# EVALUATION OF THE EFFECT OF SUBJECT AGE, HEPATIC FUNCTION AND THE CO-ADMINISTRATION OF THE $H_2$-RECEPTOR ANTAGONIST, CIMETIDINE ON THE PHARMACOKINETICS AND PHARMACODYNAMICS OF THE $H_1$-RECEPTOR ANTAGONIST, HYDROXYZINE, AND ITS ACTIVE METABOLITE CETIRIZINE IN HUMANS AND RABBITS

by

XUEYU CHEN

A THESIS SUBMITTED TO THE FACULTY OF GRADUATE STUDIES
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

Department of Chemistry and Faculty of Pharmacy
University of Manitoba
Winnipeg, Manitoba, Canada

ISBN 0-315-63373-5

Canada

# EVALUATION OF THE EFFECT OF SUBJECT AGE, HEPATIC FUNCTION AND THE CO-ADMINISTRATION OF THE $H_2$-RECEPTOR ANTAGONIST, CIMETIDINE ON THE PHARMACOKINETICS AND PHARMACODYNAMICS OF THE $H_1$-RECEPTOR ANTAGONIST, HYDROXYZINE, AND ITS ACTIVE METABOLITE CETIRIZINE IN HUMANS AND RABBITS

BY

XUEYU CHEN

A thesis submitted to the Faculty of Graduate Studies of the University of Manitoba in partial fulfillment of the requirements of the degree of

DOCTOR OF PHILOSOPHY

# Abstract

The effects of age, hepatic function, and the co-administration of cimetidine on the pharmacokinetics and pharmacodynamics of hydroxyzine and its active metabolite, cetirizine, were studied in humans and rabbits. HPLC methods were used to measure serum hydroxyzine, serum and urine cetirizine concentrations. Histamine-induced wheals and flares in the skin were used as a measure of antihistaminic activity.

Both age and hepatic dysfunction reduced the elimination of hydroxyzine and cetirizine due to decreased drug metabolism, and decreased renal excretion in humans. The elderly, and patients with primary biliary cirrhosis were more sensitive to changes in drug concentrations in the body than young adults were, and had prolonged antihistaminic effects. The pharmacokinetics of cetirizine in children were not different from those in young adults. Cetirizine significantly suppressed histamine-induced skin wheals and flares for more than 24 hours after a single oral dose of 5 mg or 10 mg cetirizine in children.

The coadministration of cimetidine inhibited the elimination of both hydroxyzine and cetirizine in rabbits. However, cimetidine did not cause any significant changes in hydroxyzine and cetirizine pharmacodynamic parameters. It was concluded that the enhanced therapeutic efficacy of hydroxyzine and cimetidine was due to the pharmacokinetic interaction, instead of the involvement of $H_2$-receptors in the histamine-induced cutaneous response.

Carbon tetrachloride induced hepatic failure in rabbits. The metabolism of hydroxyzine and cetirizine was inhibited in rabbits with hepatic dysfunction. However, results obtained in rabbits could not be directly extrapolated to humans.

Dosage regimens for hydroxyzine and cetirizine may need to be modified in patients with reduced hepatic and renal function due to age or diseases. The coadministration of cimetidine will affect the elimination of hydroxyzine and cetirizine.

# Acknowledgement

I would like to express my deep gratitude to my advisor, Dr. K. J. Simons for his guidance, encouragement, and assistance throughout this study. I am also grateful to Dr. F. E. R. Simons of Department of Pediatrics, Faculty of Medicine for kindly reading this thesis and offering many helpful criticisms.

I also wish to thank the other members of my advisory committee: Dr. C. Briggs of the Faculty of Pharmacy and Drs. A. Chow and H. Guesser of the Department of Chemistry, Faculty of Science for their advice, and helpful discussions in preparation of this thesis.

Finally, I wish to thank my parents and family for their continued support, understanding and encouragement from the other side of the world.

# Table of Contents

# List of Figures

# List of Tables

# Glossary

| | |
|---|---|
| Al.Phos.: | Alkaline Phosphatase |
| $A_0$: | the area of wheal and/or flare at time 0 |
| $A_t$: | the area of wheal and/or flare at time t |
| $AUC_{0->\infty}$: | the area under the concentration versus time curve from zero to infinity |
| $AUC_{0->t}$: | the area under the concentration versus time curve from zero to time t |
| $AUMC_{0->\infty}$: | the area under the first moment of serum concentration versus time curve |
| $\alpha$ and $\beta$: | roots of the quadratic equation $r^2 + (K12+K21+K10)\ r + K21 \cdot K10 = 0$. |
| Ce: | the hydroxyzine concentration at the effect compartment |
| Ce': | the cetirizine concentration at the effect compartment |
| Cls: | the systemic clearance |
| Clr: | the renal clearance |
| $C_{max}$: | the maximum serum concentration of hydroxyzine or cetirizine |
| CNS: | the central nervous system |
| C.V.: | the coefficient of variation |
| E: | the pharmacologic effect produced by hydroxyzine and/or cetirizine expressed as the percent suppression of histamine induced wheal and flare |
| $E_{max}$: | the maximum pharmacologic effect produced by hydroxyzine and/or cetirizine |

$EC_{50}^{H}$: the hydroxyzine concentration required to achieve half of the maximum effect

$EC_{50}^{C}$: the cetirizine concentration required to achieve half of the maximum effect

F: the oral bioavailablity

F-value: the F value for given degrees of freedom and $\alpha$

$K_{1e}$: the first-order intercompartment transfer rate constant of hydroxyzine from the central compartment to the effect compartment

$K_{1e}'$: the first-order intercompartment transfer rate constant of cetirizine from the central compartment to the effect compartment

$K_{10}$: the first-order elimination rate constant of hydroxyzine

$K_{12}$: the first-order intercompartment transfer rate constant of hydroxyzine from the central compartment to the peripheral compartment

$K_{21}$: the first-order intercompartment transfer rate constant of hydroxyzine from the peripheral compartment to the central compartment

K: the first-order elimination rate constant of cetirizine after hydroxyzine administration

$K_{e0}$: the first-order elimination rate constant of hydroxyzine from the effect compartment

$K_{e0}'$: the first-order elimination rate constant of cetirizine from the effect compartment

Km: the first-order rate constant of cetirizine formation from hydroxyzine

LDH: lactate dehydrogenase

MRT: the mean residence time

| | |
|---|---|
| PBC: | primary biliary cirrhosis |
| PR>F: | the significance probability value associated with the F value |
| PR>t: | the significance probability value associated with the t value |
| R: | the ratio of cetirizine $AUC_{0->\infty}$ to hydroxyzine $AUC_{0->\infty}$ |
| γ-GT: | γ-glutamyl transferase |
| S.D.: | standard deviation |
| S.E.: | an asymptotic valid standard error of the estimate |
| SGOT: | serum glutamic oxaloacetic transaminase |
| SGPT: | serum glutamic pyruvic transaminase |
| t-value: | the t value for a given degree of freedom and α |
| $T_{1/2}$: | the elimination half-life |
| $T_{max}$: | the time to reach the maximum serum concentration |
| $V_1$: | the volume of distribution of the central compartment |
| V': | the apparent volume of distribution of cetirizine |
| Vβ: | the apparent volume of distribution |
| $(Xu)_{0-24}$: | the total amount of cetirizine excreted in the urine from 0 to 24 hours |

# Chapter I Introduction

## 1.1 Histamine

### 1.1.1 Chemistry

Histamine ( ß-aminoethylimidazole), which is comprised of an amino group connected by a two-carbon atom chain to an imidazole ring, is a physiologically active, endogenous substance discovered in the early 1900's (1,2).

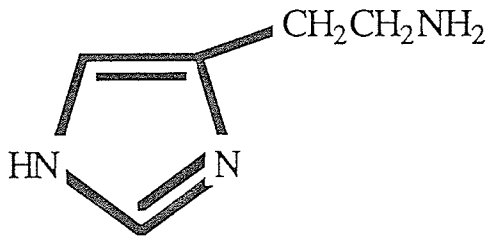



Fig.1 The chemical structure of histamine

It is formed by the decarboxylation of the amino acid histidine catalyzed by the enzyme L-histidine decarboxylase (Fig.2).

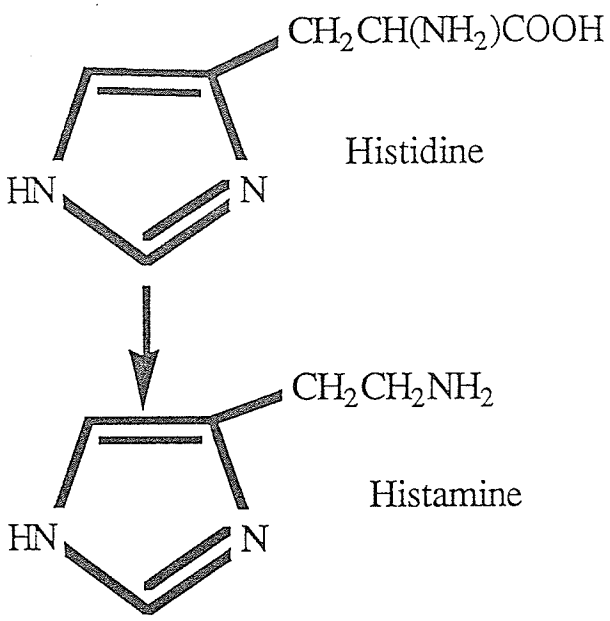



Fig.2 The biosynthesis of histamine

Both the amino and the imidazole groups of the histamine molecule are basic, and thus are protonated in acidic solutions. Titration of histamine in aqueous solution gives three pKa values. The first one (pKa=5.8) corresponds to the dissociation of the ring -NH-, and the second (pka=9.4) corresponds to dissociation of the side chain $-NH_3^+$ group. In strong alkali, the ring ionises at -N- (pKa=14) to give an anion.

The imidazole ring is rigid and planar, and is an aromatic system with $6\pi$ electrons, incorporating two types of nitrogen atoms. It is tautomeric and exists in neutral solutions in two different forms, in which only one of the nitrogen atoms carries a proton. The single carbon-carbon bonds in the side chain permit rotation, resulting in different conformations of the molecule. Thus, histamine in aqueous solution is a mixture of many species undergoing rapid interconversion, e.g., ionic forms, tautomers and conformers. These species differ in electronic charge, position of hydrogen atoms and overall shape. However, the

importance of these properties in controlling the biological activity of histamine is not yet clearly understood (2). It is generally accepted that the pharmacologically active form at both $H_1$ and $H_2$-receptor is the monocationic $N_3$-H tautomer.

Histamine is a very hydrophilic molecule. It has a strong capacity for hydrogen bonding, in which both the ammonium and imidazolium cations act as hydrogen donors and the uncharged ring acts both as hydrogen donor and acceptor. All nitrogen atoms in a histamine molecule are negatively charged, while there is little net charge on the carbon atoms. The positive charge is distributed widely over all hydrogen atoms, but tends to be concentrated on all N-H hydrogens (2).

### 1.1.2 Pharmacology

Histamine is found in most tissues of the body. It is present in high concentrations in the lung and skin. High concentrations are also found in the gastrointestinal tract, partly due to the large number of mast cells in the gastrointestinal tract and partly due to the presence of histamine in mast-cell like histaminocytes in the stomach (1,3).

At the cellular level, histamine is stored mainly in tissue mast cells, or in blood basophils. These cells can synthesize histamine by the decarboxylation of histidine and store it in secretory granules as the inactive form, histamine-glycosaminoglycan (heparin) complex, formed by ionic forces. Histamine is stored in the granules at a concentration of approximately 5 μg per million cells. Nonmast-cell sites of histamine formation and storage include cells of the human epidermis, cells in the gastric mucosa, neurons within the central nervous system, and cells in regenerating or rapidly growing tissues.

Histamine is released from its storage sites as the free active form by a secretory process during inflammatory and allergic reactions. The secretion of histamine can be initiated when an antigen, such as animal dander, pollen, food, stinging insect venom, or certain drugs such as the penicillins, combines with and bridges adjacent molecules of reaginic antibodies (IgE) attached to the mast cell and basophil surface, or when complement components $C_{3a}$ and $C_{5a}$ interact with specific receptors on the cell surface. The ensuing process involves a series of reactions that require calcium and metabolic energy and terminates with the extrusion of the contents of secretory granules by the process of exocytosis. Among the reactions involved in the process are: activation of proteases, methylation of phospholipids, opening of membrane calcium channels and mobilization of calcium ions, activation of phospholipase $A_2$ and arachidonate metabolism, reduced cyclic AMP synthesis, and enhanced protein phosphorylation. Other pro-inflammatory substances released together with histamine in allergic conditions are leukotrienes, prostaglandins, kinins, serotonin, platelet-activating factor, etc (1,3). Histamine can also be released directly from its storage sites as the active form by some drugs such as opiates, by peptides, and by other chemical agents such as compound 48/80 and other surfactants.

Each of the above mentioned classes of histamine-releasing agents can set up the classical, energy-dependent secretory response of the mast cells or the basophils, and they may produce this effect in each instance by causing a rise in the intracellular concentration of calcium ions. Some agents are ionophores and can transport calcium into the cells; others act like specific antigens to increase the membrane permeability of calcium; the rest act principally by mobilizing calcium from cellular sources.

In other clinical conditions, such as cold urticaria, vibratory urticaria, solar urticaria, unfavorable physical conditions can cause the release of histamine in susceptible patients. Histamine release also occurs whenever there is nonspecific cell damage from any causes.

Upon release from its storage sites, histamine exerts its physiological effects through two types of receptors: $H_1$ and $H_2$ receptors (1,2,3,4,5,9). The classification of these receptors is based primarily on the use of highly specific and competitive antagonists. Recently, a third type of receptor, the $H_3$ receptor, which may be involved in the feed-back control of histamine release and synthesis, has also been described (6,7,8). There is also evidence that histamine may mediate growth (124) and act as an intracellular messager (125) via low-affinity, non-$H_1$, non-$H_2$, and non-$H_3$ receptors. None of these histamine receptors have been isolated and identified. Knowledge of their structures is inferred from pharmacological studies of structure-activity relationships of histamine agonists and antagonists. Both $H_1$ and $H_2$ receptors are considered to be components of cell surface structures.

The combination of histamine with both $H_1$ and $H_2$ receptors exerts a predominantly dilatal effect on the vasculature that involves the finer blood vessels, resulting in flushing, lowered total peripheral resistance and a fall in systemic blood pressure. In addition, histamine can also increase the permeability of post-capillary venules, yielding an outward passage of plasma protein and fluid into extracellular spaces, an increase in the flow of lymph and its protein content, and the formation of edema. In skin, this process leads to the " triple response" following intradermal histamine injection:

1) A localized red spot extending a few millimetres around the site of injection. It appears within a few seconds after the injection, and reaches a maximum in about a minute. This red spot soon acquires a bluish tint. It is due to the vasodilatation of the smaller arterioles and precapillary sphincters.

2) A brighter red flush or "flare" of irregular outline, extending about 1cm or so beyond the original red spot and developing slowly. This is due to an axon reflex, which involves stimulation of sensory fibres and the passage of antidromic impulses through neighbouring branches of the same nerve with the release of a vasodilator mediator, probably substance P (1,3).

3) A wheal that is discernible in 1 to 2 minutes and occupies the same area as the original small red spot at the injection site. It fades away in about 10 minutes. This is due to the increased permeability of the post-capillary venules (1,3).

Histamine is also a powerful gastric secretagogue and evokes a copious secretion of gastric juice of high acidity as a result of $H_2$-receptor activation. Other physiological effects of histamine include direct stimulation of smooth muscles in various tissues, contraction of the gut, and contraction of large blood vessels. Histamine can also stimulate sensory nerve endings to cause itching (1,2,3).

The mechanism of the $H_1$-receptor activation is not clear, however, a mechanistic model for the activation process at the $H_2$-receptor site has been proposed. In this model, histamine, predominantly in the monocationic form, approaches the receptor as the $N_3$-H tautomer. The cationic side chain is anchored, the neutralization causes a shift in the tautomeric preference from $N_3$-H to $N_1$-H. $N_1$ then picks up a proton from

a proton donor site on the receptor, while $N_3$ acts as a proton donor for a proton acceptor site with which histamine is interacting. The change in the tautomeric preference thus leads to a proton relay process at the receptor to trigger the biological response (2,10,11).

Histamine is used clinically as a diagnostic agent, such as in the diagnosis of pheochromocytoma (4).

1.1.3 Absorption, metabolism and excretion

Histamine is readily absorbed after parenteral injection and acts rapidly when given by the subcutaneous or intramuscular route. When administered orally, a large amount of histamine can be given without causing any effects. Histamine is converted by intestinal bacteria to inactive N-acetylhistamine, and any histamine which is absorbed is rapidly inactivated as it traverses the intestinal wall or circulates through the liver (1).

There are two major routes of histamine metabolism. The more important route involving ring methylation is catalyzed by the enzyme histamine-N- methyltransferase, which is specific for histamine and is widely distributed in tissues. Most of the product, N-methylhistamine, is then converted by monoamine oxidase (MAO) to N-methylimidazole acetic acid (Fig.3) (1,3).

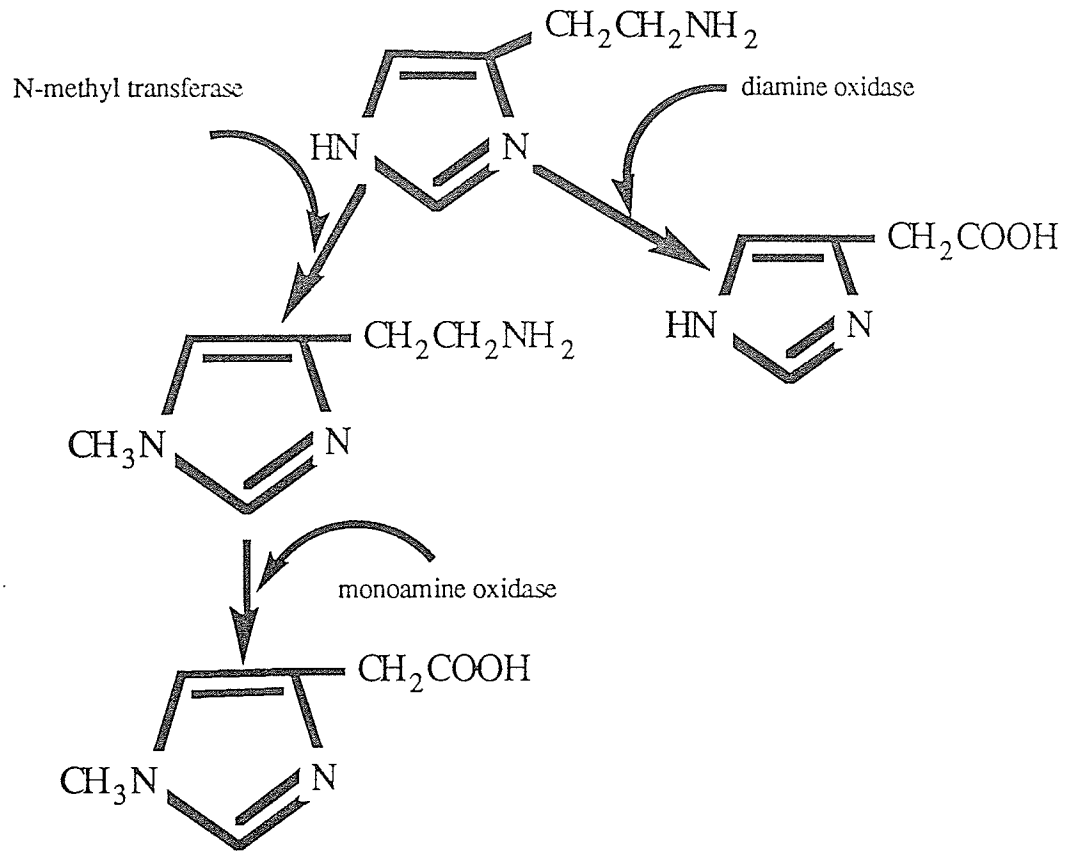



Fig.3 The metabolic pathways of histamine

Histamine also undergoes oxidative deaminization catalyzed mainly by the nonspecific enzyme diamine oxidase (DAO) to imidazole acetic acid, and eventually to its riboside. The various metabolites, which have little or no pharmacological activity, are excreted in the urine. Only 2-3% of a histamine dose is excreted unchanged in the urine after parenteral administration (1,3).

## 1.2 Histamine antagonists

### 1.2.1 Classification of histamine antagonists

Histamine antagonists are currently classified as $H_1$ and $H_2$-receptor antagonists depending on the types of receptors with which they interact. Histamine antagonists act competitively and reversibly (1,2,3,4).

### 1.2.2 $H_1$-receptor antagonists

#### 1.2.2.1 Classification and the basic structure

Histamine $H_1$-receptor antagonists, commonly known as $H_1$-receptor antagonists were discovered in the late 1930's. After the initial discovery of $H_1$-receptor antagonists reported in 1937 by Bovet and Staub (12), hundreds of compounds have been synthesized and tested for antihistaminic activity, and about 30 of them have been used clinically since the 1940's. Most classical $H_1$-receptor antagonists have the same basic structure: a substituted ethylamine-like histamine (1,4). They have a tertiary amino group linked by a two-, or three atom chain to two aromatic substituents and conform to the general structure shown in Fig.4.

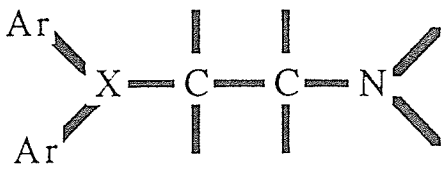



Fig.4 The general structure of $H_1$-receptor antagonists

This structure encompasses the following features:

1) one Ar could be aryl, e.g., phenyl, substituted phenyl, or heteroaryl-, e.g., 2-pyridyl-.

2) the second Ar could be arylmethyl or a second aryl group. These two Ars may together form another ring system, or related tricyclic structures.

3) X is oxygen, nitrogen, or carbon connecting the side chain to the aromatic ring system in various ways.

4) C-C represents a short chain of carbon atoms which may be saturated, branched, contain a double bond, or be part of a ring system.

5) the terminal -N- is generally a tertiary amino group, most commmonly dimethylamino-, or pyrolidino- (1,2,3,4).

The above features not only respresent general similarities in structure but also indicate a great diversity in the detailed chemistry of individual $H_1$-receptor antagonists. $H_1$-receptor antagonists can be classified on the basis of X substitutions into six groups:

1) ethylenediamine derivatives

This group of $H_1$-receptor antagonists has nitrogen in the X position. Drugs used clinically from this group include antazoline, tripelennamine, pyrilamine, and methapyrilene.

2) ethanolamine derivatives

This group has oxygen in the X position. Drugs in this group include clemastine, diphenhydramine, dimenhydrinate, bromodiphenydramine, doxylamine, carbinoxamine, diphenylpraline, and phenyltoloxamine. They have substantial anticholinergic activity, and cause considerable sedation and CNS effects.

3) propylamine (alkylamine) derivatives

The $H_1$-receptor antagonists in this group contain a carbon atom on the X position, such as chlorpheniramine, brompheniramine, pheniramine, dexchlorpheniramine, dexbropheniramine, dimethindene, pyrrobutamine, and tripolidine.

4) phenothiazine derivatives

In this group of $H_1$-receptor antagonists, nitrogen is in the X position as part of a phenothiazine nucleus. Methdilazine, promethazine and trimeprazine are among drugs from this group which are used clinically.

5) piperazine derivatives

In this group, nitrogen is present in the X position as part of a piperazine nucleus. Hydroxyzine, cetirizine, buclizine, meclizine, chlorcyclizine, and the cyclizines are in this group.

6) piperidine derivatives

In this group, nitrogen is present in the X position as part of a piperidine nucleus. Azatadine, loratadine, ketotifen, and cyproheptadine are in this group.

7) others

Drugs that can not be ascribed to the above six groups are classified into this group. Examples are terfenadine, astemizole, mequitazine, and phenindamine (1,4).

1.2.2.2 Mechanism of action

$H_1$-receptor antagonists are sufficiently similar in structure to histamine so that they bind competitively to the $H_1$-receptor sites on the target cell surface, yet sufficiently different so that it is impossible for $H_1$-receptor antagonists to act as $H_1$-receptor agonists. $H_1$-receptor antagonists do not chemically inactivate or physiologically antagonize histamine (1,4), however, some $H_1$-receptor antagonists, including terfenadine, loratadine, and azatadine, prevent release of inflammatory mediators from IgE-sensitized mast cells and basophils (126,127).

The dominant physico-chemical property of $H_1$-receptor antagonists appears to be lipophilicity, conferred by the aryl groups, and basicity determined by the amino side chain. Almost all $H_1$-receptor antagonists are tertiary amines which have pKa values sufficiently high for protonation to occur at the physiological pH of approximately 7.4. Therefore, although $H_1$-receptor antagonists and histamine appear to compete for the same receptors, they do not necessarily interact with precisely the same set of atoms at the receptor site. It is hypothesized that agonists of $H_1$-receptors, such as histamine, are highly polar and react with receptors at sites which are rich in polar groups, i.e., in a strongly hydrophilic region, while, in the vicinity, there may be a less specific lipophilic region which serves as a complementary area to the hydrophobic rings found in $H_1$-receptor antagonists (2).

1.2.2.3 Efficacy tests of $H_1$-receptor antagonists

The efficacy of $H_1$-receptor antagonists can be evaluated by using a number of pharmacodynamic models (23), including cutaneous (13,14,15), nasal (16,17), pulmonary (18,19) and central nervous system (20) models. Among these models, the cutaneous model is the most widely used and most objective model. In the cutaneous model, histamine, allergen or some histamine releasing agent is injected intradermally or epicutaneously, resulting in the formation of a wheal and flare. The presence of an $H_1$-receptor antagonist will inhibit the formation of wheal and flare. Wheal and flare produced with and without the presence of $H_1$-receptor antagonists can then be outlined on the skin and traced on paper. The resulting image can be cut and weighed on a balance (14), or the mathematical product of the crossed diameters of wheal and flare can be used to quantify drug effects (21). More recently, digitizers connected to personal computers have been used to measure areas of irregularly shaped wheal and flare (13,22).

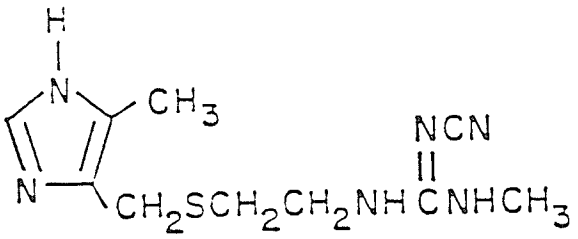
1.2.3 $H_2$-receptor antagonists

After the rapid development and wide clinical application of $H_1$-receptor antagonists, it was found that none of these drugs blocked all of the effects of histamine, particularly the stimulation of gastric acid excretion. In 1972, a new and chemically distinct class of drugs that selectively blocks the stimulant effect of histamine on gastric acid secretion was introduced after several hundreds of compounds were synthesized and tested (24,25). These agents also suppressed other responses to histamine that were refractory to the $H_1$-receptor antagonists. This discovery resulted

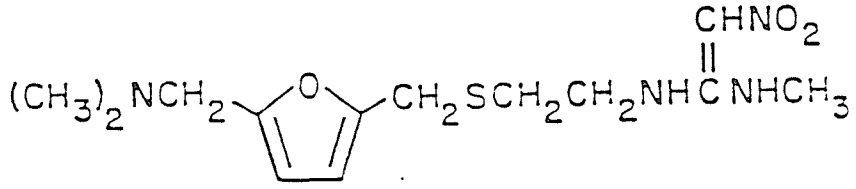
in the differentiation of two populations of histamine receptors, and this new group of drugs were subsequently named $H_2$-receptor antagonists.

The $H_2$-receptor antagonists were synthesized by the stepwise modification of the histamine molecule. Therefore, the chemical structure of some of the $H_2$-receptor antagonists are similar to that of histamine. However, they differ from histamine in two important respects: first, the side chains of $H_2$-receptor antagonists are longer, and are not basic, i.e., the side chains are not charged at the physiological pH; secondly, the imidazole ring is a base and it exists as a mixture of charged and uncharged forms at pH 7 (2). $H_2$-receptor antagonists differ remarkably in chemical structures from the $H_1$-receptor antagonists, and they are less basic and much less lipophilic. Cimetidine was the first $H_2$-receptor antagonist to be used clinically (2). Other examples of $H_2$-receptor antagonists are ranitidine and famotidine. Their chemical structures are shown in Fig.5.

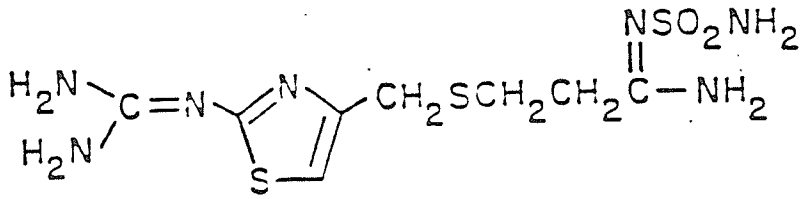
$H_2$-receptor antagonists are reversible, competitive antagonists of the actions of histamine on $H_2$-receptors. They are highly selective in their action and are without effect on $H_1$-receptors (1,3,4). $H_2$-receptor antagonists are used clinically for the treatment of gastric ulcer, Zollinger-Ellison syndrome, and other conditions such as reflex esophagitis, stress ulcers, and upper gastrointestinal tract bleeding. Their potency appears to be inversely related to hydrophilicity. It is hypothesized from many structure-activity studies that $H_2$-receptor antagonists act at a highly polar site where the dominant interactions are hydrogen bonding, probably as a result of a cluster of donor-acceptor atoms at the membrane surface (2,12).



Cimetidine



Ranitidine



Famotidine

Fig.5. Chemical structures of cimetidine, ranitidine, and famotidine

## 1.3 Hydroxyzine

### 1.3.1 Chemistry

Hydroxyzine hydrochloride, 2-[2-[4-[(4-chlorophenyl) phenylmethyl] -1-piperazinyl]ethoxy]-ethanol dihydrochloride ($C_{21}H_{27}ClN_2O_2$ . 2HCl, MW 447.8, Fig.6), is a piperazine-type $H_1$-receptor antagonist. It is structurally similar to buclizine, cyclizine, and meclizine (4,26). Hydroxyzine was one of many piperazine derivatives synthesized by Morren *et al* (27,28) in early 1950's. It occurs as a white, odorless powder and is very soluble in water and freely soluble in alcohol. Hydroxyzine has pKa values of 2.6 and 7.0 (4).

### 1.3.2 Pharmacology

The pharmacological effects of hydroxyzine are similar to those of other $H_1$-receptor antagonists. It competes competitively with histamine for $H_1$-receptor sites on cell surfaces, thereby preventing responses mediated by histamine. It has CNS depressant, anticholingeric, antispasmodic, and local anesthetic activity which may be due to a suppression of activity in certain key regions of the subcortical area of CNS. It also has sedative and antiemetic activity. These effects may be due to the fact that hydroxyzine can cross the blood-brain barrier and produce sedation by occupying $H_1$-receptors in the brain which are involved in the control of states of wakefulness. Hydroxyzine does not inhibit gastric acid secretion nor does it increase gastric pH. It may have mild anticholinergic effects (4).

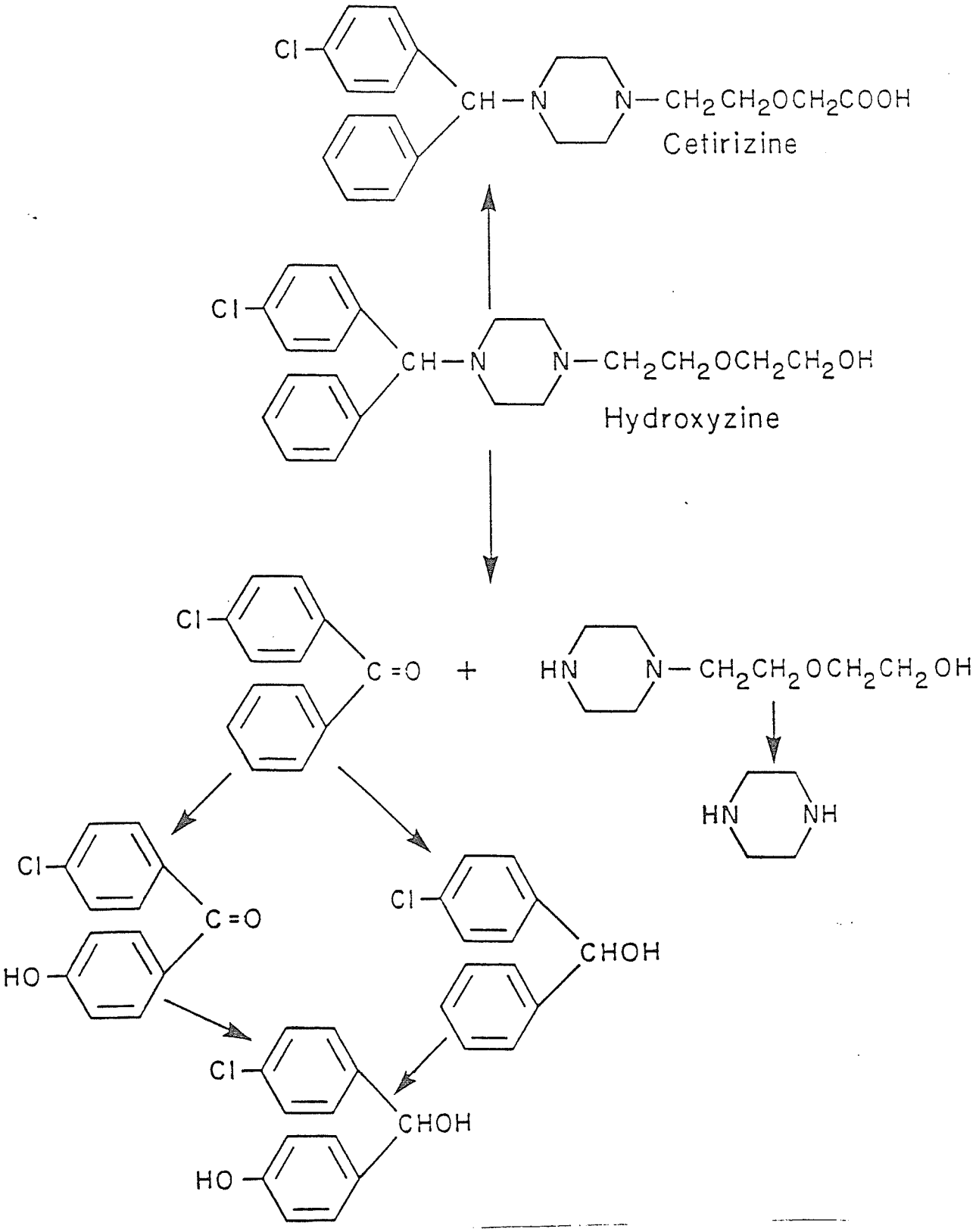



Fig.6. The metabolic pathways of hydroxyzine

Hydroxyzine is used for the symptomatic management of allergic disorders such as urticaria, atopic dermatitis (eczema), histamine-mediated pruritus, and allergic rhintis. It is also used as an adjunctive treatment in some patients with disease states associated with anxiety (4,29).

1.3.3 Analysis

There are various analytical methods for measuring $H_1$-receptor antagonists' concentrations. Procedures for hydroxyzine detection by TLC (39) and electrophoresis (40) do not have the sensitivity and specificity necessary for analysing of biological samples. GLC (41,42) methods have been described, but the flame-ionization detection was not sufficiently sensitive for measuring drug concentration in plasma samples. It was suggested that only the use of Mass Spectrometric detection following GLC separation could provide sufficient sensitivity (42).

Fouda *et al* (32) reported a GLC-MS procedure for the determination of the acetate derivative of hydroxyzine in human plasma following the administration of 100 mg hydroxyzine tablets. This method has a sensitivity of 2 ng/ml and makes use of a pentadeuterated analog as the internal standard. Gengo *et al* (35) reported a GLC method for determining serum hydroxyzine concentrations with a sensitivity of 2.5 ng/ml using ethoxy hydroxyzine as the internal standard and a thermionic detector.

An HPLC method for the analysis of hydroxyzine in blood samples was reported by Simons *et al* (33,34,92). The sensitivity of this method was reported to be 3 ng/ml. This method and modification of this method were

subsequently used to analyze serum hydroxyzine concentrations in our laboratory with the sensitivity improved from 3 ng/ml to 1 ng/ml.

1.3.4 Pharmacokinetics

Although $H_1$-receptor antagonists have been used clinically for more than four decades, little was known about their clinical pharmacokinetics until the last decade. Even now, there is still a lack of information about the pharmacokinetics of a large number of $H_1$-receptor antagonists. Furthermore, the information available is sometimes conflicting and confusing. There are several reasons for this:

1) many $H_1$-receptor antagonists were introduced into clinical practice before the concept of pharmacokinetics was developed.

2) $H_1$-receptor antagonists are generally present in low concentrations in body fluids, usually in the range of 1 ng/ml to 1 μg/ml. It is only recently that analytical instruments with sufficient sensitivity and specificity to measure serum concentrations of $H_1$-receptor antagonists and their metabolites in biological fluids have become widely available to research pharmacokineticists.

3) these drugs generally produce relatively minor adverse effects. The therapeutic range of $H_1$-receptor antagonists is considered to be relatively wide, thus making it unnecessary for routine monitoring of serum concentrations of $H_1$-receptor antagonists (30,31).

However, since $H_1$-receptor antagonists are frequently prescribed and widely used as non-prescription medications, the adverse effects produced by $H_1$-receptor antagonists such as blurred vision, drowiness, and dizziness cannot be ignored. These side effects can sometimes lead to fatal consequences, in cases where individuals perform potentially hazardous

tasks requiring mental altertness or physical coordination, such as operating machinary or driving a motor vehile. Also, these adverse effects may be aggravated by the coadministration of alcohol or other CNS depressants. It is apparent that better understanding of the clinical pharmacokinetics of the $H_1$-receptor antagonists is important.

The pharmacokinetics of hydroxyzine requires further investigation, as even recent studies (32,33,34,35) provide conflicting results.

1.3.4.1 Absorption

Hydroxyzine is believed to be absorbed quickly and consistently from the gastrointestinal tract after oral administration (4). The onset of sedation may occur 15 to 30 minutes after oral administration. Fouda *et al* (32) found that the mean maximum serum concentration of hydroxyzine of about 80 ng/ml occurred at about 3 hours in four male volunteers after oral administration of 100 mg hydroxyzine tablets. Simons *et al* (33,34) observed that the peak serum concentrations of 72.5 and 47.4 ng/ml occurred at about 2 hours in 7 adults and 12 children respectively, after an oral administration of hydroxyzine syrup, 0.7 mg/kg. Gengo *et al* (35) reported that the average peak concentrations of 29 ng/ml occurred at 2 hours in 12 male volunteers after an oral administration of 25 mg hydroxyzine capsule.

There are no bioavailability studies of hydroxyzine available, since no intravenous formulation is commercially available. Severe adverse effects, such as marked local discomfort and sterile abcesses, have occurred at the site of I.M. injections. When the I.M. formulation is administered by intra-arterial injection, thrombosis and digital gangrene necessitating

amputation have occurred, while phlebitis and hemolysis may occur following I.V. administration.

1.3.4.2 Distribution

The distribution of hydroxyzine into human body tissues and fluids has not been fully characterized.

Following the administration of hydroxyzine, it is believed that the drug is widely distributed into body tissues and fluids, with high concentrations in the liver, lung, spleen, kidney, and adipose tissues. In a fatality due to hydroxyzine (36), the following tissue concentrations were reported: blood 39 μg/ml, brain 163 μg/g, bile 122 μg/ml, liver 414 μg/g and urine 19 μg/ml.

It was found that $^{3}$H-labelled hydroxyzine was rapidly distributed to various organs after intraperitoneal administration to rats (37). Highest specific activity was found in lung, followed by fat, liver, spleen and kidney. The apparent volumes of distribution of hydroxyzine after an oral dose of 0.7 mg/kg to children and adults were found to be 18.5 l/kg and 19.5 l/kg respectively (33,34). The above volumes were calculated by assuming that the absolute bioavailability of oral hydroxyzine is 100 percent, since no intravenous data is available.

1.3.4.3 Metabolism and excretion

The metabolism of $^{3}$H-hydroxyzine was studied with differential solvent extraction and TLC, after intraperitoneal administration to rats (37). Hydroxyzine-$^{3}$H was completely metabolized. Among the metabolites were p-chloro-p'-hydroxybenzophenone, p-chlorobenzhydrol, p-chlorobenzo-phenone, piperazine and 2-[2-(1-piperazinyl)ethoxy]ethanol.

However, a metabolic pathway was not proposed by the authors. Cetirizine, formed by the oxidation of the primary alcohol side chain to a carboxylic acid, is the major metabolite of hydroxyzine in humans. It was reported that 45% to 60% of an orally administered dose of hydroxyzine was converted to cetirizine, while the rest was metabolized to other as yet unidentified compounds (38). Hydroxyzine and its major metabolites are also excreted in the urine (4,37,38). Based on the information given above, a metabolic pathway is suggested and is shown in Fig.6.

The elimination half-life of hydroxyzine was reported by Fouda *et al* (32) to be about 3 hours after an oral dose of 100 mg hydroxyzine to 4 male volunteers. However, subsequent studies in children and adults by Simons *et al* (33,34) suggested that the elimination half-life of hydroxyzine was much longer than the previously reported 3 hours. In children, the mean $t_{1/2}$ was found to be 7.1 hours, while in adults it was about 20.0 hours in adults. A close examination of the experimental design of Fouda *et al* (32) revealed that the sampling time was only to 24 hours and there was no sample between 8 and 24 hours. It was possible that the reported half-life of 3 hours was for the distribution phase, instead of the elimination phase. Gengo *et al* (35) reported a mean elimination half-life of 14 hours after an oral dose administration of 25 mg hydroxyzine.

It was observed by Simons *et al* (33) that the elimination half-life of hydroxyzine increased with increasing age in children with a correlation coefficient of 0.83 from 1 to 14 years. The mean oral systemic clearance was 32.08 ml/min/kg in children (33), which was significantly higher than that in adults, 9.78 ml/min/kg (34). This phenomenon is consistent with the fact that most drugs metabolized by the cytochrome P-450 system have shorter elimination half-lives in children than in adults. In a more recent

study (35), a systemic clearance of 69.3 l/hr was reported. If the average body weight of the 14 male subjects is taken as 70 kg, then, the systemic clearance would become 16.5 ml/min/kg. Again, the clearance values (35) were not corrected for bioavailability since there was no intravenous data available.

### 1.3.5 Pharmacodynamics of hydroxyzine

The relationship between the serum concentration of hydroxyzine and its therapeutic effects was studied in adults using the intradermally injected histamine-induced wheal and flare as indicators of efficacy (34). At the site of histamine injection, wheals and flares were significantly suppressed ($p<0.05$) from 1 to 36 hours and 60 hours respectively after the oral administration of hydroxyzine 0.7 mg/kg in young adults. Maximal suppression of the wheals was 80% and the maximal suppression of the flares was 92%.

In children with severe, extensive atopic dermatitis, a single oral dose of hydroxyzine of 0.7mg/kg significantly suppressed pruritus ($p<0.05$) from 1 to 24 hours (33). There was greater than 85% suppression of the pruritus from 1 to 12 hours, while the mean serum hydroxyzine concentrations ranged from 41.8 to 5.6 ng/ml after this single dose. In a subsequent double-blind, crossover, multiple-dose study of 2 weeks in the same pediatric patients, hydroxyzine was administered orally every 8 hours for a week in doses of 0.7 and 1.4 mg/kg. At the end of this study, mean serum hydroxyzine concentrations were 50.6 and 85.9 ng/ml for 0.7 and 1.4 mg/kg doses respectively. The scores of atopic dermatitis severity and distribution were significantly reduced at the end of both weeks of treatment ($p<0.05$) compared with the prestudy score. There was no

significant difference between the score at the end of the week in which 1.4 mg/kg t.i.d was given and the score at the end of the week in which 0.7 mg/kg t.i.d was given. However, the dose of 1.4 mg/kg t.i.d caused significantly greater sedation ($p<0.05$).

Gengo *et al* (35) observed that the wheal diameters after 25 mg oral hydroxyzine were significantly less than those after placebo at 4, 12, and 24 hours after drug administration. An average maximum 92% reduction in wheal diameters occurred. There was no difference in skin reaction 36 hours after hydroxyzine and placebo administration.

## 1.4 Cetirizine

### 1.4.1 Chemistry

Cetirizine, 2-[2-(4((4-chlorphenyl)phenylmethyl)-1-piperazinyl) ethoxyl]-acetic acid dihydrochloride ( $C_{21}H_{26}N_2O_3CCl.2HCl$, MW 461.8), is the major metabolite of hydroxyzine in human beings. It occurs as a white powder, which is freely soluble in water, soluble in methanol, and insoluble in chloroform and acetone. Cetirizine is formed *in vivo* from hydroxyzine by an oxidative metabolism (38). The chemical structure of cetirizine is shown in Fig.6.

### 1.4.2 Pharmacology

There is very little data available with regard to the pharmacology of cetirizine since it was discovered to be pharmacologically active only a few years ago, and is still being developed for use in patients (38,44,45). Oral cetirizine has been shown to possess the antihistaminic activity of

hydroxyzine, but with few CNS effects. Cetirizine also has a smaller volume of distribution than its parent compound does, which is to be expected since cetirizine is more water soluble than hydroxyzine is. The presence of the carboxylic acid group makes cetirizine more hydrophilic, thus making it more difficult for cetirizine to penetrate the blood-brain barrier. This fact could possibly explain cetirizine's lack of sedative effects.

De Vos *et al* (44) studied the inhibition of histamine, and allergen-induced skin reactions in four animal species (mice, rats, guinea pigs and dogs) by cetirizine, mepyramine, clemastine, hydroxyzine, and terfenadine. They observed that cetirizine was the most potent of the five $H_1$-receptor antagonists tested when given orally. In rats, the cetirizine dose that reduced the reaction by 50% in comparison to controls was 4.2 μmol/kg, while in other species, the dose was between 0.1 and 0.4 μmol/kg.

Snyder and Snowman (45) evaluated the activity of cetirizine, hydroxyzine and terfenadine at central $H_1$-receptor sites. They also compared the ability of cetirizine to cross the blood-brain barrier to those of three other $H_1$-receptor antagonists: hydroxyzine, chlorpheniramine and terfenadine. Cetirizine, hydroxyzine and terfenadine have similar potencies on brain $H_1$-receptors as on lung $H_1$-receptors, although hydroxyzine is four to six times more potent than either cetirizine or terfenadine. They also found that hydroxyzine and chlorpheniramine cross the blood-brain barrier much more easily than cetirizine and terfenadine do.

It was found in the same study (45) that cetirizine was highly selective for $H_1$-receptors. Cetirizine does not bind to serotonin 5-$HT_2$, dopamine $D_2$, adrenergic, dihydroporphrin, calcium-antagonist, and verapamil calcium-antagonist receptors, while both hydroxyzine and terfenadine do so. *In vivo* experiments conducted to evaluate these drugs'

occupancy of $H_1$-receptor in the brain after peripheral administration demonstrated that cetirizine did not significantly penetrate the blood-brain barrier in contrast to hydroxyzine. At 10 mg/kg, chlorpheniramine and hydroxyzine occupied the majority of the central histamine $H_1$-receptor sites, while at 30 mg/kg, terfenadine occupied 70% of brain $H_1$-receptor sites, and cetirizine occupied only about 34% of brain $H_1$-receptor sites.

### 1.4.3 Analysis

Analytical methods for determining serum cetirizine concentration by GC (38) and HPLC (46,47) have been reported, with sensitivity limits of 10 ng/ml and 2 ng/ml respectively.

### 1.4.4 Pharmacokinetics

The pharmacokinetics of cetirizine (38,43,44,45) to date have been determined in animal species.

In animals, cetirizine is rapidly absorbed after oral administration with peak concentrations occurring at about 1 hour. The bioavailability is from 80 to 100% in mice, rabbit and dogs, but only 40% in rats (38). About 30% of a dose of cetirizine is excreted unchanged in the urine in monkeys, mice and dogs, while over 60% is excreted unchanged in rabbits. The elimination half-life is 0.6 hour in rats, about 9.0 hour in dogs, 2.3 hour in rabbits, 3.2 hour in mice, and 1.4 hour in monkeys(38).

After radiolabelled cetirizine was given orally to rats, mice, rabbits and dogs, high radioactivity was found in organs such as liver, kidney, lung, spleen etc, while very low levels of radioactivity were found in cerebrum and cerebellum indicating low blood-brain barrier penetration; and no accumulation in the brain was found (38).

In a study by Wood *et al* (46), $^{14}C$-labelled cetirizine was given to six human volunteers. It was found that the drug was rapidly absorbed with peak serum concentrations of radioactivity achieved within one hour. The mean peak cetirizine concentration was found to be 359 ng/ml. The elimination half-life was 7.4 hours. About 60% of the radioactivity was excreted during the first day, with another 10% or so excreted during the next four days. About 10% of the dose was excreted in the feces. A close examination of radioactive compounds excreted in urine showed that only a small percentage of a dose of cetirizine was metabolized in man by the oxidative o-dealkylation of the side chain to $P_{026}$.

Gengo *et al* (35) found that the elimination half-life of cetirizine in 20 healthy volunteers was about 7 hours. This value was confirmed by another study by Matzke *et al* (47), who found that the mean $t_{1/2}$ of cetirizine in 14 adults was 7.4 hours. The same group of investigators (47) also found that cetirizine pharmacokinetic parameters correlated with both age and renal function, however, the effect of renal function was more important than that of age. In patients with a mean creatinine clearance of 44±11 ml/min, the half-life of cetirizine was 19.2±3.3 hours, while in patients with a mean creatinine clearance of 19±10 ml/min, the half-life was prolonged to 20.9±4.4 hours. In 16 elderly patients with various degrees of renal deficiency, the $t_{1/2}$ was 11.8 hour. This might be caused by the reduced renal function in the elderly as a consequence of the natural aging process.

Lefebvre *et al* (115) also studied the pharmacokinetics of orally administered cetirizine in 10 elderly volunteers, 60 to 90 years, and in 10 young healthy subjects, 21 to 29 years. It was found that about 60% of an oral dose of 10 mg cetirizine was excreted unchanged in the urine 32 hours

after drug administration in young healthy volunteers, while only about 50% was excreted unchanged in the elderly during the same time period. It was also found that mean plasma concentrations were slightly higher in the elderly, and pharmacokinetic parameters including $C_{max}$, $T_{max}$, $T_{1/2}$, $AUC_{0->\infty}$ were also slightly higher in the elderly, but the differences were not significant. They concluded that the slight differences in pharmacokinetics of cetirizine between young and elderly subjects could be attributed to the decreased renal clearance in the elderly.

### 1.4.5 Pharmacodynamics

There is also limited information about the pharmacodynamics of cetirizine. In a random, double blind cross-over study by Brik *et al* (48), three different doses of cetirizine 5 mg, 10 mg and 20 mg were given to 10 young adults. The bronchodilator effect and the protective effect of different doses of cetirizine against bronchospasm induced by histamine inhalation were compared to those of placebo and hydroxyzine. It was noted that all doses of cetirizine provided significantly greater protection against histamine-induced bronchospasm than hydroxyzine did ($p<0.05$).

In another study by Juhlin *et al* (49), 10 mg of oral cetirizine was found to significantly inhibit the wheal and flare induced by histamine, by 48/80, by physical factors such as pressure and cold, without any drug related adverse effects.

In a study by Rihoux and Dupont (43), the histamine cutaneous reactivity of healthy volunteers was measured after a single oral dose of placebo, terfenadine 60 mg and 180 mg, and cetirizine 2HCl 10 mg and the central nervous system side effects were evaluated by visual analog scales for drowsiness and movement coordination. It was found that the

suppression effect of cetirizine 10 mg was significantly faster, more pronounced, and longer lasting than that of terfenadine 60 mg and was equal to that of terfenadine 180 mg, while central nervous system side effects of cetirizine and terfenadine were not different from those of placebo.

In a four-way crossover study (35), single doses of hydroxyzine 25 mg, cetirizine 10 mg and 20 mg, and placebo were given to twenty volunteers. Skin wheal response to histamine, psychomotor effects, together with central nervous system effects were measured after each dose. All three active treatments produced an equivalent suppression of skin wheal response to histamine that was significantly greater than placebo ($p<0.01$). Hydroxyzine produced a significant change compared with placebo in all three CNS parameters (critical flicker frequency, Stroop word testing, and visual analog scales), while neither cetirizine 10 mg, nor cetirizine 20 mg produced any significant change in CNS parameters.

## 1.5 Factors affecting the pharmacokinetics of drugs

Pharmacokinetics is defined as the study of time course of drug absorption, distribution, metabolism and excretion, as well as the relationship of these processes to the intensity and time course of pharmacologic effects of drugs (50). It is therefore expected that many factors, such as age, sex, race, disease state and coadministration of other drugs will affect the pharmacokinetics of drugs. Although the exact mechanism of the action of many of these factors are far from certain at this time, numerous attempts have been made to clarify them (51,52,53,54,55). The effects of three of the above mentioned factors: age,

disease state and drug interaction will be discussed using hydroxyzine and cetirizine as model $H_1$-receptor antagonists.

### 1.5.1 The effect of age

Although it has long been an accepted principal in pharmacology and clinical medicine that aging in humans is one of many factors that may affect the response to drugs, the age problem is often ignored in designing appropriate dosing regimens. For the majority of drugs, the dosing regimens most frequently employed are those based upon information obtained in healthy young male adults. The elderly and children represent two distinct groups in society and there is a lack of information concerning drug response in the elderly and in children.

The elderly ( age 65 or older) represented about 10% of the world population in 1986, and this percentage is expected to increase to about 15% by the year 2000. The elderly experience a greater incidence of diseases, physical impairments and physiological disorders than younger adults do, which is supported by the fact that the elderly occupy a greater share of hospital bed and long-term health care facilities than young adults do, and they consume more drugs, about 25% of total use, than do young adults (53,56).

Generally there is a need for a great deal more information on the effect of age on drug therapy. The current literature is filled with conflicting data and contradictions arising from lack of controls for the many complicated interacting variables, improper experimental design, and inappropriate methods of data analysis or interpretation of results (55).

1.5.1.1 Absorption

Drug absorption in the elderly has not been studied extensively. Aging results in a number of alterations in the structure and function of the gastrointestinal tract (53,55,58). Among those changes which may affect drug absorption are:

1) decreased gastric acid secretion,

2) reduced gastrointestinal motility,

3) reduced splanchnic blood flow, and

4) decline in the number of, or absorptive capacity of the enterocytes.

The acidity of the gastrointestinal tract is reduced as age increases. Kekki *et al* (57) reported an age-dependent decline in gastric acid secretion in humans of both sexes and correlated this with atropic alterations in the gastric mucosa. The increase in gastric pH will probably have an adverse effect on the dissolution rates of basic drugs. It may also influence drug absorption by reducing drug stability, resulting in the production of clinically less active or inactive compounds.

The gastrointestinal muscle tone and motor activity are generally considered to be reduced in the elderly as a result of atrophy (53,55), which will result in the increase of gastric emptying time in the elderly. In one study (59), the mean gastric emptying-time was measured as the time required for 50% of initial radiolabel to exit the stomach. The investigators found that there was a significant increase in the mean gastric emptying-time, from 50 min in young adults, mean age 29, to 123 min in the elderly subjects, mean age 77. A delay in the gastric emptying may reduce the rate of absorption, but only in certain instances is it expected to influence the extent of absorption.

Gastrointestinal blood perfusion is also diminished as much as 30%-40% in some cases with age (53,55). The consequence of reduced splanchnic blood flow on drug absorption is not clear. It is likely that the rate of absorption of drugs, especially those with high lipid solubility, will decline somewhat, but there may be little effect on the extent of absorption. A reduction in blood flow may also alter the absorption of those compounds which undergo specialized transport such as iron, calcium, and galactose as a consequence of decreased delivery of oxygen and of co-factors needed to provide energy for cellular metabolism (52,53).

Aging also results in a number of changes in the structural integrity and barrier function of the gastrointestinal tract, including a proliferation of connective tissue in the lamina propria, amyloidosis, and a loss of enterocytes (53,55). Reduced intestinal absorption has been attributed to a decline in the number of viable enterocytes (112). An age-related increase in the incidence of duodenal diverticulitis (113) has also been suggested as one cause of malabsorption in the elderly. In one study (114) which examined biopsy specimens from the upper jejunum of healthy young, 16-30 years, and elderly subjects, 60-73 years, there was an average age-related reduction of about 20% in mucosal surface area. Assuming that all other factors remain constant, and that drug is absorbed by simple diffusion, the absorption rate will decrease in direct proportion to the decrease in effective absorbing membrane surface area.

Other factors that have to be considered include alteration with age of the plasma concentration of a number of hormones that influence GI action. However, the consequence of this observation is not clearly understood.

1.5.1.2 Distribution

Drug distribution in the elderly is influenced by such factors as the physiological and anatomical changes that occur with age including body composition, plasma protein binding, and tissue binding. Fat-free mass declines with age in both males and females, and fat mass increases with age from 20 to 40% (52,53,55). There is also a concomitant reduction of 10 to 25% of body water as a function of aging. The influence these changes in body composition have on drug distribution will be dependent on the physiochemical characteristics of the drug. Those compounds that distribute primarily into lean tissue or body water will probably show an age-related decrease in volume of distribution, resulting in higher peak plasma levels in the elderly versus young subjects, while compounds that distribute into fatty tissues will probably show an increase in volume of distribution.

Blood albumin concentrations decrease in the elderly, resulting in a decrease in bound drug in plasma since albumin is a major site of drug binding. The result of this decrease will be an increase in the volume of distribution (52,53,55).

It must be pointed out that the above statements concerning the effects of aging on drug distribution are only true in general terms. The results from various studies concerning specific drugs are conflicting and inclusive. Much more research must be done before firm conclusions can be reached.

1.5.1.3 Elimination

Changes in drug metabolism in the elderly are not well defined for two reasons. First of all, measurements of hepatic function have no index

of comparison that can be related to drug metabolism capacity. Attempts have been made to correlate either serum albumin concentration, or enzymatic activity such as SGOT, SGPT, or LDH to drug metabolizing capacity, but none of these correlations were statistically significant (51,60,64). Secondly, there are many variables that influence hepatic drug metabolism. Among them are disease states, concurrent drug use, nutritional status, environmental compounds, genetic difference, gender, liver mass, and blood flow (51,60).

The liver undergoes physiological and anatomic changes with age. Liver blood flow decreases at a rate of 0.5-1.5% per year after age 25, which represents a 40 to 50% decrease by the age of 65 (52,53,55). This decline in liver blood flow is partially the result of the decline in cardiac output which occurs with aging. Thus, for drugs with high hepatic extraction ratios, such as lidocaine and propanolol whose metabolism is highly dependent upon liver blood flow, such a decline in hepatic blood flow may result in reduced systemic clearance. Total liver mass also decreases with age. However, the importance of this change upon drug metabolism is not clear.

Drug metabolism can be classified into Phase I and Phase II reactions. Phase I reactions include oxidation reactions such as hydroxylation, N-dealkylation, and sulfoxidation, reduction reactions and hydrolysis reactions, while Phase II reactions include conjugation reactions with glucuronic acid, sulfate etc. The enzyme systems responsible for catalyzing Phase I reactions have been found to decrease in activity with age, leading to reduced systemic clearance for drugs undergoing Phase I metabolism such as antipyrine, diazepam and theophylline. Enzyme systems for Phase II reactions are not impaired due to aging, and drugs such as

temezepam and lorazepam which are principally eliminated by conjugation do not have reduced systemic clearances in the elderly (62,63,64)

Renal excretion is the other major route of drug elimination. The changes in renal function with age were better defined than the changes of hepatic function with age, mainly because there are standard, easily employed methods for quantitating renal function, and these measures correlate well with drug excretion (53,55).

The creatinine clearance is the most frequently used estimate of glomerular filtration rate (67), because creatinine is an endogenous compound that is readily measured in biological fluids and the test does not require the administration of an exogenous compound. Creatinine clearance decreases with age and may be reduced by approximately 30% to 40% in a person 80 years old (53,55).

The influence of aging on the renal function has been thoroughly evaluated. It is generally accepted that the renal function declines as a natural consequence of aging. The blood flow to the kidney declines at a rate of 1 to 2% per year, which represents a loss of 50% of renal function in the elderly. The glomerular filtration rate also undergoes a concomitant decline by as much as 40%, and renal tubular secretion/absorption declines at a rate of approximately 7% per decade. Additional structural changes correlating with age-dependent decline in renal function include: 1) a significant loss in the number of functional nephrons, and 2) an increased incidence of spontaneous glomerular sclerosis (53,55).

Therefore, for those drugs which are mainly eliminated by excretion as unchanged drugs in urine such as digoxin and cimetidine, reduced renal function will result in decreased elimination. Since cetirizine is excreted primarily unchanged (38), it is expected that its elimination

will be delayed in the elderly. Indeed, Matzke *et al*, and Lefebvre *et al* (47,115) found that the elimination half-life of cetirizine was increased in the elderly. Matzke *et al* (47) also found that the elimination half-life of cetirizine was increased in patients with renal insufficiency.

### 1.5.2 Children

In children, at least two $H_1$-receptor antagonists, chlorpheniramine and hydroxyzine that are eliminated primarily by hepatic metabolism, have been shown to have more rapid elimination than in adults (31). Simons *et al* (33) found that hydroxyzine half-life in children, 7.2±2.3 hours, was significantly shorter than that in adults, 20.0±4.1 hours (34), and that in children, the $t_{1/2}$ of hydroxyzine could be correlated with age (r=0.83). In a 1 year old patient, the $t_{1/2}$ was approximately 4 hours, while it was 11 hours in a 14 year old patient.

### 1.5.3 Hepatic dysfunction

Since the liver is the major site for drug metabolism, it is believed that special care should be taken in administering drugs to patients with disease states affecting hepatic function. Early studies in this area provided confusing and conflicting information, indicating that generalization about the influence of hepatic function on drug metabolism is extremely difficult (51,55,60,64). This situation can be explained as follows: first of all, liver dysfunction is actually a result of an assortment of acute and chronic inflammatory, degenerative, or neoplastic insults to the hepatobiliary system. The assessment of hepatic function can vary widely within any diagnosed condition since many of the clinical and laboratory criteria for determining the stage and severity of liver disease are relatively crude.

Therefore, patients with liver disease exhibit considerable heterogeneity of hepatic dysfunction. Secondly, patients with hepatic disorders frequently have other concurrent diseases or reduced renal function. Thirdly, these patients may have an altered nutritional status, which may either be self-generated, as, for example, in patients with alcoholic cirrhosis, or imposed by therapeutic regimen restraints, for example, protein restricted diets. Fourthly, patients with liver disease, frequently receive multiple drugs which may interact either pharmacokinetically or pharmacodynamically with the drug under investigation. Finally, whenever possible, researchers always tend to make simple generalizations about an extremely complicated situation. In this case, the liver performs a multiplicity of functions, including the elimination of drugs by metabolism and biliary excretion. Metabolic pathways, each with a different set of co-factor requirements, are numerous, and the contribution of any pathway to the total elimination varies with each drug. Therefore, attempts to generalize these situations often lead to oversimplification and conflicting conclusions.

It has been suggested that serum albumin might serve as a crude index of hepatic drug metabolizing capacity in chronic liver diseases. Patients with a depressed serum albumin level showed a prolonged half-life of antipyrine, a drug which is essentially unbound to plasma proteins and predominantly cleared by the liver (64), and a depressed intrinsic clearance of amobarbital. A low albumin value probably reflects a depressed synthesis of hepatic proteins including those involved with drug metabolism. Other biochemical parameters such as serum bilirubin, SGOT, SGPT, LDH, and alkaline phosphate (51) were also used to correlate hepatic function with some pharmacokinetic parameters, but without much success.

Recent studies (66,68) suggested that a model drug such as antipyrine instead of biochemical parameters should be used to measure the liver function of patients with hepatic diseases. The criteria for such a model drug are that it should be rapidly and evenly distributed, completely metabolized, easily measured and have few and rare side effects (66,68)

The liver is a major site for the synthesis of albumin, $\alpha_1$-acid glycoprotein, and other circulating macromolecules to which drugs bind reversibly. Therefore, it would be expected that hepatic dysfunction would lead to alterations in the unbound drug fraction present in the blood. However, when binding is less than 90%, pharmacokinetic parameters for total drug tend to be relatively insensitive to the limited pathophysiological changes in binding.

Hydroxyzine, as mentioned before, is extensively metabolized, therefore, it is naturally expected that the diminished hepatic metabolizing ability in patients with hepatic disorders will prolong the half-life of hydroxyzine.

Carbon tetrachloride has been used to induce liver damage in animals, thus providing an animal model for studying the effect of liver dysfunction on drug metabolism. Carbon tetrachloride is metabolized by the cytochrome P-450 dependent monoxygenase to a reactive metabolite, trichloromethyl free radical ( $\cdot CCl_3$), which is further metabolized to $\cdot CH_3COO^-$ in the liver. These free radicals cause the peroxidation of the polygenoic lipids of the endoplasmic reticulum, and the generation of secondary free radicals. This destructive lipid peroxidation leads to the breakdown of membrane structure and function, and if a sufficient amount of $CCl_4$ has been consumed, damage can be extended to all cellular membranes (1,69,70). This method has been employed by Kaka *et al* (71)

to study the effect of hepatic dysfunction on the disposition of bupropion in rats. However, liver dysfunction induced by $CCl_4$ probably differs from liver diseases in humans which develops over a long period of time. Therefore, it is doubtful that the results from animal studies can be extrapolated to humans.

1.5.4 Drug-drug interaction between cimetidine and hydroxyzine or cetirizine

1.5.4.1 Combined therapy with $H_1$ and $H_2$-receptor antagonists

The inability of $H_1$-receptor antagonists to provide total relief of whealing in patients with chronic urticaria could have several possible explanations. First, histamine released from skin mast cells may achieve very high local concentrations in close proximity to skin blood vessels. Systemically administered $H_1$-receptor antagonists, although possessing a greater affinity for $H_1$- receptors than histamine, may not achieve high enough local concentrations to occupy all $H_1$-receptors (109). Second, mediators other than histamine, such as kinins, prostaglandins and leukotrienes may also be involved in the allergic-induced cutaneous responses. Finally, human skin blood vessels possess both $H_1$ and $H_2$-receptors (105,110,111), both of which may be involved in histamine-induced cutaneous responses. $H_1$-receptor antagonists block only $H_1$-receptors, with $H_2$-receptors remaining available to released histamine. It would follow therefore, that the combined therapy of $H_1$ and $H_2$-receptor antagonists should be more effective than $H_1$-receptor antagonists alone in suppressing histamine-induced cutaneous responses.

Cheng *et al* (103) showed that pyrilamine shifted the histamine wheal dose-response curves to the right in a parallel manner in guinea-pigs. A combination of pyrilamine and metiamide, an $H_2$-receptor antagonist, further shifted the histamine dose-response curve to the right as compared with the group treated with pyrilamine alone. However, the participation of histamine $H_2$-receptors could only be demonstrated after $H_1$-receptors were blocked. Furthermore, a large dose of metiamide was required to show any response from $H_2$-receptor antagonists. It was therefore concluded that $H_1$-receptors were playing a major role in the mediation of the histamine skin wheal.

In recent years, several studies (79-86,104) have been carried out to investigate the combined efficacy of $H_1$ and $H_2$-receptor antagonists in treating patients with chronic urticaria. The combination of $H_1$ and $H_2$-receptor antagonists has been judged differently by various investigators. In most studies (79,80,81,82,83,84,86,104), the combination therapy was found to be superior to therapy with $H_1$-receptor antagonists alone. The combination of chlorpheniramine and cimetidine is much more effective in treating the whealing of dermographism *urticaria factitious* than chlorpheniramine alone; the combination of cimetidine and hydroxyzine is more effective than hydroxyzine alone in controlling the symptoms of chronic urticaria (86,104). On the other hand, one double blind study (85) failed to show that the combined therapy of chlorpheniramine and cimetidine had any advantage in the treatment of chronic idiopthic urticaria over chlorpheniramine alone.

1.5.4.2 Pharmacokinetic interactions

The $H_2$-receptor antagonist used in most of reported studies (79-81,83-86,104) is cimetidine. After its approval for general use in 1977, cimetidine soon became one of the most widely prescribed drugs (72). Since then, there have been a large number of reports (72,73,74) of adverse effects when cimetidine was administered in therapeutic doses concurrently with other medications. Cimetidine is believed to affect other drugs by one or several of the following four mechanisms:

1) Since cimetidine is a potent $H_2$-receptor antagonist, it can increase gastric pH. This results in an increased dissolution of dosage forms containing drugs which are weak acids and a corresponding decreased dissolution of weak bases. Cimetidine has been shown to alter the time to attain the peak plasma concentration of a number of drugs including mexiletine, ethanol and chlormethiazole following oral dosing, indicating a change in their rates of gastrointestinal absorption. However, it appears that the extent of absorption is not affected (73,74).

2) Metabolic reactions are mainly carried out in the hepatocyte, and facilitated by the presence of various enzymes. The most important enzymes with respect to the number of drugs affected are those of the microsomal enzyme oxidation system. These enzymes are located in the smooth endoplasmic reticulum of the cell, and are responsible for many Phase I and Phase II reactions. The function of this system is to insert one molecule of oxygen into endogenous or exogenous substrates. The enzyme system is composed of two enzymes, cytochrome P-450 and NADPH cytochrome P-450 reductase, which requires the cytosol component, nicotinamide adenine dinucleotide phosphate (NADPH) for its action. Cytochrome P-450 is a hemoprotein enzyme embedded in the lipid bilayer

of the smooth endoplasmic reticulum with a portion exposed to the cytosol, it binds to and metabolizes drugs. The reductase is a flavoprotein located primarily on the surface of the membrane, but in close proximity to the cytochrome P-450, it donates an electron to the cytochrome P-450 complex. The end result of this process is the production of oxidized drug, oxidized cytochrome P-450 and water (1,76,77).

The imidazole nucleus of cimetidine and the cyano portion of the side chain bind to the haem portion of cytochrome P-450, thus preventing other drugs from binding to it and being metabolized. Cimetidine binds to 2 distinct and independent classes of binding sites on cytochrome P-450, with micromolar dissociation constants of 8.3 and 100. Cimetidine has been shown to inhibit microsomal hepatic drug metabolism in both a competitive and a non-competitive manner, depending on the substrate and experimental conditions employed (73,74).

3) It was originally reported that cimetidine reduces liver blood flow in humans, based on the fact that indocyanine green and propranolol clearance in subjects given cimetidine was reduced. This assumes that indocyanine green clearance is an index solely of liver blood flow. However, indocyanine green clearance is a product of both liver blood flow and extraction across the liver. Thus changes in ICG clearance could be due to changes in one or both determinants. This mechanism is still quite controversial (73,74,75).

4) Filtration by the glomerulus and active secretion by the proximal tubule are important mechanisms for drug excretion. There are two separate active transport mechanisms; one for weak acids and the other one for weak bases. It has been shown that cimetidine reduces the renal clearance of the weakly basic drug, procainamide and its active metabolite,

N-acetylprocainamide. The mechanism which involves competition for active tubular secretion has been verified in an isolated rabbit proximal tubule model (73,74,75). This could be of great significance to the elimination of cetirizine, which is mainly eliminated by renal excretion.

Most studies (79-86,104) on the combined therapy of $H_1$ and $H_2$-receptor antagonists presumed that $H_2$-receptors were involved in histamine-induced cutaneous responses, and then set out to demonstrate that the combined therapy indeed provided a better efficacy. Only one group of investigators (87) measured the serum concentration of the $H_1$-receptor antagonist, hydroxyzine, when coadministered with cimetidine. It was found that hydroxyzine serum concentrations following the coadministration of cimetidine were significantly higher than hydroxyzine concentrations when hydroxyzine was given alone. However, there were drawbacks in the experimental design. First, the authors failed to explain why serum hydroxyzine concentrations in the blank study were different in the control and experimental groups. Therefore, the assumption that no accumulation occurred in the experimental group could be invalid. Second, blood samples were only obtained at 8, 14 and 20 hours after hydroxyzine administration. Given the current understanding of the pharmacokinetics of hydroxyzine, this design is considered to be inappropriate. Finally, both hydroxyzine and cimetidine were given orally. Since cimetine is an $H_2$-receptor antagonist, it would inhibit gastric acid secretion and increase the fraction of unionized hydroxyzine in the stomach. Therefore, it was possible that the absorption of hydroxyzine was increased due to the coadministration of cimetidine.

## 1.6 Rationale of studies

### 1.6.1 The use of rabbits in pharmacokinetic studies

In pharmacokinetic studies, the use of human subjects provides the most appropriate results, but due to difficulties in obtaining volunteers, relatively high cost and possible side effects, an animal model is often used to obtain preliminary information.

Various animals, including mice, rats, guinea pigs, rabbits, dogs, monkeys, minature swine and sheep, have been used in pharmacokinetic and pharmacodynamic studies. Rabbits are often selected as the laboratory animal for the studies which could not be performed in human subjects. Rabbits have a unique gastrointestinal structure (88) so that bioavailability studies must be designed and performed with appropriate controls (130). However, rabbits are relatively inexpensive to purchase and maintain, and of sufficient size to permit the withdrawal of the number of blood samples necessary for pharmacokinetic studies. Preliminary studies in our laboratory confirmed that rabbits metabolize hydroxyzine to cetirizine, as do human subjects.

### 1.6.2 Purpose of studies

The present study was designed to investigate several of the many factors which can affect the pharmacokinetics and pharmacodynamics of $H_1$-receptor antagonists, with hydroxyzine being the model drug. Hydroxyzine was chosen for several reasons. First, considerable research has been done on the pharmacokinetics and pharmacodynamics of hydroxyzine in children and young adults in our laboratory (33,34). A sensitive assay for hydroxyzine and an objective method of monitoring

efficacy are available. Secondly, it has been found during the past several years that the major metabolite of hydroxyzine in humans, cetirizine, is pharmacologically active. An HPLC assay for determining cetirizine was established in our laboratory (38).

The studies described in this thesis were designed to evaluate the following aspects of the pharmacokinetics and pharmacodynamics of hydroxyzine and cetirizine:

1) The pharmacokinetics and pharmacodynamics of hydroxyzine will be determined in healthy elderly subjects. The pharmacokinetics and pharmacodynamics of hydroxyzine in children (33) and in young adults (34) have already been studied in our laboratory. The elimination of hydroxyzine from the body decreases with increasing age (33,34). It is hypothesized that hydroxyzine elimination will be even more delayed in elderly subjects. The effect of increasing age on the disposition of cetirizine, the active metabolite of hydroxyzine, will also be evaluated in the elderly subjects following the administration of hydroxyzine. Serum samples from the hydroxyzine studies in children (33) and young adults (34) will be reanalyzed for cetirizine concentrations for comparison with the resutls obtained in elderly subjects. Pharmacokinetic parameters such as area under the serum concentration versus time curve, total body clearance, apparent volume of distribution and elimination half-life for hydroxyzine, and cetirizine where applicable, will be calculated for the elderly subjects and compared to the values obtained in children (33) and young adults (34).

The efficacy of hydroxyzine will be monitored in the elderly subjects by evaluation of the degree of suppression of histamine-induced wheals and flares over time, before and following the administration of hydroxyzine.

Calculation of $E_{max}$ and $EC_{50}^{H}$ values in the elderly subjects will be carried out and results will be compared to values obtained in young adults (34) to evaluate possible changes in degree of responsiveness to $H_1$-receptor antagonist treatment with age.[1]

2) The pharmacokinetics and pharmacodynamics of hydroxyzine, and its active metabolite, cetirizine, will be assessed in patients with primary biliary cirrhosis. In humans, about 60% of a dose of hydroxyzine is converted to cetirizine, of which about 60 to 80% is excreted unchanged in the urine. The basic pharmacokinetic parameters will be determined in these subjects and the values compared to those obtained in children (33), young adults (34) and elderly subjects, to determine if there is a further decrease in hydroxyzine elimination in patients with reduced hepatic function. Efficacy will also be assessed by monitoring the degree of suppression of histamine-induced wheals and flares, and the results compared to those obtained in the other subjects to evaluate possible changes in response to $H_1$-receptor antagonist treatment in subjects with reduced hepatic function.[1]

3) The pharmacokinetics and pharmacodynamics of cetirizine will be studied in children with allergic rhinitis. The pharmacokinetic and pharmacodynamic parameters calculated in children in this study will be compared to values reported in the literature for similar studies in young adults, elderly subjects, and patients with varying degrees of renal insufficiency (35,47,115) to provide further information about the effects

---

[1]Although cetirizine is currently being evaluated as an $H_1$-receptor antagonist when administered *de novo*, approval was not received from the Faculty Committee on the Use of Human Subjects in Research at the University of Manitoba for the administration of cetirizine *de novo* to the subjects in Studies 1 and 2.

of patient age on the various pharmacokinetic and pharmacodynamic parameters of cetirizine.

4) The relative bioavailability of orally administered hydroxyzine versus intramuscularly administered hydroxyzine will be evaluated in rabbits. There is no commercially available intravenous formulation of hydroxyzine and there are specific warnings against administering the intramuscular formulation by the intravenous route to humans (4,29). Results from this study could provide some preliminary information about the extent of oral absorption of hydroxyzine.

5) The effects of the $H_2$-receptor antagonist cimetidine on the pharmacokinetics and pharmacodynamics of the $H_1$-receptor antagonist hydroxyzine and cetirizine will be studied in rabbits since approval was not obtained for this study in human subjects. Based on the evidence in the literature (79-86,104), we hypothesized that cimetidine would inhibit the elimination of hydroxyzine and cetirizine, yielding higher plasma concentrations of these $H_1$-receptor antagonists. The traditional pharmacokinetic parameters for hydroxyzine, and cetirizine from hydroxyzine, will be determined before, with and after cimetidine coadministration. A similar series of experiments will be performed for cetirizine administered *de novo*. The primary objective will be to evaluate the pharmacokinetic interaction between hydroxyzine and cimetidine, and between cetirizine and cimetidine. Suppression of the histamine-induced wheals will be determined simultaneously for evaluation of possible pharmacodynamic interactions as well.

6) The effect of hepatic dysfunction, chemically induced, on the pharmacokinetics of hydroxyzine, and cetirizine from hydroxyzine, and cetirizine administered *de novo*, will be studied in rabbits. Basic

pharmacokinetic parameters for these compounds will be determined in rabbits. Hepatic dysfunction will be chemically induced in the same rabbits and the pharmacokinetic parameters for hydroxyzine and cetirizine under these test conditions will be calculated and compared to the values obtained under control conditions. The degree of changes in the pharmacokinetic parameters following reduced hepatic function will be compared to the results obtained in healthy humans and patients with primary biliary cirrhosis to determine if the animal model simulates the changes in humans.

# Chapter II Experimental

## 2.1 Chemicals and equipment

### 2.1.1 Chemicals

1. Hydroxyzine dihydrochloride: Pfizer Canada Inc., Kirkland, Quebec
2. Cetirizine dihydrochloride: Pfizer Canada Inc., Kirkland, Quebec
3. Antazoline hydrochloride: Pfizer Canada Inc., Kirkland, Quebec
4. $P_{265}$: Pfizer Canada Inc., Kirkland, Quebec
5. Phosphoric acid : Fisher Scientific Co., Fair Lawn, New Jersey, U.S.A.
6. Ammonium phosphate monobasic: Fisher Scientific Co., Fair Lawn, New Jersey, U.S.A.
7. Potassium phosphate dibasic: Fisher Scientific Co., Fair Lawn, New Jersey, U.S.A.
8. Sodium citrate: Fisher Scientific Co., Fair Lawn, New Jersey, U.S.A.
9. Citric acid: Fisher Scientific Co., Fair Lawn, New Jersey, U.S.A.
10. Potassium hydrochloride: Fisher Scientific Co., Fair Lawn, New Jersey, U.S.A.
11. Evans-Blue: Fisher Scientific Co., Fair Lawn, New Jersey, U.S.A.
12. Sodium decanesulfonate: Aldrich Chemical Company Inc., Milwaukee, Wisconsin, U.S.A.

### 2.1.2 Solvents

1. Diethyl ether: Fisher Scientific Co., Fair Lawn, New Jersey,

U.S.A.

2. Acetone: Fisher Scientific Co., Fair Lawn, New Jersey, U.S.A.
3. Acetonitrile (HPLC): Fisher Scientific Co., Fair Lawn, New Jersey, U.S.A.
4. Ethyl acetate: Fisher Scientific Co., Fair Lawn, New Jersey, U.S.A.

2.1.3 Supplies

1. Filter unit (0.45 μm, and 0.22 μm): Millipore Corporation, Bedford, Maryland, U.S.A.
2. Sure-sep II serum plasma separator: Organon Teknika Co., Morris Plains, New Jersey, U.S.A.
3. Butterfly infusion sets (23 G and 25 G): Abbott Ireland Ltd., Sligo, Rep. of Ireland
4. Syringe ( 5 cc and 1 cc): Becton, Dickinson and Co., Rutherford, New Jersey, U.S.A.
5. Needle (26 G): Becton, Dickinson and Co., Rutherford, New Jersey, U.S.A.
6. Disposable test tubes (16x100 mm): Fisher Scientific Co., Fair Lawn, New Jersey, U.S.A.

2.1.4 Equipment

1. Centrifuge: International Equipment Co., Boston, Mass., U.S.A.
2. pH meter (model 600): Fisher Scientific Co., Fair Lawn, New Jersey, U.S.A.
3. Balance (Mettler AE160): Mettler Instrument Cor., New Jersey, U.S.A

4. Vortex mixer (Vortex genie, model K-550-G): Scientific Industries Inc., Northborough, Maryland, U.S.A.
5. Evaporator (The Meyer N-Evap Analytical Evaporator): Organomatic Associates Inc., Northorough, Maryland., U.S.A.
6. Milli-Q Water System: Millipore Corporation, Bedford, Maryland, U.S.A.
7. High performance liquid chromatography: The HPLC system was comprised of a 6000A high pressure pump, a U6K injector for the analysis of hydroxyzine and a 710B automatic injector for the analysis of cetirizine. The 480 UV-LC spectrophotometric detector was set at a wavelength of 229 nm for both hydroxyzine and cetirizine. The detector was connected to a 720 data module. A Novapak 0.8 cm x 10 cm column and a radial compression module (RCM-100) were used for the separation of hydroxyzine, cetirizine and their respective internal standards. All of the above instrument are from Waters ( Waters Associates Inc., Millford, Massachusetts., U.S.A.).

2.1.5. Dosage Forms

1. Hydroxyzine I.M. injection (Atarax® U.S.P., 50 mg/ml): Pfizer Canada Inc., Kirkland, Quebec
2. Hydroxyzine syrup (Atarax® U.S.P., 10 mg/5 ml): Pfizer Canada Inc., Kirkland, Quebec
3. Cetirizine injection: a 10 mg/ml solution filtered through the 0.22 μm filter unit.*
4. Cetirizine capsule: Pfizer Canada Inc., Kirkland, Quebec
5. Histamine injection (U.S.P, 1 mg/ml): Allen & Hanburys, Toronto, Ontario

6. Evans-blue injection: a 100 mg/ml solution filtered through the 0.22 μm filter unit
7. Cimetidine injection (U.S.P., 150 mg/ml): Smith Kline & French Canada Ltd., Mississauga, Ontario
8. Hydroxyzine injection: a 10 mg/ml solution filtered through the 0.22 μm filter unit.*

* Hydroxyzine and cetirizine solutions were freshly prepared when needed in our laboratory.

## 2.2 Methodology

### 2.2.1 Pharmacokinetic and pharmacodynamic studies of hydroxyzine and cetirizine in humans

#### 2.2.1.1 Extraction procedure for hydroxyzine

The method used for extracting hydroxyzine from serum was that of Simons *et al* (33,34) without any modifications.

Twenty-five microlitres of antazoline solution (1 μg/ml) which acts as the internal standard were added to 1 ml of serum sample along with 250 μl of 10% KOH solution and 5 ml of freshly distilled ether. Extraction was achieved by mixing on a vortex mixer for 30 seconds followed by centrifuging for 5 minutes at 2000 rpm. The aqueous portion was frozen in a dry ice/acetone bath and the ether layer was transferred to a clean dry16x100 mm test tube. One hundred microlitres of 0.05% $H_3PO_4$ solution were added, followed by mixing on a vortex mixer for 30 seconds and centrifuging for 5 minutes at 2000 rpm. The aqueous layer was again frozen in a dry ice/acetone bath and the ether layer was discarded. The

aqueous portion was exposed to a stream of dry nitrogen to remove remaining traces of ether. All of the remaining aqueous solution was then taken up in a syringe and injected onto the column.

2.2.1.2 Extraction procedure for cetirizine

To 1 ml serum, 50 µl of $P_{265}$ (3 µg/ml), which acts as the internal standard, were added, together with 1 ml sodium citrate buffer (1M, pH 5.0) and 3 ml of ethyl acetate. The sample was mixed on a vortex mixer for 1 minute and centrifuged for 15 minutes at at 2000 rpm. The organic layer was transferred to a clean test tube. To the remaining serum, another 3 ml ethyl acetate were added. The sample was again mixed for 1 minute and centrifuged for 15 minutes at 2000 rpm. The ethyl acetate was mixed with that from the previous extraction. Two hundred microlitres of 1.7% $H_3PO_4$ were added, and the sample was mixed for 1 minute and centrifuged for 5 minutes at 2000 rpm. The aqueous portion was frozen in a dry ice/acetone bath, and the organic layer was discarded. The aqueous layer was then exposed to a stream of dry nitrogen to remove remaining traces of ethyl acetate. The aqueous layer was transferred to the sample tube of the automatic injector, and 100 µl of the solution were injected onto the column.

The extraction procedure for cetirizine from urine was the same as described above, except that 100 µl $P_{265}$ (3 µg/ml) was added to the urine sample at the beginning of the extraction.

2.2.1.3 Chromatographic separation and quantitation of hydroxyzine and cetirizine

The mobile phases used were acetonitrile-phosphate buffer (0.075M $NH_4H_2PO_4$, pH 2.5) (35:65, v/v) for the separation of hydroxyzine and acetonitrile-phosphate buffer (0.075M $NH_4H_2PO_4$, pH 2.9, 0.02 M sodium 1-decanesulfonate) (43:57 v/v) for the separation of cetirizine. The flow rate for separating and quantifying hydroxyzine was set at 1.5 ml/min, while the flow rate for cetirizine was set at 1.2 ml/min. The effluent from the column was monitored by UV absorption at 229 nm with 0.20 to 0.005 a.u.f.s. sensitivity settings. The chart speed for the data module was 0.25 cm/min. Peak height ratios of hydroxyzine to antazoline and cetirizine to $P_{265}$ were used for the quantitation based on the calibration curves established during the study period. The retention times were 3.0 and 5.5 minutes for antazoline and hydroxyzine, and 6.5 and 9.0 minutes for cetirizine and $P_{265}$ respectively.

The calibration curves were prepared from the results of assays on blank serum samples to which known quantities of hydroxyzine and cetirizine and corresponding internal standards antazoline, and $P_{265}$ were added. All chromatographic separations were carried out at ambient temperature. The serum concentrations of hydroxyzine and cetirizine were expressed in terms of the free base form only.

The same procedure was used for the determination of cetirizine in urine as for measuring serum cetirizine concentrations, except that the calibration curve was prepared by "spiking" blank urine samples with known quantity of cetirizine, and the calibration curve was prepared over a much wider range of concentrations.

2.2.1.4 Pharmacokinetic and pharmacodynamic studies of hydroxyzine in the elderly

The study protocol was approved by the Faculty Committee on the Use of Human Subjects in Research of the University of Manitoba, and each participant gave written, informed consent before study entry. Participants were eligible for study if they were age 65 or older, in excellent health, not requiring any medication regularly, and within 10% of normal weight for height. They were excluded if they had any acute or chronic illness, if they had ever taken an $H_1$-receptor antagonist regularly, if they had ever smoked, if they ingested alcohol or xanthine-containing beverage excessively, or if they had abnormal hepatic or renal function.

The participants visited the Health Sciences Clinical Research Center for history, physical examination, and blood samples for complete blood count, assessment of hepatic function using serum bilirubin, direct and total serum protein and albumin, alanine aminotransferase, aspartate aminotransferase, lactase dehydrogenase, and γ–glutamyl transferase; and assessment of renal function, using serum creatine and blood urea nitrogen.

After an 8 hour fast, indwelling, venous catheters were inserted in all participants. Blood samples of 5 ml for the measurement of serum hydroxyzine and cetirizine levels were collected from the indwelling catheter with "heparin lock" before and at 1, 2, 3, 4, 5, 6, 8, 10 and 12 hours, then by venipuncture at 24, 48, 72, 96, 120, and 144 hours after administration of a single dose of hydroxyzine hydrochloride, 0.7 mg/kg as Atarax® syrup, with 250 ml water. From 1 to 12 hours after administration, the first 1.0 ml of each blood sample was discarded, and after each sample was obtained the heparin lock was rinsed with 1.0 ml 0.9% saline solution, followed by 0.5 ml of a solution containing 10 U

heparin per 1.0 ml 0.9% saline solution. A standard snack was served 2 hours after the dose and standardized meals were served 4 and 9 hours after the dose.

Blood samples were collected in glass test tubes and centrifuged at 2000 rpm and serum was transferred to glass test tubes securely capped and stored at -20 $^0$ until analyzed.

The efficacy test was carried out by the method described in section 2.2.1.7.

2.2.1.5 Pharmacokinetic and pharmacodynamic studies of hydroxyzine in patients with primary biliary cirrhosis

The study protocol was approved by the Faculty Committee on the Use of Human Subjects in Research of the University of Manitoba. Each participant gave written, informed consent before study entry.

Patients were eligible for the study if they had symptomatic, biopsy-compatible primary biliary cirrhosis, with abnormal liver biochemistry tests, defined as alanine aminotransferase at least twice normal, and/or alkaline phosphatase at least 1.5 times normal, and abnormal γ-glutamyl transferase on at least two occasions over the previous six months. They were also eligible if they had not taken any sedatives or antihistamines or antihistaminic-like agents such as a tricyclic antidepressant or barbiturates within one week, a resin-binding agent such as cholestyramine within 72 hours of the study, or the long-acting $H_1$-receptor antagonist, astemizole, within the previous year. They were required to be non-smokers, within 10-15% of normal body weight for height, and to have a life expectancy of at least one year. Patients were excluded from the study if they had hepatic failure; ascites; encephalopathy; associated bowel disease, which

might impair hydroxyzine absorption; or known hypersensitivity to any $H_1$-receptor antagonist.

The participants visited the Health Sciences Clinical Research Center for history, physical examination and blood samples for complete blood count, assessment of hepatic and renal function using direct and total bilirubin, serum protein, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphate, γ-glutamyl transferase, prothrombin time, blood urea nitrogen, creatinine and urinalysis.

After an overnight fast, venous catheters were inserted in all patients. Blood samples of 5 ml for the measurement of hydroxyzine and cetirizine were withdrawn from the venous catheter with "heparin lock" before and at 1, 2, 3, 4, 5, 6, 8, 10, 12 hours, then by venipuncture at 24, 48, 72, 96, 120, and 144 hours after the oral administration of a single dose of hydroxyzine hydrochloride, 0.7 mg/kg as Atarax® syrup, with 250 ml of water. From 1 to 12 hours after dosing, the first 1.0 ml of each blood sample was discarded, and after each sample was obtained, the heparin lock was rinsed with 1.0 ml 0.9% saline solution, following by 0.5 ml of a solution containing 10 U heparin per 1.0 ml 0.9% saline solution. A standard snack was served 2 hours after the dose and standardized meals were served 4 and 9 hours after the dose.

Blood samples were collected in glass test tubes and centrifuged at 2000 rpm and serum was transferred to glass test tubes securely capped and stored at -20 $^0$ until analyzed.

The efficacy test was also carried out by the method described in section 2.2.1.7.

2.2.1.6 Pharmacokinetic and pharmacodynamic studies of cetirizine in children

The study protocol was approved by the Faculty Committee on the Use of Human Subjects in Research of the University of Manitoba. The objective and experimental procedure were explained to each subject carefully. Each subject gave written consent if possible before study entry in addition to written consents from parents or guardians.

Patients were eligible for study if they were 5 to 12 years of age, had a history of allergic rhinitis with late summer exacerbations, and had one or more positive epicutaneous tests to relevant antigens, such as weed pollens, molds, and/or grain dust. Patients were excluded if they had any disorder other than allergic rhinitis, mild asthma, or eczema, or if they had any underlying or recent disorder that would interfere with the evaluation of their response to therapy, for example, an upper respiratory tract infection. Patients were not eligible if they had abnormal hematologic, renal, or hepatic function, or if they required intranasal corticosteroids for allergic rhinitis treatment. They were also excluded if they could not stop the use of medication that had antihistaminic or sedating properties for at least 5 days before the study, if they had received astemizole within the preceding year, if they were undergoing desensitization, or if major changes were being made to their enviroment, for example, installation of air conditioning.

The participants were randomly divided into two groups, with one group receiving an oral dose of 5 mg cetirizine and the other group receiving 10 mg cetirizine in the form of capsules[1] . After an overnight

---

1 . The 5 mg and 10 mg cetirizine doses are the only therapeutic doses approved for use in young subjects with allergic rhinitis.

fast, venous catheters were inserted in all subjects. Blood samples of 5 ml for the measurement of cetirizine were withdrawn from the venous catheter with " heparin lock " before and at 0.5, 1.0, 1.5, 2.0, 4.0, 6.0, 8.0, 10.0, 12.0, and by venipuncture at 24 hours after the oral administration of cetirizine. Urine samples were collected from 0-4 hours, 4-8 hours, 8-12 hours and 12-24 hours after the drug administration.

Twenty-four hours after the first dose of cetirizine was given, cetirizine was given daily at 8 p.m. at the same dose for 5 weeks. A blood sample was withdrawn weekly in the morning during this period. Blood samples were collected in glass test tubes and centrifuged at 2000 rpm, and serum was transferred to glass test tubes securely capped. Both serum and urine samples were stored at $-20^{0}$ until analyzed.

The efficacy test was carried out by the method described in section 2.2.1.7.

2.2.1.7 The efficacy tests of hydroxyzine and cetirizine in human subjects

Each time a blood sample was obtained, an intradermal test was performed with 0.01 ml of a solution containing histamine phosphate, 0.1 mg/ml in adults, or an epicutaneous (prick) test with a histamine phosphate solution of 1 mg/ml in children. A different site on the volar surface of the forearm was used for each test, and the sequence of sites chosen was identical in all participants. Wheal and flare circumferences were traced 10 minutes after histamine injection with a felt-tipped pen and transferred to transparent papers. Injections and tracing were done by the same investigator. The wheal and flare areas were measured on a digitizer coupled with an IBM-PC computer, and stereometric measurement

software (Sigma-Scan™, version 3.10, Jandel Scientific, Sausalito, Calfornia, U.S.A.).

At the same time, participants were questioned about adverse effects such as sedation, light-headiness, feelings of disorientation or dizziness, dry mouth, visual changes, or difficulty in urinating.

2.2.2 Pharmacokinetic and pharmacodynamic studies of hydroxyzine and cetirizine in rabbits: the effects of cimetidine and hepatic dysfunction

2.2.2.1 Extraction procedure for hydroxyzine

The method used for extracting hydroxyzine from rabbit serum was that of Simons *et al* (33,34) without any modifications.

Twenty-five microlitres of antazoline solution (1 μg/ml), which acts as the internal standard, were added to 0.5 ml of serum sample along with 250 μl of 10% KOH solution and 5 ml of freshly distilled ether. Extraction was achieved by mixing on a vortex mixer for 30 seconds followed by centrifuging for 5 minutes at 2000 rpm. The aqueous portion was frozen in a dry ice/acetone bath and the ether layer was transferred to a clean 16x100 mm dry test tube. One hundred microlitres of 0.05% $H_3PO_4$ solution were added, followed by mixing on a vortex mixer for 30 seconds and centrifuging for 5 minutes at 2000 rpm. The aqueous layer was again frozen in a dry ice/acetone bath and the ether layer was discarded. The aqueous portion was exposed to a stream of dry nitrogen to remove remaining traces of ether. All of the remaining aqueous solution was then taken up in a syringe and injected onto the column.

2.2.2.2 Extraction procedure for cetirizine

To 0.5 ml serum, 50 µl of $P_{265}$ (3 µg/ml) which acts as the internal standard were added together with 1 ml sodium citrate buffer (1M, pH 5.0) and 3 ml of ethyl acetate. The sample was mixed for 1 minute and centrifuged for 15 minutes at 2000 rpm. The organic layer was transferred to a clean test tube. To the remaining serum, another 3 ml ethyl acetate were added. The sample was again mixed for 1 minute and centrifuged for 15 minutes at 2000 rpm. The ethyl acetate was mixed with that from the previous extraction. Two hundred microlitres of 1.7% $H_3PO_4$ were added, and the sample was mixed for 1 minute and centrifuged for 5 minutes at 2000 rpm. The aqueous portion was frozen in a dry ice/acetone bath, and the organic layer was discarded. The aqueous layer was then exposed to a stream of dry nitrogen to remove remaining traces of ethyl acetate. The aqueous layer was transferred to the sample tube of the automatic injector, and 100 µl of the solution were injected onto the column.

2.2.2.3 Chromatographic separation and quantitation of hydroxyzine and cetirizine

The mobile phases used were acetonitrile-phosphate buffer (0.075M $NH_4H_2PO_4$, pH 2.5) (35:65,v/v) for the separation of hydroxyzine and acetonitrile-phosphate buffer (0.075M $NH_4H_2PO_4$, pH 2.9, with 0.02M sodium 1-decanesulfonate) (45:55 v/v) for the separation of cetirizine. The flow rate for separating and quantifying hydroxyzine was set at 0.8 ml/min, while the flow rate for cetirizine was set at 1.2 ml/min. The effluent from the column was monitored by UV absorption at 229 nm with 0.50 to 0.005 a.u.f.s. sensitivity settings. The chart speed for the data module was 0.25 cm/min. Peak height ratios of hydroxyzine to antazoline

and cetirizine to $P_{265}$ were used for the quantitation based on the calibration curves established during the study period. The retention times were 5.0 and 11.0 minutes for antazoline and hydroxyzine, and 6.0 and 7.5 minutes for cetirizine and $P_{265}$ respectively.

The calibration curves were prepared from the results of assays on blank serum samples supplemented with known quantities of hydroxyzine and cetirizine and corresponding internal standards antazoline and $P_{265}$. All chromatographic separations were carried out at ambient temperature. The serum concentrations of hydroxyzine and cetirizine were expressed in terms of free base form only.

2.2.2.4 The bioavailability study of hydroxyzine in rabbits

Three New Zealand white male rabbits, obtained from the Central Animal Care Services, University of Manitoba, were used in this study. They were kept individually in metal cages fitted with wire floors to reduce coprophagy. Food and water were supplied *ad libitum.*

Each rabbit received an I.M. injection of 5 mg of hydroxyzine and an oral dose of 100 mg hydroxyzine hydrohloride solution two weeks apart. Blood samples were obtained prior to and at 5, 15, 30, 60 minutes and 2, 3, 4, 5, 6 hours after the dosing.

Blood samples were collected in 16x100 mm glass test tubes without anticoagulants. The serum was separated by placing Sure Sep-II separators on the top of glass test tubes and centrifuging for 15 minutes at 2000 rpm. Serum samples were stored frozen at -20 $^0$ until analyzed.

2.2.2.5 Pharmacokinetic and pharmacodynamic studies of hydroxyzine in rabbits: the effect of cimetidine

Five male New Zealand white rabbits obtained from the Central Animal Care Services, University of Manitoba were used in this study. They were kept individually in metal cages fitted with wire floors to reduce coprophagy. Food and water were supplied *ad libitum.*

All five rabbits received an I.V. bolus injection of 10 mg hydroxyzine hydrochloride through the ear vein. Two to three millilitres of blood were withdrawn from the ear vein using an infusion set prior to and at 5, 15, 30, 60 minutes and 2, 3, 4, 6, 8, and 12 hours after the injection. The efficacy test was carried out using the method described in section 2.2.2.9 on the depilated rabbit back at the same time of each blood sampling.

The same five rabbits were subsequently used to study the interaction between cimetidine and hydroxyzine one week later. The rabbits were given cimetidine, 100 mg/kg, intravenously twice a day for one week. On the seventh day, each rabbit received an intravenous bolus dose of 10 mg hydroxyzine hydrochloride. Blood samples were obtained prior to and at 5, 15, 30, 60 minutes and at 2, 3, 4, 6, 8, 12, and 24 hours after injection. The efficacy test was carried out as described in section 2.2.2.9 at the same time of each blood sampling. The cimetidine dosing was discontinued after this study.

Two weeks after this study, each rabbit received another intravenous bolus dose of 10 mg hydroxyzine hydrochloride. The blood samples were taken at the same time as in the control study. The efficacy test was also performed as described in section 2.2.2.9 at the same time of each blood sampling.

Blood samples were collected in 16x100 mm glass test tubes without anticoagulants. The serum was separated by placing Sure Sep-II separators on the top of glass test tubes and centrifuging for 15 minutes at 2000 rpm. Serum samples were stored frozen at -20 $^0$ until analyzed.

A blood sample was taken at the beginning of each study for enzyme tests.

2.2.2.6 The pharmacokinetic and pharmacodynamic study of cetirizine in rabbits: the effect of cimetidine

Five male New Zealand white rabbits, obtained from the Central Animal Care Services, University of Manitoba, were used in this study. They were kept individually in metal cages fitted with wire floors to reduce coprophagy. Food and water were supplied *ad libitum.*

An intravenous bolus dose of 10 mg cetirizine dihydrochloride was administered to each rabbit through the ear vein. Two to three millilitres of blood were withdrawn from the ear vein using an infusion set prior to and at 5, 15, 30, 60 minutes, and 2, 3, 4, 6, 8 and 12 hours after the drug administration. The efficacy test was carried out at the same time as each blood sample was obtained using the method described in section 2.2.2.9 on the depilated rabbit back.

The same five rabbits were employed to study the interaction between cimetidine and cetirizine. One week after the above study, cimetidine was administered intravenously at 100 mg/kg twice a day for one week. On the seventh day, each rabbit received an intravenous bolus injection of 10 mg cetirizine dihydrochloride. Blood samples were obtained prior to, and at 5, 15, 30, 60 minutes, and 2, 3, 4, 6, 8, 12, and 24 hours after drug administration. An efficacy test was carried out as described in

section 2.2.2.9 at the same time as each blood sample was obtained. The cimetidine dosing was discontinued.

Two weeks after the study, another intravenous dose of 10 mg cetirizine dihydrochloride was given, and blood samples were obtained. The efficacy test was carried out as in the control study.

Blood samples were collected in 16x100 mm glass test tubes without anticoagulants. The serum was separated by placing Sure Sep-II separators on the top of glass test tubes and centrifuging for 15 minutes at 2000 rpm. Serum samples were stored frozen at -20 $^0$ until analyzed.

At the beginning of each study, a blood sample was withdrawn for enzyme tests.

2.2.2.7 Pharmacokinetic studies of hydroxyzine in rabbits: the effect of hepatic dysfunction

Five male New Zealand white rabbits, obtained from the Central Animal Care Service, University of Manitoba, were used in this study. They were kept individually in metal cages fitted with wire floors to reduce coprophagy. Food and water were supplied *ad libitum*.

An intravenous bolus injection of 10 mg hydroxyzine hydrochloride was administered to each rabbit through the ear vein. Two to three millilitres of blood were withdrawn through the ear vein using an infusion set prior to and at 5, 15, 30, 60 minutes and 2,3,4,6,8, and 12 hours after the drug administration.

Two weeks after the above study, carbon tetrachloride ($CCl_4$) (0.5 ml/kg) was given intraperitoneally. Three days later, an intravenous bolus injection of 10 mg hydroxyzine hydrochloride was administered.

Blood samples were taken prior to and at 5, 15, 30, 60 minutes and 2, 3, 4, 6, 8, 12 and 24 hours after the drug administration.

Blood samples were collected in 16x100 mm glass test tubes without anticoagulants. The serum was separated by placing Sure Sep-II separators on the top of glass test tubes and centrifuging for 15 minutes at 2000 rpm. Serum samples were stored frozen at -20 $^0$ until analyzed.

A blood sample was taken at the beginning of each study for biochemical tests.

All rabbits were sacrificed after this study.

2.2.2.8 Pharmacokinetic studies of cetirizine in rabbits: the effect of hepatic dysfunction

Five male New Zealand white rabbits, obtained from the Central Animal Care Service, University of Manitoba, were used in this study. They were kept individually in metal cages fitted with wire floors to reduce coprophagy. Food and water were supplied *ad libitum.*

An intravenous bolus injection of 10 mg cetirizine dihydrochloride was administered to each rabbit through the ear vein. Two to three millilitres of blood were withdrawn from the ear vein using an infusion set prior to and at 5, 15, 30, 60 minutes and 2, 3,4,6,8, and 12 hours after the drug was given.

Two weeks after the above study, carbon tetrachloride ($CCl_4$) (0.5 ml/kg) was given intraperitoneally. Three days later, an intravenous bolus injection of 10 mg cetirizine dihydrochloride was administered. Blood samples were taken prior to and at 5, 15, 30, 60 minutes and 2, 3, 4, 6, 8, 12 and 24 hours after the drug administration.

Blood samples were collected in 16x100 mm glass test tubes without anticoagulants. The serum was separated by placing Sure Sep-II separators on the top of glass test tubes and centrifuging for 15 minutes at 2000 rpm. Serum samples were stored frozen at -20 $^0$ until analyzed.

A blood sample was taken at the beginning of each study for biochemistry tests.

All rabbits were sacrificed after this study.

2.2.2.9.The efficacy tests of hydroxyzine and cetirizine in rabbits.

Each time a blood sample was withdrawn, an intradermal test was performed with 0.05 ml of a solution containing histamine phosphate, 1.0 mg/ml. A different site on the depilated back of rabbits was used for each test. Prior to the first test, 0.1 ml of Evans-Blue (100 mg/ml) was injected intravenously. The cutaneous blue spots were traced 10 minutes after each histamine injection and transferred to a transparent paper using a felt-tipped pen. Wheal areas were measured with an IBM-XT compatible digitizer, and stereometric measurement software (Sigma-Scan™, version 3.10, Jandel Scientific, Sausalito, Calfornia, U.S.A.).

## 2.3 Data analysis

### 2.3.1 Pharmacokinetic data analysis

Data from the above studies were analyzed using PKCALC (89) on an IBM-XT compatible. PKCALC is a BASIC program which performs standard statistical and pharmacokinetic analysis of multisubject data sets, including means, standard deviations, standard errors of variation, half-

lives of absorption and elimination, areas under the concentration versus time curves, and mean residence time.

PKCALC is linked to an augumented copy of ESTRIP (90), which can strip serum concentration versus time data automatically using different polyexponential equations. Data from each subject were fitted independently, and models giving the least sum of squared deviations and the best coefficient of determination were selected. In addition, each fitting was visually inspected to make sure that at least three data points were used in calculating the slope of the terminal linear portion.

In PKCALC, the elimination half-life was calculated using equation (1).

$$T_{1/2} = 0.693/\beta \qquad (1)$$

where β is the slope of the terminal linear portion in the concentration versus time curve.

The area under the concentration versus time curve ($AUC_{0->\infty}$) was calculated by the trapezoidal rule from the time 0 to time t of the last sample and extrapolated to infinity according to the formula:

$$AUC_{0->\infty} = AUC_{0->t} + Ct/\beta \qquad (2)$$

where Ct is the concentration of hydroxyzine (cetirizine) in the last sample of time t. Results were expressed in terms of ng·hr per ml.

The systemic clearance (Cls) was calculated using:

$$Cls = Dose / AUC_{0->\infty} / weight \qquad (3)$$

Results were expressed as ml/min/kg.

The renal clearance of cetirizine was calculated by using equation (4):

$$Clr = (Xu)_{0-24} / AUC_{0->24} \qquad (4)$$

where $(Xu)_{0-24}$ is the amount of cetirizine excreted unchanged in urine from 0 to 24 hours, and $AUC_{0->24}$ is the area under the cetirizine concentration versus time curve from 0 to 24 hours. Results were expressed as ml/min/kg.

The apparent volume of distribution for the central compartment, $V_\beta$, was calculated using equation (5):

$$V_\beta = Cls / \beta \qquad (5)$$

Results were expressed as l/kg.

The bioavailability was calculated using equation (6):

$$F = \frac{(Dose)_{i.m}\ ß_{oral}\ (AUC_{0->\infty})_{oral}}{(Dose)_{oral}\ ß_{im}\ (AUC_{0->\infty})_{i.m.}} \qquad (6)$$

The mean residence time (MRT) was calculated using

$$MRT = AUMC_{0->\infty} / AUC_{0->\infty} \qquad (7)$$

where $AUMC_{0->\infty}$ is the area under the first moment of the serum concentration versus time curve. Results were expressed in hours.

The ratio of cetirizine $AUC_{0->\infty}$ to hydroxyzine $AUC_{0->\infty}$ was calculated as:

$$R = \frac{\text{cetirizine } AUC_{0->\infty}}{\text{hydroxyzine } AUC_{0->\infty}} \qquad (8)$$

2.3.2 Pharmacodynamic data analysis

2.3.2.1 The modified $E_{max}$ model

The efficacy was calculated as the percent suppression of wheal and flare by using equation (9):

$$E = \frac{A_0 - A_t}{A_0} \times 100\% \qquad (9)$$

where $A_0$ is the wheal and/or flare area before drug administration. $A_t$ is the wheal and/or flare area at time t after hydroxyzine and/or cetirizine administration.

The mean efficacy- mean concentration relationship was subsequently fit to equation (10):

$$E = \frac{E_{max} \cdot C}{EC_{50}^{H} + C} \qquad (10)$$

where $E_{max}$ is the maximum possible response that can be attributed to hydroxyzine (cetirizine). $EC_{50}^{H}$ is the hydroxyzine concentration that produces 50% of the maximum effect (see Appendix I for derivation). In case of hydroxyzine administration, C was calculated using equation (11).

$$C = C_{hydroxyzine} + 1/4 \cdot C_{cetirizine} \qquad (11)$$

$$EC_{50}^{C} = 4 \times EC_{50}^{H} \qquad (12)$$

The curve fitting was performed by using BMDP (P3R) (107) on an IBM-370 computer at the University of Manitoba Computer Centre. Equation (9) was defined by Fortran statements, a sample of which, together with system control languages was given below.

```
// JOB
//EXEC BIMEDT, PROG=BMDP3R
//FUN  DD *
          DF(1) = X(1)/(P(2) + X(1))
          DF(2) =- P(1) * X(1) / (P(2) + X(1))**2
          F = DF(1) * P(1)
```

```
//SYSIN DD *
/ FUN     EFFECT = Emax * C / (EC50  + C)
/PROBLEM  TITLE IS ' Emax  MODEL  FITTING'.
/INPUT    VARIABLES ARE 2.
                FORMAT IS FREE.
/VARIABLE   NAMES ARE EFFECT, CONC.
/REGRESS      DEPENDENT IS EFFECT.
                  PARAMETERS ARE 2.
/PARAMETER   INITIAL ARE 90, 10.0.
/END
 DATA
//
```

where F is the effect expressed as the percent suppression of wheal and flare. P(1), P(2) and X are $E_{max}$, $EC_{50}^{H}$ and the modified concentration in Eq.(10) respectively. DF(1) and DF(2) are derivatives of Eq.(10) with respect to P(1) and P(2) respectively. This method was used to analyse effect-concentration data obtained from the elderly subjects, patients with primary biliary cirrhosis, and rabbits given hydroxyzine.

2.3.2.2 The effect-compartment model

This model was used to develop an integrated pharmacokinetic and pharmacodynamic model of hydroxyzine after an intravenous bolus injection in rabbits. The efficacy was also calculated using equation (9)

The serum hydroxyzine concentration versus time data after intravenous bolus injections of 10 mg hydroxyzine can be best described by a two-compartment model as indicated by equation (13).

$$C = \frac{X_0 (K_{21}-\alpha)}{V_1 (\beta-\alpha)} e^{-\alpha t} + \frac{X_0 (K_{21}-\beta)}{V_1 (\alpha-\beta)} e^{-\beta t} \qquad (13)$$

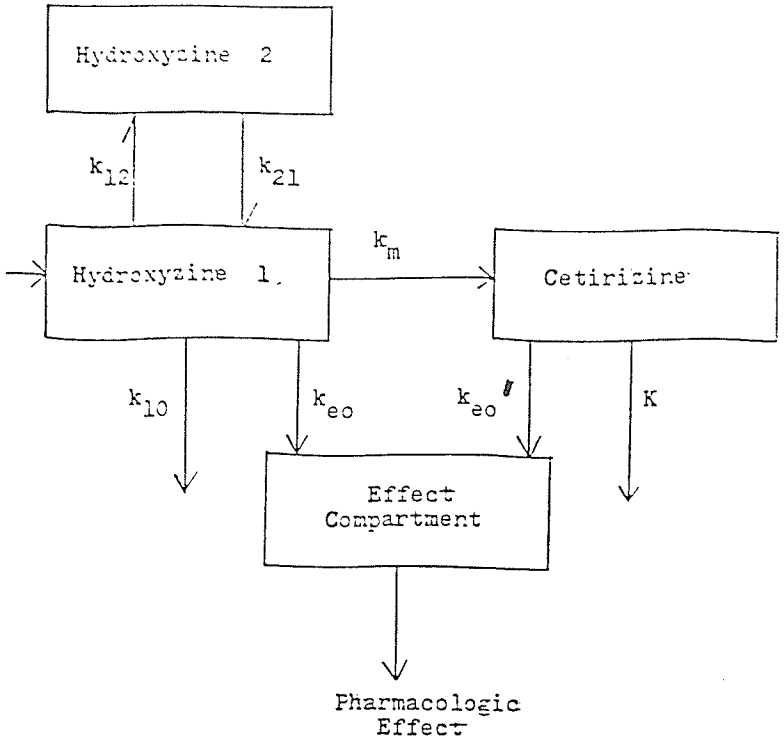
where Xo is the dose of hydroxyzine given intravenously, and $V_1$ is the volume of distribution of the central compartment. $\alpha$ and $\beta$ are roots of the quadratic equation $r^2 + (K12+K21+K10)\, r + K21 \cdot K10 = 0$.

The serum cetirizine concentration versus time data after intravenous bolus injections of 10 mg hydroxyzine can be best described by a one-compartment model with a first-order formation process.

$$C = \frac{X_0' K_m}{V'(K_m-K)} (e^{-Kt} - e^{-K_m t}) \qquad (14)$$

where Km is the formation rate constant of cetirizine from hydroxyzine, K is the elimination rate constant of cetirizine, Xo' is the amount of cetirizine formed from hydroxyzine after an intravenous bolus injection of 10 mg hydroxyzine, and V' is the volume of distribution of cetirizine.

A hypothetical effect-compartment similar to that of Sheiner *et al* (120,121,122,123,128) was postulated. The effect-compartment is connected to the central compartment by a link model, the properties of which are not known and are of no consequence here. The model is shown in the following scheme.




The hydroxyzine concentration in the effect-compartment is given by equation (15) (see Appendix II for derivation):

$$C_e = \frac{X_0 K_{eo}}{V_1}\left(\frac{K_{21}-\alpha}{(\beta-\alpha)(K_{eo}-\alpha)}e^{-\alpha t} + \frac{K_{21}-\beta}{(\alpha-\beta)(K_{eo}-\beta)}e^{-\beta t} + \frac{K_{21}-K_{eo}}{(\alpha-K_{eo})(\beta-K_{eo})}e^{-K_{eo}t}\right)$$

The cetirizine concentration in the effect-compartment is given by equation (16):

$$C_e' = \frac{X_0' K_m K_{eo}'}{V}\left(\frac{e^{-K_m t}}{(K-K_m)(K_{eo}'-K_m)} + \frac{e^{-Kt}}{(K_m-K)(K_{eo}'-K)} + \frac{e^{-K_{eo}' t}}{(K_m-K_{eo}')(K-K_{eo}')}\right)$$

The pharmacodynamic effect can be related to concentrations of hydroxyzine and cetirizine in the effect compartment through equation (10) by substituting Ce and Ce' for $C_H$ and $C_C$ .

The data analysis was carried out in two steps. First, the effect-concentration data from all hydroxyzine studies in rabbits were fitted using Eq.(10) to obtain estimates of $E_{max}$ and $EC_{50}^H$. Then, in Method A, mean plasma hydroxyzine and cetirizine concentrations were fitted into equations (13) and (14) to obtain estimates of $\alpha$, $\beta$, $K_{21}$, $V_1$, Km, Xo'/V', and K.

These parameters were brought into equation (15) and (16). Then, Ce and Ce' were put into equation (10), and PCNONLIN was used to fit the data to get estimates of Keo, and Keo'.

In Method B, plasma hydroxyzine and cetirizine concentrations from each individual rabbit were fitted into equations (13) and (14) to obtain estimates of $\alpha$, $\beta$, $K_{21}$, $V_1$, Km, Xo'/V', and K for each individual rabbit. These parameters were brought into equation (15) and (16). Then, Ce and Ce' were put into equation (10), and PCNONLIN was used to fit the data to get estimates of Keo, and Keo' for each individual rabbit.

2.3.3 Statistical analysis

Statistical analysis was also carried out on an IBM-370 computer at the Univeristy of Manitoba Computer Centre. The two-way ANOVA (116) ( $\alpha$=0.05), using subject and sample time as the criteria for classification, was used to compare effects produced by hydroxyzine or/and cetirizine. The Tukey and Bonferroni multiple range tests ( $\alpha$=0.05) were used to compare pharmacokinetic parameters of hydroxyzine and cetirizine obtained from different patient populations, and from rabbits with and without the coadministration of cimetidine. Balanced paired t-tests ($\alpha$=0.05) were used to compare pharmacokinetic parameters of hydroxyzine and cetirizine obtained from rabbits with and without $CCl_4$-induced hepatic dysfunction.

# Chapter III Results

## 3.1 Pharmacokinetic and pharmacodynamic studies of hydroxyzine and cetirizine in humans

### 3.1.1 HPLC assays

#### 3.1.1.1 HPLC assay of hydroxyzine

Representative HPLC chromatograms for hydroxyzine and the internal standard antazoline are shown in Fig. 7.

The retention times of hydroxyzine and antazoline are 5.5 and 3.0 minutes respectively. There were no interfering peaks.

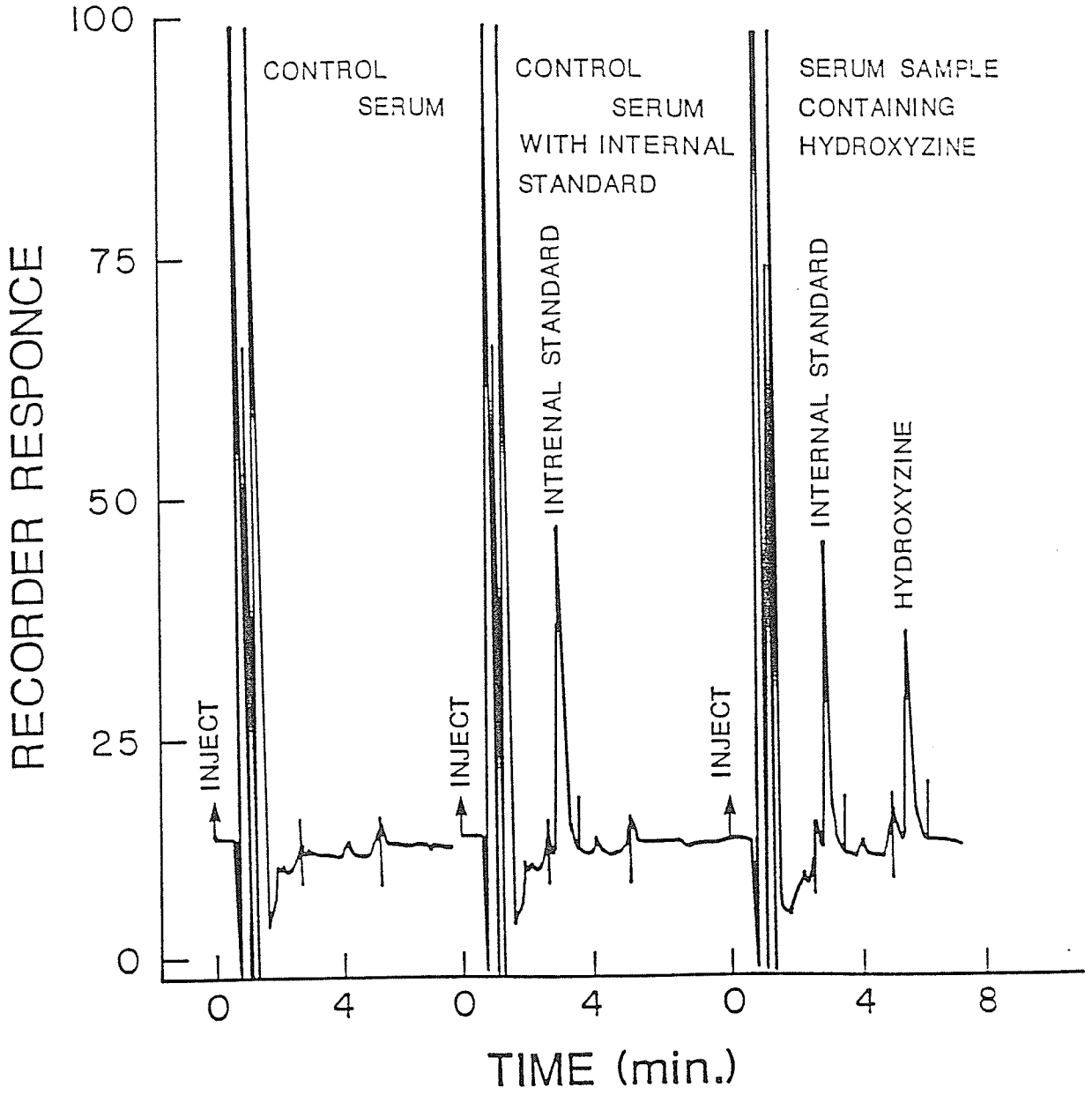



Fig.7 The HPLC chromatograms of hydroxyzine

3.1.1.2 Calibration curves for hydroxyzine

The calibration curves for hydroxyzine were constructed by plotting peak height ratios of hydroxyzine to antazoline versus concentrations of hydroxyzine. Calibration curves were analyzed periodically during the study period using concentrations of hydroxyzine from 2.0 ng/ml to 203.8 ng/ml. over which range the calibration curve is linear. The variability in the calibration curves over a period of 12 months were calculated from six calibration curves, each having six samples at every concentration. The variability is expressed as the coefficient of variation and shown in Table 1, and the curve is shown in Fig.8. The variability is not shown in Fig.8 and following figures in order to maintain the clearity of the mean data. All variances are provided in corresponding tables.

Table 1. Variability in HPLC calibration curves for hydroxyzine

| Concentration(ng/ml) | Peak Height Ratio | C.V. |
|---|---|---|
| 2.0 | 0.036 | 10.5% |
| 5.1 | 0.083 | 11.7% |
| 10.2 | 0.158 | 6.6% |
| 20.4 | 0.302 | 4.5% |
| 25.5 | 0.405 | 1.5% |
| 51.0. | 0.822 | 5.0% |
| 101.9 | 1.683 | 4.6% |
| 203.8 | 3.280 | 4.0% |

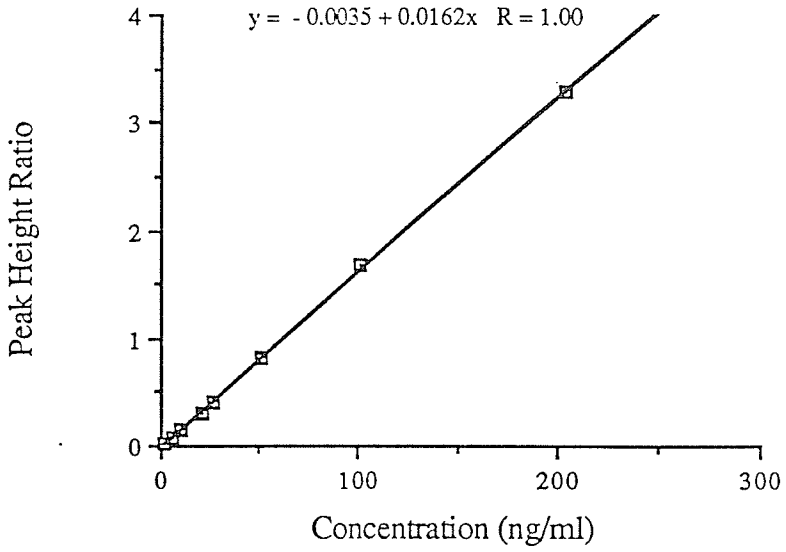



Fig.8 The HPLC calibration curve for hydroxyzine

3.1.1.3 HPLC assay for cetirizine

Representative chromatograms for cetirizine and its internal standard $P_{265}$ in serum and urine are shown in Fig.9 and Fig.10 respectively.

The retention times of cetirizine and $P_{265}$ are 6.5 and 9.0 minutes respectively. No interfering peaks were observed.

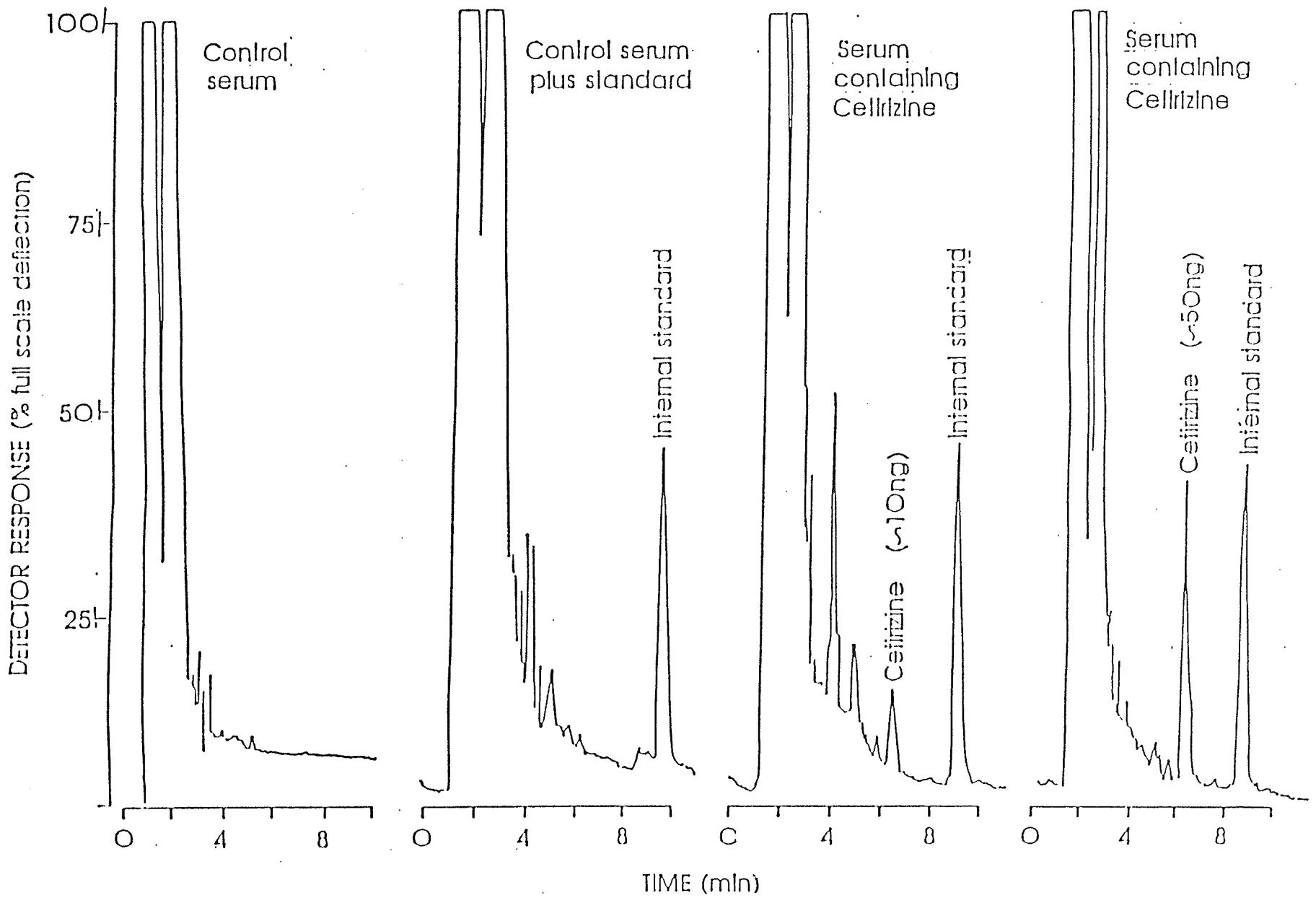



Fig.9 The HPLC chromatograms of serum cetirizine

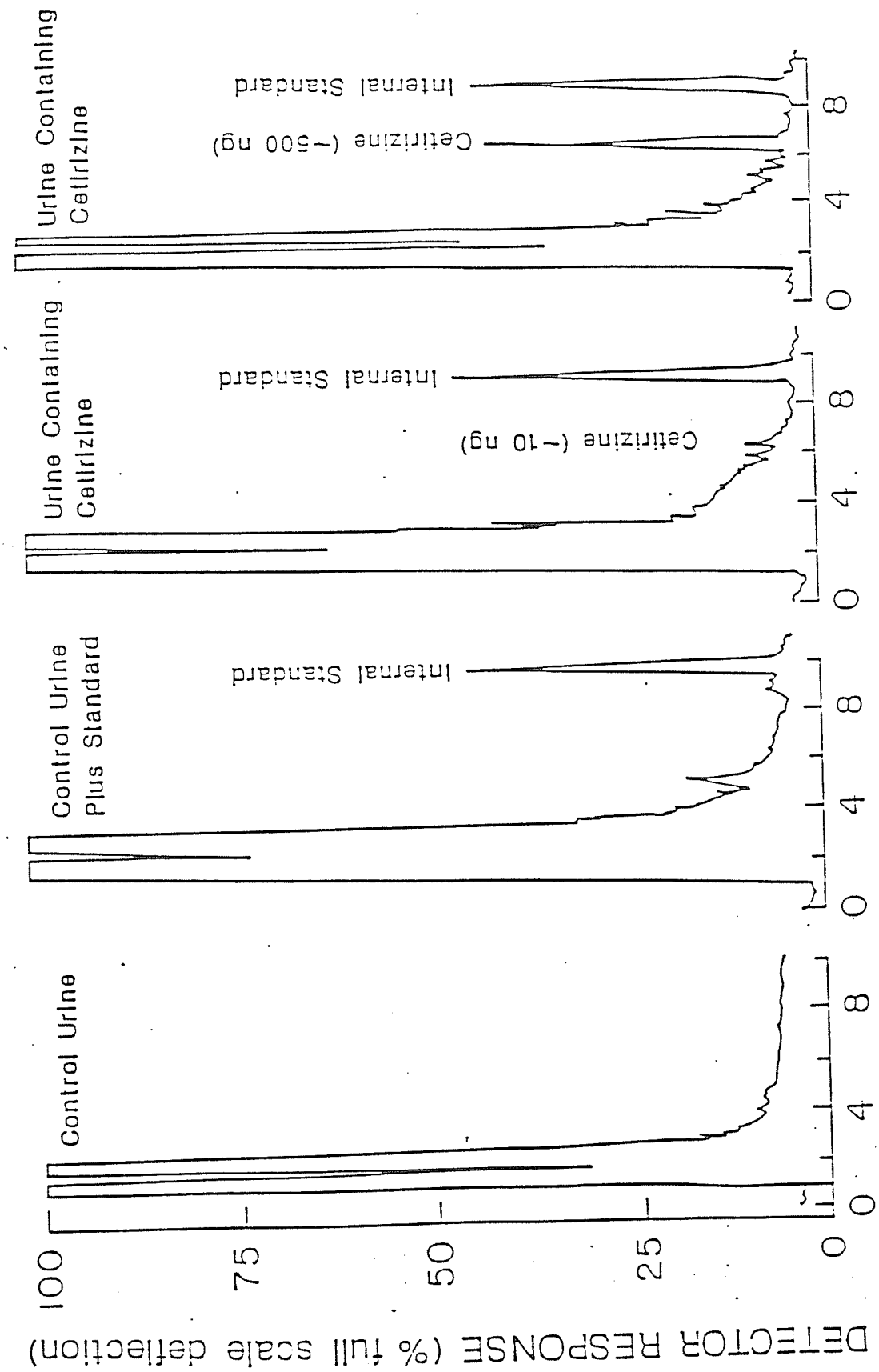



Fig.10 The HPLC chromatograms of urine cetirizine

3.1.1.4 Calibration curves for cetirizine

The calibration curves for cetirizine were constructed by plotting peak height ratios of cetirizine to $P_{265}$ versus concentrations of cetirizine. The calibration curve was analyzed periodically during the study period using concentrations of cetirizine from 2.1 ng/ml to 211.0 ng/ml, and from 10.6 ng/ml to 4220.0 ng/ml in case of measuring urine cetirizine. The calibration curves are linear over these ranges of concentrations. The variabilities in the serum cetirizine calibration curves over a period of 12 months were calculated from six calibration curves, each having six samples at every concentration. The variability is expressed as the coefficient of variation and shown in Table 2. The variabilities in the urine cetirizine calibration curves over a period of 2 months were calculated from two calibration curves, each having six samples at every concentration. The variability is expressed as the coefficient of variation and shown in Table 3, and the calibration curves are shown in Fig.11 and Fig.12.

Table 2. Variability in HPLC calibration curves for serum cetirizine

| Concentration(ng/ml) | Peak Height Ratio | C.V. |
|---|---|---|
| 2.1 | 0.056 | 14.0% |
| 5.3 | 0.088 | 14.2% |
| 10.6 | 0.138 | 7.4% |
| 26.4 | 0.345 | 3.3% |
| 52.8 | 0.698 | 3.6% |
| 105.5 | 1.368 | 4.7% |
| 211.0 | 2.390 | 2.8% |

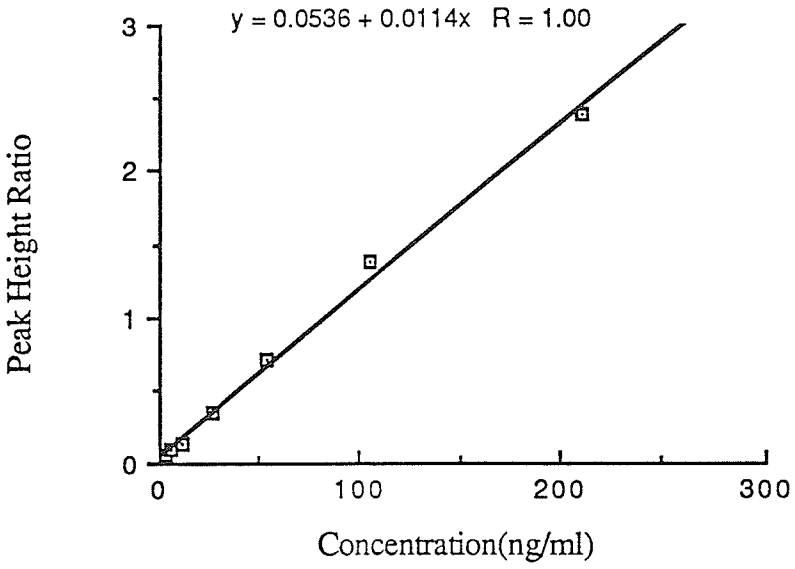



Fig.11 The HPLC calibration curve for serum cetirizine

Table 3. Variability in HPLC calibration curves for urine cetirizine

| Concentration(ng/ml) | Peak Height Ratio | C.V. |
|---|---|---|
| 10.6 | 0.060 | 12.7% |
| 52.8 | 0.278 | 3.8% |
| 105.5 | 0.559 | 1.1% |
| 211.0 | 1.160 | 1.5% |
| 527.5 | 2.352 | 4.0% |
| 1055.0 | 4.499 | 7.3% |
| 1582.5 | 7.000 | 5.0% |
| 2110.0 | 9.594 | 6.0% |
| 4220.0 | 18.772 | 12.4% |

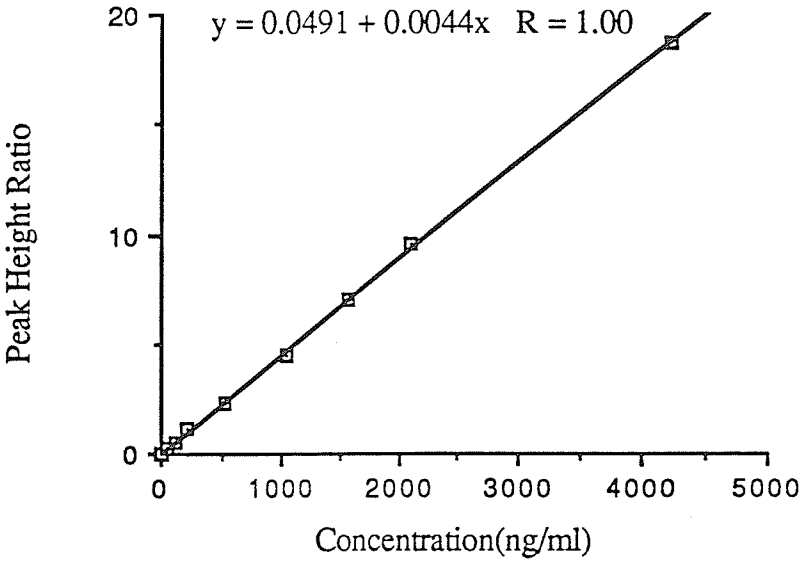



Fig.12 The HPLC calibration curve for urine cetirizine

3.1.2 Pharmacokinetic and pharmacodynamic studies of hydroxyzine in the elderly

3.1. 2.1 Serum concentrations of hydroxyzine and cetirizine

Nine healthy, white, retired clerical and professional people were recruited in response to advertisement at the Health Science Center. All subjects were well nourished but nonobese, did not require any medication in the month preceding the study, or during the study. None of them had taken $H_1$-receptor antagonists chronically, and had never taken hydroxyzine or cetirizine. All had normal hepatic and renal function. The mean age of the participants (seven females and two males) was 69.5±3.7 years, their mean weight was 70.0±9.6 kg.

The serum concentrations of hydroxyzine and cetirizine after the oral administration of 0.7 mg/kg hydroxyzine in these subjects are listed in Table 4 and Table 5, and the mean serum concentrations of hydroxyzine and cetirizine are plotted against time using a semilogarithm scale and are shown in Fig.13.

Table 4. Serum hydroxyzine concentrations in the elderly after an oral dose of hydroxyzine 0.7 mg/kg

| Time /Subject | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | Mean | S.D. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 57.0 | 20.6 | 80.8 | 42.6 | 48.9 | 94.5 | 70.6 | 50.5 | 42.2 | 56.4 | 22.4 |
| 2 | 82.8 | 42.4 | 93.3 | 63.9 | 70.0 | 70.6 | 54.7 | 57.4 | 80.5 | 68.4 | 15.8 |
| 3 | 74.8 | 41.1 | 72.9 | 58.0 | 58.9 | 61.2 | 33.2 | 64.3 | 87.3 | 61.3 | 16.6 |
| 4 | 50.6 | 40.6 | 54.6 | 44.9 | 57.6 | 61.0 | 29.4 | 70.4 | 51.0 | 51.0 | 12.0 |
| 5 | 38.7 | 34.0 | 42.1 | 35.4 | 46.7 | 50.2 | 26.3 | 52.3 | 56.7 | 42.5 | 9.8 |
| 6 | 33.6 | 31.2 | 36.9 | 30.5 | 39.2 | 45.7 | 24.5 | 83.5 | 44.9 | 41.1 | 17.3 |
| 8 | 28.6 | 32.7 | 31.7 | 20.6 | 29.2 | 36.0 | 20.5 | 57.6 | 38.5 | 32.8 | 11.1 |
| 10 | 27.5 | 23.5 | 25.6 | 19.1 | 25.7 | 22.1 | 18.5 | 59.0 | 33.0 | 28.2 | 17.4 |
| 12 | 11.9 | 21.7 | 23.7 | 16.6 | 20.6 | 19.3 | 10.4 | 49.9 | 29.1 | 22.6 | 11.7 |
| 24 | 6.3 | 12.6 | 12.1 | 11.7 | 12.6 | 14.8 | 6.1 | 44.3 | 21.7 | 15.8 | 11.6 |
| 48 | 3.6 | 4.8 | 7.0 | 5.5 | 5.0 | 7.7 | 4.5 | 32.1 | 12.4 | 9.2 | 9.0 |
| 72 | 1.4 | 3.5 | 2.5 | 3.3 | 3.4 | 2.8 | 2.9 | 23.6 | 9.4 | 5.9 | 7.0 |
| 96 | N.D | N.D | 4.3 | 1.7 | 1.4 | 1.3 | N.D | 17.8 | 5.2 | 5.3 | 6.3 |
| 120 | N.D | N.D | 1.7 | N.D | N.D | N.D | N.D | 15.3 | 3.0 | 6.7 | 7.5 |
| 144 | N.D | N.D | 1.1 | N.D | N.D | N.D | N.D | 8.8 | N.D | 4.9 | 5.4 |

* N.D: below the minimum detectable concentration (1ng/ml).

Table 5. Serum concentrations of cetirizine produced *in vivo* from hydroxyzine in the elderly after an oral dose of hydroxyzine 0.7 mg/kg

| Time /Subject | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | Mean | S.D. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 140.2 | 151.2 | 212.3 | 281.1 | 203.0 | 321.7 | 284.2 | 254.2 | 262.5 | 234.5 | 62.0 |
| 2 | 275.2 | 290.1 | 540.8 | 321.6 | 326.6 | 368.3 | 420.7 | 356.1 | 333.3 | 359.2 | 80.5 |
| 3 | 314.9 | 481.4 | 520.3 | 322.3 | 309.0 | 487.0 | 451.6 | 365.5 | 366.3 | 402.0 | 83.1 |
| 4 | 314.9 | 314.3 | 503.9 | 343.1 | 374.7 | 542.4 | 475.7 | 437.2 | 271.3 | 409.3 | 90.6 |
| 5 | 421.3 | 287.1 | 417.3 | 243.9 | 344.1 | 343.9 | 493.0 | 506.3 | 273.2 | 356.2 | 95.6 |
| 6 | 296.5 | 281.5 | 348.5 | 235.1 | 346.2 | 313.5 | 406.4 | 397.6 | 275.2 | 318.3 | 60.4 |
| 8 | 260.7 | 252.4 | 449.4 | 230.1 | 308.3 | 319.9 | 363.0 | 315.4 | 295.5 | 306.4 | 70.5 |
| 10 | 223.2 | 258.2 | 401.6 | 217.6 | 286.8 | 348.1 | 344.9 | 285.1 | 262.5 | 286.7 | 69.8 |
| 12 | 175.2 | 258.6 | 351.5 | 233.9 | 338.8 | 282.5 | 297.4 | 266.4 | 259.4 | 271.1 | 58.9 |
| 24 | 152.2 | 191.3 | 223.7 | 141.0 | 188.9 | 195.9 | 212.8 | 165.2 | 273.8 | 185.2 | 55.6 |
| 48 | 75.1 | 67.2 | 68.1 | 83.9 | 88.3 | 90.5 | 34.8 | 88.9 | 103.4 | 72.3 | 26.4 |
| 72 | 25.9 | 27.9 | 26.7 | 29.3 | 37.6 | 23.4 | 20.3 | 47.9 | 40.0 | 29.7 | 10.5 |
| 96 | 11.4 | 17.2 | 13.1 | 14.3 | 16.5 | 9.8 | 11.2 | 39.5 | 21.9 | 17.2 | 9.1 |
| 120 | 5.9 | 6.9 | 6.9 | N.D. | 5.6 | 4.6 | 5.8 | 21.3 | 16.6 | 9.2 | 6.2 |
| 144 | 2.0 | 3.5 | 2.9 | N.D. | N.D. | 2.1 | N.D. | 19.0 | N.D. | 5.9 | 7.3 |

* N.D: below the minimum detectable concentration (2ng/ml).

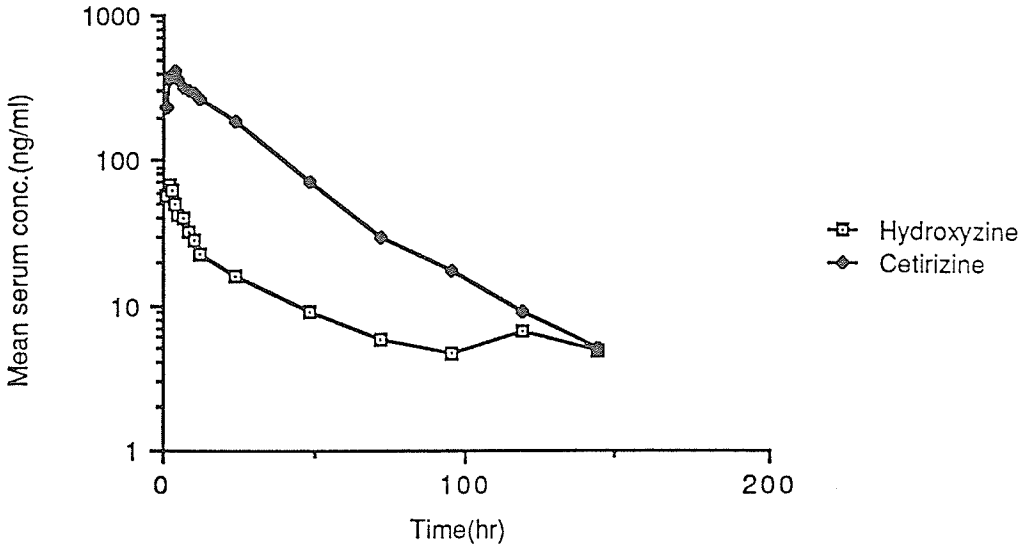



Fig.13 Mean serum concentrations of hydroxyzine and cetirizine produced *in vivo* from hydroxyzine after an oral dose of hydroxyzine 0.7 mg/kg in the elderly

3.1.2.2 Pharmacodynamic studies of hydroxyzine in the elderly

The results of the efficacy tests calculated as the percent suppression of wheals and flares induced by the intradermally injected histamine are listed in Table 6 and Table 7, and are plotted in Fig.14 and Fig.15. The mean percent suppression of wheals and flares in the elimination phase is plotted against the modified concentration in Fig.16.

Table 6. The percent suppression of wheals induced by intradermally injected histamine after an oral dose of hydroxyzine 0.7 mg/kg in the elderly

| Subject / Time | 1 | 2 | 3 | 4 | 5 | 6 | 8 | 10 | 12 | 24 | 48 | 72 | 96 | 120 | 144 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 35.6 | 72.8 | 72.2 | 82.3 | 77.4 | 79.0 | 80.2 | 72.3 | 72.1 | 65.1 | 54.7 | 46.9 | 53.3 | 61.2 | 36.9 |
| 2 | 43.5 | 70.5 | 70.4 | 73.0 | 72.2 | 70.7 | 73.8 | 69.5 | 57.6 | 49.6 | 28.4 | 36.7 | 20.6 | 4.5 | 11.7 |
| 3 | 55.0 | 81.4 | 79.4 | 79.3 | 80.5 | 75.4 | 75.7 | 82.6 | 79.6 | 74.9 | 70.3 | 47.7 | 48.3 | 24.8 | 52.4 |
| 4 | 39.0 | 41.7 | 70.5 | 75.3 | 73.7 | 78.3 | 67.9 | 76.1 | 70.4 | 66.4 | 68.9 | 49.2 | 37.0 | 62.8 | 44.9 |
| 5 | 31.6 | 69.9 | 73.6 | 83.3 | 88.9 | 85.8 | 82.0 | 79.1 | 80.3 | 58.5 | 69.9 | 59.6 | 59.1 | 25.0 | 9.3 |
| 6 | 46.8 | 54.2 | 53.9 | 73.8 | 76.2 | 69.0 | 73.5 | 68.9 | 54.9 | 59.5 | 62.8 | 56.9 | 51.6 | 22.9 | 31.5 |
| 7 | 44.7 | 59.0 | 78.9 | 78.8 | 76.8 | 83.5 | 82.4 | 73.9 | 81.1 | 67.5 | 64.1 | 60.4 | 48.7 | 60.8 | 26.8 |
| 8 | 20.8 | 48.2 | 60.6 | 77.6 | 76.8 | 77.9 | 62.7 | 66.5 | 67.4 | 64.3 | 72.9 | 61.0 | 61.9 | 46.7 | 24.0 |
| 9 | 36.5 | 72.9 | 75.0 | 100 | 100 | 100 | 76.1 | 85.6 | 74.6 | 90.4 | 73.4 | 65.1 | 42.9 | 37.3 | 37.7 |
| Mean | 39.3 | 63.4 | 70.5 | 80.4 | 80.3 | 80.0 | 74.9 | 74.9 | 70.9 | 66.2 | 62.8 | 53.7 | 47.0 | 38.4 | 30.6 |
| S.D. | 9.8 | 13.2 | 8.3 | 8.2 | 8.8 | 9.2 | 6.5 | 6.5 | 9.5 | 1.5 | 14.2 | 9.1 | 12.5 | 20.7 | 14.3 |

Table 7 The percent suppression of flares induced by intradermally injected histamine after an oral dose of hydroxyzine 0.7 mg/kg in the elderly

| Subject / Time | 1 | 2 | 3 | 4 | 5 | 6 | 8 | 10 | 12 | 24 | 48 | 72 | 96 | 120 | 144 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 13.5 | 67.6 | 78.6 | 84.4 | 81.0 | 83.1 | 69.5 | 79.6 | 74.3 | 75.3 | 77.5 | 83.1 | 83.2 | 77.8 | 5.0 |
| 2 | 64.0 | 91.2 | 92.3 | 92.1 | 97.3 | 93.9 | 84.7 | 70.0 | 82.7 | 87.4 | 80.7 | 82.3 | 68.8 | 92.4 | 36.9 |
| 3 | 71.2 | 88.0 | 90.5 | 89.0 | 88.4 | 87.8 | 92.4 | 87.7 | 92.7 | 83.4 | 90.6 | 89.7 | 80.9 | 87.0 | 82.1 |
| 4 | 60.4 | 84.0 | 88.5 | 90.4 | 91.8 | 91.3 | 90.0 | 86.6 | 92.6 | 89.4 | 83.1 | 81.7 | 65.6 | 58.0 | 23.7 |
| 5 | 82.9 | 83.4 | 74.3 | 84.3 | 83.1 | 89.9 | 86.1 | 86.4 | 81.8 | 83.5 | 75.5 | 70.2 | 84.7 | 83.1 | 77.0 |
| 6 | 44.2 | 72.4 | 79.2 | 82.4 | 72.2 | 63.2 | 63.4 | 50.8 | 63.7 | 48.0 | 15.0 | 54.9 | 57.1 | 43.1 | 43.8 |
| 7 | 20.9 | 65.1 | 81.8 | 82.8 | 76.3 | 77.9 | 82.9 | 88.7 | 74.4 | 76.9 | 80.1 | 66.8 | 68.0 | 2.7 | 20.0 |
| 8 | 57.0 | 53.5 | 69.1 | 70.2 | 63.7 | 80.8 | 75.6 | 80.7 | 77.6 | 85.0 | 84.0 | 70.1 | 60.4 | 79.8 | 61.1 |
| 9 | 43.2 | 84.6 | 78.6 | 64.2 | 77.6 | 79.1 | 79.0 | 80.1 | 78.9 | 83.3 | 76.2 | 76.0 | 75.1 | 60.5 | 50.4 |
| M | 50.8 | 76.6 | 81.4 | 82.2 | 81.3 | 83.0 | 80.4 | 79.0 | 79.9 | 79.1 | 73.6 | 75.0 | 70.9 | 64.9 | 44.5 |
| S.D. | 22.7 | 12.6 | 7.7 | 9.3 | 10.3 | 9.3 | 9.5 | 12.0 | 9.1 | 12.5 | 22.5 | 10.6 | 11.2 | 28.2 | 26.1 |

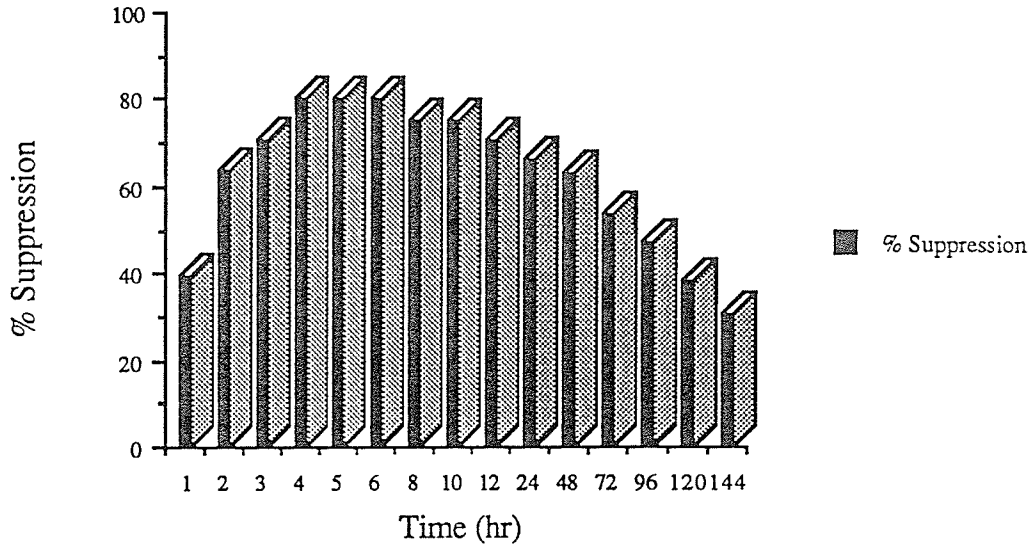



Fig.14 The mean percent suppression of wheals induced by intradermally injected histamine in the elderly after an oral dose of hydroxyzine 0.7 mg/kg

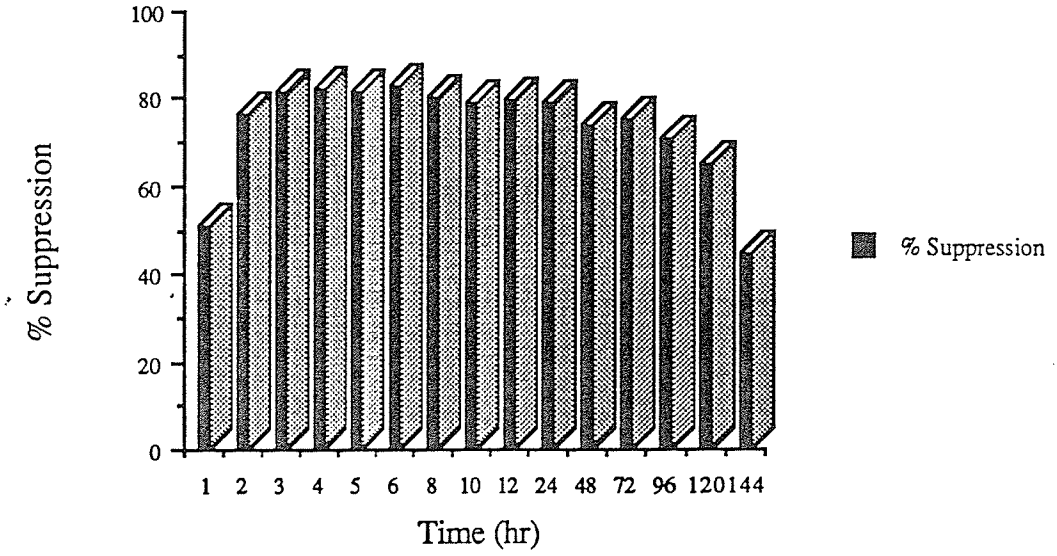
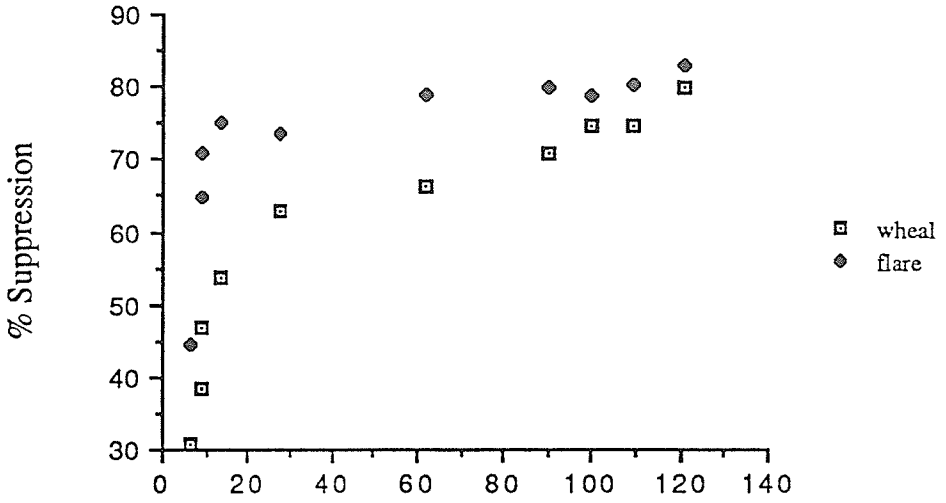



Fig.15 The mean percent suppression of flares induced by intradermally injected histamine in the elderly after an oral dose of hydroxyzine 0.7 mg/kg




$C_{Hydroyzine} + 1/4\ C_{Cetirizine}$

Fig.16 The mean effect- mean concentration relationship of hydroxyzine in the elderly after an oral dose of hydroxyzine 0.7 mg/kg

3.1.2.3 Curve fitting, pharmacokinetic and pharmacodynamic parameters

The serum hydroxyzine concentrations after an oral dose of 0.7 mg/kg in the elderly are best described by a triexponential equation, corresponding to an absorption phase, a distribution phase and an elimination phase. However, the serum cetirizine concentrations after an oral dose of hydroxyzine 0.7 mg/kg in the elderly are best described by either a biexponential or triexponential equation.

Pharmacokinetic parameters calculated are listed in Table 8 and Table 9. The systemic clearance and the apparent volume of distribution for the central compartment of hydroxyzine were calculated by assuming that hydroxyzine administered orally was totally absorbed(F=1).

Pharmacodynamic parameters are listed in Table 10.

Table 8. Pharmacokinetic parameters of hydroxyzine in the elderly after an oral dose of hydroxyzine 0.7 mg/kg

| Patient | $C_{max}$ ng/ml | $T_{max}$ hr | $T_{1/2}$ hr | $AUC_{0->\infty}$ ng·hr/ml | Oral Cls ml/min/kg | $V_\beta$ l/kg |
|---|---|---|---|---|---|---|
| 1 | 83 | 2 | 20.7 | 854 | 9.1 | 16.3 |
| 2 | 42 | 2 | 26.3 | 864 | 13.5 | 30.7 |
| 3 | 93 | 2 | 29.7 | 1243 | 9.4 | 24.2 |
| 4 | 64 | 2 | 25.6 | 907 | 12.1 | 26.8 |
| 5 | 70 | 2 | 23.9 | 1016 | 11.5 | 23.8 |
| 6 | 95 | 1 | 20.2 | 1145 | 9.8 | 17.1 |
| 7 | 71 | 1 | 29.8 | 619 | 11.8 | 30.6 |
| 8 | 84 | 6 | 53.3 | 4010 | 2.9 | 13.4 |
| 9 | 87 | 3 | 34.5 | 1789 | 6.5 | 19.4 |
| Mean | 77 | 2.3 | 29.3 | 1383 | 9.6 | 22.5 |
| S.D. | 17 | 1.5 | 10.1 | 1039 | 3.2 | 6.3 |

Table 9. Pharmacokinetic parameters of cetirizine produced *in vivo* from hydroxyzine in the elderly after an oral dose of hydroxyzine 0.7 mg/kg

| Patient | $C_{max}$ ng/ml | $T_{max}$ hr | T1/2 hr | $AUC_{0->\infty}$ ng·hr/ml | R |
|---|---|---|---|---|---|
| 1 | 421 | 4 | 19.8 | 6178 | 7.2 |
| 2 | 481 | 3 | 21.3 | 11048 | 12.8 |
| 3 | 541 | 2 | 22.9 | 13214 | 10.6 |
| 4 | 343 | 4 | 21.4 | 9683 | 10.7 |
| 5 | 375 | 4 | 19.3 | 12509 | 12.3 |
| 6 | 542 | 4 | 18.0 | 12346 | 10.8 |
| 7 | 493 | 5 | 24.8 | 11574 | 18.7 |
| 8 | 506 | 5 | 38.0 | 13396 | 3.3 |
| 9 | 366 | 3 | 37.8 | 13814 | 7.7 |
| Mean | 462 | 3.8 | 24.8 | 11529 | 10.4 |
| S.D. | 77 | 1.0 | 7.7 | 2383 | 4.3 |

Table 10. Pharmacodynamic parameters of hydroxyzine in the elderly after an oral dose of hydroxyzine 0.7 mg/kg

| Parameter | $E_{max}$ (%) ( S.E.) | $EC_{50}^{H}$ (ng/ml) (S.E.) |
|---|---|---|
| Wheal | 80.5 (0.7) | 8.2 (0.3) |
| Flare | 83.6 (1.0) | 3.0 (0.3) |

### 3.1.3 Pharmacokinetic and pharmacodynamic studies of hydroxyzine in patients with primary biliary cirrhosis

#### 3.1.3.1 Serum concentrations of hydroxyzine and cetirizine

Eight patients, 7 females and 1 male, completed the study. Their mean age was 53.4 ±11.2 years. All had abnormal liver biochemistry tests, all had biopsies compatible with primary biliary cirrhosis, and seven out of eight had positive test results for anti-antimitochondrial antibodies. No patient had a history of hepatic failure, esophageal varices, or shunts, and none were in-patients at the time of the study. The results of biochemical tests are shown in Table 11.

The serum concentrations of hydroxyzine and cetirizine in the patients after an oral dose of hydroxyzine 0.7 mg/kg are listed in Table 12 and Table 13, and the mean serum concentrations of hydroxyzine and cetirizine are plotted against time in Fig.17.

Table 11. Demographic data of patients with primary biliary cirrhosis

| Parameter | Mean±S.D. | range | normal range |
|---|---|---|---|
| age (yr) | 53.4±11.2 | 41-69 | ------- |
| weight (kg) | 62.4±8.8 | 47.2-72.0 | ------- |
| dose (mg) | 43.9±6.6 | 33.0-52.8 | ------- |
| bilirubin(μmol/l) | 33.0±23.6 | 10-74 | 3-18 |
| γ-GT (U/L) | 882.3±167.1 | 632-995 | 5-55 |
| SGOT (U/L) | 117.6±52.6 | 56-213 | <50 |
| SGPT (U/L) | 130.0±48.4 | 76-217 | 10-40 |
| Alk.Phos. (U/L) | 693.9±434.1 | 136-1449 | 3-125 |

Table 12. Serum hydroxyzine concentrations in patients with primary biliary cirrhosis after an oral dose of hydroxyzine 0.7 mg/kg

| Time / Subject | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | Mean | S.D |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 101.3 | 41.1 | 57.0 | 251.8 | 115.7 | 157.2 | 59.5 | 10.5 | 23.5 | 90.8 | 76.3 |
| 2 | 102.0 | 62.5 | 112.2 | 179.1 | N.S | 100.9 | 70.8 | 65.2 | 88.0 | 97.6 | 37.8 |
| 3 | 109.5 | 53.1 | 88.1 | 119.9 | 120.9 | 68.3 | 77.9 | 62.0 | 132.5 | 92.5 | 29.0 |
| 4 | 77.0 | 37.4 | 80.0 | 108.0 | 84.3 | 64.5 | 68.8 | 59.1 | 67.3 | 71.8 | 19.3 |
| 5 | 56.1 | 32.9 | 71.7 | N.S | 98.3 | 49.4 | 41.3 | 37.3 | 74.5 | 57.7 | 22.4 |
| 6 | 44.3 | 26.9 | 54.8 | 85.0 | 80.8 | 38.3 | 47.3 | 29.2 | 80.4 | 54.1 | 22.7 |
| 8 | 32.1 | 17.4 | 49.9 | 78.3 | 78.7 | 26.7 | 51.3 | 14.9 | 55.3 | 45.0 | 23.9 |
| 10 | 18.4 | 14.5 | 39.3 | 61.5 | 57.7 | 23.8 | 37.2 | 14.8 | 58.1 | 36.2 | 19.3 |
| 12 | 16.9 | 11.3 | 31.8 | 66.2 | 63.3 | 17.5 | 37.1 | 5.7 | 39.1 | 32.1 | 21.8 |
| 24 | 16.9 | 8.8 | 20.7 | 55.9 | 38.2 | 7.5 | 15.0 | 3.1 | 21.4 | 20.9 | 16.6 |
| 48 | 10.1 | 8.1 | 5.2 | 25.0 | 28.4 | 4.8 | 5.5 | 1.2 | 15.0 | 11.5 | 9.5 |
| 72 | 6.8 | 6.6 | N.D | 22.1 | 13.6 | 2.7 | N.S | N.D | 7.9 | 10.0 | 6.9 |
| 96 | 5.2 | 2.7 | N.D | 11.6 | 8.5 | 1.7 | 2.2 | N.D | 6.6 | 5.5 | 3.7 |
| 120 | 3.8 | N.D | N.D | 8.6 | 7.8 | N.D | N.D | N.D | 5.1 | 6.3 | 2.3 |
| 144 | 2.9 | N.D | N.D | 7.3 | 7.2 | N.D | N.D | N.D | N.D | 5.8 | 2.5 |

* N.S.: No Sample

** N.D: below the minimum detectable concentration (1ng/ml).

Table 13. Serum concentrations of cetirizine produced *in vivo* from hydroxyzine in patients with primary biliary cirrhosis after an oral dose of hydroxyzine 0.7 mg/kg

| Time / Subject | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | Mean | S.D. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 297.5 | 384.1 | 239.2 | 216.8 | 347.0 | 176.9 | 135.4 | 30.8 | 241.4 | 229.9 | 108.3 |
| 2 | 674.8 | 369.9 | 414.9 | 165.2 | N.S. | 355.3 | 234.0 | 220.2 | 323.8 | 344.7 | 158.1 |
| 3 | 497.6 | 799.7 | 415.9 | 221.2 | N.S. | 339.6 | 299.8 | 227.6 | 240.4 | 386.5 | 190.3 |
| 4 | 566.0 | 1125.0 | 457.4 | 149.7 | 446.7 | 371.4 | 346.6 | 269.2 | 245.3 | 430.8 | 286.8 |
| 5 | 474.9 | 1168.0 | 458.0 | 183.6 | 347.0 | 329.6 | 215.5 | 198.0 | 302.0 | 419.5 | 302.8 |
| 6 | 405.1 | 1075.9 | 455.5 | 244.8 | 388.4 | 303.2 | 275.4 | 136.7 | 245.7 | 392.3 | 274.2 |
| 8 | 361.0 | 860.0 | 382.9 | 202.8 | 397.6 | 275.0 | 347.5 | 84.5 | 251.4 | 351.4 | 215.4 |
| 10 | 388.8 | 650.3 | 396.3 | 77.2 | 491.0 | 263.2 | 286.6 | 37.6 | 274.0 | 318.3 | 191.7 |
| 12 | 367.0 | 489.6 | 359.9 | 99.7 | 341.5 | 253.7 | 303.3 | 351.0 | 254.8 | 313.6 | 106.8 |
| 24 | 207.1 | 265.8 | 175.3 | 109.1 | 191.1 | 125.5 | 149.5 | 40.4 | 150.8 | 157.2 | 64.1 |
| 48 | 103.1 | 100.3 | 69.9 | 65.7 | 108.2 | 31.2 | 112.0 | 4.4 | 63.6 | 73.2 | 37.1 |
| 72 | 34.1 | 52.2 | 24.4 | 42.5 | 35.5 | 15.3 | N.S. | N.D. | 14.8 | 31.3 | 13.9 |
| 96 | 13.3 | 18.7 | 8.8 | 13.9 | 16.4 | 12.9 | 22.4 | N.D. | 9.8 | 14.5 | 4.5 |
| 120 | 6.4 | 24.6 | 6.6 | 7.8 | 9.4 | 5.7 | 12.1 | N.D. | 4.7 | 9.7 | 6.5 |
| 144 | 3.5 | 11.1 | 4.5 | 2.6 | 7.8 | 6.5 | 9.9 | N.D. | 2.4 | 6.0 | 3.3 |

* N.S.: No Sample

** N.D: below the minimum detectable concentration (2 ng/ml).

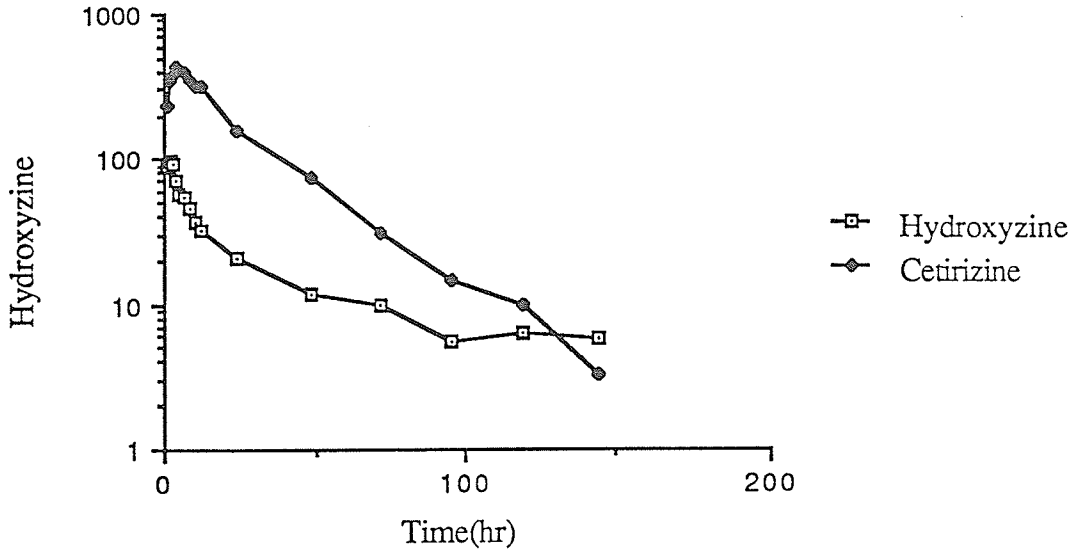



Fig.17 Mean serum concentrations of hydroxyzine and cetirizine produced *in vivo* from hydroxyzine in patients with primary biliary cirrhosis after an oral dose of hydroxyzine 0.7 mg/kg

3.1.3.2 Pharmacodynamic studies of hydroxyzine in patients with primary biliary cirrhosis

The results of efficacy tests calculated as the percent of suppression of wheals and flares induced by the intradermally injected histamine are listed in Table 14 and Table 15, and the mean percent suppression of wheal and flare in these patients are plotted against time separately in Fig.18 and Fig.19. The mean percent suppression of wheal and flare in the elimination phase is plotted against the modified concentration in Fig.20.

Table 14. The percent suppression of wheals induced by intradermally injected histamine in patients with primary biliary cirrhosis after an oral dose of hydroxyzine 0.7 mg/kg

| Subject / Time | 1 | 2 | 3 | 4 | 5 | 6 | 8 | 10 | 12 | 24 | 48 | 72 | 96 | 120 | 144 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 8.0 | 40.8 | 57.2 | 51.1 | 41.5 | 60.1 | 69.1 | 58.0 | 62.2 | 56.9 | 43.3 | 4.7 | 0 | 0 | 0 |
| 2 | 40.5 | 58.2 | 54.7 | 48.0 | 47.3 | 59.0 | 100 | 100 | 100 | 100 | 100 | 24.1 | 45.2 | 11.5 | 23.2 |
| 3 | 54.1 | 79.6 | 82.9 | 87.4 | 80.5 | 83.7 | 80.6 | 78.2 | 84.6 | 80.7 | 84.4 | 76.9 | 76.8 | 69.8 | 73.0 |
| 4 | 47.9 | 54.8 | 77.8 | 72.7 | 80.1 | 75.6 | 73.7 | 68.5 | 70.4 | 64.3 | 56.6 | 62.6 | 57.0 | 51.7 | 30.0 |
| 5 | 60.4 | 76.7 | 81.3 | 84.2 | 88.9 | 89.4 | 88.7 | 87.2 | 80.2 | 73.8 | 75.7 | 68.3 | 66.9 | 66.6 | 56.4 |
| 6 | 44.4 | 42.9 | 58.7 | 48.9 | 67.3 | 72.7 | 67.7 | 58.4 | 64.9 | 51.0 | 42.0 | 36.2 | 44.0 | 36.1 | 0 |
| 7 | 18.5 | 52.2 | 60.2 | 66.6 | 58.1 | 57.5 | 61.5 | 56.4 | 56.1 | 52.7 | 29.4 | 20.6 | 1.6 | 1.6 | 0 |
| 8 | 25.6 | 37.3 | 50.5 | 74.1 | 73.3 | 77.1 | 72.5 | 66.0 | 74.1 | 65.1 | 54.9 | 44.4 | 38.4 | 4.3 | 0 |
| 9 | 35.5 | 53.7 | 62.3 | 68.0 | 60.9 | 72.6 | 65.8 | 69.5 | 56.6 | 60.0 | 42.6 | 40.1 | 29.0 | 8.2 | 6.5 |
| M | 37.2 | 55.1 | 65.1 | 66.8 | 66.4 | 72.0 | 75.5 | 71.4 | 72.1 | 67.2 | 58.8 | 42.0 | 39.9 | 27.8 | 21.0 |
| S.D. | 17.1 | 14.8 | 12.2 | 14.7 | 15.9 | 11.2 | 12.3 | 14.7 | 14.4 | 15.6 | 23.2 | 23.8 | 26.5 | 28.7 | 27.4 |

Table 15. The percent suppression of flares induced by intradermally injected histamine in patients with primary biliary cirrhosis after an oral dose of hydroxyzine 0.7 mg/kg

| Subject / Time | 1 | 2 | 3 | 4 | 5 | 6 | 8 | 10 | 12 | 24 | 48 | 72 | 96 | 120 | 144 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 45.4 | 82.5 | 77.2 | 82.7 | 82.2 | 77.8 | 82.6 | 91.3 | 82.5 | 84.8 | 88.3 | 68.4 | 73.6 | 9.3 | 0 |
| 2 | 52.7 | 59.0 | 75.5 | 56.1 | 73.0 | 68.7 | 88.6 | 86.9 | 87.1 | 81.2 | 80.7 | 33.5 | 23.9 | 0 | 7 |
| 3 | 72.9 | 87.8 | 87.6 | 85.7 | 86.7 | 91.1 | 91.2 | 79.8 | 90.3 | 88.6 | 88.8 | 90.6 | 88.1 | 73.2 | 62.5 |
| 4 | 45.9 | 77.2 | 97.2 | 96.2 | 96.2 | 95.6 | 65.0 | 82.8 | 71.9 | 95.0 | 82.0 | 72.7 | 60.2 | 46.6 | 41.3 |
| 5 | 37.5 | 80.5 | 92.5 | 88.1 | 89.3 | 93.2 | 92.0 | 89.8 | 83.9 | 81.4 | 55.9 | 62.7 | 50.3 | 47.3 | 27.5 |
| 6 | 62.6 | 59.3 | 72.5 | 70.4 | 91.7 | 87.1 | 82.4 | 80.3 | 81.8 | 83.8 | 76.4 | 73.1 | 67.5 | 47.2 | 20.4 |
| 7 | 38.1 | 93.9 | 94.5 | 95.0 | 88.8 | 93.0 | 92.9 | 80.3 | 87.2 | 82.4 | 73.1 | 20.3 | 32.6 | 1.9 | 0 |
| 8 | 24.6 | 84.2 | 87.1 | 83.0 | 91.5 | 90.6 | 83.1 | 80.5 | 88.7 | 76.6 | 77.6 | 74.8 | 51.0 | 26.8 | 52.4 |
| 9 | 56.9 | 71.8 | 85.5 | 83.8 | 84.8 | 90.1 | 86.8 | 83.7 | 75.5 | 84.8 | 84.8 | 75.7 | 73.0 | 50.3 | 44.7 |
| M | 48.5 | 77.4 | 85.5 | 82.3 | 87.1 | 87.5 | 85.0 | 83.9 | 83.2 | 84.3 | 78.6 | 63.5 | 57.8 | 33.6 | 28.4 |
| S.D. | 14.6 | 12.0 | 8.7 | 12.4 | 6.7 | 8.7 | 8.5 | 4.4 | 6.1 | 5.2 | 10.0 | 22.3 | 20.6 | 25.4 | 23.2 |

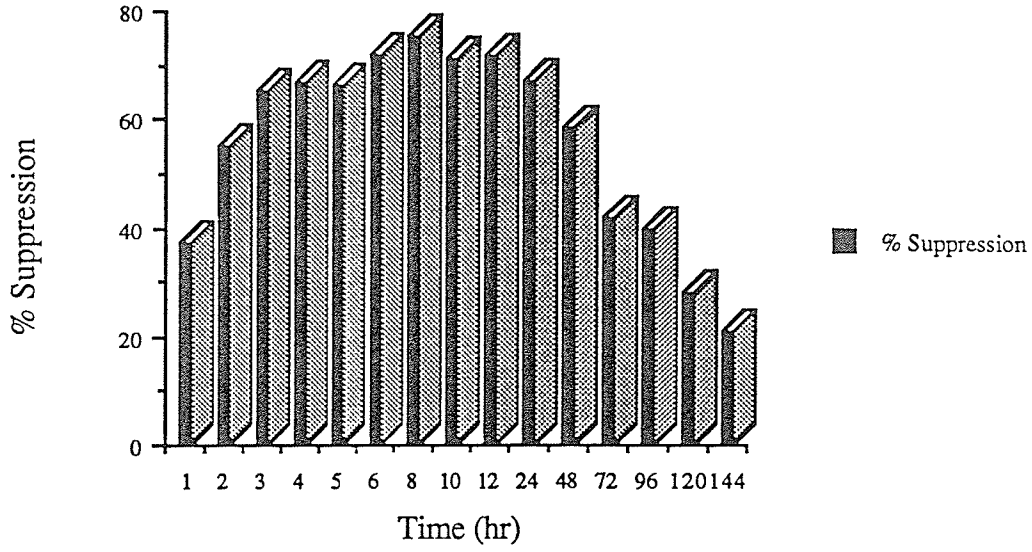



Fig.18 The mean percent suppression of wheals induced by intradermally injected histamine in patients with primary biliary cirrhosis after an oral dose of hydroxyzine 0.7 mg/kg

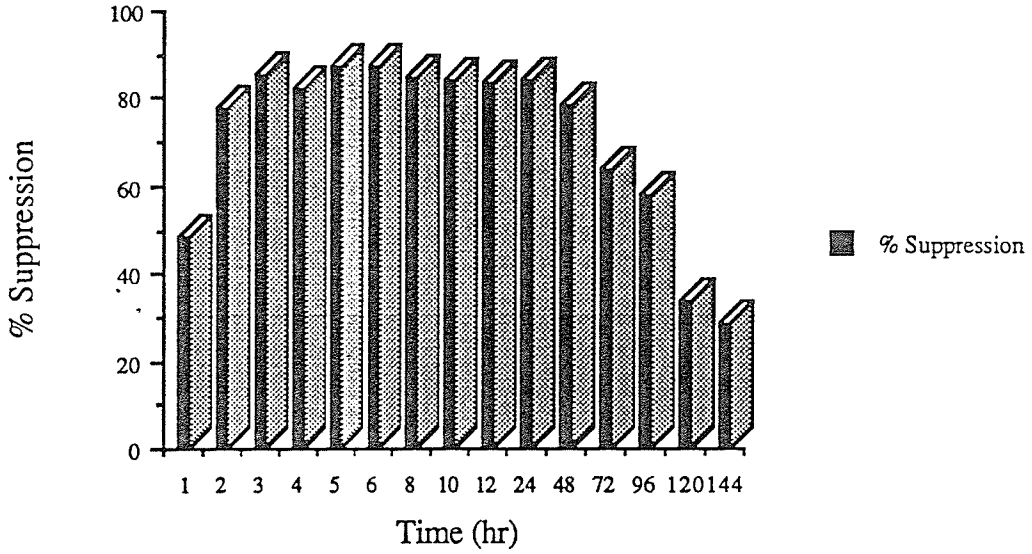



Fig.19 The mean percent suppression of flares induced by intradermally injected histamine in patients with primary biliary cirrhosis after an oral dose of hydroxyzine 0.7 mg/kg

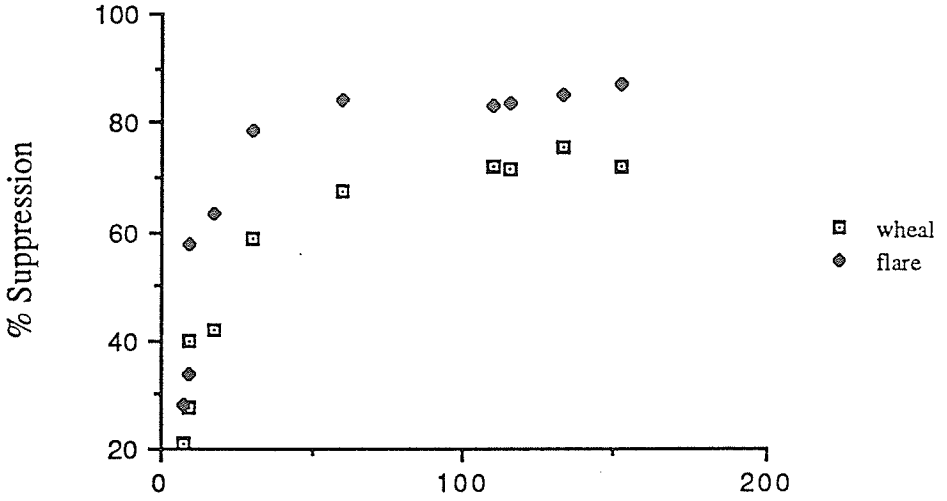



Fig.20 The effect-concentration relationship of hydroxyzine in patients with primary biliary cirrhosis after an oral dose of hyroxyzine 0.7 mg/kg

3.1.3.3 Curve fitting, pharmacokinetic and pharmacodynamic parameters

The serum hydroxyzine concentrations after the oral administration of hydroxyzine are best described by a triexponential equation, corresponding to an absorption phase, a distribution phase and an elimination phase. The coefficients of determination are from 0.89 to 0.99.

The serum concentrations of cetirizine after the oral administration of hydroxyzine 0.7 mg/kg in these patients could be best described by either a triexponential or quatrexponential equation, with the coefficient of determination ranging from 0.81 to 0.99.

Pharmacokinetic parameters calculated are listed in Table 16 and Table 17 . The systemic clearance and the apparent volume of distribution were calculated by assuming that hydroxyzine was totally absorbed (F=1) after the oral administration.

Pharmacodynamic parameters are listed in Table 18.

Table 16. Pharmacokinetic parameters of hydroxyzine in patients with primary biliary cirrhosis after an oral dose of hydroxyzine 0.7 mg/kg

| Subject | $C_{max}$ ng/ml | $T_{max}$ hr | $T_{1/2}$ hr | $AUC_{0->\infty}$ ng·hr/ml | Oral Cls ml/min/kg | $V_\beta$ l/kg |
|---|---|---|---|---|---|---|
| 1 | 109 | 3 | 44.6 | 1827 | 6.4 | 24.7 |
| 2 | 62 | 2 | 47.2 | 1117 | 10.4 | 42.6 |
| 3 | 112 | 2 | 13.6 | 1402 | 8.3 | 9.8 |
| 4 | 252 | 1 | 36.6 | 4719 | 2.5 | 7.8 |
| 5 | 121 | 2 | 40.8 | 3965 | 2.9 | 10.4 |
| 6 | 157 | 1 | 38.8 | 1171 | 10.0 | 33.5 |
| 7 | 78 | 3 | 36.4 | 1462 | 8.0 | 25.1 |
| 8 | 65 | 2 | 17.7 | 451 | 25.9 | 39.7 |
| 9 | 132 | 3 | 48.1 | 2406 | 4.9 | 20.2 |
| Mean | 121 | 2.1 | 36.0 | 2058 | 8.8 | 23.8 |
| S.D. | 58 | 0.8 | 12.3 | 1411 | 7.0 | 13.0 |

Table 17. Pharmacokinetic parameters of cetirizine produced *in vivo* from hydroxyzine in patients with primary biliary cirrhosis after an oral dose of hydroxyzine 0.7 mg/kg

| Subject | $C_{max}$ ng/ml | $T_{max}$ hr | $T_{1/2}$ hr | $AUC_{0->\infty}$ ng·hr/ml | R |
|---|---|---|---|---|---|
| 1 | 675 | 2 | 19.2 | 14615 | 8.0 |
| 2 | 1168 | 5 | 38.1 | 21944 | 19.6 |
| 3 | 458 | 5 | 49.2 | 12787 | 9.1 |
| 4 | 271 | 3 | 24.8 | 7817 | 1.7 |
| 5 | 491 | 10 | 32.7 | 14555 | 3.7 |
| 6 | 371 | 4 | 40.2 | 9066 | 7.7 |
| 7 | 347 | 8 | 26.3 | 13281 | 9.1 |
| 8 | 269 | 4 | 11.9 | 2180 | 4.8 |
| 9 | 324 | 2 | 26.9 | 9747 | 4.1 |
| Mean | 486 | 4.8 | 29.9 | 11777 | 7.5 |
| S.D. | 286 | 2.7 | 11.4 | 5496 | 5.2 |

Table 18. Pharmacodynamic parameters of hydroxyzine in patients with primary biliary cirrhosis after an oral dose of hydroxyzine 0.7 mg/kg

| Parameter | $E_{max}$ (%) ( S.E.) | $EC_{50}^{H}$ (ng/ml) ( S.E.) |
|---|---|---|
| Wheal | 82.9 (1.2) | 14.9 (0.8) |
| Flare | 93.9 (1.6) | 9.9 (0.7) |

### 3.1.4. Pharmacokinetic and pharmacodynamic studies of cetirizine in children

#### 3.1.4.1. Serum concentrations of cetirizine

Nineteen children, age 5-12 years, with allergic rhinitis, participated in this study. Serum concentrations of cetirizine in these children after two doses of cetirizine are listed in Table 19 and Table 20, and are plotted against time in Fig.21. Table 21 lists amounts of cetirizine excreted in the urine in different time periods in the first 24 hours after the drug administration. Serum cetirizine concentrations in the following 5 week period are listed in Table 22 and Table 23. The mean steady-state concentrations are plotted in Fig.22.

Table 19 . Serum concentrations of cetirizine in children after an oral dose of 5 mg cetirizine

| Subject | 0.5 (hr) | 1.0 (hr) | 1.5 (hr) | 2.0 (hr) | 4.0 (hr) | 6.0 (hr) | 8.0 (hr) | 10.0 (hr) | 12.0 (hr) | 24.0 (hr) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 36.3 | 296.9 | 383.4 | 312.5 | 172.3 | 100.5 | 86.0 | 70.8 | N.S. | 26.3 |
| 2 | 290.2 | 292.6 | 298.6 | 258.3 | 170.8 | 142.8 | 98.4 | 63.3 | 54.4 | 20.9 |
| 3 | 684.6 | 515.7 | 489.0 | 465.4 | 312.7 | 216.0 | 169.6 | 117.0 | 89.3 | 32.3 |
| 4 | 204.6 | 465.2 | 496.4 | 436.7 | 309.1 | 188.0 | 150.1 | 111.7 | 83.7 | 27.9 |
| 5 | 572.4 | 475.5 | 321.6 | 332.1 | 229.4 | 190.2 | 108.9 | 97.1 | 88.0 | 34.1 |
| 6 | 128.2 | 199.3 | 118.8 | 158.8 | 223.2 | 133.6 | 123.2 | 83.5 | 49.8 | 18.6 |
| 7 | 73.4 | 214.9 | 254.5 | 160.9 | 118.7 | 69.8 | 60.0 | 52.7 | 36.1 | 10.8 |
| 8 | 426.2 | 398.2 | 314.9 | 369.3 | 214.4 | 192.1 | 125.6 | 99.3 | 66.5 | 13.1 |
| 9 | 175.2 | 365.5 | 438.3 | 436.7 | 274.4 | 208.2 | 109.8 | 74.6 | 73.4 | 11.9 |
| 10 | 497.9 | 494.5 | 380.3 | 343.2 | 233.4 | 174.4 | N.S. | 99.3 | 63.8 | 20.4 |
| Mean | 308.9 | 371.8 | 349.6 | 327.4 | 225.9 | 161.6 | 114.6 | 86.9 | 67.2 | 21.6 |
| S.D. | 224.0 | 116.5 | 114.4 | 108.6 | 61.8 | 48.3 | 32.8 | 21.3 | 18.3 | 8.3 |

* N.S.: No Sample

Table 20. Serum concentrations of cetirizine
in children after an oral dose of 10 mg cetirizine

| Subject | 0.5 (hr) | 1.0 (hr) | 1.5 (hr) | 2.0 (hr) | 4.0 (hr) | 6.0 (hr) | 8.0 (hr) | 10.0 (hr) | 12.0 (hr) | 24.0 (hr) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 464.3 | 585.6 | 496.1 | 456.1 | 307.9 | 241.8 | 183.7 | 141.8 | 111.9 | 38.9 |
| 2 | 943.8 | 648.2 | 641.8 | 622.7 | 526.1 | 467.2 | 303.0 | 198.8 | 127.6 | 87.6 |
| 3 | 1354 | 1034 | 1042 | 1071 | 801.0 | 571.1 | 367.9 | 219.0 | 195.6 | 86.5 |
| 4 | 833.2 | 711.1 | 765.3 | 755.1 | 737.4 | 324.4 | 187.2 | N.S. | 105.4 | 28.6 |
| 5 | 622.8 | 691.8 | 608.3 | 588.7 | 377.7 | 311.1 | 274.4 | 109.5 | 93.3 | 18.0 |
| 6 | 1387 | 1101 | 1039 | 983.9 | 558.9 | 351.4 | 253.4 | 205.2 | 148.0 | 46.7 |
| 7 | 153.4 | 714.6 | 765.4 | 676.5 | 557.9 | 299.0 | 216.7 | 158.5 | 136.0 | 46.7 |
| 8 | 417.5 | 751.6 | 646.3 | 594.8 | 365.5 | 272.4 | 219.2 | 157.5 | 124.6 | 33.4 |
| 9 | 1492 | 1031 | 761.6 | 574.8 | 430.7 | 365.5 | 195.5 | N.S. | 169.1 | 57.0 |
| Mean | 852.2 | 807.8 | 751.9 | 702.6 | 518.1 | 356.0 | 244.5 | 170.0 | 134.6 | 49.3 |
| S.D. | 479.2 | 192.7 | 186.1 | 202.0 | 168.2 | 103.1 | 61.7 | 39.2 | 32.2 | 24.2 |

* N.S.: No Sample

Table 21. Urinary excretion of cetirizine in the first 24 hours after the 5 mg and 10 mg doses in children

| Subject\Time | 0-4 h | 4-8 h | 8-12 h | 12-24 h | Total |
|---|---|---|---|---|---|
| 5mg | | | | | |
| 1 | 1.48 | 1.03 | 0.44 | 0.52 | 3.47 |
| 2 | 0.15 | 0.83 | 0.31 | 0.39 | 1.68 |
| 3 | 0.86 | 1.00 | 0.56 | 0.71 | 2.13 |
| 4 | 2.23 | 0.58 | 0.47 | 0.21 | 3.49 |
| 5 | 0.81 | 0.50 | 0.28 | 0.28 | 1.88 |
| 6 | 0.15 | 0.68 | 0.40 | 0.17 | 1.40 |
| 7 | 0.89 | 0.55 | 0.08 | 0.24 | 1.77 |
| 8 | 0.60 | 0.31 | 0.32 | 0.44 | 1.67 |
| 9 | 0.77 | 0.68 | 0.39 | 0.20 | 2.04 |
| 10 | 0.41 | 0.31 | 0.30 | 0.38 | 1.41 |
| Mean | 0.84 | 0.65 | 0.36 | 0.35 | 2.19 |
| S.D. | 0.63 | 0.25 | 0.13 | 0.17 | 0.83 |
| 10mg | | | | | |
| 1 | 4.54 | 1.46 | 0.18 | 0.69 | 6.87 |
| 2 | 0.29 | 0.98 | 0.50 | 0.49 | 2.26 |
| 3 | 1.00 | 1.58 | 0.81 | 0.83 | 4.22 |
| 4 | 1.19 | 1.17 | 0.56 | 0.33 | 3.25 |
| 5 | 1.63 | 0.77 | 0.27 | 0.37 | 3.04 |
| 6 | 1.58 | 1.50 | 0.96 | 0.80 | 4.84 |
| 7 | 0.52 | 1.35 | 0.29 | 0.37 | 2.53 |
| 8 | 1.56 | 1.19 | 0.84 | 0.71 | 4.31 |
| 9 | 1.36 | 1.23 | 0.36 | 0.69 | 3.64 |
| Mean | 1.52 | 1.25 | 0.53 | 0.59 | 3.88 |
| S.D. | 1.23 | 0.26 | 0.28 | 0.20 | 1.40 |

Table 22. Serum cetirizine concentrations at the steady-state after the oral administration of 5 mg cetirizine in children

| Subject\Time | 1 week | 2 week | 3 week | 4 week | 5 week |
|---|---|---|---|---|---|
| 1 | 114.4 | 62.3 | 83.5 | 72.6 | 71.4 |
| 2 | 111.4 | 124.5 | 112.2 | 121.6 | 95.3 |
| 3 | 78.6 | 201.6 | 327.7 | 125.3 | 219.8 |
| 4 | 141.6 | 189.0 | 171.5 | 163.0 | 171.8 |
| 5 | 106.1 | 105.1 | 137.1 | 112.2 | 49.8 |
| 6 | 103.0 | 100.8 | 84.9 | 67.1 | 101.0 |
| 7 | 89.6 | 57.8 | 68.8 | 182.0 | 39.2 |
| 8 | 136.9 | N.S. | 85.9 | N.S. | 125.6 |
| 9 | 75.3 | 126.8 | 84.0 | N.S. | N.S. |
| 10 | 120.5 | 124.3 | 114.7 | 115.3 | 92.3 |
| Mean | 107.7 | 121.4 | 127.0 | 119.9 | 107.3 |
| S.D. | 22.3 | 49.1 | 77.0 | 39.4 | 57.9 |

* N.S.: No Sample

Table 23. Serum cetirizine concentrations at the steady-state after the oral administration of 10 mg cetirizine in children

| Subject\Time | 1 Week | 2 Week | 3 Week | 4 Week | 5 Week |
|---|---|---|---|---|---|
| 1 | 145.3 | 156.2 | 105.1 | 121.0 | 118.0 |
| 2 | 279.5 | 206.6 | 241.9 | 163.6 | 165.4 |
| 3 | 348.9 | 245.8 | 179.8 | 16.4 | 128.7 |
| 4 | 211.9 | 237.9 | 9.1 | 91.0 | 179.8 |
| 5 | N.S. | 185.8 | 276.6 | 146.9 | N.S. |
| 6 | 154.1 | N.S. | 327.1 | N.S. | 240.8 |
| 7 | 192.0 | 140.0 | 148.5 | 202.4 | 190.1 |
| 8 | 305.3 | 203.0 | 109.5 | 195.6 | 284.9 |
| 9 | 191.8 | 204.8 | 285.3 | 77.4 | 164.2 |
| Mean | 228.6 | 197.5 | 209.2 | 142.6 | 184.0 |
| S.D. | 74.1 | 36.4 | 85.0 | 48.7 | 55.6 |

* N.S.: No Sample

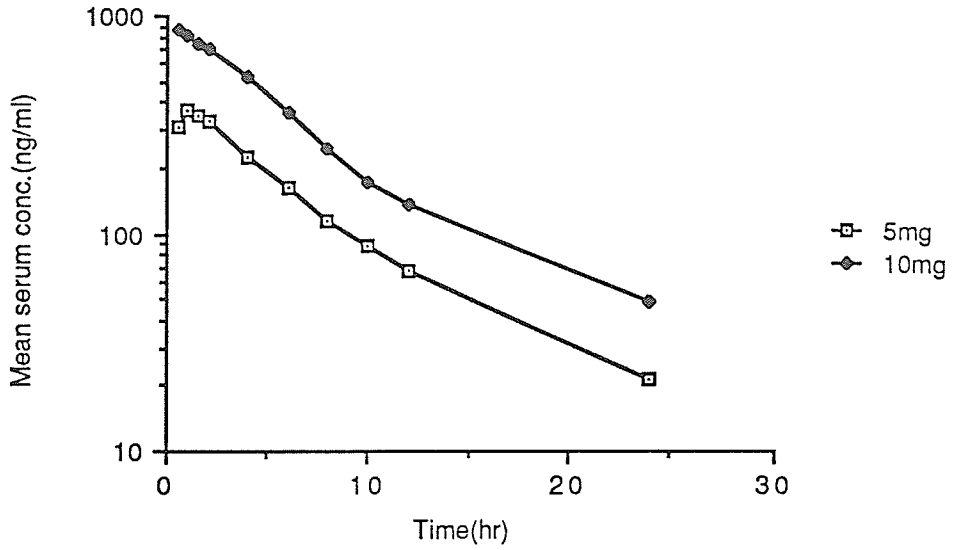



Fig.21 Mean serum concentrations of cetirizine in children after oral administration of 5 mg and 10 mg of cetirizine

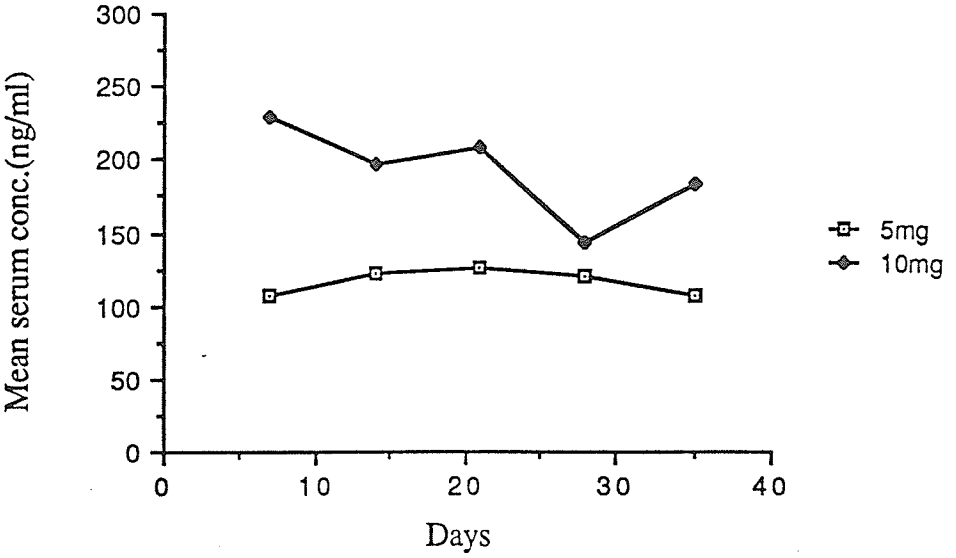



Fig.22 Mean serum cetirizine concentration at the steady-state after oral administrations of 5 mg and 10 mg of hydroxyzine

3.1.4.2 Pharmacodynamic studies of cetirizine in children

The results of efficacy tests calculated as the percent suppression of wheal and flare induced by epicutaneous histamine after the oral administration of cetirizine in children are listed from Table 24 to Table 27. The mean percent suppression are plotted against time in Fig. 23 and Fig. 24. The percent suppression of wheal and flare in the steady-state after the continuous administration of two cetirizine dosage forms are listed from Table 28 to Table 31, and the mean percent suppression are plotted in Fig.25 and Fig.26.

Table 24. The percent suppression of wheals induced by epicutaneous histamine in children after the oral administration of 5 mg cetirizine

| Subject | 0.5 (hr) | 1.0 (hr) | 1.5 (hr) | 2.0 (hr) | 4.0 (hr) | 6.0 (hr) | 8.0 (hr) | 10.0 (hr) | 12.0 (hr) | 24.0 (hr) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 28.2 | 32.0 | 79.7 | 76.9 | 100 | 100 | 100 | 100 | 100 | 60.5 |
| 2 | 0 | 34.2 | 85.4 | 57.8 | 100 | 81.9 | 83.0 | 84.9 | 60.7 | 59.4 |
| 3 | 84.7 | 97.9 | 88.5 | 55.5 | 100 | 83.4 | 88.7 | 90.7 | 100 | 100 |
| 4 | 46.4 | 38.0 | 80.1 | 82.4 | 100 | 100 | 96.0 | 90.7 | 96.3 | 91.0 |
| 5 | 69.5 | 71.6 | 81.6 | 100 | 100 | 100 | 100 | 90.6 | 88.5 | 74.8 |
| 6 | 56.5 | 68.9 | 69.5 | 73.7 | 100 | 100 | 100 | 90.6 | 88.6 | 66.8 |
| 7 | 60.1 | 11.1 | 57.0 | 62.4 | 93.8 | 83.9 | 84.0 | 93.5 | 74.2 | 36.4 |
| 8 | 0 | 60.8 | 54.2 | 64.1 | 73.2 | 100 | 91.0 | 66.2 | 84.8 | 68.6 |
| 9 | 58.9 | 63.2 | 77.6 | 81.7 | 66.5 | 80.9 | 82.1 | 61.7 | 90.6 | 44.1 |
| 10 | 0 | 37.9 | 53.6 | 78.7 | 61.6 | 100 | 100 | 74.5 | 70.4 | 23.8 |
| Mean | 40.4 | 51.6 | 72.7 | 73.3 | 89.5 | 93.0 | 91.5 | 83.2 | 85.4 | 61.5 |
| S.D. | 31.4 | 25.3 | 13.3 | 13.6 | 15.8 | 9.1 | 8.5 | 12.7 | 13.1 | 22.3 |

Table 25. The percent suppression of flares induced by epicutaneous histamine in children after the oral administration of 5 mg cetirizine

| Subject | 0.5 (hr) | 1.0 (hr) | 1.5 (hr) | 2.0 (hr) | 4.0 (hr) | 6.0 (hr) | 8.0 (hr) | 10.0 (hr) | 12.0 (hr) | 24.0 (hr) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0 | 0 | 93.5 | 91.2 | 96.6 | 96.4 | 96.0 | 97.7 | 96.0 | 94.8 |
| 2 | 0 | 75.9 | 82.9 | 81.5 | 76.9 | 62.0 | 69.5 | 55.2 | 49.3 | 56.3 |
| 3 | 76.3 | 88.4 | 80.1 | 87.8 | 88.7 | 87.7 | 84.2 | 90.7 | 92.1 | 90.5 |
| 4 | 0 | 20.5 | 0 | 87.7 | 94.0 | 90.7 | 94.7 | 89.7 | 88.8 | 87.3 |
| 5 | 82.7 | 97.1 | 96.6 | 98.9 | 97.9 | 97.1 | 97.9 | 97.1 | 96.7 | 94.8 |
| 6 | 8.1 | 69.1 | 77.4 | 83.8 | 93.9 | 94.2 | 93.9 | 93.9 | 93.8 | 71.5 |
| 7 | 95.8 | 85.1 | 89.3 | 60.2 | 95.2 | 94.9 | 91.2 | 95.1 | 92.6 | 91.4 |
| 8 | 0 | 0 | 91.8 | 90.6 | 93.0 | 93.7 | 93.5 | 92.5 | 93.0 | 94.5 |
| 9 | 46.9 | 90.8 | 82.9 | 97.7 | 97.5 | 95.9 | 95.9 | 94.9 | 94.4 | 90.3 |
| 10 | 58.9 | 65.5 | 95.1 | 97.6 | 97.7 | 98.0 | 97.8 | 98.5 | 97.1 | 97.0 |
| Mean | 36.9 | 59.2 | 79.0 | 90.7 | 93.1 | 91.1 | 91.5 | 90.5 | 89.3 | 85.8 |
| S.D. | 39.4 | 37.8 | 8.5 | 5.9 | 6.3 | 10.7 | 8.7 | 12.7 | 14.3 | 12.6 |

Table 26. The percent suppression of wheals induced by epicutaneous histamine in children after the oral administration of 10 mg cetirizine

| Subject | 0.5 (hr) | 1.0 (hr) | 1.5 (hr) | 2.0 (hr) | 4.0 (hr) | 6.0 (hr) | 8.0 (hr) | 10.0 (hr) | 12.0 (hr) | 24.0 (hr) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 52.9 | 62.9 | 100 | 23.6 | 100 | 100 | 100 | 96.8 | 100 | 37.3 |
| 2 | 100 | 89.4 | 100 | 87.7 | 87.5 | 83.9 | 74.9 | 100 | 87.4 | 81.3 |
| 3 | 100 | 97.6 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 93.8 |
| 4 | 54.1 | 100 | 100 | 85.1 | 100 | 83.9 | 87.6 | 84.7 | 100 | 36.2 |
| 5 | 68.5 | 100 | 100 | 100 | 100 | 88.5 | 93.8 | 100 | 100 | 0.3 |
| 6 | 70.3 | 100 | 100 | 100 | 100 | 100 | 74.1 | 79.1 | 68.4 | 63.9 |
| 7 | 52.5 | 88.8 | 70.8 | 69.3 | 61.0 | 100 | 100 | 75.0 | 100 | 100 |
| 8 | 0 | 100 | 70.3 | 100 | 100 | 100 | 100 | 100 | 100 | 28.0 |
| 9 | 54.6 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Mean | 61.4 | 93.2 | 93.5 | 85.1 | 94.3 | 95.1 | 92.3 | 92.8 | 95.1 | 60.1 |
| S.D. | 29.9 | 12.3 | 13.0 | 25.4 | 13.1 | 7.4 | 10.9 | 10.3 | 10.8 | 36.2 |

Table 27. The percent suppression of flares induced by epicutaneous histamine in children after the oral administration of 10 mg cetirizine

| Subject | 0.5 (hr) | 1.0 (hr) | 1.5 (hr) | 2.0 (hr) | 4.0 (hr) | 6.0 (hr) | 8.0 (hr) | 10.0 (hr) | 12.0 (hr) | 24.0 (hr) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 36.1 | 34.5 | 70.8 | 73.3 | 67.3 | 74.7 | 73.3 | 68.3 | 72.1 | 42.8 |
| 2 | 96.4 | 95.7 | 96.2 | 96.1 | 87.8 | 95.1 | 94.6 | 94.7 | 94.1 | 92.5 |
| 3 | 95.8 | 97.4 | 97.5 | 97.5 | 97.3 | 97.7 | 97.3 | 97.8 | 96.9 | 96.6 |
| 4 | 31.2 | 87.6 | 93.9 | 94.6 | 93.3 | 89.1 | 84.0 | 77.4 | 86.2 | 45.4 |
| 5 | N.S | 60.9 | 97.4 | 97.1 | 97.8 | 98.7 | 98.3 | 97.3 | 97.0 | 94.7 |
| 6 | 96.0 | 95.6 | 94.5 | 95.3 | 92.9 | 93.2 | 93.5 | 91.9 | 93.3 | 91.3 |
| 7 | 54.7 | 81.8 | 98.3 | 96.7 | 96.8 | 97.4 | 97.7 | 98.1 | 97.0 | 97.8 |
| 8 | 54.0 | 92.3 | 93.8 | 96.8 | 91.8 | 95.8 | 95.1 | 94.4 | 91.9 | 87.0 |
| 9 | 51.1 | 93.1 | 93.3 | 93.8 | 91.8 | 92.3 | 92.8 | 91.6 | 93.9 | 92.0 |
| Mean | 64.4 | 82.1 | 92.9 | 93.5 | 90.8 | 92.7 | 91.8 | 90.2 | 91.4 | 82.3 |
| S.D. | 27.5 | 21.1 | 8.5 | 7.7 | 9.4 | 7.4 | 8.1 | 10.3 | 8.0 | 21.9 |

Table 28 The percent suppression of wheals induced by epicutaneous histamine in children at the steady-state after the oral administration of 5 mg cetirizine

| Subject\Day | 7 | 14 | 21 | 28 | 35 |
|---|---|---|---|---|---|
| 1 | 100 | 100 | 100 | 100 | 74.1 |
| 2 | 100 | 100 | 100 | 100 | 100 |
| 3 | 100 | 100 | 100 | 100 | 100 |
| 4 | 100 | 100 | 100 | 100 | 100 |
| 5 | 100 | 80.2 | 100 | 83.3 | 100 |
| 6 | 100 | 93.3 | 100 | 93.4 | 100 |
| 7 | 100 | 78.9 | 83.0 | 73.8 | 74.4 |
| 8 | 100 | 62.4 | 100 | 67.9 | 100 |
| 9 | 75.4 | 54.0 | 89.1 | 79.2 | 100 |
| 10 | 91.7 | 100 | 100 | 69.3 | 32.7 |
| Mean | 93.0 | 86.9 | 96.5 | 86.7 | 87.2 |
| S.D. | 13.2 | 17.3 | 6.1 | 13.5 | 21.9 |

Table 29 The percent suppression of flares induced by epicutaneous histamine in children at the steady-state after the oral administration of 5 mg cetirizine

| Subject\Day | 7 | 14 | 21 | 28 | 35 |
|---|---|---|---|---|---|
| 1 | 94.1 | 94.3 | 95.4 | 93.0 | 94.0 |
| 2 | 46.9 | 73.4 | 66.9 | 71.7 | 76.3 |
| 3 | 91.0 | 79.0 | 87.2 | 86.5 | 84.7 |
| 4 | 90.1 | 91.5 | 91.7 | 94.3 | 84.6 |
| 5 | 96.6 | 96.2 | 98.0 | 95.7 | 98.6 |
| 6 | 93.4 | 93.8 | 90.6 | 95.5 | 94.7 |
| 7 | 94.8 | 93.5 | 94.4 | 92.5 | 92.6 |
| 8 | 90.1 | 90.7 | 91.1 | 91.7 | 91.5 |
| 9 | 97.2 | 96.3 | 97.4 | 95.7 | 96.2 |
| 10 | 98.0 | 98.0 | 98.4 | 95.9 | 96.3 |
| Mean | 89.2 | 90.7 | 91.1 | 91.3 | 90.9 |
| S.D. | 15.1 | 8.0 | 9.2 | 7.5 | 6.9 |

Table 30 The percent suppression of wheals induced by epicutaneous histamine in children at the steady-state after the oral administration of 10 mg cetirizine

| Subject\Day | 7 | 14 | 21 | 28 | 35 |
|---|---|---|---|---|---|
| 1 | 74.7 | 100 | 100 | 100 | 100 |
| 2 | 100 | 90.3 | 100 | 91.7 | 100 |
| 3 | 100 | 85.1 | 100 | N.S. | 100 |
| 4 | 100 | 85.6 | 100 | 100 | 100 |
| 5 | 100 | 100 | N.S. | 100 | 100 |
| 6 | N.S. | 64.2 | 100 | N.S. | N.S. |
| 7 | 100 | N.S. | 100 | N.S. | 100 |
| 8 | 100 | 100 | 100 | 100 | 100 |
| 9 | 100 | 100 | 100 | 100 | 100 |
| Mean | 96.8 | 90.7 | 100 | 98.6 | 100 |
| S.D. | 8.9 | 12.6 | 0 | 3.4 | 0 |

*N.S: No sample

Table 31 The percent suppression of flares induced by epicutaneous histamine in children at the steady-state after the oral administration of 10 mg cetirizine

| Subject\Day | 7 | 14 | 21 | 28 | 35 |
|---|---|---|---|---|---|
| 1 | 56.4 | 36.8 | 66.3 | 48.0 | 64.2 |
| 2 | 96.4 | 93.5 | 95.8 | 95.0 | 95.7 |
| 3 | 96.9 | 96.3 | 96.6 | N.S. | 96.8 |
| 4 | 89.8 | 90.3 | 87.9 | 87.7 | 90.2 |
| 5 | 97.4 | 96.3 | N.S. | 97.6 | 98.1 |
| 6 | N.S. | 90.1 | 95.7 | N.S. | N.S. |
| 7 | 96.9 | N.S. | 97.3 | N.S. | 95.6 |
| 8 | 89.1 | 89.7 | 90.9 | 94.0 | 91.1 |
| 9 | 88.5 | 87.8 | 94.6 | 93.5 | 93.3 |
| Mean | 88.9 | 85.1 | 90.6 | 86.0 | 90.6 |
| S.D. | 13.7 | 19.8 | 10.3 | 18.9 | 11.0 |

*N.S: No sample

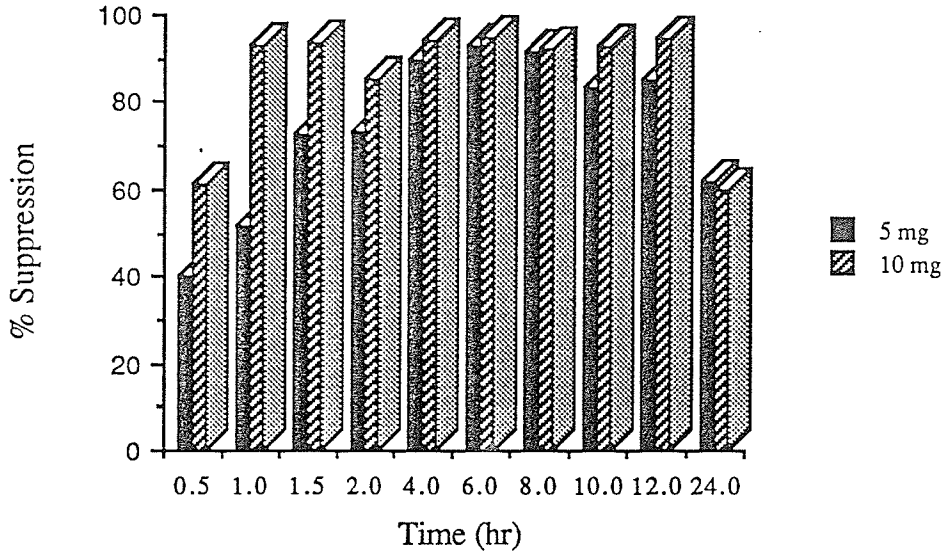



Fig.23 The mean percent suppression of wheals induced by epicutaneous histamine in children after oral administrations of 5 mg and 10 mg cetirizine

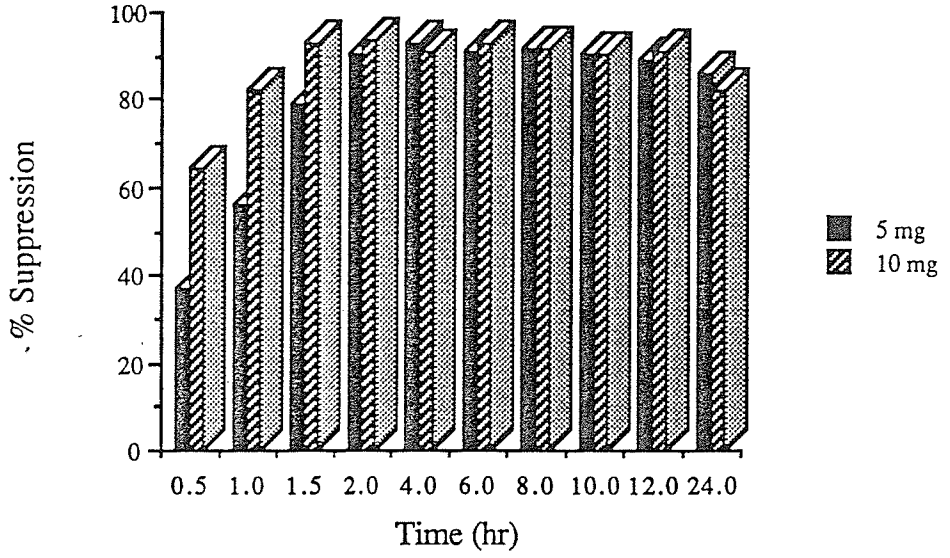



Fig.24 The mean percent suppression of flares induced by epicutaneous histamine in children after oral administrations of 5 mg and 10 mg cetirizine

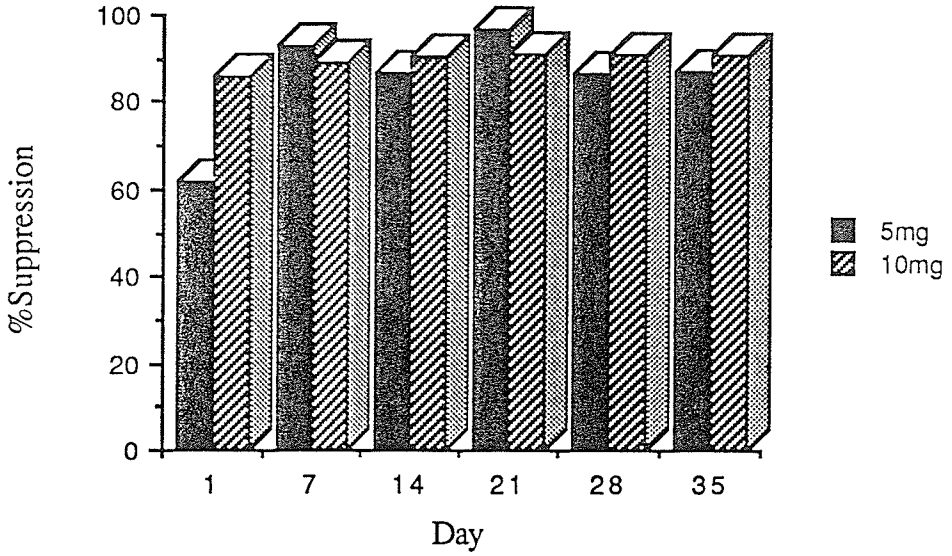



Fig.25 The mean percent suppression of wheals induced by epicutaneous histamine in children at the steady-state after oral administrations of 5 mg and 10 mg cetirizine q 24 hr

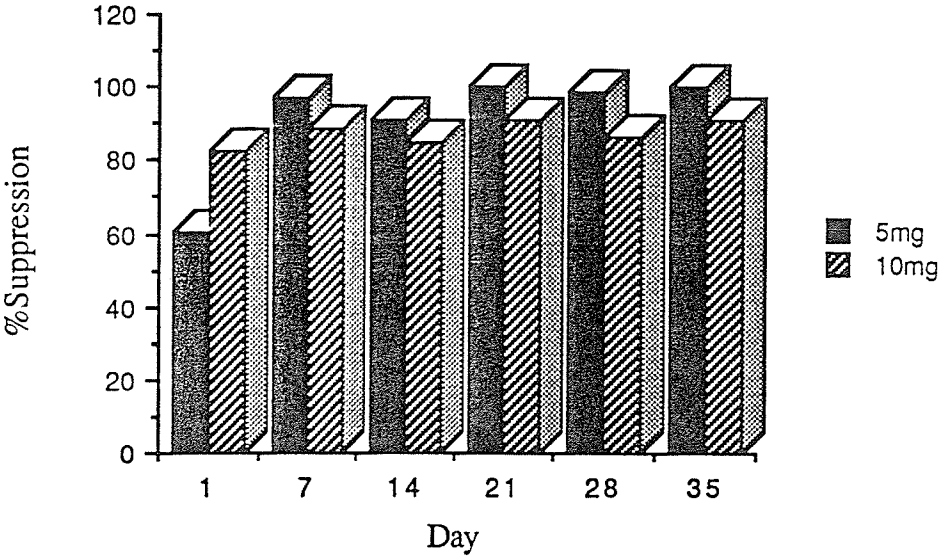



Fig.26 The mean percent suppression of flares induced by epicutaneous histamine in children at the steady-state after oral administrations of 5 mg and 10 mg cetirizine q 24 hr

3.1.4.3 Curve fitting and pharmacokinetic parameters

Serum cetirizine concentration versus time data were fitted into polyexponential equations. In these two groups, the serum cetirizine versus time data could be best described by a triexponential equation, corresponding to an absorption phase, a distribution phase and an elimination phase. Pharmacokinetic parameters calculated are listed in Table 32. and 33.

Table 32. Pharmacokinetic parameters of cetirizine in children after the oral administration of 5 mg cetirizine

| Subject | $C_{max}$ ng/ml | $T_{max}$ hr | T1/2 hr | AUC ng·hr/ml | Oral Cls ml/min/kg | $V_\beta$ l/kg | Xu mg | Clr ml/min/kg |
|---|---|---|---|---|---|---|---|---|
| 1 | 383 | 1.5 | 9.4 | 2524 | 1.16 | 0.94 | 3.47 | 0.94 |
| 2 | 299 | 1.5 | 8.8 | 2537 | 0.94 | 0.72 | 1.67 | 0.35 |
| 3 | 685 | 0.5 | 8.2 | 4199 | 0.99 | 0.70 | 4.59 | 1.00 |
| 4 | 496 | 1.5 | 7.6 | 3587 | 1.18 | 0.77 | 3.49 | 0.90 |
| 5 | 572 | 0.5 | 6.9 | 3416 | 0.95 | 0.57 | 1.88 | 0.40 |
| 6 | 223 | 4.0 | 8.5 | 2162 | 1.43 | 1.04 | 1.39 | 0.44 |
| 7 | 255 | 1.5 | 6.4 | 1474 | 1.20 | 0.66 | 1.77 | 0.45 |
| 8 | 426 | 0.5 | 5.1 | 2837 | 0.92 | 0.41 | 1.67 | 0.32 |
| 9 | 438 | 1.5 | 4.7 | 2875 | 0.92 | 0.37 | 2.04 | 0.39 |
| 10 | 498 | 0.5 | 5.7 | 3103 | 0.70 | 0.34 | 1.40 | 0.21 |
| Mean | 428 | 1.4 | 7.1 | 2871 | 1.04 | 0.65 | 2.34 | 0.54 |
| S.D. | 144 | 1.1 | 1.6 | 768 | 0.20 | 0.23 | 1.10 | 0.29 |

Table 33. Pharmacokinetic parameters of cetirizine in children after the oral administration of 10 mg cetirizine

| Subject | $C_{max}$ ng/ml | $T_{max}$ hr | T1/2 hr | AUC ng·hr/ml | Oral Cls ml/min/kg | $V_\beta$ l/kg | Xu mg | Clr ml/min/kg |
|---|---|---|---|---|---|---|---|---|
| 1 | 586 | 1.0 | 7.0 | 4383 | 1.10 | 0.67 | 3.13 | 0.38 |
| 2 | 944 | 0.5 | 7.1 | 6798 | 1.04 | 0.64 | 2.26 | 0.26 |
| 3 | 1355 | 0.5 | 10.4 | 10374 | 0.88 | 0.79 | 4.21 | 0.42 |
| 4 | 833 | 0.5 | 6.0 | 6256 | 1.20 | 0.62 | 3.24 | 0.40 |
| 5 | 692 | 1.0 | 4.4 | 4490 | 1.12 | 0.42 | 3.03 | 0.35 |
| 6 | 1388 | 0.5 | 7.2 | 7486 | 1.01 | 0.63 | 4.84 | 0.52 |
| 7 | 765 | 1.5 | 7.5 | 5714 | 1.34 | 0.87 | 2.53 | 0.37 |
| 8 | 752 | 1.0 | 6.1 | 4858 | 1.17 | 0.62 | 4.30 | 0.54 |
| 9 | 1492 | 0.5 | 6.7 | 7022 | 1.01 | 0.59 | 3.65 | 0.40 |
| Mean | 978 | 0.8 | 6.9 | 6376 | 1.10 | 0.65 | 3.47 | 0.40 |
| S.D. | 341 | 0.4 | 1.6 | 1874 | 0.13 | 0.13 | 0.86 | 0.08 |

## 3.2 Pharmacokinetic and pharmacodynamic studies of hydroxyzine and cetirizine in rabbits

### 3.2.1 HPLC assays

#### 3.2.1.1 HPLC assay of hydroxyzine

Representative HPLC chromatograms for hydroxyzine and its internal standard antazoline are shown in Fig. 27.

The retention times of hydroxyzine and antazoline are 11.0 and 5.0 minutes respectively. There were no interfering peaks.

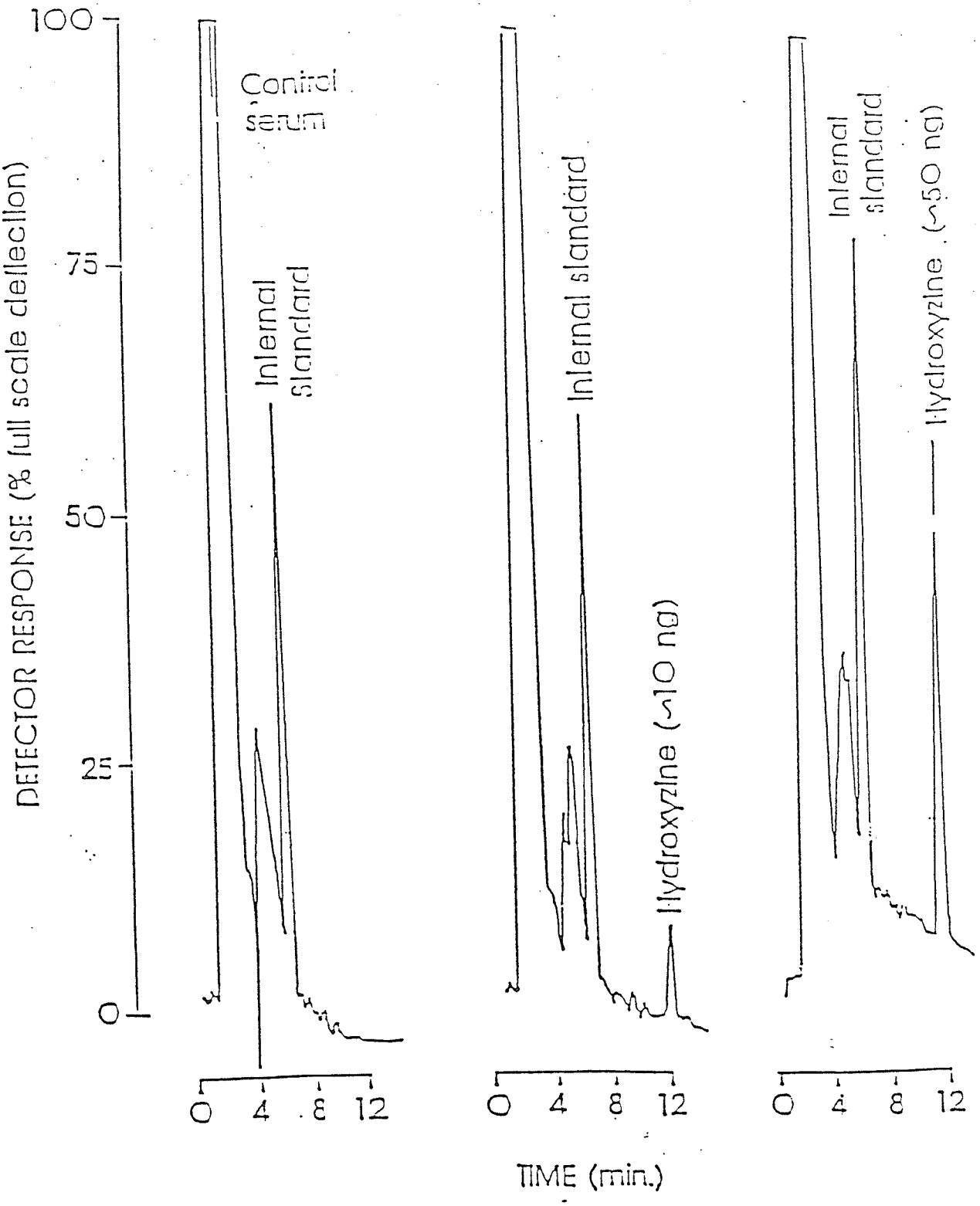



Fig.27 The HPLC chromatograms of hydroxyzine in rabbit serum

3.2.1.2. Calibration curves for hydroxyzine

The calibration curves for hydroxyzine were constructed by plotting peak height ratios of hydroxyzine to antazoline versus concentrations of hydroxyzine. Calibration curves were analyzed periodically during a 12 month study period using concentrations of hydroxyzine from 2.0 ng/ml to 509.5 ng/ml, over which range the calibration curve was linear. The variability in the calibration curves over a period of 12 months were calculated from six calibration curves, each having six samples at every concentration. The variability is expressed as the coefficient of variation and is shown in Table 34, and the calibration curve is shown in Fig.28.

Table 34. Variability in HPLC calibration curves for hydroxyzine

| Concentration(ng/ml) | Peak Height Ratio | C.V. |
|---|---|---|
| 2.0 | 0.036 | 6.8% |
| 5.1 | 0.091 | 3.9% |
| 10.2 | 0.167 | 4.2% |
| 20.4 | 0.358 | 4.0% |
| 51.0 | 0.965 | 5.9% |
| 101.9 | 1.850 | 1.3% |
| 203.8 | 3.626 | 1.5% |
| 509.5 | 9.030 | 2.0% |

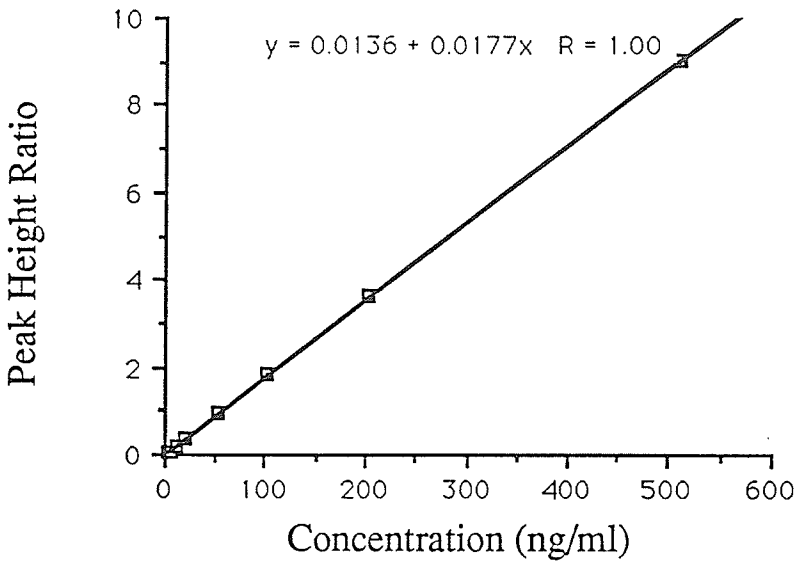



Fig. 28. The calibration curve for hydroxyzine

3.2.1.3 HPLC assay of cetirizine

Representative HPLC chromatograms for cetirizine and its internal standard $P_{265}$ are shown in Fig. 29.

The retention times of cetirizine and $P_{265}$ are 6.0 and 7.5 minutes respectively. There were no interfering peaks.

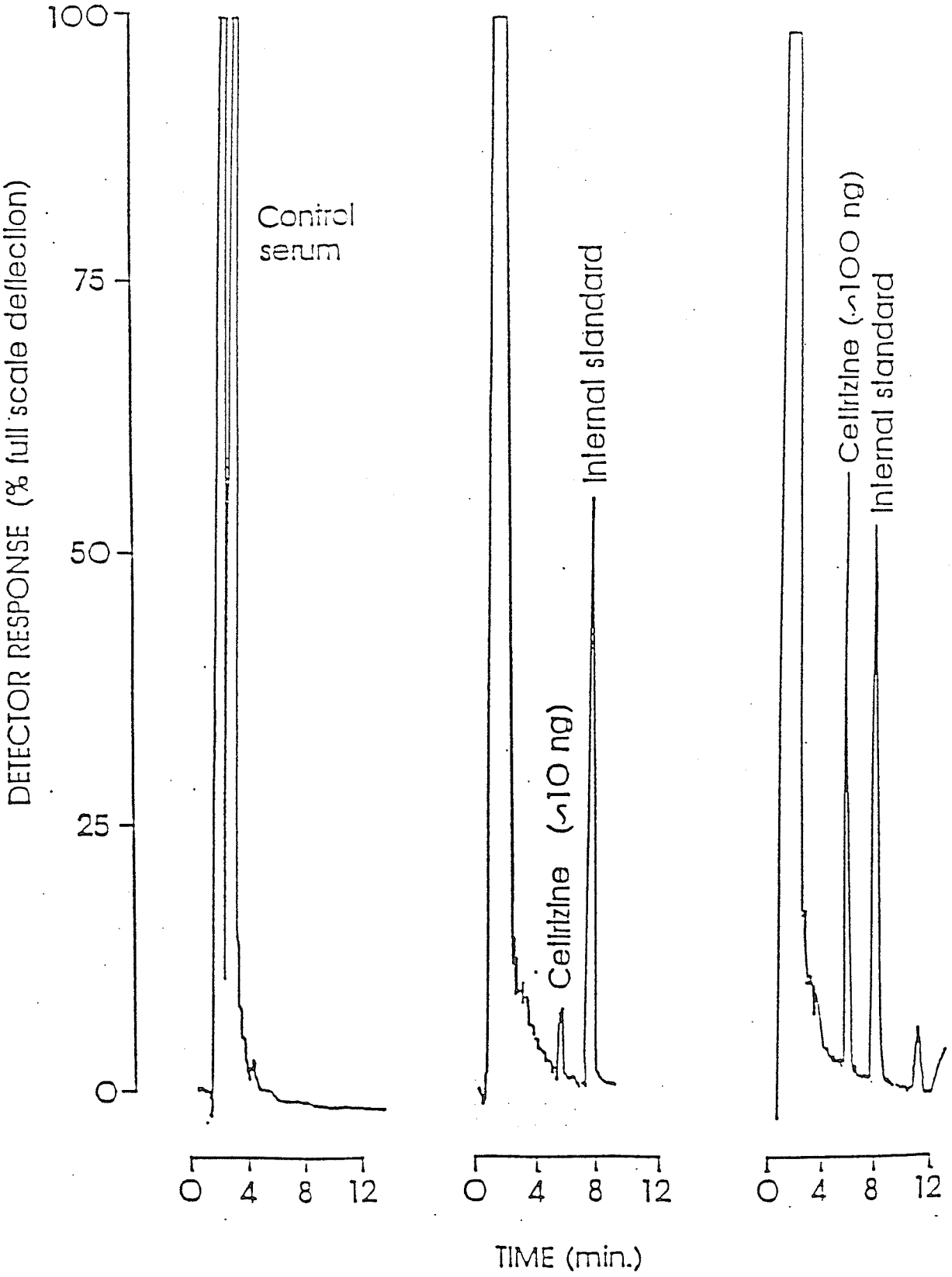



Fig.29 The HPLC chromatograms of cetirizine in rabbit serum

3.2.1.4 Calibration curves for cetirizine

The calibration curves for cetirizine were constructed by plotting peak height ratios of cetirizine to $P_{265}$ versus concentrations of cetirizine. Calibration curves were analyzed periodically during a 12 month study period using concentrations of cetirizine from 5.3 ng/ml to 527.5 ng/ml, over which range the calibration curve was linear. The variability in the calibration curves over a period of 12 months were calculated from six calibration curves, each having six samples at every concentration. The varability is expressed as the coefficient of variation and is shown in Table 35, and the calibration curve is shown in Fig.30.

Table 35. Variability in HPLC calibration curves for cetirizine

| Concentration(ng/ml) | Peak Height Ratio | C.V. |
|---|---|---|
| 5.3 | 0.067 | 1.1% |
| 10.6 | 0.116 | 4.3% |
| 21.1 | 0.242 | 2.6% |
| 52.8 | 0.573 | 1.7% |
| 105.5 | 1.149 | 3.7% |
| 211.0 | 2.425 | 1.8% |
| 527.5 | 6.050 | 1.9% |

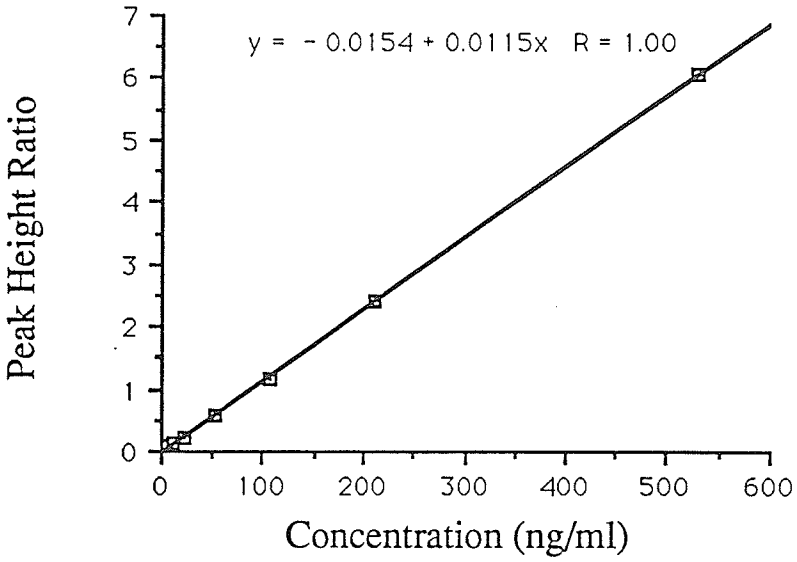



Fig. 30. The calibration curve for cetirizine

3.2.2 Bioavailability studies of hydroxyzine

3.2.2.1 Serum concentrations of hydroxyzine after intramuscular and oral administrations.

Table 36 and Table 37 list serum concentrations of hydroxyzine after the intramuscular injection of 5 mg hydroxyzine hydrochloride and the oral administration of 100 mg hydroxyzine hydrochloride solution in three rabbits.

Serum concentrations were plotted versus time using a semilogarithmic scale, and are shown in Fig.31 and Fig.32 respectively.

Table 36. Serum concentrations of hydroxyzine after intramuscular doses of 5 mg hydroxyzine

| Time (hr)\Subject | 1 | 2 | 3 |
|---|---|---|---|
| 0.083 | 43.7 | 90.0 | 61.9 |
| 0.25 | 83.5 | 137.7 | 66.1 |
| 0.5 | 97.8 | 177.7 | 56.4 |
| 1.0 | 143.5 | 243.1 | 43.5 |
| 1.5 | 114.6 | 185.4 | 40.6 |
| 2.0 | 103.1 | 159.8 | 35.0 |
| 3.0 | 61.5 | 103.2 | 23.0 |
| 4.0 | 31.9 | 60.2 | 20.1 |
| 5.0 | 24.6 | 21.9 | 14.3 |
| 6.0 | 18.0 | 16.7 | 11.9 |

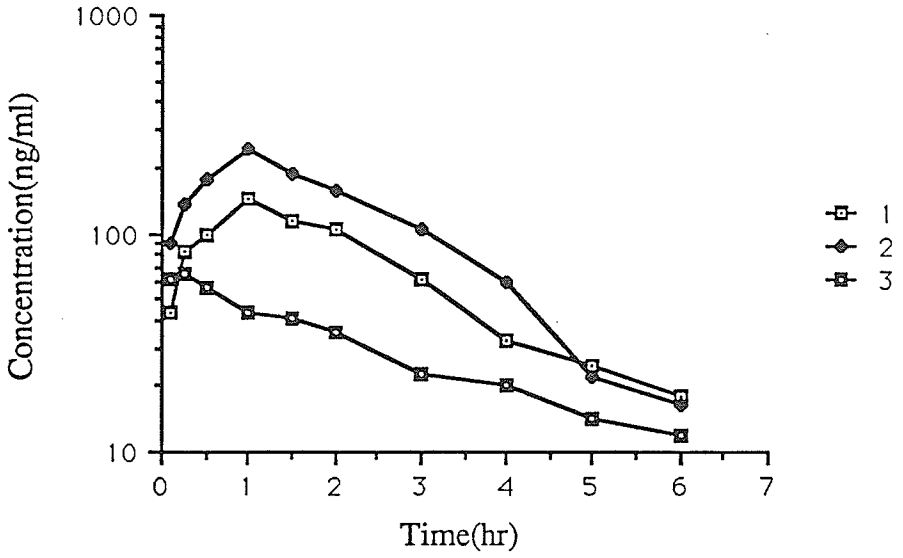



Fig.31. Serum concentrations of hydroxyzine in rabbits after I.M. doses of 5mg hydroxyzine

Table 37. Serum concentrations of hydroxyzine after the oral administration of 100 mg hydroxyzine

| Time (hr)\Subject | 1 | 2 | 3 |
|---|---|---|---|
| 0.083 | 220.3 | 93.2 | 73.6 |
| 0.25 | 720.6 | 190.4 | 106.8 |
| 0.5 | N.S. | 585.3 | 162.6 |
| 1.0 | 477.6 | 484.2 | 110.6 |
| 1.5 | 305.1 | 387.7 | N.S. |
| 2.0 | 248.5 | 184.2 | 83.8 |
| 3.0 | 120.1 | 106.1 | 64.5 |
| 4.0 | 58.7 | 71.1 | 40.1 |
| 5.0 | 39.1 | 34.0 | 28.4 |
| 6.0 | 21.0 | 25.2 | N.S. |

* N.S.: No Sample

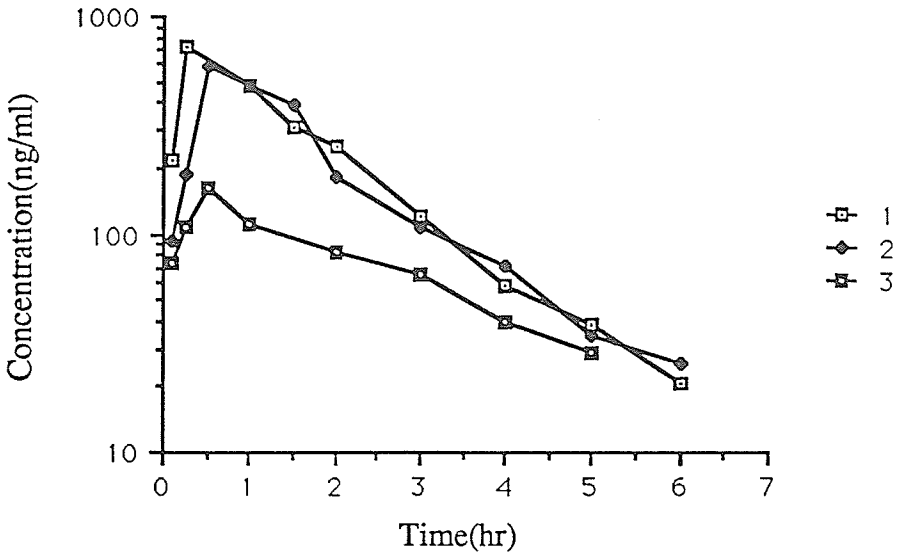



Fig.32. Serum concentrations of hydroxyzine in rabbits after the oral administration of 100 mg hydroxyzine

3.2.2.2 Curve fitting and pharmacokinetic parameters

The serum concentration versus time curves following the intramuscular and oral administrations of hydroxyzine were best described by biexponential equations, corresponding to one absorption phase and one elimination phase. The coefficient of determination was from 0.91 to 0.99, with the exception of oral administration in rabbit 2 which was 0.71.

Pharmacokinetic parameters are calculated and summarized in Table 38.

Table 38. Pharmacokinetic parameters of hydroxyzine following intramuscular and oral administrations

| Parameter\Subject | A | B | C |
|---|---|---|---|
| I.M. | | | |
| Dose (mg) | 5.0 | 5.0 | 5.0 |
| $T_{1/2}$ (hr) | 1.59 | 1.14 | 2.37 |
| $C_{max}$ (ng/ml) | 143.5 | 243.1 | 66.1 |
| $T_{max}$ (hr) | 1.0 | 1.0 | 0.25 |
| $AUC_{0->\infty}$ | 392.7 | 633.8 | 174.1 |
| MRT(hr) | 2.79 | 2.23 | 3.44 |
| Oral | | | |
| Dose(mg) | 100.0 | 100.0 | 100.0 |
| $T_{1/2}$ (hr) | 1.12 | 1.19 | 1.89 |
| $C_{max}$ (ng/ml) | 720.6 | 585.3 | 162.6 |
| $T_{max}$ (hr) | 0.25 | 0.5 | 0.5 |
| $AUC_{0->\infty}$ | 1212.3 | 1068.2 | 377.7 |
| MRT(hr) | 1.69 | 2.15 | 2.95 |
| F | 0.15 | 0.08 | 0.11 |

3.2.3 Pharmacokinetics and pharmacodynamics of hydroxyzine in rabbits: the effect of cimetidine

3.2.3.1 Serum concentrations of hydroxyzine and cetirizine

Serum concentrations of hydroxyzine and cetirizine following the intravenous bolus dose of 10 mg hydroxyzine two weeks before cimetidine, with cimetidine and two weeks after cimetidine was discontinued are listed from Table 39 to Table 44. The mean serum concentrations are plotted against time in Fig.33 and Fig.34.

Table 39. Serum hydroxyzine concentrations after an i.v. bolus dose of 10 mg hydroxyzine

| Time (hr) | 1 | 2 | 3 | 4 | 5 | Mean±S.D. (ng/ml) |
|---|---|---|---|---|---|---|
| 0.083 | 1414.5 | 1504.2 | 2556.4 | 726.2 | 1916.9 | 1623.6±674.4 |
| 0.25 | 529.2 | 690.0 | 564.9 | 682.7 | 599.8 | 613.3±71.2 |
| 0.5 | 374.4 | 395.1 | 361.3 | 447.3 | 287.3 | 373.1±58.1 |
| 1.0 | 227.5 | 369.8 | 247.2 | 116.3 | 164.8 | 225.1±96.1 |
| 2.0 | 221.6 | 284.1 | 69.2 | 56.1 | 60.5 | 138.3±107.0 |
| 3.0 | 178.2 | 87.9 | 28.1 | 23.2 | 31.9 | 69.9±66.0 |
| 4.0 | 62.4 | 85.6 | 9.8 | 9.9 | 12.5 | 36.0±35.6 |
| 6.0 | 21.0 | 31.8 | 5.5 | 4.2 | 3.0 | 13.1±12.8 |
| 8.0 | 19.5 | 12.2 | N.D. | N.D. | N.D. | 15.9±5.2 |
| 12.0 | 5.1 | N.D. | N.D. | N.D. | N.D. | 5.1 |

* N.D: below the minimum detectable concentration (1 ng/ml).

Table 40. Serum hydroxyzine concentrations after an i.v. bolus dose of 10 mg hydroxyzine with the coadministration of cimetidine

| Time (hr) | 1 | 2 | 3 | 4 | 5 | Mean±S.D. (ng/ml) |
|---|---|---|---|---|---|---|
| 0.083 | 3936.6 | 855.8 | 2565.9 | 1316.8 | N.S. | 2168.8±1382.3 |
| 0.25 | 908.5 | 804.1 | 1297.8 | N.S. | N.S. | 1003.4±260.1 |
| 0.5 | 581.3 | 662.1 | 908.5 | N.S. | 745.1 | 724.2±139.9 |
| 1.0 | 377.6 | 466.9 | 802.3 | 595.8 | 593.8 | 567.3±160.3 |
| 2.0 | 278.8 | 194.8 | 383.1 | 293.5 | 230.6 | 276.1±71.5 |
| 3.0 | 203.5 | 195.5 | 219.7 | 168.9 | N.S. | 196.9±21.2 |
| 4.0 | 197.5 | 132.0 | 113.4 | 124.6 | 73.4 | 128.2±44.9 |
| 6.0 | 107.7 | 85.7 | 30.5 | 119.1 | 55.5 | 79.7±36.7 |
| 8.0 | 9.5 | 40.0 | 18.7 | 90.5 | 20.7 | 35.8±32.5 |
| 12.0 | 6.3 | 13.7 | 8.5 | N.S. | 12.5 | 10.2±3.5 |
| 24.0 | 2.1 | N.S. | N.D. | 13.4 | 6.1 | 7.2±5.7 |

* N.S.: No Sample

** N.D: below the minimum detectable concentration (1 ng/ml).

Table 41. Serum hydroxyzine concentrations after an i.v bolus dose of 10 mg hydroxyzine two weeks after cimetidine was discontinued

| Time (hr) | 1 | 2 | 3 | 5 | Mean±S.D. (ng/ml) |
|---|---|---|---|---|---|
| 0.083 | 961.1 | 1432.2 | 1282.5 | 1373.9 | 1262.4±210.1 |
| 0.25 | 611.7 | 508.0 | 545.0 | 851.3 | 629.0±154.3 |
| 0.5 | 446.9 | 482.1 | 345.0 | 638.9 | 478.3±121.9 |
| 1.0 | 317.9 | 324.9 | 187.1 | 233.6 | 265.9±66.9 |
| 2.0 | 133.9 | 316.3 | 59.1 | 83.2 | 148.1±116.4 |
| 3.0 | 65.5 | 116.4 | 22.5 | 36.9 | 60.3±41.5 |
| 4.0 | 39.0 | 64.9 | 13.1 | 19.4 | 34.1±23.3 |
| 6.0 | N.S. | 29.8 | N.D. | 8.0 | 18.9±15.5 |
| 8.0 | 6.2 | 13.4 | N.D. | N.D. | 9.8±5.1 |

* N.S.: No Sample

* N.D: below the minimum detectable concentration (1 ng/ml).

*** Rabbit 4 suffered a back injury sometime after the study in which cimetidine was coadministered. The rabbit was sacrificed and not available for study after the discontinuation of cimetidine.

Table 42. Serum cetirizine concentrations after an i.v. bolus dose of 10 mg hydroxyzine

| Time (hr) | 1 | 2 | 3 | 4 | 5 | Mean±S.D. (ng/ml) |
|---|---|---|---|---|---|---|
| 0.083 | 78.7 | 20.6 | 45.2 | 136.5 | 96.2 | 75.4±45.0 |
| 0.25 | 147.2 | 46.1 | 168.4 | 349.2 | 173.5 | 176.9±109.2 |
| 0.5 | 171.0 | 89.3 | 180.4 | 403.1 | 283.3 | 225.4±120.9 |
| 1.0 | 171.7 | 115.2 | 145.1 | 346.1 | 225.8 | 200.8±90.9 |
| 2.0 | 188.9 | 159.6 | 157.0 | 206.2 | 114.0 | 165.2±35.2 |
| 3.0 | 65.5 | 163.5 | 55.3 | 100.8 | 43.5 | 85.7±48.5 |
| 4.0 | 60.1 | 140.0 | 18.3 | 55.8 | N.S. | 68.5±51.2 |
| 6.0 | 20.2 | 72.1 | 6.5 | 10.5 | 23.0 | 26.5±26.4 |
| 8.0 | 8.9 | 30.1 | N.D. | 3.7 | N.D. | 14.2±12.2 |
| 12.0 | 6.7 | N.S. | N.D. | 0.8 | N.D. | 6.7±4.2 |

* N.S.: No Sample

** N.D: below the minimum detectable concentration (2 ng/ml).

Table 43. Serum cetirizine concentrations after an i.v. bolus dose of 10 mg hydroxyzine with the coadministration of cimetidine

| Time (hr) | 1 | 2 | 3 | 4 | 5 | Mean±S.D. (ng/ml) |
|---|---|---|---|---|---|---|
| 0.083 | 57.0 | 31.9 | 62.6 | 94.1 | 43.6 | 57.8±23.5 |
| 0.25 | 440.7 | 130.0 | 454.6 | 203.9 | 162.1 | 278.2±156.9 |
| 0.5 | 693.4 | 231.4 | 708.0 | 418.5 | 271.3 | 464.5±226.6 |
| 1.0 | 873.6 | 385.9 | 960.9 | 662.5 | 358.2 | 648.2±274.6 |
| 2.0 | 567.0 | 357.4 | 795.9 | 548.3 | 239.9 | 501.7±213.5 |
| 3.0 | 433.4 | 334.4 | 473.7 | 339.7 | 192.9 | 354.8±108.6 |
| 4.0 | 259.4 | 338.0 | 339.8 | 299.7 | 106.3 | 268.6±96.6 |
| 6.0 | 99.6 | 100.9 | 144.9 | 211.7 | 39.3 | 119.3±63.9 |
| 8.0 | 35.6 | 91.3 | 56.2 | 111.8 | 15.3 | 62.0±39.5 |
| 12.0 | 3.1 | N.S. | 9.3 | 22.0 | 8.8 | 10.8±8.0 |
| 24.0 | N.D. | 19.8 | N.D. | N.D. | 2.1 | 10.9±12.5 |

* N.S.: No Sample

** N.D: below the minimum detectable concentration (2 ng/ml).

Table 44. Serum cetirizine concentrations after an i.v. bolus dose of 10 mg hydroxyzine two weeks after cimetidine was discontinued

| Time (hr) | 1 | 2 | 3 | 5 | Mean±S.D. (ng/ml) |
|---|---|---|---|---|---|
| 0.083 | 85.4 | 27.3 | 41.9 | 169.4 | 81.0±63.9 |
| 0.25 | 114.0 | 46.3 | 153.4 | 241.3 | 138.8±81.4 |
| 0.5 | 188.0 | 81.6 | 192.3 | 258.2 | 180.0±73.0 |
| 1.0 | 197.0 | 92.1 | 192.3 | 236.9 | 179.6±61.6 |
| 2.0 | 127.0 | 85.3 | 107.5 | 109.4 | 107.3±17.1 |
| 3.0 | 108.3 | 70.8 | 70.7 | 51.2 | 75.2±23.9 |
| 4.0 | 70.2 | 46.6 | 39.9 | 26.6 | 45.8±18.3 |
| 6.0 | 35.2 | 25.0 | 9.3 | 11.9 | 20.4±12.1 |
| 8.0 | 11.4 | 11.3 | N.D. | 6.3 | 9.7±3.0 |

* N.D: below the minimum detectable concentration (2 ng/ml).

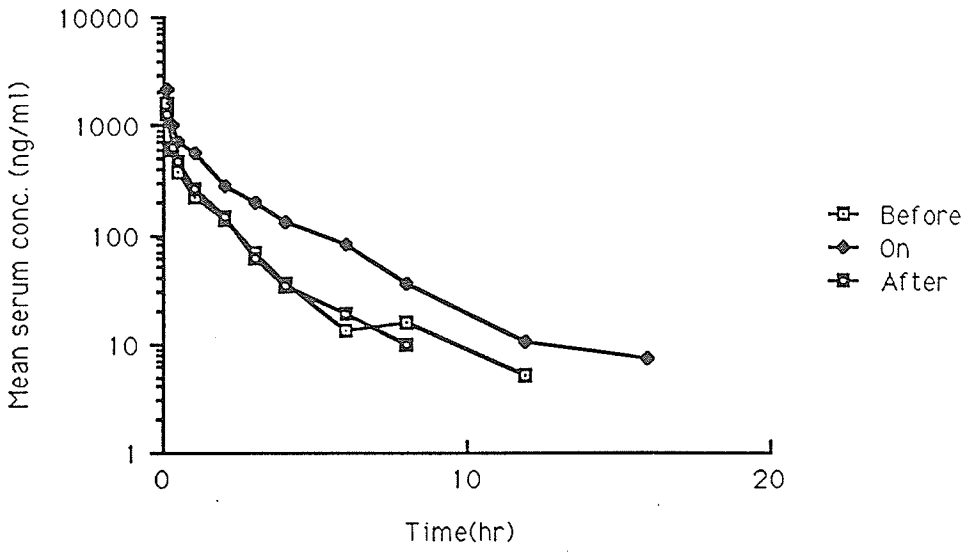



Fig.33. Mean serum hydroxyzine concentrations in rabbits after an i.v. bolus dose of 10 mg hydroxyzine with and without the coadministration of cimetidine

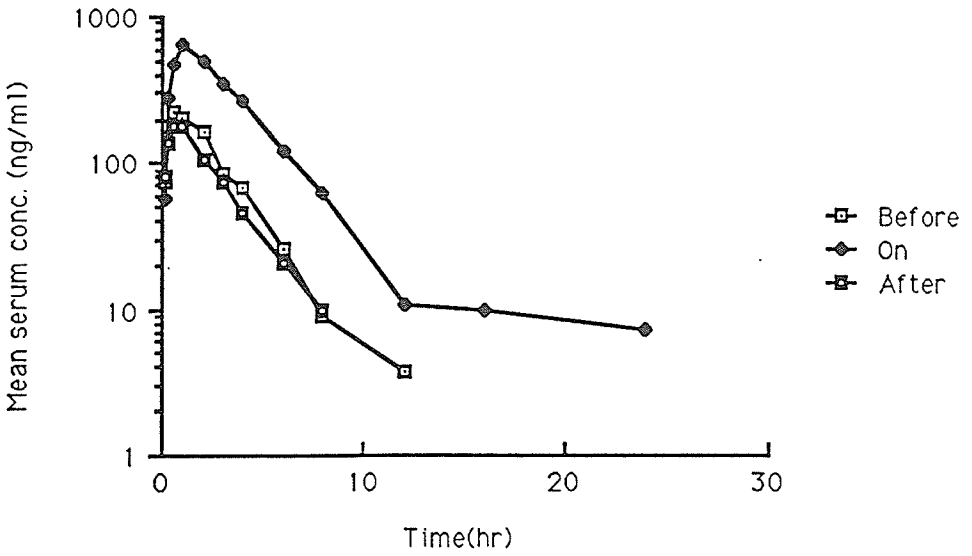



Fig.34. Mean serum cetirizine concentrations in rabbits after an i.v. bolus dose of 10 mg hydroxyzine with and without the coadministration of cimetidine

3.2.3.2 Pharmacodynamic studies of hydroxyzine

Results of the efficacy tests calculated as the percent suppression of wheals induced by intradermally injected histamine after an i.v. bolus injection of 10 mg hydroxyzine in rabbits with and without the coadministration of cetirizine are listed in Tables 45 to Table 47. Mean percent suppression is plotted against time in Fig.35 to Fig.37.

Table 45. The percent suppression of wheals induced by intradermally injected histamine after an i.v. bolus dose of 10 mg hydroxyzine in rabbits

| Time (hr) | 1 | 2 | 3 | 4 | 5 | Mean±S.D |
|---|---|---|---|---|---|---|
| 0.083 | 28.3 | 20.0 | 52.8 | 56.4 | 65.6 | 44.6±19.5 |
| 0.25 | 83.7 | 62.3 | 55.2 | 94.9 | 76.5 | 74.5±16.0 |
| 0.5 | 87.2 | 93.4 | 80.3 | 98.2 | 86.7 | 89.2±6.9 |
| 1.0 | 83.0 | 90.9 | 74.6 | 98.4 | 86.7 | 86.7±8.9 |
| 2.0 | 62.7 | 89.1 | 92.3 | 94.9 | 94.9 | 86.8±13.7 |
| 3.0 | 63.0 | 90.0 | 82.2 | 94.2 | 97.9 | 85.5±13.8 |
| 4.0 | 44.1 | 86.2 | 98.2 | 91.0 | 75.5 | 79.0±21.2 |
| 6.0 | 38.7 | 65.1 | 73.4 | 84.2 | 87.0 | 69.7±19.4 |
| 8.0 | 41.6 | 68.5 | 77.4 | 74.0 | 50.2 | 62.3±15.5 |
| 12.0 | 0 | 40.0 | 32.4 | 47.9 | 33.3 | 30.7±18.3 |

Table 46. The percent suppression of wheals induced by intradermally injected histamine after an i.v. bolus dose of 10 mg hydroxyzine with the coadministration of cimetidine in rabbits

| Time (hr) | 1 | 2 | 3 | 4 | 5 | Mean±S.D |
|---|---|---|---|---|---|---|
| 0.083 | 66.2 | 83.2 | 57.5 | 53.8 | 50.8 | 62.3±13.0 |
| 0.25 | 65.2 | 100 | 100 | 95.2 | 72.9 | 86.7±16.4 |
| 0.5 | 97.1 | 98.1 | 100 | 98.8 | 100 | 98.8±1.3 |
| 1.0 | 92.2 | 97.7 | 100 | 100 | 100 | 98.0±3.4 |
| 2.0 | 59.2 | 95.2 | 100 | 98.4 | 96.9 | 89.9±17.3 |
| 3.0 | 90.5 | 88.8 | 99.0 | 98.5 | 97.1 | 94.8±4.8 |
| 4.0 | 91.3 | 97.3 | 97.0 | 98.4 | 94.6 | 95.7±2.8 |
| 6.0 | 78.8 | 95.7 | 97.7 | 98.1 | 83.9 | 90.8±8.9 |
| 8.0 | 49.1 | 90.9 | 97.5 | 81.1 | 68.2 | 77.4±19.3 |
| 12.0 | 28.5 | 43.3 | 85.1 | 33.9 | 40.5 | 46.3±22.5 |
| 24.0 | 7.4 | 26.9 | 62.4 | 33.1 | 24.4 | 30.8±20.0 |

Table 47. The percent suppression of wheals induced by intradermally injected histamine after an i.v. bolus dose of 10 mg hydroxyzine two weeks after cimetidine was discontinued

| Time (hr) | 1 | 2 | 3 | 5 | Mean±S.D |
|---|---|---|---|---|---|
| 0.083 | 56.2 | 74.7 | 40.7 | 58.3 | 54.5±13.9 |
| 0.25 | 74.9 | 82.7 | 88.7 | 78.9 | 81.3±5.9 |
| 0.5 | 88.6 | 96.1 | 94.1 | 93.6 | 93.1±3.2 |
| 1.0 | 97.7 | 89.7 | 97.5 | 92.0 | 94.2±4.0 |
| 2.0 | 91.6 | 94.9 | 100 | 79.1 | 91.4±8.9 |
| 3.0 | 85.5 | 87.4 | 98.5 | 71.1 | 85.6±11.3 |
| 4.0 | 79.3 | 69.9 | 93.6 | 68.7 | 77.9±11.5 |
| 6.0 | 66.8 | 61.4 | 89.5 | 62.5 | 70.1±13.2 |
| 8.0 | 54.3 | 53.2 | 78.9 | 33.8 | 55.1±18.5 |
| 12.0 | 10.2 | 26.5 | 40.6 | 18.7 | 24.0±12.9 |

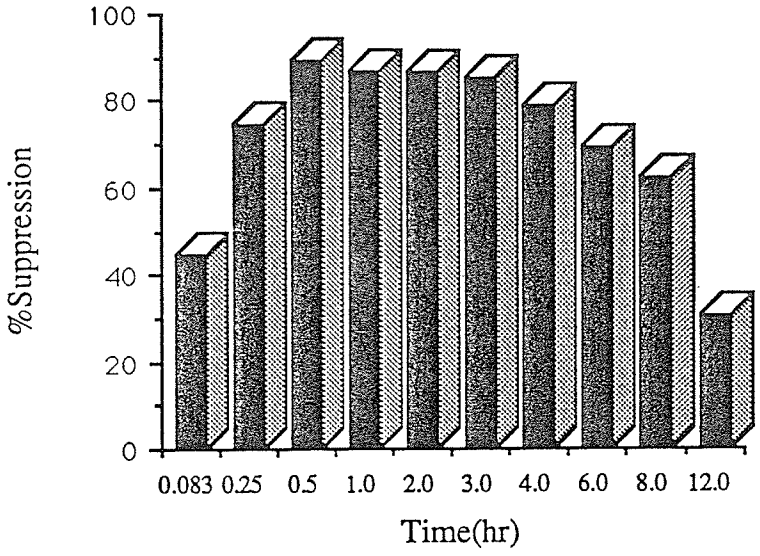



Fig.35 Mean percent suppression of wheals induced by intradermally injected histamine in rabbits after an i.v. bolus dose of 10 mg hydroxyzine

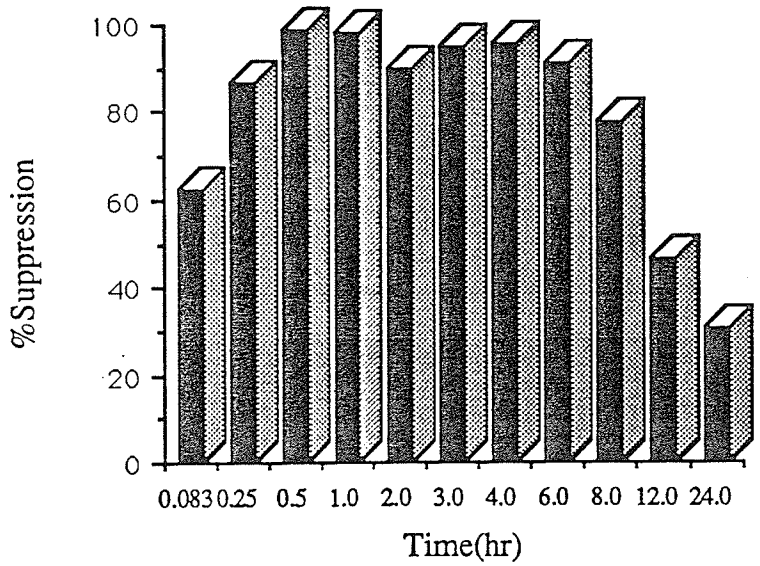



Fig.36. Mean percent suppression of wheals induced by intradermally injected histamine in rabbits after an i.v. bolus dose of 10 mg hydroxyzine with the coadministration of cimetidine

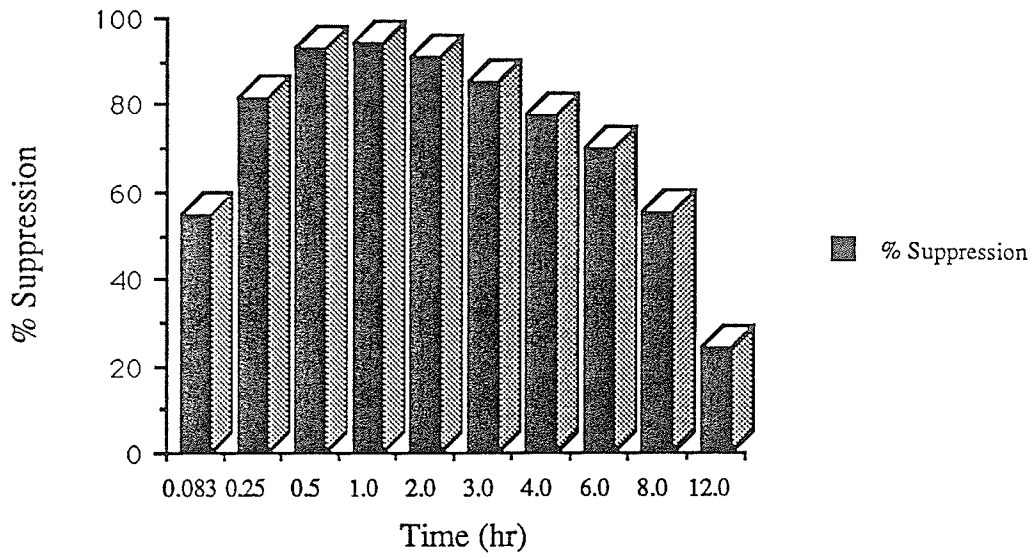



Fig.37. Mean percent suppression of wheals induced by intradermally injected histamine in rabbits after an i.v. bolus dose of 10 mg hydroxyzine two weeks after cimetidine was discontinued

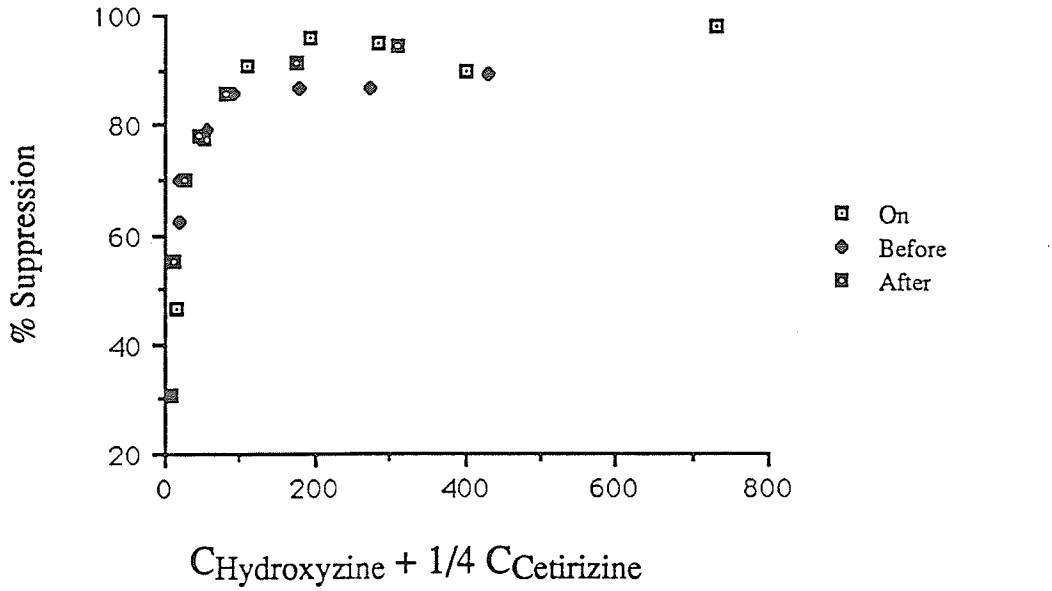



Fig.38. The mean effect-mean concentration relationship of hydroxyzine in rabbits after an intravenous bolus dose of 10 mg hydroxyzine with and without the coadministration of cimetidine

3.2.3.3 Curve fitting, pharmacokinetic and pharmacodynamic parameters

The results of the relevant biochemistry tests are listed in Table 48.

After an I.V. bolus dose of 10 mg hydroxyzine, the resulting serum hydroxyzine concentration versus time curve could be best described by two-compartment model, corresponding to a distribution phase and an elimination phase. The coefficient of determination varied from 0.95 to 0.99. Pharmacokinetic parameters are listed in Table 49 to Table 51.

Pharmacodynamic parameters are listed in Table 55.

Table 48. Results of biochemical tests

| Parameter | 1 | 2 | 3 |
|---|---|---|---|
| SGOT (U/L) | 21.0±11.0 | 29.0±17.6 | 23.3±13.1 |
| SGPT (U/L) | 29.0±10.1 | 34.3±15.9 | 40.0±12.3 |
| LDH (U/L) | 179.3±32.2 | 274.0±82.9 | 169.3±19.3 |
| AL.PHOS. (U/L) | 48.5±39.5 | 56.5±40.9 | 35.3±19.9 |

* 1: Before cimetidine was given. 2: With the coadministration of cimetidine. 3: Two weeks after cimetidine was discontinued.

Table 49. Pharmacokinetic parameters of hydroxyzine in rabbits after an i.v. bolus dose of 10 mg hydroxyzine

| Subject | Wt kg | β $hr^{-1}$ | $T_{1/2}$ hr | AUC ng·hr/ml | MRT hr | Cls ml/min/kg | $V_\beta$ l/kg |
|---|---|---|---|---|---|---|---|
| 1 | 4.75 | 0.3801 | 1.82 | 1144 | 2.15 | 30.7 | 4.8 |
| 2 | 3.83 | 0.4785 | 1.45 | 1271 | 1.76 | 34.2 | 4.3 |
| 3 | 4.80 | 0.2922 | 0.86 | 770 | 0.65 | 45.1 | 9.3 |
| 4 | 3.40 | 0.5490 | 1.26 | 556 | 0.95 | 88.1 | 9.6 |
| 5 | 4.05 | 0.7135 | 0.97 | 631 | 0.72 | 63.4 | 5.3 |
| Mean | 4.17 | 0.4827 | 1.27 | 874 | 1.25 | 52.3 | 6.7 |
| S.D. | 0.6 | 0.1616 | 0.39 | 317 | 0.67 | 23.7 | 2.6 |

Table 50. Pharmacokinetic parameters of hydroxyzine in rabbits after an i.v.bolus dose of 10 mg hydroxyzine with the coadministration of cimetidine

| Subject | β $hr^{-1}$ | T1/2 hr | AUC ng·hr/ml | MRT hr | Cls ml/min/kg | $V_\beta$ l/kg |
|---|---|---|---|---|---|---|
| 1 | 0.1086 | 6.38 | 1423 | 3.62 | 24.7 | 13.6 |
| 2 | 0.1177 | 5.89 | 2984 | 5.81 | 14.6 | 7.4 |
| 3 | 0.2406 | 2.88 | 2361 | 2.00 | 14.7 | 3.7 |
| 4 | 0.2333 | 2.97 | 1793 | 3.29 | 27.3 | 7.0 |
| 5 | 0.2137 | 3.24 | 2104 | 2.33 | 19.6 | 5.5 |
| Mean | 0.1828 | 4.27 | 2133 | 3.41 | 20.2 | 7.5 |
| S.D. | 0.064 | 1.71 | 591 | 1.50 | 5.8 | 3.8 |

Table 51. Pharmacokinetic parameters of hydroxyzine after an i.v. bolus dose of 10 mg hydroxyzine two weeks after cimetidine was discontinued

| Subject | $\beta$ $hr^{-1}$ | $T_{1/2}$ hr | AUC ng·hr/ml | MRT hr | Cls ml/min/kg | $V_\beta$ l/kg |
|---|---|---|---|---|---|---|
| 1 | 0.4674 | 1.48 | 923 | 1.44 | 38.0 | 4.9 |
| 2 | 0.4891 | 1.42 | 1253 | 1.65 | 34.7 | 4.3 |
| 3 | 0.7536 | 0.92 | 578 | 0.80 | 60.0 | 4.8 |
| 5 | 0.5021 | 1.38 | 864 | 0.97 | 56.7 | 5.7 |
| Mean | 0.5531 | 1.30 | 905 | 1.22 | 45.1 | 4.9 |
| S.D. | 0.1345 | 0.27 | 277 | 0.40 | 11.4 | 0.6 |

After an intravenous bolus dose of 10 mg hydroxyzine, the resulting serum cetirizine concentration versus time curves could be best described by either a two-compartment model or a three-compartment model, with coefficients of determination varying from 0.85 to 0.99. Pharmacokinetic parameters of cetirizine are listed from Table 52 to Table 54.

Table 52. Pharmacokinetic parameters of cetirizine after an i.v. bolus dose of 10 mg hydroxyzine

| Subject | $\beta$ $hr^{-1}$ | $T_{1/2}$ hr | AUC ng·hr/ml | R | MRT hr | $C_{max}$ ng/ml | $T_{max}$ hr |
|---|---|---|---|---|---|---|---|
| 1 | 0.3335 | 2.08 | 658 | 0.6 | 3.19 | 188.9 | 2.0 |
| 2 | 0.3440 | 2.01 | 839 | 0.7 | 4.12 | 163.5 | 3.0 |
| 3 | 0.4461 | 1.55 | 620 | 0.8 | 2.40 | 180.4 | 0.5 |
| 4 | 0.4315 | 1.61 | 919 | 1.7 | 1.95 | 403.1 | 0.5 |
| 5 | 0.6877 | 1.01 | 583 | 0.9 | 1.75 | 283.3 | 0.5 |
| Mean | 0.4486 | 1.65 | 724 | 0.9 | 2.68 | 243.8 | 1.3 |
| S.D. | 0.1429 | 0.43 | 147 | 0.4 | 0.98 | 100.5 | 1.2 |

Table 53. Pharmacokinetic parameters of cetirizine after an i.v. bolus dose of 10 mg hydroxyzine with the coadministration of cimetidine

| Subject | $\beta$ $hr^{-1}$ | T1/2 hr | AUC ng·hr/ml | R | MRT hr | $C_{max}$ ng/ml | $T_{max}$ hr |
|---|---|---|---|---|---|---|---|
| 1 | 0.5110 | 1.36 | 2714 | 1.9 | 2.44 | 873.6 | 1.0 |
| 2 | 0.1267 | 5.46 | 2786 | 0.9 | 8.07 | 385.9 | 1.0 |
| 3 | 0.2131 | 3.25 | 3380 | 1.4 | 2.76 | 960.9 | 1.0 |
| 4 | 0.2639 | 2.63 | 2922 | 1.6 | 4.30 | 662.5 | 1.0 |
| 5 | 0.1245 | 5.56 | 1207 | 0.6 | 3.75 | 358.2 | 1.0 |
| Mean | 0.2479 | 3.65 | 2602 | 1.3 | 4.26 | 648.2 | 1.0 |
| S.D. | 0.1586 | 1.83 | 822 | 0.5 | 2.26 | 274.6 | ---- |

Table 54. Pharmacokinetic parameters of cetirizine after an i.v. bolus dose of 10 mg hydroxyzine two weeks after cimetidine was discontinued

| Subject | $\beta$ $hr^{-1}$ | T1/2 hr | AUC ng·hr/ml | R | MRT hr | $C_{max}$ ng/ml | $T_{max}$ hr |
|---|---|---|---|---|---|---|---|
| 1 | 0.3927 | 1.76 | 675 | 0.7 | 2.89 | 197.0 | 1.0 |
| 2 | 0.3421 | 2.03 | 400 | 0.3 | 3.56 | 92.1 | 1.0 |
| 3 | 0.5977 | 1.16 | 501 | 0.9 | 2.01 | 192.3 | 1.0 |
| 5 | 0.4105 | 1.69 | 576 | 0.7 | 2.10 | 258.2 | 0.5 |
| Mean | 0.4358 | 1.66 | 538 | 0.7 | 2.64 | 184.7 | 0.88 |
| S.D. | 0.1118 | 0.36 | 117 | 0.3 | 0.73 | 68.8 | 0.25 |

Table 55 A. Pharmacodynamic parameters of hydroxyzine in rabbits using the modified $E_{max}$ model and the effect-compartment model

| Parameters | 1 | 2 | 3 |
|---|---|---|---|
| the $E_{max}$ model* | | | |
| $E_{max}$ (%) (S.E.) | 92.0 (1.5) | 99.2 (2.3) | 96.1 (0.9) |
| $EC_{50}^{H}$ (ng/ml) (S.E) | 8.9 (1.1) | 9.3 (1.6) | 9.2 (0.7) |
| the effect-compartment model** | | Studies 1, 2, 3 | |
| $E_{max}$ (%) (S.E.) | | 92.5 (3.0) | |
| $EC_{50}^{H}$ (ng/ml) (S.E) | | 6.9 (1.7) | |

1: Before cimetidine was given. , 2: With the coadministration of cimetidine. 3: Two weeks after cimetidine was discontinued.

* Calculated from mean data in five rabbits in each study.

**Pooled data from rabbits in studies 1, 2 and 3.

Table 55 B. Pharmacodynamic parameters of hydroxyzine in rabbits using the effect-compartment model

| Groups \ Parameters | | Keo (S.E.) $hr^{-1}$ | Keo' (S.E.) $hr^{-1}$ |
|---|---|---|---|
| Method A | | | |
| I | | 0.49 (0.32) | 0.083 (0.03) |
| II | | 1.56 (2.05) | 0.33 (0.24) |
| III | | 1.19 (0.61) | 0.33 (0.10) |
| Method B | | | |
| | 1 | 1.17 (1.14) | 0.05 (0.17) |
| | 2 | 1.08 (1.04) | 0.62 (0.50) |
| I | 3 | 0.21 (0.33) | 0.05 (0.14) |
| | 4 | 0.33 (0.22) | 0.35 (0.40) |
| | 5 | 0.48 (0.33) | 0.15 (0.2) |
| | 1 | very large* | very large * |
| | 2 | very large * | very large * |
| II | 3 | 0.22 (0.24) | 0.18 (0.42) |
| | 4 | 14.3 (5.78) | 1.16 (1.66) |
| | 5 | very large * | very large * |
| | 1 | 8.19 (2.68) | 0.81 (0.85) |
| III | 2 | 2.12 (1.00) | 0.41 (0.44) |
| | 3 | 0.31 (0.33) | 0.24 (0.45) |
| | 5 | 2.59 (1.42) | 0.36 (0.33) |

* The value is larger than $10^4$.

** I. Before cimetidine was given. II. With the coadministration of cimetidine. III. Two weeks after cimetidine was discontinued.

3.2.3.4 Statistical tests of pharmacokinetic parameters

Various pharmacokinetic parameters of hydroxyzine and cetirizine with and without the coadminsitration of cimetidine were compared by using Turkey and Bonferroni multiple range tests($\alpha$=0.05) to measure whether there was any change in pharmacokinetic characteristics of hydroxyzine and cetirizine when cimetidine was given at the same time. Results are listed in Table 56. Only parameters which showed significant difference with the coadministration of cimetidine are listed.

Table 56. Multiple range tests of pharmacokinetic parameters of hydroxyzine and cetirizine in rabbits with and without the coadministration of cimetidine

| Parameters | Mean | Grouping* | F | PR>F |
|---|---|---|---|---|
| Hydroxyzine T1/2 | | | | |
| | | | 12.4 | 0.0015 |
| **1 | 1.27 | A | | |
| **2 | 4.27 | B | | |
| **3 | 1.30 | A | | |
| Hydroxyzine AUC0->∞ | | | | |
| | | | 13.5 | 0.0011 |
| 1 | 874 | A | | |
| 2 | 2133 | B | | |
| 3 | 905 | A | | |
| Hydroxyzine CLs | | | | |
| | | | 5.6 | 0.0210 |
| 1 | 52.3 | A | | |
| 2 | 20.2 | B | | |
| 3 | 45.1 | A | | |
| Cetirizine AUC0->∞ | | | | |
| | | | 24.2 | 0.0001 |
| 1 | 724 | A | | |
| 2 | 2602 | B | | |
| 3 | 538 | A | | |
| Cetirizine $C_{max}$ | | | | |
| | | | 9.32 | 0.0043 |
| 1 | 243.8 | A | | |
| 2 | 648.2 | B | | |
| 3 | 184.7 | A | | |

* Groups with the same letter are not significantly different ( $\alpha$=0.05)

** 1: Before cimetidine was given. 2: With the coadministration of cimetidine. 3: Two weeks after cimetidine was discontinued.

3.2.4 Pharmacokinetic and pharmacodynamic studies of cetirizine in rabbits: the effect of cimetidine

3.2.4.1 Serum concentrations of cetirizine

Serum concentrations of cetirizine after an intravenous bolus injection of cetirizine two weeks before cimetidine, with the coadministration of cimetidine and two weeks after the discontinuation of cimetidine are listed in Table 57 to Table 59. They are plotted against time in Fig.39.

Table 57. Serum cetirizine concentration after an intravenous bolus dose of 10 mg cetirizine

| Time (hr) | 1 | 2 | 3 | 4 | 5 | Mean±S.D. (ng/ml) |
|---|---|---|---|---|---|---|
| 0.083 | 7018.1 | 5188.1 | 9784.0 | 7333.9 | 8799.8 | 7624.8±1763.0 |
| 0.25 | 4737.2 | 4150.0 | 6621.2 | 4886.5 | 5578.0 | 5194.6±945.7 |
| 0.5 | 2725.4 | 3711.9 | N.S. | 3870.6 | 2869.6 | 3294.4±580.4 |
| 1.0 | 1629.8 | 2449.9 | 1570.7 | 2457.9 | 2122.2 | 2046.1±429.5 |
| 2.0 | 493.9 | 1222.1 | 484.9 | 1108.7 | 634.7 | 788.9±351.1 |
| 3.0 | 319.5 | 632.5 | 196.3 | 463.8 | 285.5 | 379.5±171.1 |
| 4.0 | 99.2 | 258.0 | 89.0 | 180.7 | 136.2 | 152.6±69.0 |
| 6.0 | 36.7 | 87.9 | 24.5 | 50.9 | 95.0 | 59.0±31.2 |
| 8.0 | 17.9 | 32.6 | 12.2 | 29.1 | 26.3 | 23.6±8.4 |
| 12.0 | N.D. | 5.0 | N.D. | 4.0 | 2.4 | 3.8±1.3 |

* N.S.: No Sample

** N.D: below the minimum detectable concentration (2 ng/ml).

Table 58. Serum cetirizine concentrations after an intravenous bolus dose of 10 mg cetirizine with the coadministration of cimetidine

| Time (hr) | 1 | 2 | 3 | 4 | 5 | Mean±S.D. (ng/ml) |
|---|---|---|---|---|---|---|
| 0.083 | 11299.2 | 9450.0 | 9350.0 | 12788.8 | 7779.9 | 10133.6±1938.4 |
| 0.25 | 7108.7 | 6711.9 | 6852.0 | 8142.6 | 5605.4 | 6884.1±908.3 |
| 0.5 | 4228.8 | 4759.5 | 4433.0 | 5564.4 | 4732.3 | 4743.6±508.8 |
| 1.0 | 1793.5 | 2783.3 | 2842.0 | 3871.6 | 2956.3 | 2849.3±737.5 |
| 2.0 | 623.4 | 854.8 | 765.0 | 1061.7 | 1225.1 | 906.0±239.0 |
| 3.0 | 201.7 | 655.3 | 235.7 | 610.7 | 479.4 | 436.6±209.5 |
| 4.0 | 92.8 | 224.3 | 136.4 | 348.8 | 182.1 | 196.9±98.2 |
| 6.0 | 41.8 | 59.0 | 42.0 | 140.6 | 49.7 | 66.6±42.0 |
| 8.0 | 33.6 | 38.8 | N.S. | 63.8 | 24.8 | 40.3±16.7 |
| 12.0 | 19.1 | 30.9 | 8.3 | 30.3 | 9.8 | 19.7±10.8 |
| 24.0 | 9.1 | 7.4 | 3.0 | 5.2 | N.D. | 6.2±2.7 |

* N.S.: No Sample

* N.D: below the minimum detectable concentration (2 ng/ml).

Table 59. Serum cetirizine concentrations after an intravenous bolus dose of 10 mg cetirizine two weeks after cimetidine was discontinued

| Time (hr) | 1 | 2 | 3 | 4 | 5 | Mean±S.D. (ng/ml) |
|---|---|---|---|---|---|---|
| 0.083 | 7457.9 | 6854.7 | 6664.2 | 6056.6 | 5677.8 | 6542.2±695.4 |
| 0.25 | 5511.3 | 4894.5 | 4473.8 | 5561.4 | 3970.5 | 4882.3±681.0 |
| 0.5 | 3807.1 | 2812.4 | 3521.4 | 5417.7 | 3076.7 | 3727.1±1020.6 |
| 1.0 | 2029.3 | 1616.3 | N.S. | 2839.6 | 2212.2 | 2174.4±508.7 |
| 2.0 | 510.4 | 454.0 | 759.5 | 846.3 | 739.7 | 662.0±170.1 |
| 3.0 | 218.5 | 163.0 | 281.1 | 246.3 | 294.1 | 240.6±52.6 |
| 4.0 | 113.7 | 64.5 | 115.5 | 172.5 | 122.4 | 117.7±38.3 |
| 6.0 | 38.0 | 33.6 | 63.7 | 54.8 | 37.9 | 45.6±13.0 |
| 8.0 | 22.4 | 10.5 | 20.5 | 33.1 | 37.5 | 24.8±10.7 |
| 12.0 | 3.5 | N.D. | 2.4 | 8.0 | 7.6 | 5.4±2.8 |

* N.S.: No Sample

** N.D: below the minimum detectable concentration (2 ng/ml).

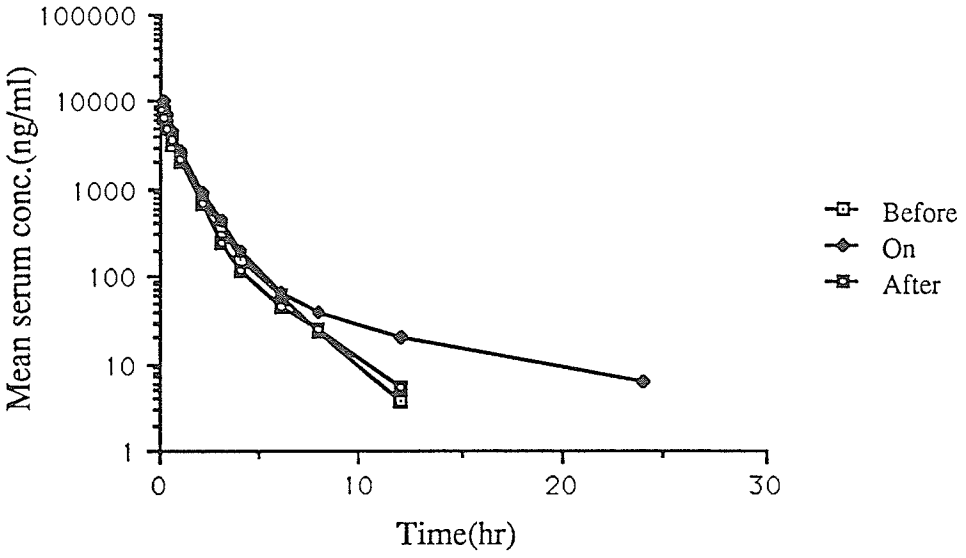



Fig.39. Mean serum cetirizine concentrations after an i.v. bolus dose of 10 mg cetirizine in rabbits with and without the coadministration of cimetidine

3.2.4.2 Pharmacodynamic studies of cetirizine

Results of the efficacy test calculated as the percent suppression of wheals induced by intradermally injected histamine after an intravenous bolus injection of 10 mg cetirizine with and without the coadministration of cimetidine in rabbits are listed in Table 60 to Table 62. They are plotted against time in Fig.40 to Fig.42.

Table 60. The percent suppression of wheals induced by intradermally injected histamine in rabbits after an i.v. bolus dose of 10 mg cetirizine

| Time (hr) | 1 | 2 | 3 | 4 | 5 | Mean±S.D |
|---|---|---|---|---|---|---|
| 0.083 | 87.6 | 92.2 | 97.0 | 97.4 | 83.5 | 91.5±6.0 |
| 0.25 | 89.5 | 99.0 | 99.1 | 97.4 | 93.2 | 95.6±4.2 |
| 0.5 | 91.8 | 99.0 | 99.4 | 95.7 | 92.0 | 95.6±3.7 |
| 1.0 | 90.7 | 99.0 | 97.4 | 97.7 | 92.9 | 95.5±3.5 |
| 2.0 | 94.7 | 98.6 | 100 | 98.1 | 97.8 | 97.8±1.9 |
| 3.0 | 98.1 | 99.6 | 100 | 99.4 | 97.8 | 98.9±1.0 |
| 4.0 | 86.4 | 94.6 | 97.2 | 99.7 | 95.6 | 94.7±5.0 |
| 6.0 | 75.0 | 85.6 | 95.0 | 97.0 | 95.3 | 89.6±9.3 |
| 8.0 | 59.5 | 83.4 | 90.2 | 87.5 | 83.5 | 80.8±12.3 |
| 12.0 | 49.5 | 72.6 | 75.0 | 76.3 | 72.0 | 69.1±11.1 |

Table 61. The percent suppression of wheals induced by intradermally injected histamine in rabbits after an i.v. bolus dose of 10 mg cetirizine with the coadministration of cimetidine

| Time (hr) | 1 | 2 | 3 | 4 | 5 | Mean±S.D |
|---|---|---|---|---|---|---|
| 0.083 | 59.5 | 43.8 | 93.2 | 98.5 | 85.0 | 76.0±23.4 |
| 0.25 | 96.0 | 48.8 | 97.2 | 99.4 | 96.8 | 87.6±21.7 |
| 0.5 | 98.3 | 85.1 | 98.8 | 98.5 | 98.8 | 95.9±6.0 |
| 1.0 | 96.8 | 88.1 | 100 | 98.7 | 99.0 | 96.5±4.8 |
| 2.0 | 100 | 97.8 | 98.8 | 97.5 | 98.0 | 98.4±1.0 |
| 3.0 | 100 | 99.2 | 98.5 | 98.5 | 95.4 | 98.3±1.7 |
| 4.0 | 96.2 | 96.4 | 97.8 | 98.2 | 90.7 | 95.9±3.0 |
| 6.0 | 91.9 | 91.9 | 95.2 | 90.0 | 88.2 | 91.4±2.6 |
| 8.0 | 72.0 | 82.1 | 90.6 | 88.4 | 80.8 | 82.8±7.3 |
| 12.0 | 74.2 | 72.8 | 77.8 | 77.5 | 75.2 | 75.5±2.1 |
| 24.0 | 20.0 | 15.9 | 70.3 | 34.0 | 34.8 | 35.0±21.4 |

Table 62. The percent suppression of wheals induced by intradermally injected histamine in rabbits after an i.v. bolus dose of 10 mg cetirizine two weeks after cimetidine was discontinued

| Time (hr) | 1 | 2 | 3 | 4 | 5 | Mean±S.D |
|---|---|---|---|---|---|---|
| 0.083 | 97.1 | 93.9 | 65.4 | 96.2 | 60.7 | 82.7±18.0 |
| 0.25 | 99.5 | 98.4 | 92.5 | 99.6 | 94.3 | 96.9±3.3 |
| 0.5 | 99.7 | 97.6 | 95.4 | 99.4 | 90.5 | 96.3±3.8 |
| 1.0 | 97.4 | 97.7 | 98.2 | 98.7 | 93.8 | 97.2±1.9 |
| 2.0 | 97.9 | 97.9 | 99.5 | 99.1 | 96.3 | 98.1±1.3 |
| 3.0 | 95.0 | 98.4 | 99.7 | 99.1 | 95.2 | 97.5±2.2 |
| 4.0 | 93.2 | 95.1 | 93.2 | 93.6 | 89.9 | 93.0±1.9 |
| 6.0 | 87.0 | 91.9 | 89.5 | 87.0 | 89.9 | 89.1±2.1 |
| 8.0 | 71.4 | 75.7 | 82.5 | 73.4 | 84.9 | 77.6±5.9 |
| 12.0 | 45.0 | 52.1 | 55.6 | 18.7 | 58.5 | 46.0±16.1 |

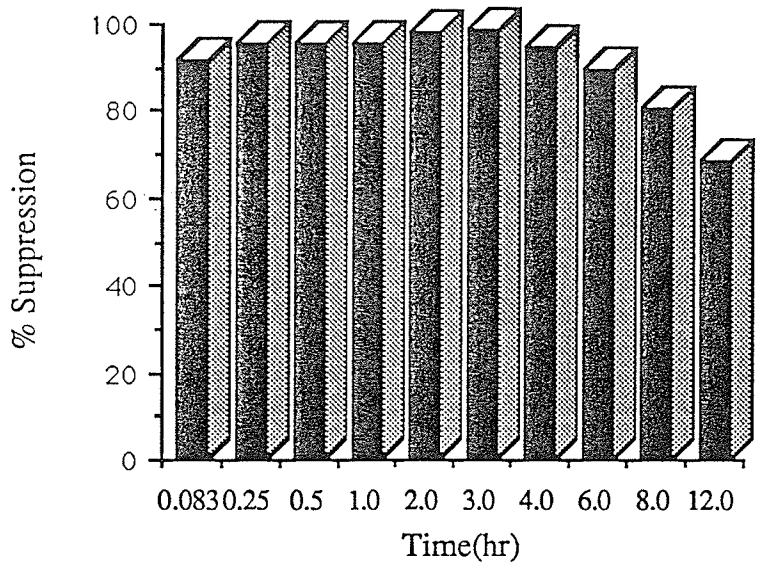



Fig.40. Mean percent suppression of wheals induced by intradermally injected histamine in rabbits after an i.v. bolus dose of 10 mg cetirizine

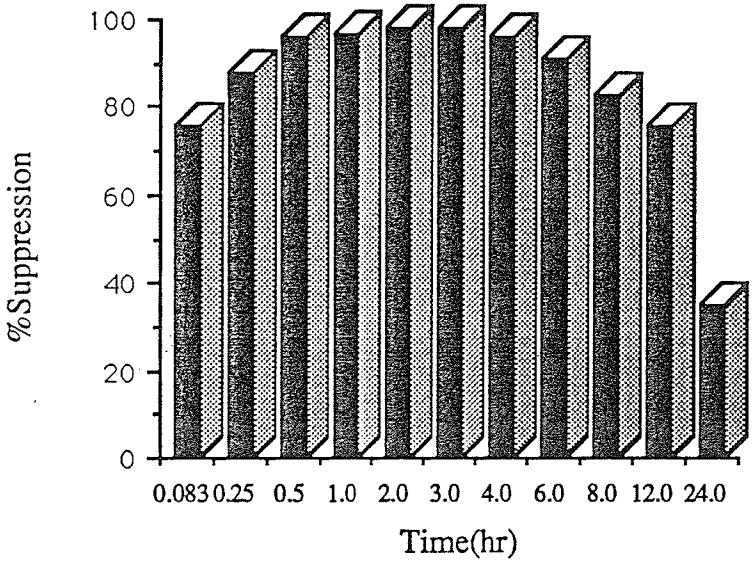



Fig.41. Mean percent suppression of wheals induced by intradermally injected histamine in rabbits after an i.v. bolus dose of 10 mg cetirizine with the coadministration of cimetidine

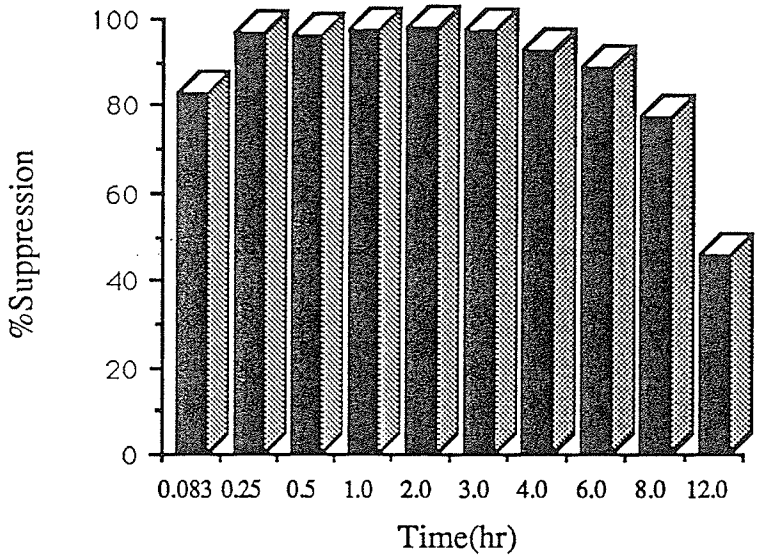



Fig.42. Mean percent suppression of wheals induced by intradermally injected histamine in rabbits after an i.v. bolus dose of 10 mg cetirizine two weeks after cimetidine was discontinued

3.2.4.3 Curve fitting, and pharmacokinetic parameters

The serum cetirizine concentration versus time curves in rabbits after an intravenous bolus dose of 10 mg cetirizine were best described by a two-compartment model, corresponding to a distribution phase and an elimination phase, with coefficients of determination varying from 0.98 to 1.00. Pharmacokinetic parameters are listed from Table 64 to Table 66, while Table 63 lists results of biochemical tests.

Table 63. Results of biochemical tests

| Parameter | 1 | 2 | 3 |
|---|---|---|---|
| SGOT (U/L) | 15.2±3.2 | 24.0±8.4 | 21.0±5.7 |
| SGPT (U/L) | 35.6±13.2 | 41.2±23.4 | 37.4±20.6 |
| LDH (U/L) | 138.0±41.2 | 171.2±68.9 | 77.8±22.5 |
| AL. Phos. (U/L) | 40.8±10.9 | 44.4±13.8 | 50.3±19.9 |

* 1: Before cimetidine was given. 2: With the coadministration of cimetidine. 3: Two weeks after cimetidine was discontinued.

Table 64. Pharmacokinetic parameters of cetirizine after an i.v. bolus dose of 10 mg cetirizine

| | Wt | $\beta$ | $T_{1/2}$ | AUC | MRT | Cls | $V_\beta$ |
|---|---|---|---|---|---|---|---|
| Subject | kg | $hr^{-1}$ | hr | ng·hr/ml | hr | ml/min/kg | l/kg |
| 1 | 4.45 | 0.6769 | 1.02 | 4872 | 1.10 | 7.7 | 0.7 |
| 2 | 3.75 | 0.5445 | 1.27 | 7053 | 1.55 | 6.3 | 0.7 |
| 3 | 4.30 | 0.6859 | 1.01 | 6103 | 0.85 | 6.4 | 0.6 |
| 4 | 3.11 | 0.5033 | 1.38 | 6967 | 1.31 | 7.7 | 0.9 |
| 5 | 4.09 | 0.5893 | 1.18 | 5964 | 1.21 | 6.8 | 0.7 |
| Mean | 3.94 | 0.6000 | 1.17 | 6192 | 1.20 | 7.0 | 0.7 |
| S.D. | 0.53 | 0.0804 | 0.16 | 887 | 0.26 | 0.7 | 0.1 |

Table 65. Pharmacokinetic parameters of cetirizine after an i.v. bolus dose of 10 mg cetirizine with the coadministration of cimetidine

| Subject | $\beta$ $hr^{-1}$ | $T_{1/2}$ hr | AUC ng·hr/ml | MRT hr | Cls ml/min/kg | $V_\beta$ l/kg |
|---|---|---|---|---|---|---|
| 1 | 0.1022 | 6.78 | 6713 | 1.70 | 5.6 | 3.3 |
| 2 | 0.2008 | 3.45 | 8433 | 1.91 | 5.3 | 1.6 |
| 3 | 0.1378 | 5.03 | 7469 | 1.22 | 5.2 | 3.3 |
| 4 | 0.1951 | 3.55 | 10698 | 1.68 | 5.0 | 1.5 |
| 5 | 0.4156 | 1.67 | 7981 | 1.30 | 5.1 | 0.7 |
| Mean | 0.2103 | 4.10 | 8259 | 1.56 | 5.2 | 1.9 |
| S.D. | 0.1219 | 1.92 | 1506 | 0.29 | 0.2 | 1.0 |

Table 66. Pharmacokinetic parameters of cetirizine after an i.v. bolus dose of 10 mg cetirizine two weeks after cimetidine was discontinued

| Subject | $\beta$ $hr^{-1}$ | $T_{1/2}$ hr | AUC ng·hr/ml | MRT hr | Cls ml/min/kg | $V_\beta$ l/kg |
|---|---|---|---|---|---|---|
| 1 | 0.4238 | 1.64 | 5771 | 1.00 | 6.5 | 0.9 |
| 2 | 0.7319 | 0.95 | 4651 | 0.98 | 9.6 | 0.8 |
| 3 | 0.5114 | 1.36 | 6168 | 1.16 | 6.3 | 0.7 |
| 4 | 0.4331 | 1.60 | 7403 | 1.43 | 7.2 | 1.0 |
| 5 | 0.4253 | 1.63 | 5536 | 1.60 | 7.4 | 1.0 |
| Mean | 0.5051 | 1.44 | 5906 | 1.23 | 7.4 | 0.9 |
| S.D. | 0.1319 | 0.30 | 1005 | 0.27 | 1.3 | 0.1 |

3.2.4.4. Statistical tests of pharmacokinetic parameters

Various pharmacokinetic parameters of cetirizine with and without the coadministration of cimetidine were analyzed ($\alpha$=0.05) by using Tukey and Bonferroni multiple range tests to measure whether there was any change in pharmacokinetic properties of cetirizine when cimetidine was given at the same time. Results are shown in Table 67, only parameters showing significant differences are listed.

Table 67. Multiple range tests of pharmacokinetic parameters of cetirizine in rabbits with and without the coadministration of cimetidine

| | Mean | Grouping* | F | PR>F |
|---|---|---|---|---|
| Cetirizine $T_{1/2}$ | | | | |
| | | | 10.69 | 0.0022 |
| **1 | 1.17 | A | | |
| 2 | 4.10 | B | | |
| 3 | 1.44 | A | | |
| Cetirizine AUC0->∞ | | | | |
| | | | 6.09 | 0.0150 |
| 1 | 6192 | A | | |
| 2 | 8259 | B | | |
| 3 | 5906 | A | | |
| Cetirizine Cls | | | | |
| | | | 8.76 | 0.0045 |
| 1 | 7.0 | A | | |
| 2 | 5.2 | B | | |
| 3 | 7.4 | A | | |

* Groups with the same letter are not significantly different ( $\alpha$=0.05).
** 1: Before cimetidine was given. 2: With the coadministration of cimetidine. 3: Two weeks after cimetidine was discontinued.

3.2.5 Pharmacokinetic studies of hydroxyzine in rabbits: the effect of hepatic dysfunction

3.2.5.1 Serum concentrations of hydroxyzine and cetirizine

Table 68 and Table 69 list hydroxyzine and cetirizine concentrations in the rabbits before hepatic dysfunction was induced. Serum hydroxyzine and cetirizine concentrations in the same rabbits with induced hepatic dysfunction after an intravenous bolus injection of 10 mg hydroxyzine are listed in Table 70 and Table 71. The mean serum concentrations are plotted against time in Fig. 43 and Fig.44.

Table 68. Serum hydroxyzine concentrations in rabbits after an i.v. bolus dose of 10 mg hydroxyzine

| Time (hr) | 1 | 2 | 3 | 4 | 5 | Mean±S.D. (ng/ml) |
|---|---|---|---|---|---|---|
| 0.083 | 961.1 | 1282.5 | 1262.8 | 1584.3 | 1214.9 | 1261.1±222.0 |
| 0.25 | 611.7 | 545.0 | N.S. | 680.3 | 589.5 | 606.6±56.4 |
| 0.5 | 446.9 | 345.0 | 952.4 | 347.8 | 402.4 | 498.9±257.0 |
| 1.0 | 317.9 | 187.1 | 473.1 | 127.4 | 196.7 | 260.4±137.5 |
| 2.0 | 133.9 | 59.1 | 155.8 | 63.4 | 61.1 | 94.7±46.5 |
| 3.0 | 65.5 | 22.5 | 66.9 | 32.5 | 38.9 | 45.3±20.0 |
| 4.0 | 39.0 | 13.1 | 33.1 | 8.7 | 30.2 | 24.8±13.2 |
| 6.0 | N.S. | N.S. | 9.7 | 3.0 | 13.3 | 8.7±5.2 |
| 8.0 | 6.2 | N.D. | 6.4 | N.D. | 5.4 | 6.0±0.5 |
| 12.0 | N.D. | N.D. | N.D. | N.D. | 2.7 | 2.7±0.9 |

* N.S.: No sample

* N.D: below the minimum detectable concentration (1 ng/ml).

Table 69. Serum cetirizine concentrations in rabbits after an i.v. bolus dose of 10 mg hydroxyzine

| Time (hr) | 1 | 2 | 3 | 4 | 5 | Mean±S.D. (ng/ml) |
|---|---|---|---|---|---|---|
| 0.083 | 85.4 | 41.9 | 69.5 | 56.3 | 65.6 | 63.7±16.1 |
| 0.25 | 114.0 | 153.4 | 128.5 | 131.6 | 91.5 | 123.8±22.9 |
| 0.5 | 188.0 | 192.3 | 182.9 | 172.0 | 109.5 | 168.9±34.1 |
| 1.0 | 197.0 | 192.3 | 203.9 | 265.6 | 134.8 | 198.7±46.5 |
| 2.0 | 127.0 | 107.5 | N.S. | 169.7 | 86.6 | 122.7±35.4 |
| 3.0 | 108.3 | 70.7 | 59.3 | 167.4 | 73.8 | 95.9±44.0 |
| 4.0 | 70.2 | 39.9 | 56.3 | 66.8 | 40.3 | 54.7±14.3 |
| 6.0 | 35.2 | 9.3 | 15.3 | 50.4 | 17.8 | 25.6±16.9 |
| 8.0 | 11.4 | N.D. | N.D. | 17.7 | 13.1 | 14.1±3.3 |
| 12.0 | N.D. | N.D. | N.D. | 8.6 | 9.3 | 9.0±0.5 |

* N.S.: No sample

** N.D: below the minimum detectable concentration (2 ng/ml).

Table 70. Serum hydroxyzine concentrations in rabbits with hepatic dysfunction after an i.v. bolus dose of 10 mg hydroxyzine

| Time (hr) | 1 | 2 | 3 | 4 | 5 | Mean±S.D. (ng/ml) |
|---|---|---|---|---|---|---|
| 0.083 | 1524.7 | 1005.9 | 1122.4 | 1900.4 | 1584.5 | 1427.6±363.5 |
| 0.25 | 722.3 | 693.5 | 650.4 | 820.5 | 739.4 | 725.2±63.0 |
| 0.5 | 283.4 | 545.7 | 417.6 | 560.7 | 602.5 | 482.0±130.7 |
| 1.0 | 203.4 | 391.1 | 475.4 | 325.5 | 400.5 | 359.2±102.0 |
| 2.0 | 157.5 | 210.8 | 316.2 | 260.6 | 275.3 | 244.1±61.3 |
| 3.0 | 116.3 | 54.1 | 219.2 | 150.8 | 160.7 | 140.2±60.7 |
| 4.0 | 69.9 | 47.7 | 103.6 | 78.7 | 100.2 | 80.0±23.0 |
| 6.0 | 26.4 | 24.7 | 53.4 | 40.2 | 54.5 | 39.8±14.2 |
| 8.0 | 15.5 | 16.2 | 15.2 | 25.5 | 26.0 | 19.7±5.6 |
| 12.0 | 8.0 | 5.3 | 3.6 | 5.8 | 6.6 | 5.9±1.6 |
| 24.0 | N.D. | N.D. | N.D. | N.D. | 1.2 | 1.2±0 |

* N.D: below the minimum detectable concentration (1 ng/ml).

Table 71. Serum cetirizine concentrations in rabbits with hepatic dysfunction after an i.v. bolus dose of 10 mg hydroxyzine

| Time (hr) | 1 | 2 | 3 | 4 | 5 | Mean±S.D. (ng/ml) |
|---|---|---|---|---|---|---|
| 0.083 | 40.3 | 53.1 | 30.4 | 57.4 | 55.9 | 47.4±11.7 |
| 0.25 | 56.2 | 124.6 | 68.6 | 100.6 | 80.4 | 86.1±27.0 |
| 0.5 | 106.1 | 170.1 | 150.5 | 143.8 | 100.8 | 134.3±29.8 |
| 1.0 | 123.4 | 162.7 | 142.6 | 180.9 | 120.5 | 146.0±25.8 |
| 2.0 | 93.5 | 99.7 | 70.7 | 140.6 | 75.3 | 96.0±27.7 |
| 3.0 | 90.7 | 73.8 | 46.2 | 87.5 | 54.6 | 70.6±19.7 |
| 4.0 | 43.0 | 55.5 | 25.3 | 58.4 | 37.8 | 44.0±13.5 |
| 6.0 | 22.7 | 25.0 | 18.8 | 23.2 | 20.5 | 22.0±2.4 |
| 8.0 | 11.3 | N.S. | 9.6 | 10.8 | 13.6 | 11.3±1.7 |
| 12.0 | 2.9 | 10.3 | 6.0 | 7.0 | 9.2 | 7.1±2.9 |
| 24.0 | N.D. | N.D. | N.D. | 2.5 | 4.0 | 3.3±1.1 |

* N.S.: No sample

* *N.D: below the minimum detectable concentration (2 ng/ml).

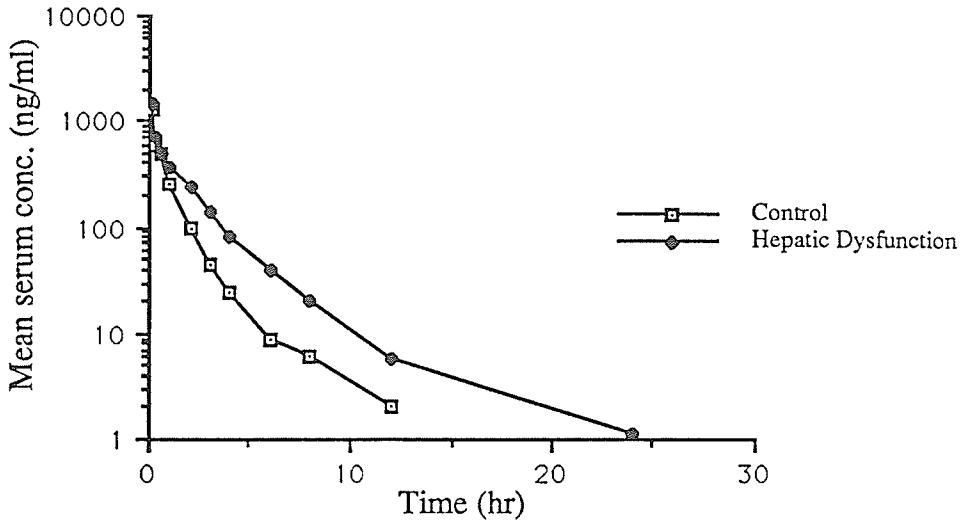



Fig.43. Mean serum concentrations of hydroxyzine in rabbits with and without hepatic dysfunction after an i.v. bolus dose of 10 mg hydroxyzine

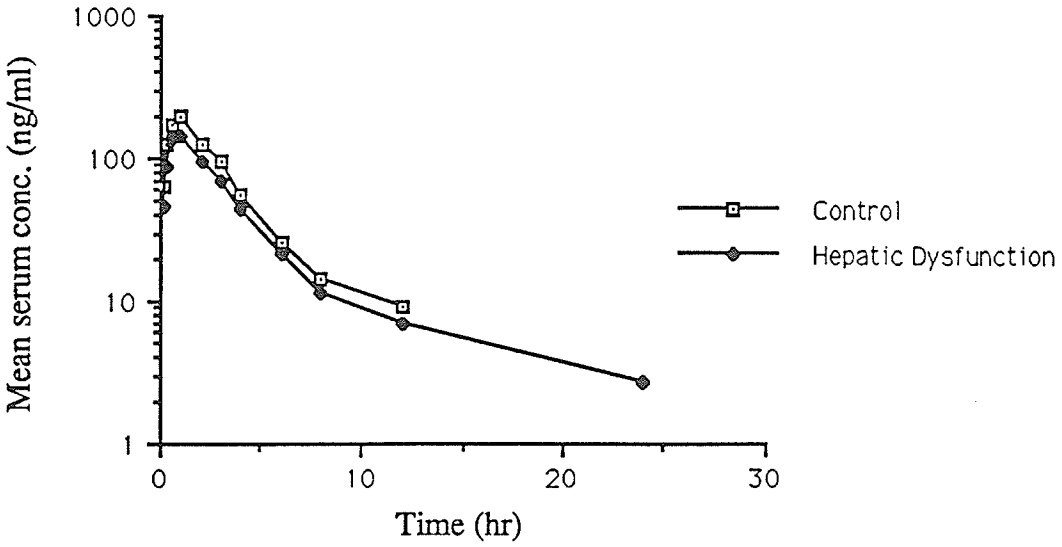



Fig.44. Mean serum cetirizine concentrations in rabbits with and without hepatic dysfunction after an i.v. bolus dose of 10 mg hydroxyzine

3.2.5.2 Curve fitting and pharmacokinetic parameters

The serum hydroxyzine concentration versus time curves were best described by a two-compartment model after an intravenous bolus injection of 10 mg hydroxyzine in control rabbits, while a three-compartment model was needed sometimes to describe the serum concentration versus time curves after an intravenous bolus dose of 10 mg hydroxyzine in rabbits with hepatic dysfunction. Coefficients of determination varied from 0.98 to 1.00.

The serum cetirizine concentration versus time curves after an intravenous bolus injection of 10 mg hydroxyzine in control rabbits were best described by a two-compartment model., with a coefficient of determination from 0.91 to 0.99. However, most of the serum cetirizine concentration versus time curves after an intravenous bolus injection of 10 mg hydroxyzine in rabbits with hepatic dysfunction were best described by a three-compartment model, with a coefficient of determination from 0.96 to 0.99, except rabbit 2 which had a coefficient of determination of 0.78.

Table 72 lists results of biochemical tests. Various pharmacokinetic parameters are listed in Table 73 to Table 76.

Table 72. Results of biochemical tests

| Parameter | 1 | 2 |
|---|---|---|
| SGOT (U/L) | 20.5±4.6 | 320.3±311.9 |
| SGPT(U/L) | 35.8±15.5 | 501.0±202.5 |
| LDH (U/L) | 160.0±70.2 | 418.0±319.7 |
| Al. Phos. (U/L) | 42.3±11.8 | 41.0±9.6 |

1: Control; 2: $CCl_4$-treated

Table 73. Pharmacokinetic parameters of hydroxyzine after an i.v. bolus dose of 10 mg hydroxyzine

| Subject\Parmeter | Wt | $\beta$ | $T_{1/2}$ | $AUC_{0->\infty}$ | Cls | $V\beta$ |
|---|---|---|---|---|---|---|
| | kg | $hr^{-1}$ | hr | ng·hr/ml | ml/min/kg | l/kg |
| 1 | 4.75 | 0.5669 | 1.22 | 923.1 | 38.1 | 4.0 |
| 2 | 4.80 | 0.9539 | 0.73 | 578.6 | 60.0 | 3.8 |
| 3 | 4.50 | 0.3185 | 2.18 | 1368.7 | 27.1 | 5.1 |
| 4 | 4.30 | 0.8439 | 0.82 | 612.1 | 63.3 | 4.5 |
| 5 | 4.60 | 0.3222 | 2.15 | 716.3 | 50.6 | 9.4 |
| Mean | 4.59 | 0.6011 | 1.42 | 839.8 | 47.8 | 5.4 |
| S.D. | 0.20 | 0.2925 | 0.70 | 324.8 | 15.2 | 2.3 |

Table 74. Pharmacokinetic parameters of hydroxyzine in rabbits with hepatic dysfunction after an i.v. bolus dose of 10 mg hydroxyzine

| Subject\Parameter | ß | $T_{1/2}$ | $AUC_{0->\infty}$ | Cls | Vβ |
|---|---|---|---|---|---|
| | $hr^{-1}$ | hr | ng·hr/ml | ml/min/kg | l/kg |
| 1 | 0.3256 | 2.13 | 1030.7 | 34.0 | 6.3 |
| 2 | 0.2624 | 2.64 | 1171.6 | 29.6 | 6.8 |
| 3 | 0.4424 | 1.57 | 1592.9 | 23.2 | 3.2 |
| 4 | 0.2206 | 3.14 | 1522.3 | 25.5 | 6.9 |
| 5 | 0.2025 | 3.42 | 1646.1 | 22.0 | 6.5 |
| Mean | 0.2907 | 2.58 | 1392.7 | 26.9 | 4.7 |
| S.D. | 0.097 | 0.75 | 274.3 | 4.9 | 2.6 |

Table 75. Pharmacokinetic parameters of cetirizine after an i.v. bolus dose of 10 mg hydroxyzine

| Subject\Parameter | ß | $T_{1/2}$ | $AUC_{0->\infty}$ | R | $C_{max}$ | $T_{max}$ |
|---|---|---|---|---|---|---|
| | $hr^{-1}$ | hr | ng·hr/ml | | ng/ml | hr |
| 1 | 0.3931 | 1.76 | 675.1 | 0.7 | 197.0 | 1.0 |
| 2 | 0.5974 | 1.16 | 499.2 | 0.9 | 192.3 | 0.5 |
| 3 | 0.5000 | 1.39 | 547.6 | 0.4 | 203.9 | 1.0 |
| 4 | 0.3231 | 2.14 | 906.6 | 1.5 | 265.6 | 1.0 |
| 5 | 0.2551 | 2.72 | 483.8 | 0.7 | 134.8 | 1.0 |
| Mean | 0.4137 | 1.83 | 662.5 | 0.8 | 198.7 | 0.9 |
| S.D. | 0.1368 | 0.62 | 175.7 | 0.4 | 46.4 | 0.2 |

Table 76. Pharmacokinetic parameters of cetirizine after an i.v. bolus dose of 10 mg hydroxyzine in rabbits with hepatic dysfunction

| Subject\Parameter | $\beta$ | $T_{1/2}$ | $AUC_{0->\infty}$ | R | $C_{max}$ | $T_{max}$ |
|---|---|---|---|---|---|---|
| | $hr^{-1}$ | hr | ng·hr/ml | | ng/ml | hr |
| 1 | 0.3592 | 1.93 | 482.9 | 0.5 | 123.4 | 1.0 |
| 2 | 0.2136 | 3.24 | 603.9 | 0.5 | 170.1 | 0.5 |
| 3 | 0.1101 | 6.29 | 459.1 | 0.3 | 150.5 | 0.5 |
| 4 | 0.1913 | 3.62 | 683.2 | 0.4 | 180.9 | 1.0 |
| 5 | 0.1460 | 4.75 | 517.9 | 0.3 | 120.5 | 1.0 |
| Mean | 0.2040 | 4.00 | 549.4 | 0.4 | 149.1 | 0.8 |
| S.D. | 0.0956 | 1.64 | 92.8 | 0.1 | 27.1 | 0.3 |

3.2.5.3. Statistical tests of pharmacokinetic parameters

Various pharmacokinetic parameters of hydroxyzine and cetirizine in control rabbits and rabbits with hepatic dysfunction were compared using balanced paired t-tests ($\alpha$=0.05). Parameters showing significant differences are listed in Table 77.

Table 77. Multiple range tests of hydroxyzine pharmacokinetic parameters in rabbits with and without hepatic dysfunction

| | Mean | Grouping* | t | PR>t |
|---|---|---|---|---|
| Hydroxyzine $AUC_{0->\infty}$ | | | | |
| | | | 3.25 | 0.0314 |
| **1 | 839.8 | A | | |
| 2 | 1392.7 | B | | |
| Hydroxyzine Cls | | | | |
| | | | 2.97 | 0.0410 |
| 1 | 47.8 | A | | |
| 2 | 26.9 | B | | |

* Groups with the same letter are not significantly different ( $\alpha$=0.05).

** 1: Control; 2:$CCl_4$-treated

3.2.6. Pharmacokinetic studies of cetirizine in rabbits: the effect of hepatic dysfunction

3.2.6.1 Serum concentrations of cetirizine

Serum cetirizine concentrations after an intravenous bolus injection of 10 mg cetirizine in rabbits with and without hepatic dysfunction are listed in Table 78 and Table 79. The mean serum cetirizine concentrations are plotted against time in Fig.45.

Table 78. Serum cetirizine concentrations in rabbits after an i.v. bolus dose of 10 mg cetirizine

| Time (hr) | 1 | 2 | 3 | 4 | 5 | Mean±S.D. (ng/ml) |
|---|---|---|---|---|---|---|
| 0.083 | 6664.2 | 3618.8 | 5677.8 | 6056.6 | 6854.5 | 5774.4±1293.6 |
| 0.25 | 4473.8 | 2729.9 | 3970.5 | 5561.4 | 4894.5 | 4326.0±1065.9 |
| 0.5 | 3521.4 | 2261.7 | 3076.7 | 5417.7 | 2812.4 | 3417.9±1207.2 |
| 1.0 | N.S. | 2818.8 | 2212.2 | 2839.6 | 1616.6 | 2371.8±581.5 |
| 2.0 | 759.5 | 952.1 | 739.7 | 846.3 | 454.7 | 750.5±185.4 |
| 3.0 | 281.1 | 647.4 | 294.1 | 246.3 | 163.0 | 326.4±186.6 |
| 4.0 | 115.5 | 253.7 | 122.4 | 172.5 | 64.5 | 145.7±71.5 |
| 6.0 | 63.7 | 138.9 | 37.9 | 54.8 | 33.6 | 65.8±42.7 |
| 8.0 | 20.4 | 62.4 | 27.5 | 33.1 | 10.5 | 30.8±19.6 |
| 12.0 | 2.4 | 13.2 | 7.6 | 8.0 | N.D. | 7.8±4.4 |

* N.S.: No sample

** N.D: below the minimum detectable concentration (2 ng/ml).

Table 79. Serum cetirizine concentrations in rabbits with hepatic dysfunction after an i.v. bolus dose of 10 mg cetirizine

| Time (hr) | 1 | 2 | 3 | 4 | 5 | Mean±S.D. (ng/ml) |
|---|---|---|---|---|---|---|
| 0.083 | 15713.9 | 4162.4 | 11482.5 | 8516.5 | 9288.1 | 9832.7±4227.6 |
| 0.25 | 9110.9 | 2968.0 | 8837.9 | 6250.0 | 6253.5 | 6684.1±2485.5 |
| 0.5 | 7999.9 | 3130.2 | 4829.7 | 4612.3 | 3482.4 | 4810.9±1923.5 |
| 1.0 | 4920.2 | 2703.8 | 4253.7 | 2710.6 | N.S. | 3647.1±1118.9 |
| 2.0 | 2055.6 | 2008.4 | N.S. | 612.8 | 1093.6 | 1442.6±708.6 |
| 3.0 | 1269.6 | 1161.7 | 2228.3 | 295.6 | 652.2 | 1121.5±733.3 |
| 4.0 | 607.1 | 761.7 | 647.4 | 211.3 | 498.4 | 545.2±209.1 |
| 6.0 | 205.4 | 237.9 | N.S. | 133.1 | 115.9 | 173.1±58.1 |
| 8.0 | 107.1 | 81.4 | 283.6 | 80.2 | 52.0 | 120.9±93.0 |
| 12.0 | 52.5 | 37.9 | 44.6 | 50.5 | 23.6 | 41.8±11.7 |
| 24.0 | 10.3 | 8.0 | 17.7 | 8.4 | 5.5 | 10.0±4.6 |

* N.S.: No sample

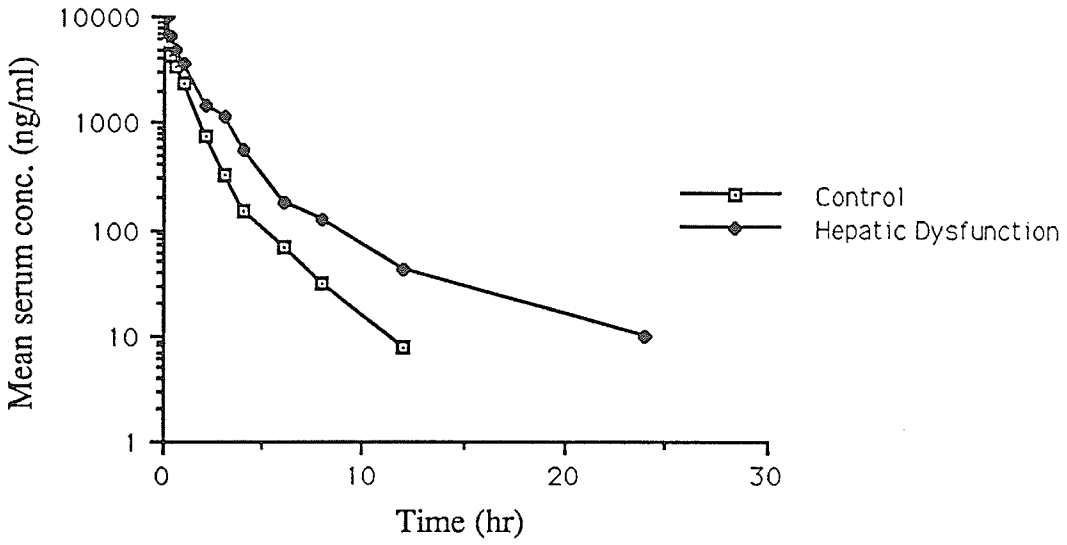



Fig.45. Mean serum cetirizine concentrations in rabbits with and without hepatic dysfunction after an i.v. bolus dose of 10 mg cetirizine

3.2.6.2 Curve fitting and pharmacokinetic parameters

The serum cetirizine concentration versus time curves in control rabbits after an intravenous bolus injection of 10 mg cetirizine were best described by a two-compartment model, with a coefficient of determination varying from 0.93 to 1.00.

The serum cetirizine concentration versus time curves in rabbits with hepatic dysfunction after an intravenous bolus injection of 10 mg cetirizine were also best described by a two-compartment model. The coefficients of determination varied from 0.97 to 1.00. Pharmacokinetic parameters are listed in Table 81 and Table 82. Table 80 lists the results of biochemical tests.

Table 80. Results of biochemical tests

| Parameter | 1 | 2 |
|---|---|---|
| SGOT (U/L) | 8.4±4.0 | 434.2±441.8 |
| SGPT (U/L) | 19.4±6.7 | 516.0±425.1 |
| LDH (U/L) | 105.3±41.5 | 272.8±175.3 |
| AL. Phos. (U/L) | 62.9±14.2 | 89.4 ± 5.37 |

1: Control; 2: CCl4-treated

Table 81. Pharmacokinetic parameters of cetirizine in rabbits after an i.v. bolus dose of 10 mg cetirizine

| Subject | Wt kg | β $hr^{-1}$ | $T_{1/2}$ hr | AUC ng·hr/mll | Cls ml/min/kg | $V_\beta$ l/kg |
|---|---|---|---|---|---|---|
| 1 | 4.30 | 0.5114 | 1.36 | 6168 | 6.28 | 0.74 |
| 2 | 4.00 | 0.3743 | 1.85 | 6305 | 6.61 | 1.06 |
| 3 | 3.11 | 0.3284 | 2.11 | 5506 | 9.73 | 1.78 |
| 4 | 4.09 | 0.4331 | 1.60 | 7403 | 5.50 | 0.76 |
| 5 | 4.70 | 0.7319 | 0.95 | 4652 | 7.62 | 0.62 |
| Mean | 4.04 | 0.4758 | 1.57 | 6007 | 7.15 | 0.99 |
| S.D. | 0.59 | 0.1587 | 0.45 | 1019 | 1.63 | 0.47 |

Table 82. Pharmacokinetic parameters of cetirizine in rabbits with hepatic dysfunction after an i.v. bolus dose of 10 mg cetirizine

| Subject | β $hr^{-1}$ | $T_{1/2}$ hr | AUC0->∞ ng·hr/ml | Cls ml/min/kg | $V_\beta$ l/kg |
|---|---|---|---|---|---|
| 1 | 0.2529 | 2.74 | 15352 | 2.52 | 0.60 |
| 2 | 0.1706 | 4.06 | 9552 | 4.36 | 1.53 |
| 3 | 0.2490 | 2.78 | 16488 | 3.25 | 0.78 |
| 4 | 0.1776 | 3.90 | 7963 | 5.12 | 1.73 |
| 5 | 0.2623 | 2.64 | 8503 | 4.17 | 0.95 |
| Mean | 0.2225 | 3.22 | 11572 | 3.88 | 1.12 |
| S.D. | 0.0445 | 0.69 | 4030 | 1.01 | 0.9 |

3.2.6.3 Statistical tests of pharmacokinetic parameters

Various pharmacokinetic parameters of cetirizine after an intravenous bolus injection of 10 mg cetirizine in rabbits with and without hepatic dysfunction were analyzed by balanced paired t-tests ($\alpha$=0.05). Parameters showing significant differences in rabbits with hepatic dysfunction are listed in Table 83.

Table 83. Multiple range tests of cetirizine pharmacokinetic parameter in rabbits with and without hepatic dysfunction

| | Mean | Grouping* | t | PR>t |
|---|---|---|---|---|
| Cetirizine Cls | | | | |
| | | | 3.28 | 0.0304 |
| **1 | 7.1 | A | | |
| 2 | 3.9 | B | | |
| Cetirizine $T_{1/2}$ | | | | |
| | | | 5.42 | 0.0056 |
| 1 | 1.57 | A | | |
| 2 | 3.22 | B | | |
| Cetirizine $AUC_{0->\infty}$ | | | | |
| | | | 3.86 | 0.0460 |
| 1 | 6006.7 | A | | |
| 2 | 11571.6 | B | | |

* Groups with the same letter are not significantly different ( $\alpha$=0.05).

** 1: Control; 2: $CCl_4$-treated

# Chapter IV. Discussion

## 4.1 Pharmacokinetic and pharmacodynamic studies of hydroxyzine and cetirizine in humans

### 4.1.1 HPLC assays

Various analytical methods for analyzing hydroxyzine have been reported. The TLC (39) and electrophoresis (40) methods were not sensitive and specific enough to be used for measuring serum hydroxyzine concentrations. Fouda *et al* (32) reported a GLC-MS method for the determination of the acetate derivative of hydroxyzine in human plasma with a sensitivity of 2 ng/ml, however, the pharmacokinetic parameters obtained with this method are inconsistent with other literature values (33,34,35).

Simons *et al* (33,34,92) reported an HPLC method for measuring the serum concentration of hydroxyzine with a sensitivity of 3 ng/ml. In the present study, the method was modified by substituting a Nova-pak $C_{18}$ Radial-pak, 0.8 cm × 10 cm cartridge (91) for the μBondapak $C_{18}$ stainless steel column. The Nova-pak $C_{18}$ cartridge is composed of a flexible tube packed with particles of 4 μm in diameter, while spherical particles of 10 μm are used in the μBondapak $C_{18}$ stainless steel column. The cartridge is compressed in a Radial Compression Module when used for HPLC analysis. By applying pressure with the Radial Compression Module along the radial axis of the flexible tube, the cartridge wall is molded around the column packing, thereby reducing void spaces within the column bed. This results in a more homogeneously packed structure,

and yields increased column efficiency (91). For example, at a flow rate of 1.0 ml/min, an μBondapak $C_{18}$ stainless steel column gives a plate number of 40000 plates per meter, while a Nova-pak $C_{18}$ Radial-pak cartridge delivers a plate number of 100000 plates per meter. In addition, there is no difficulty in producing a uniform packing structure throughout the cartridge. Therefore, particles of 4 μm or even smaller particles can be used without creating non-uniformity. The Nova-pak $C_{18}$ packing is less hydrophobic than that of μBondapak $C_{18}$ packing, so the retention times of hydroxyzine, cetirizine and the internal standards were reduced which resulted in a shorter analysis time (91). The sensitivity of the assay was improved to 1 ng/ml without changing any other components of the HPLC system.

Mobile phases of different compositions were evaluated to optimize the degree of resolution. The mobile phase used in the present study was acetonitrile-phosphate buffer (0.075M $NH_4H_2PO_4$, pH 2.5) (35: 65 v/v). The retention times for hydroxyzine and antazoline were 5.5 and 3.0 minutes respectively. No interfering peaks were observed.

Within the concentration range of 2.0 ng/ml to 203.8 ng/ml, the hydroxyzine -antazoline peak height ratios were found to be linear. The coefficient of variation obtained over a period of 12 months was less than 15% at all concentrations.

The extraction of hydroxyzine from serum samples is a relatively easy, but efficient process. The recovery rate of a known quantity of hydroxyzine using the present method was around 80%.

GC (35) and HPLC (38,46,47) methods for measuring serum cetirizine concentrations have been reported with a limit of sensitivity of 10 ng/ml and 2 ng/ml respectively. In the present study, the serum

cetirizine concentration was measured by using a modified version of the method reported by Matzke *et al* (47). A Nova-pak $C_{18}$ Radial-pak cartridge was used instead of a Brownlee RP-8, 4.6 mm ×10 cm column, and sodium decanesulfonate was substituted for sodium octanesulfonate in the mobile phase. The mobile phase was composed of acetonitrile-phosphate buffer (0.075M $NH_4H_2PO_4$, pH 2.9, with 0.02M sodium decanesulfonate) (43:57 v/v). Under these conditions, a serum cetirizine concentration of 2 ng/ml could be detected. The retention times for cetirizine and $P_{265}$ were 6.5 and 9.0 minutes respectively.

Within the concentration range of 2.1 ng/ml to 211.0 ng/ml, the drug-internal standard peak height ratios were found to be linear. The coefficient of variation calculated over a period of 12 months was less than 15% percent at all concentrations. In urine samples, the calibration curve was linear from 10.6 ng/ml to 4220.0 ng/ml. The coefficients of variation at both ends of this concentration range were larger compared to others, probably due to the error in handling very small or very large volumes of stock solutions.

The extraction of cetirizine from serum and urine samples was not as efficient as that of hydroxyzine. The recovery rate of a known quantity of cetirizine was around 55%. The low recovery rate could be attributed to the fact that cetirizine is an oxidative derivative of hydroxyzine. There is a carboxylic acid group instead of a hydroxyl group at the end of its side chain, thus making it more difficult to maintain cetirizine in a non-ionized form in solution. Therefore, the pH of the buffer added to serum and urine samples at the beginning of the study is very critical. Since the pKa value of cetirizine was not available, different citrate buffers were tried to

improve extraction efficiency. The citrate buffer of pH 5.0 gave the best result.

Another problem associated with the cetirizine extraction process was that serum samples became emulsified easily during vortexing. There was no solution to this problem, except increasing centrifugation time and being careful during the whole extraction process.

4.1.2 Pharmacokinetic and pharmacodynamic studies of hydroxyzine in the elderly

4.1.2.1 Pharmacokinetics of hydroxyzine in the elderly

The serum hydroxyzine concentration versus time curve after the oral administration of 0.7 mg/kg hydroxyzine in the elderly could be best described by a triexponential equation, corresponding to an absorption phase, a distribution phase and an elimination phase. Since hydroxyzine was rapidly absorbed as indicated by the mean $T_{max}$ of 2.3±1.5 hours, and there were usually only two data points before the maximum concentration was reached, the absorption phase was not well defined.

The resulting serum cetirizine concentration versus time curve could be best described by biexponential or triexponential equations. This was probably due to the fact that insufficient samples were taken during the formation and distribution phases of cetirizine. The pharmacokinetics of cetirizine observed after the oral administration of hydroxyzine should differ from the true pharmacokinetics of cetirizine when only cetirizine was given (50,93), because cetirizine is a metabolite of hydroxyzine. Changes in the pharmacokinetics of hydroxyzine would certainly affect the time course of cetirizine. According to Gibaldi and Perrier (50), at least

five exponential terms are needed to describe the time course of the metabolite of a drug displaying multiple compartment properties. Therefore, it was not possible to distinguish different kinetic processes of cetirizine occurring in the body after the oral administration of hydroxyzine. The terminal elimination phase observed in the cetirizine concentration versus time curve should reflect the elimination of hydroxyzine (50,93).

The mean maximum serum hydroxyzine concentration of 77±17 ng/ml occurred at a mean time of 2.3±1.5 hours in the elderly (Table 8), which indicated that hydroxyzine was absorbed rapidly. These values were not significantly different from the values of 72.5±11.1 ng/ml at 2.1±0.4 hours in the young adults (34) and 47.4±17.3 ng/ml at 2.0±0.9 hours in children (33). Fouda *et al* (32) reported a mean peak concentration of 78 ng/ml occurring at about 3.0 hours after the oral administration of 100 mg hydroxyzine tablets to 4 male volunteers. Gengo *et al* (35) reported a mean peak concentration of 29±17 ng/ml occurring at 2 hours after the oral administration of a 25 mg hydroxyzine capsule. One possible explanation for the differences in Cmax observed in our studies from others (32,35) could be that different dosage forms were used and that the bioavailability of tablets and capsules used in other studies (32,35) is less than that of the syrup used in our studies (33,34).

In the elderly, the mean maximum cetirizine concentration was 462±77 ng/ml, and it occurred at a mean time of 3.8±1.0 hours (Table 9), while in young adults, a mean maximum cetirizine concentration of 374±158 ng/ml occurred at a mean time of 3.8±0.9 hours. There were no significant differences between these parameters in these two groups. Gengo *et al* (35) also measured cetirizine concentrations after the oral

administration of a 25 mg hydroxyzine capsule. A mean peak cetirizine concentration of 127 ±35 ng/ml was reported.

The mean elimination half-life of hydroxyzine, 29.3±10.1 hours, was significantly longer ($p<0.05$) in the elderly than the previously reported 7.1±2.3 hour in children (33), but not significantly different from the value of 20.0±4.1 hour in young adults (34). The systemic clearance of hydroxyzine in the elderly, 9.6±3.2 ml/min/kg, was not significantly different from the value of 9.8±3.3 ml/min/kg in young adults (34). However, both of them were significantly ($p<0.05$) lower than the systemic clearance of 32.1±11.1 ml/min/kg observed in children (33).

The apparent volume of distribution of hydroxyzine in the elderly, 22.5±6.3 l/kg, was larger, but not significantly so, than that in the young adults, 16.0±3.0 l/kg. This was probably due to the fact that adipose tissue increases as a fraction of the body weight and lean body mass decreases as a result of normal aging process (52,53,55). Therefore, hydroxyzine, being lipophilic, would distribute more extensively in the body in the elderly than in young adults. The change of the apparent volume of distribution of hydroxyzine in the elderly may partly explain why the elimination half-life of hydroxyzine in the elderly was prolonged since the elimination half-life of a drug is directly proportional to its apparent volume of distribution, and inversely proportional to its systemic clearance.

It must be pointed out, however, that all of the above calculations of systemic clearances and apparent volumes of distribution were based on the assumption that the bioavailability of orally administered hydroxyzine was 100 percent. It was impossible to calculate the absolute bioavailability of hydroxyzine, because there is no commercial dosage form for

intravenous hydroxyzine administration, and no serum hydroxyzine concentrations after intravenous administration were available for comparison. Any deviation from the 100 percent bioavailability could introduce large errors in the conclusions made.

The mean hydroxyzine $AUC_{0->\infty}$ of 1383±1039 ng·hr/ml was obtained in the elderly, which was not significantly different from the mean value of 1095±353 ng·hr/ml obtained in young adults (34). However, the mean $AUC_{0->\infty}$ of cetirizine after an oral administration of 0.7 mg/kg hydroxyzine in the elderly, 11529±2383 ng·hr/ml, was significantly different ($p<0.05$) from the value of 6608±2243 ng·hr/ml obtained in young adults (94) after the same dose of hydroxyzine.

Cetirizine is a compound eliminated mainly through renal excretion. Renal function in the elderly is reduced as a natural consequence of aging (53,55). Since similar $AUC_{0->\infty}$ values of hydroxyzine were obtained in the elderly and in young adults after the same dose of hydroxyzine, it is unlikely that more cetirizine would be produced in the elderly than in young adults from the same amount of hydroxyzine. In addition, there is the possiblity of reduced hepatic function in the elderly due to aging (53,55). Reduced renal function in the elderly probably prolonged the elimination of cetirizine, resulting in the elevated values of cetirizine $AUC_{0->\infty}$ in the elderly.

Cetirizine is the major metabolite of hydroxyzine in humans, it is eliminated more rapidly than hydroxyzine (35,47,115). This means that the slope of the terminal linear segment of the semilogarithmic plot of cetirizine concentration versus time will probably be equal to $\beta/2.303$, where $\beta$ is the slope of the terminal linear segment of hydroxyzine concentration versus time curve. It has been reported that the elimination

half-life of cetirizine after oral administration of cetirizine was about 7.4 hours in young adults (47,115). Therefore, the half-life calculated from the cetirizine concentration versus time curve after the oral administration of hydroxyzine would reflect the half-life of hydroxyzine. In the present study, the half-life calculated from the resulting cetirizine concentration versus time curve in the elderly was 24.8±7.7 hours, significantly longer than the $t_{1/2}$ of cetirizine of 11.4±3.1 hour in young adults (94) after the same dose of hydroxyzine. However, these two half-lives were not significantly different from their corresponding hydroxyzine half-lives supporting the hypothesis that cetirizine elimination half-lives obtained from the cetirizine concentration versus time curves after the oral administration of hydroxyzine 0.7 mg/kg is a reflection of the elimination half-life of hydroxyzine (50,93).

4.1.2.2 Pharmacodynamics of hydroxyzine in the elderly

The histamine skin test is a well-standardized quantitative test of antihistamine efficacy (14,15,21). In the present study, areas of irregularly shaped wheals and flares were measured by a digitizer connected to a personal computer with better accuracy and consistency than the cut-and-weigh method (14) or the longest diameter approach (21).

The mean wheal areas after intradermal injection of 0.01ml (0.1 mg/ml) histamine phosphate solution were significantly ($p<0.01$) suppressed from 1 to 144 hours after a single dose of hydroxyzine, compared with the predose value. Maximum wheal suppression occurred between 4 and 10 hours, compared with all other wheal areas measured during the study, when wheals were 74.9±6.5% to 80.4±8.2% suppressed (Table 6).

The mean flare areas after intradermal injection of histamine were also significantly suppressed from 1 to 144 hours, compared with the predose flare areas ($p<0.01$). Maximum flare suppression, compared with all other flare areas measured during the study ($p<0.01$), occurred from 2 to 72 hours, when flare areas were 73.6±22.5 % to 83.0±9.3 % suppressed (Table 7).

In an earlier study in 7 young adults (34), 60 hours after a single dose of hydroxyzine of 0.7 mg/kg, mean hydroxyzine and cetirizine concentrations were found to be 5.6±1.3 ng/ml and 13.4±9.6 ng/ml respectively, while wheals and flares were not significantly suppressed compared with predose values. In another study in 10 young adults (35), 36 hours after a 25 mg dose of hydroxyzine, mean serum hydroxyzine and cetirizine concentrations were found to be 3 ng/ml and 120 ng/ml respectively, yet wheal suppression was not significantly different from the predose value. Rihoux and Polderman (95) showed that hydroxyzine produced 77% wheal suppression 24 hours after the oral administration of 25 mg hydroxyzine, however, no drug concentrations were reported in their study. One hundred and forty-four hours after 0.7 mg/kg hydroxyzine was given, two elderly subjects had serum hydroxyzine concentrations of 1.1 ng/ml and 8.8 ng/ml, while the other seven subjects had serum hydroxyzine concentration of less than 1ng/ml. The mean cetirizine concentration was 5.2±6.8 ng/ml. However, both wheal and flare areas were still significantly suppressed compared to pre-dose values.

Various mathematical models have been used to describe the effect-concentration relationship for many classes of drugs (96,97,98,99,100,101). These mathematical models include the linear model, the log-linear model, the $E_{max}$ model and the Sigmoid $E_{max}$ model.

The linear model was used by Bilzer *et al* (118) to describe the correlation between the inhibitory activity of diphenhydramine on the size of histamine-induced wheals and its plasma levels in 4 of the 6 volunteers studied. Carruthers *et al* (119) also used the linear model to describe the correlation between plasma diphenhydramine level and antihistaminic effects.

Since both hydroxyzine and cetirizine are $H_1$-receptor antagonists, it is assumed that they will compete competitively for the same receptors. It is further assumed that the maximum effects produced by hydroxyzine and cetirizine are equal, and $EC_{50}^{C}$ of cetirizine is four times that of hydroxyzine $EC_{50}^{H}$ because it was demonstrated by *in vitro* experiments (45) that hydroxyzine is about four times more potent than cetirizine is. An equation similar to that of the $E_{max}$ model was derivated ( see Appendix I for derivation), and the model is named the modified $E_{max}$ model.

There are also two parameters in the modified $E_{max}$ model, $E_{max}$ and $EC_{50}^{H}$. $E_{max}$ is the maximum possible response that can be attributed to the drug, and $EC_{50}^{H}$ is the hydroxyzine concentration that produces 50% of the maximum effect.

The pharmacodynamic modelling process in the present study was complicated by two factors. First, hydroxyzine was given orally in the present study and the central compartment is unlikely the effect compartment. Therefore, only concentrations in the elimination phase could be used. This was based on the assumption that drug concentrations in the effect compartment and blood would be in equilibrium during that phase so that changes in hydroxyzine and cetirizine serum concentrations would reflect changes in hydroxyzine and cetirizine concentrations in the effect compartment. Secondly, mean percent wheal and flare suppression

values and mean serum concentrations had to be used in the modelling process. It was not possible to fit the data from individual subjects to the modified $E_{max}$ model due to considerable scatter of wheal and flare areas and relatively consistent serum hydroxyzine and cetirizine concentrations. Therefore, statistical analysis of the results obtained from the different age groups was not possible.

In the elderly, the maximum wheal suppression, $E_{max}$, was 80.5%, which was less than the calculated $E_{max}$ of 99.8% obtained in young adults (94). However, a much smaller hydroxyzine concentration ($EC_{50}^{H}$) was needed to achieve the half maximum effect in the elderly than in young adults, 8.2 ng/ml versus 30.4 ng/ml respectively (94).

The maximum flare suppression, $E_{max}$, was 83.6% in the elderly, which was also less than its counterpart of 100.7% in young adults (94). A hydroxyzine concentration of 3.6 ng/ml was needed to achieve the half maximum effect in the elderly, while a hydroxyzine concentration of 10.7 ng/ml was needed to achieve the half maximum effect in young adults (94) (Table 10).

Two conclusions could be drawn from these results. First, although wheal and flare were suppressed for longer time periods in the elderly than in young adults, the maximum effect in the elderly was not increased. Second, the elderly were more sensitive to changes of drug concentrations in the body than young adults, as indicated by smaller $EC_{50}^{H}$ values obtained in the elderly.

The above results seem to lend support to the hypothesis that alterations in the quality and quantity of drug receptors might account for the enhanced sensitivity in drug response in the elderly (53,55). However, the fact that the apparent volume of distribution of hydroxyzine was

increased in the elderly may present a different explanation. Hydroxyzine was distributed more extensively in the elderly than in young adults. If the rate constant at which hydroxyzine is transferred from the peripheral compartment to the central compartment was reduced, an accumulation of hydroxyzine in the tissues, presumably belonging to the peripheral and effect compartment, will be expected, resulting in an enhanced, persistent response, but the sensitivity may remain the same or even be reduced. In addition, cetirizine is also pharmacologically active in suppressing wheal and flare formation. The increased cetirizine concentrations in the elderly may also contribute to the enhanced response observed. It was impossible to draw any definite conclusions from the data presented here as to which hypothesis is correct.

### 4.1.3 Pharmacokinetic and pharmacodynamic studies of hydroxyzine in patients with primary biliary cirrhosis

#### 4.1.3.1 Pharmacokinetics of hydroxyzine in patients with primary biliary cirrhosis

The serum hydroxyzine concentration versus time curve after oral administration of 0.7 mg/kg hydroxyzine in patients with hepatic dysfunction could be best described by a triexponential equation, corresponding to an absorption phase, a distribution phase and an elimination phase. Hydroxyzine was rapidly absorbed as indicated by the mean $T_{max}$ of 2.1±0.8 hours, so there were usually only two or three data points before the maximum serum concentration was reached. Thus, the absorption phase was not well defined.

The resulting serum cetirizine concentration versus time curves could be best described by a triexponential or a quatrexponential equation. The meaning of each exponential term, except the terminal elimination phase, was not clear because there were insufficient data points to clearly distinguish each kinetic process of cetirizine. As discussed in section 4.1.2.1, the terminal elimination phase should reflect the elimination of hydroxyzine instead of cetirizine itself.

The mean maximum serum hydroxyzine concentration of 116.5±60.6 ng/ml occurred at a mean time of 2.1±0.8 hours (Table 16) which was consistent with results from the elderly, young adults (34) and children (33) and indicated that hydroxyzine was absorbed rapidly. The mean maximum serum hydroxyzine concentration was not significantly higher than those in the elderly and young adults (94) due to a large intersubject variation, but it was significantly higher than that in children (33).

The mean maximum cetirizine concentration of 500±302 ng/ml occurred at a mean time of 4.8±2.8 hours (Table 17). There were no significant differences among maximum cetirizine concentrations after an oral dose of 0.7 mg/kg hydroxyzine in different groups studied in our laboratory.

The mean elimination half-life of hydroxyzine was 35.6±12.3 hours, significantly longer ($p<0.05$) than those values obtained in young adults (34) and in children (33), but not significantly longer than that found in the elderly subjects. This was primarily due to a large intersubject variation in the elderly and in patients with primary biliary cirrhosis and the small number of subjects. The oral systemic clearance of hydroxyzine in patients with hepatic dysfunction was 8.7±7.5 ml/min/kg, not significantly different

from those obtained in young adults (34) and in the elderly, although the clearance in children (33) was significantly higher than the values obtained in the three other groups. The apparent volume of distribution in patients with hepatic dysfunction was 22.7±13.3 l/kg. This was also not statistically significantly different from those values obtained from other groups due to the large intersubject variation.

The elimination half-life of a drug is directly proportional to its apparent volume of distribution and inversely proportional to its systemic clearance. In patients with hepatic dysfunction, the apparent volume of distribution was increased, while the systemic clearance was reduced compared to other groups. Therefore, the increase of the elimination half-life of hydroxyzine in these patients was affected by both factors.

The mean area under the serum hydroxyzine concentration versus time curve $AUC_{0->\infty}$ of 2169±1466 ng·hr/ml was larger than those found in children (33), young adults (34) and the elderly, but not significantly different due to a large intersubject variation. The mean area under the serum cetirizine concentration versus time curve $AUC_{0->\infty}$ of 12116±5774 ng·hr/ml was significantly larger than that in young adults (34) ($p<0.05$), but not different from that in the elderly. The elimination half-life of cetirizine in these patients with primary biliary cirrhosis was 28.6 hours, reflecting the elimination half-life of hydroxyzine.

The increase of cetirizine $AUC_{0->\infty}$ in patients with hepatic dysfunction was probably caused by a different reason from that which caused an increase of cetirizine $AUC_{0->\infty}$ in the elderly subjects in the previous study. Since the average age of these patients with hepatic dysfunction was about 15 years younger than the elderly subjects, the reduction in the renal function due to the natural aging process is probably

not as significant as in the case of the elderly. There are two possible reasons why cetirizine $AUC_{0->\infty}$ was increased in patients with primary biliary cirrhosis. First, cetirizine is only 50-60% excreted unchanged in the urine in humans, the rest is metabolized to unidentified metabolites. Therefore, an impairment in hepatic function could mean slower cetirizine metabolism. Second, a chronic impairment in hepatic function is usually accompanied by renal dysfunction, therefore, urinary excretion of cetirizine could also be reduced.

Attempts were made to correlate biochemical parameters, such as bilirubin, γ-GT, SGOT, SGPT and alkaline phosphatase concentrations with pharmacokinetic parameters. As shown in Table 11 , values of these parameters with the exception of serum bilirubin in one patient were all outside the normal range. The degree of liver function is poorly defined by these serum enzymes, so it is not possible to associate the extent of variation from normal of a particular biochemical parameter with the extent of liver dysfunction. Therefore, none of these biochemical parameters produced any significant linear correlation with any of hydroxyzine pharmacokinetic parameters, such as elimination half-life or oral clearance, as indicated by slopes not significantly different from zero. In the present patient group, it seems that renal function is more important in determining pharmacokinetics of hydroxyzine than mild hepatic dysfunction since there was some correlation ($r=0.608$) between age and the elimination half-life of hydroxyzine.

4.1.3.2. Pharmacodynamics of hydroxyzine in patients with primary biliary cirrhosis

The mean wheal areas were significantly ($p<0.01$) suppressed from 1 to 120 hours compared to the mean pre-dose wheal area, and the mean

flare areas were significantly suppressed from 1 to 144 hours compared to the mean predose flare area ($p<0.01$). Maximum wheal suppression occurred from 2 to 48 hours, when wheals were between 55.1±14.8% and 75.5±12.3% suppressed. Maximum flare suppression occurred from 3 to 24 hours, when flares were 82.3±12.4% to 87.5±8.7% suppressed (Tables 14 and 15).

The effect-concentration relationship could also be described by the modified $E_{max}$ model. As in the case of the elderly, only concentrations in the elimination phase were used. All concentrations were modified by adding one fourth of the cetirizine concentrations to the respective hydroxyzine concentrations. Furthermore, mean wheal and flare suppression data, and mean hydroxyzine and cetirizine plasma concentrations were used as before.

The maximum wheal suppression, $E_{max}$, was 82.9%, which was similar to that of 80.5% in the elderly, but smaller than the value of 99.8% in young adults. A hydroxyzine concentration of 14.9 ng/ml was needed to achieve the half maximum effect, again, this value was closer to that of 8.2 ng/ml in the elderly, but smaller than the value of 30.4 ng/ml found in young adults (94) (Table 18).

The maximum flare suppression was 93.9%, which was larger than that of 83.6% in the elderly and smaller than that of 100.7% in the young adults. A hydroxyzine concentration of 9.9 ng/ml was needed to achieve the half maximum effect, which again was larger than that of 3.6 ng/ml in the elderly, but of the same order as that of 10.7 ng/ml in young adults.

4.1.4 Comparison of pharmacokinetics and pharmacodynamics of hydroxyzine in different population groups

The pharmacokinetics and pharmacodynamics of hydroxyzine in children (33), young adults (34) were studied in our laboratory several years ago. At that time, it was not known that cetirizine, the major metabolite of hydroxyzine, was also pharmacologically active in inhibiting $H_1$-receptors, therefore, cetirizine serum concentrations were not measured. Serum samples left from the young adults study (34) were reanalyzed to measure serum cetirizine concentrations. However, measurement of serum cetirizine concentrations in children could only be carried out in two subjects because insufficient serum samples were left from the previous study (33).

Nonetheless, it was possible to compare pharmacokinetic and pharmacodynamic parameters obtained in different groups. Table 84 lists results from different groups.

The maximum serum hydroxyzine concentrations obtained in different groups were not significantly different from each other due to a large intersubject variation especially in patients with primary biliary cirrhosis. The Cmax in patients with primary biliary cirrhosis was the highest, and that in children was the lowest. The $T_{max}$ from different groups was essentially the same, about 2 hours indicating that hydroxyzine was rapidly absorbed and that absorption was probably not affected by age of different groups. The elimination half-life of hydroxyzine in children, 7.1±2.3 hours, was significantly ($p<0.05$) shorter than those in three other groups, 20.0±4.1, 29.3±10.1, and 36.6±13.1 hours in young adults, the elderly and patients with primary biliary cirrhosis respectively.

The elimination half-lives of hydroxyzine in the elderly and patients with hepatic dysfunction were not different from each other, but they were longer than those observed in children and young adults (33,34). The

Table 84. Comparison of pharmacokinetic and pharmacodynamic parameters of hydroxyzine in different populations

| Population | Elderly | Young Adults[1] | Children[2] | Patient PBC |
|---|---|---|---|---|
| No. | 9 | 7 | 12 | 8 |
| Age(yr) | 69.5±3.7 | 26.3±9.4 | 6.1±4.6 | 53.4±11.2 |
| Hydroxyzine | | | | |
| Cmax(ng/ml) | 76.5±16.6 | 72.5±11.1 | 47.4±17.3 | 116.5±60.6 |
| $T_{max}$(hr) | 2.3±1.5 | 2.1±0.4 | 2.0±0.9 | 2.3±0.7 |
| $T_{1/2}$ (hr) | 29.3±10.1 | 20.0±4.1 | 7.1±2.3 | 35.6±13.1 |
| Cls(ml/min/kg) | 9.6±3.2 | 9.8±3.2 | 32.1±11.1 | 8.7±7.5 |
| Vβ(l/kg) | 22.5±6.3 | 16.0±3.0 | 18.5±8.6 | 22.7±13.3 |
| $AUC_{0->\infty}$ | 1383±1039 | 1095±353 | 432±155 | 2058±1411 |
| Cetirizine | | | | |
| Cmax(ng/ml) | 462±77 | 374±158 | 412.2±76.7[3] | 500±302 |
| $T_{max}$(hr) | 3.8±1.0 | 3.8±0.9 | 2.0±0 | 4.8±2.8 |
| $AUC_{0->\infty}$ | 11529±2383 | 6608±2243 | 4999±668 | 12116±5774 |
| Ratio[4] | 10.5±4.3 | 6.3±2.1 | --------- | 7.5±5.6 |
| Wheal Suppression | 1 to 144 | 2 to 36 | not done[5] | 1 to 120 |
| Wheal $E_{max}$ | 80.5 | 99.8 | not done | 82.9 |
| Wheal $EC_{50}^{H}$ | 8.2 | 30.4 | not done | 14.9 |
| Flare suppression | 1 to 144 | 2 to 60 | not done | 1 to 144 |
| Flare $E_{max}$ | 83.6 | 100.7 | not done | 93.9 |
| Flare $EC_{50}^{H}$ | 3.6 | 10.7 | not done | 9.9 |

1 From Ref.34.

2 From Ref.33.

3 Results were from two complete sets of samples.

4 The ratio was that of cetirizine $AUC_{0->\infty}$ to hydroxyzine $AUC_{0->\infty}$.

5 Histamine-induced wheal and flare challenge was not performed, only degree of pruritus was scored in the children with atropic dermatitis.

elimination half-life of hydroxyzine observed in the present study and in studies done previously in our laboratory was longer than those reported in the literature (32,35). This could be caused by a number of reasons. First, the sampling time in our studies, except the study in children (33), was much longer than other studies (32,35). Blood samples were taken up to 60 hours in young adults and up to 144 hours in the elderly and in patients with primary biliary cirrhosis, while blood samples were only taken upto 24 hours in the study by Fouda *et al* (32) with no samples between 8 and 24 hours. In the other study (35), blood samples were drawn up to 36 hours. Second, the sensitivity of the analytical method was better in our studies, 1 ng/ml, than in other studies, 2.5 ng/ml by Gengo *et al* (35) and 10 ng/ml by Fouda *et al* (32). Therefore, it was possible for us to fully describe the time course of hydroxyzine in the body after the oral administration of hydroxyzine, and to calculate the elimination rate constant more accurately. Third, hydroxyzine was given as tablets (32) and capsules (35) in other studies, while it was given as syrup in all our studies. Thus, absorption might be more complete in our studies. This might explain the fact that the mean peak concentration was only 78 ng/ml after the oral administration of 100 mg hydroxyzine tablet (32), while the oral administration of about 50 mg hydroxyzine syrup gave the same peak concentration.

The systemic clearance of hydroxyzine in children was significantly higher than those in the other three groups. The apparent volumes of distribution were not different from each other among four groups. However, the volumes of distribution in the elderly and patients with primary biliary cirrhosis were larger than those in young adults (34) and in children (33). The prolonged elimination half-life of hydroxyzine was thus likely caused by an increase of the apparent volumes of distribution in

the elderly and by both an increase in the apparent volume of distribution and a reduction in systemic clearance in patients with primary biliary cirrhosis.

In all four studies, the systemic clearance and the apparent volume of distribution were calculated by assuming that the bioavailability of orally administered hydroxyzine was 100 percent, or that the bioavailability of orally administered hydroxyzine was the same in all four population groups.

The hydroxyzine $AUC_{0->\infty}$ values were not significantly different from each other among the four groups due to a large intersubject variability.

The Cmax values of cetirizine in children, young adults (94), the elderly, and patients with primary biliary cirrhosis were not different from each other, nor were their respective $T_{max}$ values. Cetirizine $AUC_{0->\infty}$ in the elderly and in patients with primary biliary cirrhosis were not different from each other, but both of them were significantly ($p<0.05$) larger than those in young adults and children (94). This was probably caused by a reduced renal function in the elderly, and by a combination of reduced hepatic metabolism and renal function in patients with primary biliary cirrhosis. This argument could be further illustrated by comparing the ratio of $AUC_{0->\infty}$ cetirizine to $AUC_{0->\infty}$ hydroxyzine in young adults, the elderly and patients with primary biliary cirrhosis. If the ratio in young adults, 6.3, was taken as the normal value and the ratio in the elderly, 10.5, as the value caused only by reduced renal function, then the ratio in patients with primary biliary cirrhosis, 7.5, should be between these two values due to slightly reduced hepatic and renal function.

Wheals and flares induced by intradermally injected histamine in young adults, elderly adults, and patients with primary biliary cirrhosis were significantly suppressed after the oral administration of hydroxyzine for more than twenty-four hours. Twenty-four hours after drug administration, the wheals were more than 60% suppressed, while flares were about 80% suppressed in all three groups.

Since mean percent wheal and flare suppression values were used in the pharmacodynamic model fitting process, it was not possible to compare $E_{max}$ and $EC_{50}^{H}$ obtained from different groups statistically. However, an examination of results obtained revealed that the $E_{max}$ was highest in young adults and lowest in the elderly for both wheal and flare suppression. The hydroxyzine concentration needed to achieve the half maximum effect ($EC_{50}^{H}$) was lowest in the elderly and highest in young adults for both wheal and flare. These results suggest that the elderly might be more sensitive to drug changes in the body than young adults. What causes more sensitive response in elderly than in young adults was not clear.

Adverse effects of hydroxyzine were observed in all four patient groups. Children (33) experienced significant ($p<0.05$) drowiness from 1 to 8 hours after an oral dose of hydroxyzine 0.7 mg/kg. Five of the seven subjects in the young adult study (34) reported transient dry mouth, drowiness, and light-headedness from 1 to 6 hours after the administration of hydroxyzine. Eight of the nine subjects in the elderly study fell asleep between 2 and 6 hours after an oral dose of hydroxyzine 0.7 mg/kg. One subject noted blurred vision from 6 to 9 hours after the hydroxyzine dose. After a single dose of hydroxyzine of 0.7 mg/kg, all patients with primary biliary cirrhosis became sleepy from 0.5 to 6 hours. Six patients slept from 1 to 5.5 hours. Two out of eight patients complained of blurred vision, two

complained of dry mouth, and two complained of light headedness and dizziness.

The recommended dosing regimen for hydroxyzine is 25 to 100 mg three to four times daily (14,29). It is evident that the dosing regimen should be amended in light of results from the present studies, studies carried out previously in our laboratory (33,34) and other studies reported in literature (35,95). In the present studies, a single oral dose of approximately 50 mg hydroxyzine provides greater than 60% suppression of histamine-induced wheals and greater than 80% suppression of histamine-induced flares twenty-four hours after drug administration. A dose regimen for hydroxyzine of 50 mg each 24 hours will result in much less accumulation than the dosage regimen of 25 to 100 mg three to four time daily (every 6 to 8 hours), which should result in fewer adverse affects. It is proposed that hydroxyzine, 50 mg, be given once a day, at bedtime to young adults. This dosage regimen has been used clinically with good results, but no kinetic data is available. The dose or dosage regimen should be further adjusted in the elderly and in patients with hepatic dysfunction. However, until the serum concentration-effect relationship is fully understood, dosage regimen adjustments based solely on pharmacokinetic data require clinical evaluation.

4.1.5 Pharmacokinetic and pharmacodynamic studies of cetirizine in children

4. 1.5.1 Pharmacokinetics of cetirizine in children

The serum cetirizine concentration versus time curve after an oral dose of cetirizine of 5 mg and 10 mg in children could be best described by a biexponential equation, corresponding to an absorption phase and an elimination phase. However, the absorption phase was not well defined

since there were only one or two data points before the maximum concentration was reached.

The mean maximum cetirizine concentrations of 428±144 ng/ml and 978±341 ng/ml occurred at 1.4±1.1 and 0.8±0.4 hours after the 5 mg and 10 mg doses respectively (Tables 32 and 33), indicating that cetirizine was rapidly absorbed. The maximum concentration after the 10 mg dose, 978±341 ng/ml, was twice as large as that after the 5 mg dose, 428±144 ng/ml, suggesting that the absorption of cetirizine could be described by first-order kinetic processes with no dose-dependent kinetics in the dose range tested.

Matzke *et al* (47) studied the pharmacokinetics of cetirizine in young adults, in elderly adults and in patients with different degrees of renal insufficiency after an oral dose of 10 mg cetirizine in capsule. The Cmax values observed in their study were 384±103 ng/ml in adults, 460±59 ng/ml in the elderly, and about 300 ng/ml in various groups of patients with renal insufficiency. Gengo *et al* (35) studied the pharmacokinetics and pharmacodynamics of cetirizine in 12 subjects after the oral administration of 10 mg and 20 mg capsules. The Cmax values of 257±148 ng/ml and 580±203 ng/ml were reported. Lefebvre *et al* (115) observed mean maximum cetirizine concentrations of 337 ng/ml and 362 ng/ml in 10 young healthy subjects and in 10 elderly volunteers respectively after the oral administration of 10 mg cetirizine. All of these results were significantly lower than the results obtained after the same dose in the present study in children. The differences could be caused by the fact that the body weight of children was less than that of adults, therefore, the mg/kg dose was actually higher in children after the administration of the same dose of cetirizine as that in adults (35,47,115).

The elimination half-life values of cetirizine in children were 7.1±1.6 hours after the 5 mg dose and 6.9±1.6 hours after the 10 mg dose. They were not significantly different from each other, and they were not different from the reported values of about 7 hours in adults, but were lower than the values of 11.8 hours in the elderly (47,115) and about 20 hours in patients with mild and moderate renal insufficiency (47). Since cetirizine is eliminated mainly by excretion of unchanged drug in urine, it was expected that the reduced renal function in the elderly and in patients with renal insufficiency would prolong the elimination of cetirizine.

The values of the systemic clearance of cetirizine after 5 mg and 10 mg doses of cetirizine of 1.04±0.20 ml/min/kg and 1.10±0.13 ml/min/kg, were not statistically different from each other. These values could not be compared to most results in the literature (35,47) because different units were used. Lefebvre *et al* (115) reported an apparent oral clearance of 0.64 ml/min/kg in young adults, and 0.54 ml/min/kg in the elderly, both of which were lower than what was observed in the present study.

The apparent volumes of distribution, 0.65±0.23 l/kg and 0.65±0.13 l/kg respectively, were not different after the 5 mg and 10 mg doses. They were larger than the values of 0.39±0.05 l/kg in adults and 0.38±0.06 l/kg in the elderly (47).

The mean $AUC_{0->\infty}$ of 6376±1874 ng·hr/ml after the 10 mg dose was twice as large as that of 2871±768 ng·hr/ml after the 5 mg dose. This result, together with results presented above, suggested that cetirizine displays linear kinetics after oral administration. There appeared to be no saturation of the absorption and elimination processes for cetirizine at the dose range tested in the present study.

The renal clearance was calculated by assuming that the renal clearance of cetirizine was constant. The renal clearance after the 5 mg dose was 0.54±0.29 ml/min/kg, and it was 0.40±0.08 ml/min/kg after the 10 mg dose. They were not significantly different from each other ($p<0.05$). The fraction of cetirizine excreted unchanged in the urine could be calculated by using fe= renal clearance / systemic clearance. However, the extent of cetirizine absorbed after oral administration was not known, and the systemic clearance was calculated in the present study by assuming that cetirizine was completely absorbed after oral administration, which might lead to the overestimation of the fraction excreted unchanged. Therefore, no attempts were made to calculate the fraction of cetirizine excreted unchanged after oral administrations of 5 mg and 10 mg cetirizine.

The steady-state cetirizine concentrations after the 10 mg dose were about twice as high as those after the 5 mg dose, which was to be expected. There was a large fluctuation in the steady-state concentration after the 10 mg dose, which might be caused by reduced uniformity in the time of dose administration in the multiple dose study. Since serum samples were collected 12 hours after cetirizine administration, any deviation in the dose administration time would yield errors in the time post dose at which serum cetirizine concentration was determined. This was more of problem than it would have been if serum cetirizine concentrations had been determined at $C_{min}$ just before the next dose.

4.1.5.2 Pharmacodynamics of cetirizine in children

The mean wheal areas after epicutaneous challenge of histamine phosphate solution, 1 mg/ml, were significantly suppressed ($p<0.01$) from

1 to 24 hours after a single dose of cetirizine of 5 mg and 10 mg, compared with the predose values. There were no significant differences in wheal suppression induced by doses of 5 mg and 10 mg cetirizine, except at the 0.5 hour after drug administration, when wheals were 51.6%±25.3% suppressed after the 5 mg dose, and 93.2%±12.3% suppressed after the 10 mg dose (Tables 24 and 25).

The mean flare areas after epicutaneous challenge of histamine phosphate solution, 1 mg/ml, were significantly suppressed ($p<0.01$) from 1 to 24 hours after a single dose of cetirizine of 5 mg and 10 mg, compared with the predose values. There were no differences in flare suppression induced by doses of 5 mg and 10 mg cetirizine.

Cetirizine is very effective in suppressing both histamine-induced wheals and flares. This fact might explain why no differences in wheal and flare suppressions were observed after two different doses. In addition, a large intersubject variability made it very difficult to observe any significant increase in efficacy.

The pharmacodynamic data could not be fitted into the modified $E_{max}$ model, because cetirizine is a very potent $H_1$-receptor antagonist. Wheals and flares were still significantly suppressed twenty-four hours after a single oral dose of 5 mg cetirizine and insufficient data were available in the phase when the extent of wheal and flare suppression was reduced to fully describe the effect-concentration relationship in the present study. However, doses less than 5 mg have not been considered therapeutically or approved for use at this time for administration to patients with allergic rhinitis.

At steady-state during multiple dosing, both wheals and flares were about 90% suppressed 12 hours after drug administration. There were no differences between the 5 mg and 10 mg doses of cetirizine.

Cetirizine has been shown to very effective in suppressing the histamine-induced cutaneous responses (35,44,49,108). In the present study, histamine-induced wheals were about 60% suppressed and flares were about 90% suppressed 24 hours after a single oral dose of 5 mg or 10 mg of cetirizine. In the steady-state, wheals and flares were about 90% suppressed 12 hours after drug administration. It was therefore concluded that cetirizine administered 5 mg once every day could provide effective suppression of the histamine-induced wheals and flares.

## 4.2 Pharmacokinetic and pharmacodynamic studies of hydroxyzine and cetirizine in rabbits

### 4.2.1 HPLC assays

The HPLC assay for measuring hydroxyzine concentrations in rabbits was slightly modified from that used for human sera in order to get a better separation of hydroxyzine and the internal standard and to avoid interfering peaks. The flow rate in hydroxyzine analysis was set at 0.8 ml/min, while other conditions remained the same. The retention times of hydroxyzine and the internal standard were 11.0 and 5.0 minutes respectively. The assay for measuring cetirizine concentrations was the same as that used for measuring cetirizine in human sera.

Within the concentration range of 2.0 ng/ml to 509.8 ng/ml for hydroxyzine, and 5.3 ng/ml to 527.5 ng/ml for cetirizine, the calibration

curves were linear. Coefficients of variation at all concentrations were less than 15% over a 12 month period.

4.2.2 Bioavailability study of hydroxyzine in rabbits

It was decided that the bioavailability of orally administered hydroxyzine should be investigated because there were no bioavailability data available. The bioavailability of orally administered hydroxyzine in humans was assumed to be 100% in all previous studies (33,34,35) and in the present study in the elderly and in patients with primary biliary cirrhosis.

Only three dosage forms of hydroxyzine, the intramuscular injection, oral syrup and capsule are commercially available as Atarax® . It was found in preliminary studies that a large volume of syrup had to be administered to rabbits in order to achieve concentrations sufficiently high to be detected. Therefore, a solution diluted from the I.M. injection was used as the oral liquid dosage form, and the same injection was given intramuscularly as the standard in the bioavailability study. No intravenous studies were carried out because there is no intravenous dosage form commercially available. When hydroxyzine pure substance was made available, solutions for i.v. administration were prepared in our laboratory. Later studies using i.v. administration in rabbits yielded similar $AUC_{0->\infty}$ values as those obtained in these studies using i.m. administration.

Hydroxyzine was rapidly absorbed after both intramuscular injection and oral absorption, with maximum serum concentrations appearing from 0.25 to 1 hour after I.M. injection, and from 0.25 to 0.5 hour after oral administration.

There was a large intersubject variability among three rabbits. Rabbit 3 gave the lowest concentration after both I.M. and oral administration. The mean maximum serum concentration after intramuscular injection was 150.9±88.7 ng/ml, while it was 489.5±291.1 ng/ml in case of oral administration (Table 38).

The elimination half-lives of hydroxyzine after intramuscular injection and oral administration were from 1.12 to 2.37 hour, not different from those calculated from intravenous injections in later studies ( see 4.2.3).

The mean $AUC_{0->\infty}$ after an intramuscular injection of 5 mg hydroxyzine was 400 ng·hr/ml, while the mean $AUC_{0->\infty}$ after an intravenous injection of 10 mg hydroxyzine, obtained from the hydroxyzine-cimetidine interaction study, was about 870 ng·hr/ml indicating that hydroxyzine was totally absorbed after intramuscular injections, and that the intramuscular injection was bioavailably equivalent to the intravenous injection. However, the oral administration of 100 mg hydroxyzine only yielded a mean $AUC_{0->\infty}$ of 870 ng·hr/ml, resulting in an absolute bioavailability of 11.3±3.5 %. If it is assumed that there is no loss of hydroxyzine from the gastrointestinal tract after oral administration, then the hepatic extraction ratio of hydroxyzine is about 0.9, which means that orally administered hydroxyzine will be subjected to extensive first-pass metabolism.

It was not possible to compare results obtained in this animal study to hydroxyzine studies reported in humans (32,33,34,35,92) as no bioavailability data was reported because no intravenous dosage form is available for humans. Therefore, it was not possible to determine whether the results obtained in rabbits could be extrapolated to humans because of

the differences in the gastrointestinal anatomy between rabbits and humans. This study did confirm that hydroxyzine was rapidly absorbed after oral administration to rabbits as indicated by a mean $T_{max}$ of 0.42±0.14 hour. In light of such a low bioavailability of orally administered hydroxyzine in rabbits, it could be assumed that the bioavailability of orally administered hydroxyzine in humans was also probably much less than 100%, possibly due to a large first-pass effect. Future bioavailability studies in humans are needed to clear up this problem. Since it was demonstrated in this study that the intramuscular dose has bioavailablity of about 100% when compared to the intravenous dose, intramuscular dose administration might be used in humans to determine the true bioavailability of orally administered hydroxyzine. However, the intramuscular injection of hydroxyzine is not recommended except under conditions where strict informed consent has been obtained and under clinical supervision because of adverse effects such as marked local discomfort and sterile abcesses at the site of intramuscular injection.

### 4.2.3 Pharmacokinetics and pharmacodynamics of hydroxyzine in rabbits: the effect of cimetidine

#### 4.2.3.1 Pharmacokinetics of hydroxyzine in rabbits: the effect of cimetidine

Routine biochemical tests were performed in the Health Sciences Centre Clinical Chemistry Department to measure the serum concentrations of SGOT, SGPT, LDH, and alkaline phosphatase in rabbits before and after the administration of cimetidine. These results were used to determine if the effect of cimetidine on hepatic function could be evaluated by these

enzymes, and to determine if the biochemical parameters could be correlated with hydroxyzine pharmacokinetic parameters. The values of LDH and alkaline phosphatase were elevated following the administration of cimetidine, but, these values were not significantly different from control values due to a large intersubject variability. The values of SGOT and SGPT remained virtually constant before, with the coadministration of cimetidine and two weeks after cimetidine was discontinued. Judging from these results, it is possible that acute cimetidine administration causes little measurable liver damage. No correlation between serum enzyme concentrations and hydroxyzine pharmacokinetic parameters were observed.

The serum hydroxyzine concentration versus time curve after an intravenous injection of 10 mg hydroxyzine could be best described by a biexponential equation indicating a distribution phase and an elimination phase, while the resulting serum cetirizine concentration versus time curve could be best described by a biexponential or triexponential equation. Theoretically, the time course of cetirizine after an intravenous injection of hydroxyzine needs more than three exponential terms to fully describe (50). In this study, insufficient blood samples were probably collected during the formation and distribution of cetirizine which resulted in a lack of discrimination of individual kinetic processes of cetirizine. The significance of each exponential term was not clear. In theory, the last exponential term should reflect the elimination phase of hydroxyzine not of cetirizine (50,93). This might not be detected in the current study because the elimination half-lives of hydroxyzine and cetirizine were not significantly different in rabbits. Therefore, the slope calculated from the terminal linear portion of the cetirizine concentration versus time curve

was probably a hybrid constant that cannot be related to either hydroxyzine or cetirizine elimination.

The elimination half-life of hydroxyzine after an intravenous bolus injection of 10 mg hydroxyzine was 1.27±0.39 hour. When cimetidine was given at the same time, the value was increased to 4.27±1.71 hours, while two weeks after the discontinuation of cimetidine, the value returned to 1.30±0.27 hours. The elimination half-lives of hydroxyzine before the coadministration of cimetidine, 1.27±0.39 hour, and two weeks after the discontinuation of cimetidine, 1.30±0.27 hour, were not significantly different from each other, but they were significantly ($p<0.05$) shorter than the value of 4.27±1.71 hours, when cimetidine was given concomitantly (Tables 49,50,51).

The apparent volumes of distribution of hydroxyzine after an intravenous bolus injection of 10 mg hydroxyzine was 6.7±2.6 l/kg. When cimetidine was given concomitantly, the value was increased to 7.5±3.8 l/kg, while two weeks after the discontinuation of cimetidine, the value returned to 4.9±0.6 l/kg. These values were not significantly different from each other. However, the systemic clearance of hydroxyzine, 52.3±23.7 ml/min/kg, was significantly ($p<0.05$) reduced to 20.2±5.8 when cimetidine was given concomitantly with hydroxyzine, indicating that cimetidine inhibits the elimination of hydroxyzine. Two weeks after the discontinuation of cimetidine, the systemic clearance, 45.1±11.4 ml/min/kg, was not significantly different from the pretreatment value, 52.3±23.7 ml/min/kg, which suggested that the effect of cimetidine on hydroxyzine metabolism was reversible. In a preliminary study, indocyanine green was given intravenously before and after cimetidine was administered 100 mg/kg b.i.d. for one week. There was no statistically significant difference

in indocyanine green clearance with and without the treatment of cimetidine, suggesting that cimetidine causes little measureable change in the hepatic blood flow in rabbits. From the above results, it was concluded that the prolonged hydroxyzine elimination half-life was due to the significant reduction of its systemic clearance when cimetidine was given at the same time, since a drug's elimination half-life is directly proportional to its volume of distribution and inversely proportional to its systemic clearance.

The hydroxyzine $AUC_{0->\infty}$ after an intravenous bolus injection of 10 mg hydroxyzine was 874±317 ng·hr/ml. When cimetidine was given at the same time, the value was significantly ($p<0.05$) increased to 2133±591 ng·hr/ml, while two weeks after the discontinuation of cimetidine, the value returned to 905±277 ng·hr/ml, not significantly different from pre-cimetidine values.

The cetirizine $AUC_{0->\infty}$ after an intravenous bolus injection of 10 mg hydroxyzine was 724±147 ng·hr/ml. When cimetidine was given at the same time, the value was significantly ($p<0.05$) increased to 2602±822 ng·hr/ml, while two weeks after the discontinuation of cimetidine, the value returned to 538±117 ng·hr/ml. Cetirizine Cmax of 648.2±275.6 ng/ml was also significantly ($p<0.05$) increased when cimetidine was given concomitantly, compared with pre- and post-treatment values of 243.8±100.5 ng/ml and 184.7±68.8 ng/ml respectively. These parameters all returned to pre-treatment values after the discontinuation of cimetidine. MRT values were increased when cimetidine was given at the same time, 4.26±2.26 hour, but not significantly different from pre-treatment, 2.68±0.98 hour, and after treatment, 2.64±0.73 hour, values probably due to large intersubject variability (Tables 52,53, and 54).

Cimetidine can inhibit drug elimination through three mechanisms: the inhibition of cytochrome P-450, the reduction of liver blood flow and the inhibition of renal excretion (72,73,74,75,76,77). The results obtained in the present study indicated that cimetidine could inhibit the elimination of hydroxyzine, possibly by inhibiting the hepatic metabolism. The effect of cimetidine on hepatic metabolism was reversible in this acute study, and it was unlikely that short-term administration of cimetidine caused any permanent liver damage since all pharmacokinetic parameters returned to pretreatment values two weeks after the discontinuation of cimetidine. At the same time, cimetidine also inhibited the elimination of cetirizine since cetirizine $AUC_{0->\infty}$ was increased when cimetidine was coadministered, possibly by competitively competing for the renal cationic transport system and by inhibiting cetirizine hepatic metabolism.

4.2.3.2 Comparison of the modified $E_{max}$ model and the effect-compartment model

Various mathematical methods have been proposed to relate drug effects to serum or tissue concentrations (98,99,100,101). The $E_{max}$ model is one of the most widely used pharmacodynamic models. This model is useful in situations where effect increases as drug concentration increases and it also predicts that there will be no effect when drug concentration is zero. The $E_{max}$ model is also consistent with what is often observed clinically that large increases in drug concentration are required to elicit small increases in effect as the asymptote is approached.

In the present study, the presence of pharmacologically active cetirizine after an intravenous injection of hydroxyzine makes it inappropriate to use the $E_{max}$ model unmodified. Since hydroxyzine and

cetirizine are $H_1$-receptor antagonists, it is assumed that they compete for the same receptors. It is further assumed that the maximum effects produced by hydroxyzine and cetirizine are the same, and $EC_{50}^{C}$ is four times $EC_{50}^{H}$. An equation similar to that of the $E_{max}$ model was derivated (see Appendix I for derivation), and the new model is named the modified $E_{max}$ model.

However, the $E_{max}$ model and the modified $E_{max}$ model assume that the plasma, central compartment, or some other pharmacokinetically identifible compartment is associated with the pharmacologic effect. In the present study, a time lag between the maximum pharmacologic effect and the maximum serum drug concentration was observed when mean percent suppressions of histamine-induced wheals were plotted against the mean serum hydroxyzine concentrations. Therefore, only drug concentrations in the elimination phase can be used in the pharmacodynamic modeling process if the modified $E_{max}$ model is employed.

By hypothesizing an effect compartment (120,121,122,123, 128), the effect-compartment model can explain the time lag between the maximum pharmacologic effect and the maximum serum drug concentration. In the present study, the effect compartment was assumed to be the skin.

The application of the effect-compartment model was carried out in two steps. First, the effect-concentration data from all three hydroxyzine studies in rabbits were pooled together in an attempt to obtain a full description of the effect-concentration relationship curve, and to get good estimates of $E_{max}$ and $EC_{50}^{H}$ by assuming that every rabbit exhibits similar $E_{max}$ and $EC_{50}^{H}$. Theoretically, the effect-concentration data from cetirizine studies in rabbits could also be included to increase the statistical reliability of estimates of $E_{max}$ and $EC_{50}^{H}$ . However, as shown in section 4.2.4.2,

most of the effect data points obtained in cetirizine studies are located on the part of the effect-concentration curve close to $E_{max}$. Therefore, inclusion of those data points will not help to get a better estimate of $EC_{50}^{H}$.

After the estimates of $E_{max}$ and $EC_{50}^{H}$ were obtained, two methods of data analysis were used. In Method A, mean plasma concentrations and mean effect data from each study were fitted independently using $E_{max}$ and $EC_{50}^{H}$ obtained from the previous step. Mean data were used because of large variability in plasma hydroxyzine and cetirizine concentrations, and in effects produced by hydroxyzine and cetirizine in each rabbit. In Method B, data from each individual rabbit were fitted independently to get estimates of Keo and Keo' for each individual rabbit, again using $E_{max}$ and $EC_{50}^{H}$ from the previous step.

An examination of the results obtained revealed that neither of the two data analysis methods could provide a good description of the effect-concentration relationship, as indicated by large asymptotic standard errors associated with estimated Keo and Keo', and the fact that the 95% confidence intervals of some estimates embrace the zero point. It is thought that this result was caused by the fact that hydroxyzine was so potent that most effect data obtained were larger than 50% $E_{max}$, and a full description of the effect-concentration relationship was not obtained in the present study. Ideally, one could give a smaller dose of hydroxyzine to elucidate a better description of the effect-concentration curve, especially when $C_H < EC_{50}^{H}$. This idea was raised and considered during the present study. However, the main purpose of the present study was to demonstrate the pharmacokinetic interaction between hydroxyzine and cimetidine. It would not be possible to monitor hydroxyzine plasma concentrations up to to 12 hours as it was done in the present study if a smaller dose of

given, thereby making it difficult to show the pharmacokinetic interaction between hydroxyzine and cimetidine. Another possible solution to this problem would be to give a $H_1$-receptor antagonist less potent than hydroxyzine is, such as chlorpheniramine.

Attempts were also made to normalize the plasma hydroxyzine and cetirizine concentrations to get unit dose responses first, then to fit the effect-concentration data to the effect-compartment model. However, results obtained using this method, which are not presented in this thesis, were not any better than those obtained from methods reported here.

Based on the discussion above, it was decided that only estimates obtained using the modified $E_{max}$ model would be discussed and compared among different studies.

4.2.3.3 Pharmacodynamics of hydroxyzine in rabbits: the effect of cimetidine

Intradermal injection of histamine experimentally induces the "triple response" at the site of injection (1). This objective, well-standardized biologic assay (21) provides an unique tool in assessing the effect of $H_1$-receptor antagonists. Cheng and Woodward (103,102) first adapted this method for use in animals and studied the efficacy of terfenadine using Evans-blue as the marker for wheals. Since intradermal injection of histamine induces permeability changes in post-capillary venules, resulting in the outward passage of plasma protein, fluid and dyes into the extracellular spaces, the presence of Evans-blue at the wheal site will clearly distinguish wheal sites from surrounding areas. De Vos *et al* (44) used the same method to study the efficacy of cetirizine in four animal species: rats, mice, guinea pigs and dogs. In the present study, rabbits were

used to suit the purpose of studying both pharmacokinetics and pharmacodynamics of hydroxyzine. The dose of Evans-blue injected, 10 mg, was reduced due to the requirement of long sampling times. If a large dose of Evans-blue was injected at the beginning of the study, the skin color of rabbit's depilated back would turn blue in a few hours, thus making it impossible to measure skin response to histamine after that time point. It is not possible to observe flares in rabbits due to the small differences between rabbit's natural skin color and that of the flares.

After a single intravenous injection of 10 mg hydroxyzine, wheals were significantly ($p<0.01$) suppressed for up to 12 hours compared to predose values, at which time the study terminated. The maximum suppression occurred from 0.25 to 6.0 hours, when the wheals were 69.7% to 89.7% suppressed (Tables 45,46, and 47). Serum hydroxyzine and cetirizine concentrations were no longer detectable after 12 hours.

When cimetidine was given at the same time, significant suppression ($p<0.01$) of wheals persisted for 24 hours compared to predose values. Maximum suppression, compared to all other wheal areas measured during the study ($p<0.05$), occurred from 0.25 to 8 hours, when wheals were 77.4% to 98.8% suppressed. The suppression of wheals with the coadministration of cimetidine was generally greater than the suppression when hydroxyzine was given alone, but not significant, except at 0.5 hour after drug administration. There were two reasons for being unable to detect any significant increase in wheal suppression when cimetidine was given at the same time with hydroxyzine. First, a single dose of hydroxyzine provided considerable protection against histamine. The maximum suppression of histamine-induced wheals was about 90% after a single dose of 10 mg hydroxyzine. There was little room left for

improvement. Secondly, a large intersubject variation in drug response was observed.

The effect-concentration relationship could also be described by the modified $E_{max}$ model. Problems encountered in the model fitting process of pharmacodynamic data in humans were also encountered here, and the same methods as described in section 4.1.2.2 were used to solve these problems. The calculated maximum wheal suppression after an intravenous dose of 10 mg hydroxyzine was 92.0%, and a hydroxyzine concentration of 8.9 ng/ml was needed to achieve half of the maximum effect. The calculated maximum effect was 99.2% when cimetidine was given at the same time, and a hydroxyzine concentration of 9.3 ng/ml was needed to achieve half of the maximum effect.

Two weeks after the discontinuation of cimetidine, the efficacy of hydroxyzine returned to pretreatment values. The calculated maximum effect was 96.1% and $EC_{50}^{H}$ was 9.2 ng/ml.

There have been some reports (78,79,80,81,84,86,104,106) suggesting an enhanced efficacy of the combination of an $H_1$-receptor antagonist and an $H_2$-receptor antagonist, usually cimetidine, on allergen responses and histamine cutaneous response. The identification of $H_2$-receptors in skin blood vessels (105) in addition to $H_1$-receptors further added support to the suggestion that $H_2$-receptors were also involved in allergic responses. A combination of $H_1$ and $H_2$-receptor antagonists may be beneficial in dermatological conditions such as chronic idiopathic urticaria, where histamine was implicated, but which responded poorly to a $H_1$-receptor antagonist alone. However, Cheng *et al* (103) reported that the participation of histamine $H_2$-receptor in histamine-induced skin wheals was only of minor importance.

Cimetidine has been documented in many studies ( 73,74,75,76,77) to inhibit drug elimination. It was hypothesized that the coadministration of cimetidine might inhibit the elimination of $H_1$-receptor antagonists, causing the accumulation of the drug in the body, thereby resulting in an enhanced efficacy. Unfortunately in previous studies (78,79,80,81,84,86,104,106), most of the attention was given to the enhanced therapeutic efficacy. Only one report (87) in the literature examined the interaction of $H_1$-receptor antagonists and cimetidine from the pharmacokinetic perspective. Salo *et al* (87) showed that serum hydroxyzine concentrations were increased when cimetidine was coadministered. In that study (87), seven subjects hospitalized for chronic urticaria were first given 25 mg hydroxyzine three times daily. Blood samples were taken in the morning, at 2 pm and 8 pm before hydroxyzine was administered on the second day. On the third and fourth days, 200 mg cimetidine was administered together with hydroxyzine. Blood samples were drawn on the fourth day as on day 2. It was shown that the mean concentrations obtained during combination treatment of hydroxyzine and cimetidine were significantly higher than those obtained with hydroxyzine alone.

It was clear, however, that the investigators failed to explain why there was a difference in serum hydroxyzine concentrations on the second day between the control and the experimental groups. In additon, since hydroxyzine and cimetidine were given orally in this study, there was a possiblity that cimetidine inhibited gastric acid secretion and increased gastric pH. Therefore, the fraction of unionized hydroxyzine in the stomach would be increased and as a consequence the absorption of hydroxyzine might be improved when cimetidine was given at the same

time with hydroxyzine. Therefore, results from that study (87) were not overwhelmingly convincing.

To clarify this problem, the present study was designed to show:

1) whether cimetidine inhibited the elimination of one of the most widely prescribed antihistamines, hydroxyzine. As shown in the previous section, when cimetidine was given at the same time with hydroxyzine, the systemic clearance of hydroxyzine was significantly reduced, its half-life was significantly prolonged, and its $AUC_{0->\infty}$ was significantly increased, while the $AUC_{0->\infty}$ and Cmax for cetirizine were also significantly increased. All these results confirmed that the elimination of hydroxyzine was inhibited by cimetidine.

2) whether cimetidine alone had any effect on the intradermally injected histamine-induced wheals. If, as assumed, the $H_2$-receptors were also involved in histamine cutaneous responses, then areas of wheals induced by intradermally injected histamine should be reduced in the presence of cimetidine alone. An examination of our results failed to support this assumption. The wheals at baseline induced by intradermally injected histamine in 10 control rabbits produced an average area of $0.676\pm0.120$ $cm^2$, while in 10 rabbits treated with cimetidine 100 mg/kg b.i.d for one week, the mean wheal area was $0.700\pm0.150$ $cm^2$. The fact that $E_{max}$ and $EC_{50}$ values were almost the same among the three treatment groups further indicated that cimetidine was not measurably involved in suppressing the histamine cutaneous response.

3) whether the combination of cimetidine and hydroxyzine provided a greater protection against intradermally injected histamine than hydroxyzine alone. It was found that the coadministration of cimetidine did give a greater, but not significant, protection against intradermally injected

histamine. In light of the above results, it was concluded that cimetidine alone did not provide any measurable protection against histamine in this model, but the combination of cimetidine and hydroxyzine did provide a greater protection against histamine. However, the increased protection was more likely due to the fact that cimetidine inhibited the elimination of hydroxyzine and cetirizine, increasing their concentrations, thereby, improving efficacy. Whether the same reasoning could be applied to other antihistamines is not clear and should be further investigated.

### 4.2.4 Pharmacokinetics and pharmacodynamics of cetirizine in rabbits: the effect of cimetidine

#### 4.2.4.1 Pharmacokinetics of cetirizine in rabbits: the effect of cimetidine

A new set of five rabbits were used for this study instead of reusing the five rabbits in which the hydroxyzine-cimetidine interaction had been studied. This was done to ensure that the reduction of hepatic function by cimetidine would be studied in rabbits which had not previously been exposed to cimetidine. This was considered to be the optimal experimental design based on information about cimetidine interaction in the literature (73,74,75,76,77).

Blood samples were withdrawn at the beginning of each study for enzyme assays. Although LDH, SGPT, and SGOT levels were increased when cimetidine was given at the same time, none of these parameters were significantly larger than control values due to a large intersubject variation.

Attempts were made to correlate biochemical parameters to various cetirizine pharmacokinetic parameters without any success.

The serum cetirizine concentration versus time curves could be best described by a biexponential equation, corresponding to a distribution phase and an elimination phase. The elimination half-life of cetirizine after an intravenous bolus injection of 10 mg cetirizine was 1.17±0.16 hour, not different from the company literature values (38). When cimetidine was given at the same time, the mean elimination half-life of cetirizine was significantly ($p<0.05$) increased from 1.17±0.16 hour to 4.10±1.92 hour, but was reduced to 1.44±0.30 hour two weeks after the discontinuation of cimetidine (Tables 64,65, and 66).

The apparent volumes of distribution were not different following the three treatments. The mean systemic clearance of 7.4±1.3 ml/min/kg was significantly reduced to 5.2±0.2 ml/min/kg when cimetidine was given at the same time, but returned to 7.0±0.7 ml/min/kg two weeks after the discontinuation of cimetidine. Considering that the elimination half-life is directly proportional to the apparent volume of distribution and inversely proportional to the systemic clearance, it could be concluded that the increase of the elimination half-life of cetirizine was caused by the reduction of the systemic clearance.

There was a slight increase in MRT, 1.56±0.25 hour, when cimetidine was given at the same time, but it was not significantly different from pre-cimetidine, 1.20±0.26 hour, and post-cimetidine values, 1.23±0.27 hours.

When cimetidine was given at the same time, cetirizine $AUC_{0->\infty}$, 8259±1506 ng·hr/ml, was significantly ($p<0.05$) increased from the pre-cimetidine value of 6192±887 ng·hr/ml. Two weeks after the

discontinuation of cimetidine, it was 5906±1005 ng·hr/ml, not significantly different from the pre-cimetidine values. All of the above results indicated that cimetidine did affect cetirizine elimination, but that the effect was reversible.

A large part, 50-80%, of an administered dose of cetirizine was excreted unchanged in the urine in rabbits (38). Therefore, the prolonged cetirizine elimination could be caused by the fact that cimetidine competitively competes with cetirizine for active renal tubular secretion via the cationic transport system (72,73,74). Inhibition of the fraction of the cetirizine dose that is metabolized by cimetidine might also contribute to the significant change in pharmacokinetic parameters observed.

The effect of cimetidine on cetirizine elimination would also account for the increase of cetirizine $AUC_{0->\infty}$ when cimetidine was given at the same time with hydroxyzine. Since the metabolism of hydroxyzine was inhibited, it was expected that the amount of cetirizine formed would be reduced resulting in a decreased cetirizine $AUC_{0->\infty}$. However, an increase in cetirizine $AUC_{0->\infty}$ was observed probably due to the inhibition of cetirizine elimination by competition of cimetidine for cetirizine renal tubular secretion.

More information about the effect of cimetidine on the elimination of hydroxyzine and cetirizine could have been obtained by collecting urine during the present study and determining the amount of cetirizine excreted in the urine under control and test conditions. However, this approach was hindered by two factors. First of all, the rabbits often urinated while blood sampling and histamine challenge were carried out, so it would not be possible to get an accurate estimate of the total amount of urine collected. Secondly, there was very little urine output in any study, which

meant that the rabbits would have had to be confined in the metabolic cages for a long period of time. This may have been caused by the anticholinergic effect of the $H_1$-receptor antagonists. Therefore, urine collection was not carried out.

4.2.4.2 Pharmacodynamics of cetirizine

After an intravenous bolus injection of 10 mg cetirizine, wheals induced by intradermally injected histamine were significantly suppressed ($p<0.01$) for up to 12 hours compared to baseline. Maximum suppression occurred from 0.083 to 8 hours when suppression ranged from 80.8% to 98.9%. When cimetidine was given at the same time, wheals were significantly suppressed ($p<0.01$) up to 24 hours compared to baseline. Maximum suppression occurred from 0.083 to 12 hours, when the suppression was from 75.5% to 98.4%. Two weeks after the discontinuation of cimetidine, wheals were significantly ($p<0.01$) suppressed for up to 12 hours, maximum suppression occurred from 0.083 to 8 hours, when the suppression was from 77.6% to 98.1%. (Tables 60,61, and 62).

There were no significant differences of cetirizine wheal suppression among cimetidine pre-treatment, cimetidine treated and after cimetidine treatment rabbits, possibly due to two reasons: 1) cetirizine alone is very effective in suppressing wheal formation. A single dose of 10 mg cetirizine gave a maximum suppression of 98.9%. Therefore, there is no room left for improvement; 2) a large intersubject variation was observed.

The wheal suppression data could not be fitted into the modified $E_{max}$ model or any other model due to the fact that cetirizine was very effective in inhibiting histamine cutaneous response. Wheals were still

significantly suppressed 12 hours after a single intravenous injection of 10 mg cetirizine. There were no data available in the phase where decreased wheal suppression occurred so the effect-concentration relationship could not be defined. Also, serum cetirizine concentrations were not detectable after 12 hours.

From the standpoint of understanding the pharmacodynamics of cetirizine, a smaller dose of cetirizine should be given to get a better description of the effect-concentration relationship. However, the main purpose of this study was to demonstrate the pharmacokinetic interaction between cetirizine and cimetidine. A reduced cetirizine dose will result in lower plasma cetirizine concentrations, which will make it more difficult to monitor plasma cetirizine concentrations to 12 hours as in this study. Therefore, a study with a reduced dose of cetirizine was not carried out.

4.2.5 Pharmacokinetic studies of hydroxyzine in rabbits: the effect of hepatic dysfunction

After an intraperitoneal injection of carbon tetrachloride ($CCl_4$, 0.5ml/kg) to rabbits, SGOT, SGPT, and LDH levels were all increased, indicating that a large number of cellular structures in the liver were destroyed. However, only SGOT and SGPT levels were significantly ($p<0.05$) higher than those in control animals. No changes in any biochemical parameters could be correlated to changes in hydroxyzine or cetirizine pharmacokinetic parameters.

The survival rate of rabbits after the intraperitoneal injection of carbon tetrachloride ($CCl_4$, 0.5 ml/kg) was about 50%. All rabbits who survived became listless and showed loss of appetite. Therefore, only pharmacokinetic evaluations were performed on these rabbits.

The serum hydroxyzine concentration versus time curves after an intravenous bolus injection of 10 mg hydroxyzine could be best described by an open two-compartment model, while after the treatment of carbon tetrachloride ($CCl_4$), serum hydroxyzine concentration versus time curves can be best described by a triexponential equation, the significance of each exponential term, except the terminal elimination phase, was not clear.

The half-life of hydroxyzine in untreated rabbits was 1.42±0.70 hours, which was not different from the values obtained in the previous hydroxyzine -cimetidine interaction study. The half-life of hydroxyzine in $CCl_4$-treated rabbits was 2.58±0.75 hours, which was not significantly larger than that in the untreated rabbits (Tables 73 and 74).

The systemic clearance of hydroxyzine in untreated rabbits was 47.8±15.2 ml/min/kg, which was not different from that in the previous study. In $CCl_4$-treated rabbits, the systemic clearance was significantly ($p<0.05$) reduced to 26.9 ml/min/kg. The apparent volumes of distribution in untreated and $CCl_4$-treated rabbits, 5.4±2.3 vs 4.7±2.6 l/kg respectively, were not different from each other, and both values were not different from results obtained in the control rabbits in the previous study.

The mean area under the serum hydroxyzine concentration versus time curve in untreated rabbits was 839.8±324.8 ng·hr/ml, while it increased to 1392.7±274.3 ng·hr/ml in $CCl_4$ -treated rabbits. These values were significantly ($p<0.05$) different from each other.

The serum cetirizine concentration versus time curves after a bolus intravenous injection of 10 mg hydroxyzine in controlled rabbits could be best described by a biexponential equation, while in $CCl_4$-treated rabbits, the serum cetirizine concentration versus time curves could be best described by a triexponential equation. The mean maximum cetirizine

concentration in control rabbits was 198.7±46.4 ng/ml. It was not different from that in $CCl_4$-treated rabbits, 149.1±27.1 ng/ml. There was no difference in $T_{max}$ of cetirizine between the control and $CCl_4$-treated rabbits.

The cetirizine $AUC_{0->\infty}$ in $CCl_4$-treated rabbits, 549.4±92.8 ng·hr/ml, was slightly lower than that in control rabbits, 662.5±175.7 ng·hr/ml. Considering the fact that hydroxyzine $AUC_{0->\infty}$ was significantly increased in $CCl_4$-treated rabbits, it was concluded that $CCl_4$ induced hepatic dysfunction resulting in the inhibition of hydroxyzine metabolism, yielding less cetirizine than normal. An examination of the ratio of cetirizine $AUC_{0->\infty}$ / hydroxyzine $AUC_{0->\infty}$ showed that the average ratio was 0.8 in control rabbits, while it was reduced to 0.4 in $CCl_4$-treated rabbits.

4.2.6 Pharmacokinetic studies of cetirizine in rabbits: the effect of hepatic dysfunction

After an intraperitoneal injection of carbon tetrachloride ($CCl_4$, 0.5 ml/kg), SGOT, SGPT, LDH and alkaline phosphatase levels were increased, indicating that a large number of cellular structures were destroyed. However, only SGOT and SGPT values were significantly increased ($p<0.05$).

The serum cetirizine concentration versus time curves after an intravenous bolus injection of 10 mg cetirizine in control and $CCl_4$-treated rabbits could be best described by an open two-compartment model, corresponding to a distribution phase and an elimination phase.

Pharmacokinetic parameters of cetirizine in control rabbits including $t_{1/2}$, $AUC_{0->\infty}$, Cls and Vd were not different from those obtained in the

previous cetirizine-cimetidine study and in the literature (38). In $CCl_4$-treated rabbits, the systemic clearance was significantly ($p<0.05$) reduced from 7.2±1.6 ml/min/kg to 3.9±1.0 ml/min/kg, the half-life of cetirizine was significantly ($p<0.05$) prolonged from 1.57±0.45 hour to 3.22±0.69 hour, and cetirizine $AUC_{0->\infty}$ was also significantly ($p<0.05$) increased from 6007±1019 ng·hr/ml to 11572±4030 ng·hr/ml.

The above results indicated that hepatic dysfunction would affect the elimination of cetirizine. If the fraction of cetirizine eliminated through hepatic metabolism is 50%, then a two-fold increase in the elimination half-life will be expected if the hepatic function is totally destroyed by $CCl_4$ and the renal function remains unaffected. Unfortunately, it was not possible to collect urine in this study because the rabbit drank very little water and produced minimal urine after the induction of hepatic dysfunction. No biochemical parameters could be correlated with changes in pharmacokinetic parameters.

As much as 50-80% of a dose of cetirizine is reported to be eliminated by excretion as unchanged drug in the urine, while the rest is metabolized to unidentified metabolites. In the hepatic dysfunction rabbit model, the hepatic function of rabbits was severely impaired, which resulted in the prolonged cetirizine metabolism in these rabbits.

### 4.2.7 The evaluation of the hepatic dysfunction model

Carbon tetrachloride has been used to induce hepatic dysfunction in experimental animals (69,70) and to study the effect of hepatic dysfunction on drug pharmacokinetics (71). However, it is not clear whether results obtained from these animal studies could be correctly extrapolated to humans. It was possible to evaluate the hepatic dysfunction model in the

present study, having studied the pharmacokinetics of hydroxyzine in children (33), young adults (34), elderly adults, patients with primary biliary cirrhosis, and in rabbits with the coadministration of cimetidine and with $CCl_4$ -induced hepatic dysfunction.

In young adults, the ratio (R) of $AUC_{0->\infty}$ cetirizine/$AUC_{0->\infty}$ hydroxyzine, 6.3, could be considered to be the normal value when both hepatic function and renal function were normal. When renal function is reduced, the ratio should be increased, while in case of hepatic dysfunction, the ratio should be reduced, considering the fact that cetirizine was mainly eliminated through renal excretion and hydroxyzine was mainly metabolized.

The elderly have reduced renal function and some reduction in hepatic function. The hydroxyzine $AUC_{0->\infty}$ in the elderly after an oral dose of 0.7mg/kg hydroxyzine was not different from that in young adults after the same dose, but the ratio (R) was increased to 10.5. In the case of patients with primary biliary cirrhosis, the hydroxyzine $AUC_{0->\infty}$ was increased, but the ratio, 7.5, was not lower than the normal value of 6.3, suggesting that the renal function may also be compromised in these patients.

In rabbits, when cimetidine was given at the same time as hydroxyzine, both $AUC_{0->\infty}$ hydroxyzine and $AUC_{0->\infty}$ cetirizine was significantly increased, indicating the compromise of both hepatic and renal clearances. The ratio (R) of $AUC_{0->\infty}$ cetirizine/$AUC_{0->\infty}$ hydroxyzine was slightly increased from a pretreatment value of 0.9 to 1.3 when cimetidine was given at the same time. It returned to 0.7 two weeks after the discontinuation of cimetidine. The effect of cimetidine on the elimination of hydroxyzine and cetirizine in rabbits is similar to the effect

of primary biliary cirrhosis on the elimination of hydroxyzine and cetirizine in patients with hepatic dysfunction.

When carbon tetrachloride was injected intraperitoneally, the liver tissues were damaged as judged by the large increase of such biochemical parameters as SGOT, SGPT, and LDH. The $AUC_{0->\infty}$ hydroxyzine was significantly increased but not the $AUC_{0->\infty}$ cetirizine. The ratio was reduced to 0.4 from the pretreatment value of 0.8, indicating that hydroxyzine metabolism was inhibited, but that there was little effect on cetirizine elimination.

It was therefore concluded that carbon tetrachloride induced hepatic dysfunction in rabbits was different from that caused by primary biliary cirrhosis in humans. This might be due to reduced renal function in humans as a result of chronic hepatic dysfunction. In addition, patients with primary biliary cirrhosis only had mild hepatic dysfunction, none of them had liver failure. The severity of hepatic dysfunction is different from the acute liver failure induced by $CCl_4$ in rabbits. Therefore, the hepatic dysfunction animal model might be useful only for drugs eliminated by hepatic metabolism producing metabolites which require further metabolism. For drugs eliminated both by renal excretion and hepatic metabolism, the cimetidine- induced hepatic dysfunction and renal competition model might be more suitable.

# Chapter V. Summary and Conclusion

The objectives of the present study were to evaluate the effect of patient age, degree of hepatic function and drug-drug interaction on the pharmacokinetics and pharmacodynamics of hydroxyzine and cetirizine. Studies of hydroxyzine were carried out in 9 elderly volunteers and in 8 patients with primary biliary cirrhosis. Studies of cetirizine were carried out in 19 children with allergic dermatitis or allergic rhinitis. Both hydroxyzine and cetirizine were studied in rabbits with and without the coadministration of cimetidine, and in rabbits with induced hepatic dysfunction. Blood samples were taken at pre-selected times after drug administration. HPLC systems were used to measure serum hydroxyzine and cetirizine concentrations with detection limits of 1 ng/ml and 2 ng/ml respectively.

Pharmacokinetic data obtained in different studies were fitted into compartment models using a BASIC program: PKCALC, and various parameters such as the elimination rate constant, the elimination half-life, apparent volume of distribution, systemic clearance, and $AUC_{0->\infty}$ were calculated. Pharmacodynamic data were fitted into the modified $E_{max}$ model, and $E_{max}$ and $EC_{50}^{H}$ were calculated. Tukey and Bonferroni multiple range tests were used to test statistical differences between pharmacokinetic parameters under various conditions.

The pharmacokinetics and pharmacodynamics of hydroxyzine in the elderly were studied after the oral administration of hydroxyzine 0.7 mg/kg. It was found that the elimination half-life and the apparent volume of distribution of hydroxyzine were increased in the elderly, compared to results in young adults and children. The cetirizine $AUC_{0->\infty}$ was also

increased in the elderly, while there were no differences in other cetirizine pharmacokinetic parameters. It was concluded that the delay in hydroxyzine elimination was probably due to the increased volume of distribution in the elderly and the reduced renal function in the elderly resulted in an accumulation of cetirizine in the elderly compared to young adults.

Wheals and flares were significantly suppressed for 144 hours after a single dose of hydroxyzine 0.7 mg/kg. The calculated maximum suppression was lower than that in young adults, but a lower serum hydroxyzine concentration ($EC_{50}^{H}$) was needed to achieve half of the maximum effect, indicating that the elderly were more sensitive to drug changes in the body.

The effect of hepatic function on the pharmacokinetics and pharmacodynamics of hydroxyzine was also evaluated in 8 patients with primary biliary cirrhosis. It was found that the elimination half-life, the maximum serum hydroxyzine and cetirizine concentraions, the apparent volume of distribution, and hydroxyzine and cetirizine $AUC_{0->\infty}$ were increased in these patients compared to children and young adults. However, no significant differences to results in the elderly could be detected due to large intersubject variations. It was concluded that the reduced hepatic function resulted in an accumulation of hydroxyzine and that the accumulation of cetirizine was probably caused by both reduced hepatic function and reduced renal function in these patients.

Wheals were significantly suppressed for 120 hours, while flares were significantly suppressed for 144 hours after a single dose of hydroxyzine 0.7 mg/kg in patients with primary biliary cirrhosis. The calculated maximum suppressions for both wheals and flares were lower

than the values in young adults, and lower serum concentrations were required to achieve half of the maximum effects.

Based on the above results, it is recommended that the current dosage regimen of hydroxyzine be amended from 25-50 mg t.i.d. to once a day at bedtime in young adults, and that the dosage regimen be further reduced in the elderly and in patients with hepatic dysfunction.

The pharmacokinetics and pharmacodynamics of cetirizine were studied in 19 children following oral administrations of 5 mg and 10 mg cetirizine. Results obtained from the current study were compared to literature values. It was observed that the values of the pharmacokinetic parameters of cetirizine after oral administrations of 5 mg and 10 mg cetirizine were the same, except $AUC_{0->\infty}$ and Cmax which were twice as large after the 10 mg dose as after the 5 mg dose, indicating that the absorption and elimination of cetirizine was linear over the dose range studied. It was also found that age did not affect the pharmacokinetics of cetirizine, as the elimination half-life of cetirizine in children and young adults are about the same. However, the elimination half-life of cetirizine in the elderly and subjects with various degrees of renal insufficiency was prolonged, indicating that degree of renal function is an important factor in determining the pharmacokinetics of cetirizine.

In rabbits, the coadministration of cimetidine resulted in the significant increase in the elimination half-life, $AUC_{0->\infty}$ of hydroxyzine, and a significant reduction in systemic clearance of hydroxyzine, and an significant increase in both cetirizine Cmax and $AUC_{0->\infty}$. It was concluded that cimetidine inhibited the metabolism of hydroxyzine. Pharmacodynamic studies showed that cimetidine was not significantly involved in suppressing intradermally injected histamine-induced wheals.

These results suggested that the enhanced therapeutic efficacy of hydroxyzine and cimetidine was probably due to the inhibition of hydroxyzine metabolism by cimetidine, not due to the involvement of $H_2$-receptors in histamine-induced cutaneous responses.

The coadministration of cimetidine also resulted in a significant increase in both cetirizine elimination half-life and $AUC_{0->\infty}$, and a significant decrease in its systemic clearance, possibly through competition with cetirizine active tubular excretion pathways.

In those acute studies, the effect of cimetidine on the pharmacokinetics and pharmacodynamics of hydroxyzine and cetirizine was reversible, as indicated by the fact that all pharmacokinetic and pharmacodynamic parameters returned to the pre-treatment values two weeks after the discontinuation of cimetidine.

In rabbits, intraperitoneal injection of carbon tetrachloride caused the destruction of liver tissues as indicated by the large increase of SGPT, SGOT, and LDH values. The elimination half-life and $AUC_{0->\infty}$ of hydroxyzine and cetirizine were significantly increased in $CCl_4$-treated rabbits, while systemic clearances were significantly reduced. These results suggested that the metabolism of both hydroxyzine and cetirizine was inhibited. There appeared to be no change in renal function in $CCl_4$-treated rabbits, contrary to patients with primary biliary cirrhosis. Results obtained in these rabbits, therefore, could not be safely extrapolated to humans.

## Bibliography

1. Douglas, W.W., Histamine and 5-hydroxytryptamine (serotonin) and their antagonists, in Goodman and Gilman's The pharmacological basis of therapeutics, Gilman, A.G., Goodman, L.S., and Gilman, A., eds, 7th ed., Collier Macmillan Canada Ltd.: Toronto, 1985, pp. 605-638

2. Ganellin, C.R., Chemistry and structure-activity relationship of drugs acting at histamine receptors, in Pharmcology of histamine receptors, Ganellin, C.R., and Parsons, M.E., eds, Wright/PSG: Bristol, 1982, pp.11-102

3. Rang, H.P., and Dale, M.M., Pharmacology, Churchill Livingstone: New York, 1987, pp. 187-192

4. AHFS Drug information, American Society of Hospital Pharmacists: Bethesda, MD, 1989, pp.2-5, 1163-1164

5. Coulson, C.J., Molecular mechanisms of drug action, Taylor & Francis: London, 1988, pp. 179-182

6. Arrang, J.M., Garbarg, M., and Schwartz, J.C., Auto-inhibition of brain histamine release mediated by a novel class ($H_3$) of histamine receptor Nature, 1983, 302: 832-837

7. Ishikawa, S., and Sperelakis, N., A novel class ($H_3$) of histamine receptors on perivascular nerve terminals, Nature, 1987, 327: 158-160

8. Arrang, J.M., Garbarg, M., Lancelot, J.C., Lecomte, J.M., Pollard, H., Robba, M., Schunack, W., and Schwartz, J.C., Highly potent and selective ligands for histamine $H_3$-receptors, Nature, 1987, 327: 117-123

9. Ash, A.S.F., and Schild, H.O., Receptors mediating some actions of histamine, Br. J. Pharmacol. Chemother., 1966, 27: 427-439

10. Weinstein, H., Chou, D., Johnson, C.L., Kang, S., and Green, J.P., Tautomerism and the receptor action of histamine: a mechanistic model, Mol. Pharmacol., 1976, 12: 738-745

11. Weinstein, H., Mazurek, A.P., Osman, R., and Topiol, S., Theoretical studies on the activation mechanism of the histamine $H_2$-receptor: the proton transfer between histamine and a receptor model, Mol. Pharmacol., 1986, 29: 28-33

12. Bovet, D., and Staub, A., Action protectrice des ethers phenoliques au cours de l'intoxication histaminique, C.R.Soc.Biol.(Paris), 1937, 124: 547-549

13. Simons, K.J., Singh, M., Gillespie, C.A., and Simons, F.E.R., An investigation of the $H_1$-receptor antagonist triprolidine: pharmacokinetics and antihistaminic effects, J. Allergy. Clin. Immunol., 1986, 77: 326-330

14. Joubert, L., Gaut, Z., and Abrams, W.B., A new approach to the use of histamine skin tests in the study of antihistamine drugs, Clin. Pharmacol. Ther., 1969, 10: 250-257

15. Galant, S.P., Bullock, J., Wong, D., and Maibach, H.I., The inhibitory effect of antiallergy drugs on allergen and histamine induced wheal and flare response, J. Allergy Clin. Immunol., 1973, 51: 11-21

16. Fireman, P., Skoner, D., Tanner, E., and Doyle, W., A primate model for the evaluation of antihistamines, Ann. Allergy , 1987, 59 (Part 2): 9-12

17. Kolly, M., and Pecoud, A., Comparison of levocabastine, a new selective $H_1$-receptor antagonist, and DSCG in a nasal-provocation test with allergen, Br.J.Clin. Pharmacol., 1986, 22: 389-394

18. Dorward, A.J., and Patel, K.R., A comparison of ketotifen with clemastine, ipratropium bromide, and sodium cromoglycate in exercise-induced asthma, Clin.Allergy, 1982, 12: 355-361

19. Patel, K.R., Terfenadine in exercise-induced asthma, Br. Med.J., 1984, 288: 1496-1497

20. Levander, S., Hagermark, O., and Stahle, M., Peripheral antihistamine and central sedative effects of three $H_1$-receptor antagonists, Eur.J.Clin.Pharmacol., 1985, 28: 523-529

21. Skassa-Brociek, W., Manderscheid, J.C., Michel, F.B., and Bousquet, J., Skin test reactivity to histamine from infancy to old age, J.Allergy Clin.Immunol., 1987, 80: 711-716

22. Simons, F.E.R., Watson, W.T.A., and Simons, K.J., Lack of subsensitivity to terfenadine during long-term terfenadine treatment, J. Allergy Clin. Immunol., 1988, 82: 1068-1075

23. Maddox, D.E., and Reed, C.E., Clinical Pharmacodynamics of antihistamines, Ann. Allergy , 1987, 59 ( Part 2): 43-48

24. Black, J.W., Duncan, W.A.M., and Durant, G.J., Definition and antagonism of histamine $H_2$-receptors, Nature, 1972, 236: 385-390

25. Ganellin, C.R., Selectivity and the design of histamine $H_2$-receptor antagonists, J.Appl.Chem.Biotechnol., 1978, 28: 183-200

26. Moffat, A.C., Jackson, J.V., Moss, M.S., and Widdop, B., Clark's isolation and identification of drugs, 2nd ed., The Pharmaceutical Press: London, 1986, pp. 673-674

27. Morren, H., Trolin, S., Denayer, R., Grivsky, E., and Maricq, J., New long-acting antihistamines: the 1,4-bisaralcoyl piperazines, Bull. Soc. Chim. Belg., 1951, 60: 282-295

28. Morren, H., Denayer, R., Trolin, S., Grivsky, E., Linz, R., Strubbe, H., Dony, G., and Maricq, J., Study of antihistaminic propterties of new 1,4-disubstitutes of piperazine, Ind.Chim.Belg., 1954, 19: 1176-1196

29. Compendium of Pharmaceuticals and Specialties, Gillis, M.C., ed., 24th ed., Candian Pharmaceutical Association: Ottawa, 1989, pp. 80-81

30. Paton, D.M., and Webster, D.R., Clinical pharmacokinetics of $H_1$ receptor antagonists (the antihistamines), Clin. Pharmacokinet., 1985,10: 477-497

31.Simons, F.E.R., and Simons, K.J., $H_1$-receptor antagonists: clinical pharmacology and use in allergic disease, Pediatric Clinics of North America, 1983, 30: 899-914

32. Fouda, H.G., Hobbs, D.C., and Stambaugh, J.E., Sensitive assay for determination of hydroxyzine in plasma and its human pharmacokinetics, J. Pharm. Sci., 1979, 68: 1456-1458

33. Simons, F.E.R., Simons, K.J., Becker, A.B., and Haydey, R.P., Pharmacokinetics and antipruritic effects of hydroxyzine in children with atopic dermatitis, J. Pediatr., 1984, 104: 123-127

34. Simons, F.E.R., Simons, K.J., and Frith, E.M., The pharmacokinetics and antihistaminic of the $H_1$-receptor antagonist hydroxyzine, J. Allergy Clin. Immunol., 1984, 73: 69-75

35. Gengo, F.M., Dabronzo, J., Yurchak, A., Love, S., and Miller, J.K., The relative antihistaminic and psychomotor effects of hydroxyzine and cetirizine, Clin. Pharmacol. Ther., 1987, 42: 265-272

36. Johnson, G.R., A fatal case involving hydroxyzine, J.Analyt.Toxicol., 1982, 6: 69-70

37. Pong, S.F., and Huang, C.L., Comparative studies on distribution, excretion, and metabolism of hydroxyzine-$^{3}$H and its methiodide-$^{14}$C in rats, J. Pharm. Sci., 1974, 63: 1527-1532

38. Informational material for the investigational antihistamine cetirizine, UCB Pharmaceutical Sector, Bruxelles, 1987

39. Mule, S.J., Routine identification of drugs of abuse in human urine I: application of fluorometry, thin-layer and gas-liquid chromatography, J.Chromatog., 1971, 55: 255-266

40. Tewari, S. N., Detection of synthetic psychotropic drugs by thin-layer electrophoresis, Z. Anal.Chem., 1975, 275: 31-31

41. Cardini, C., Quercia, V., and Calo, A., Systemic application of Gas Chromatography to the analysis of pharmaceutical preparations, J.Chromatog., 1968, 37: 190-193

42. van der Kleijn, E., Beelen, G.C., and Frederick, M.A., Determination of tranquilizers by GLC in biological fluids, Clin.Chim.Acta, 1971, 34: 345-356

43. Rihoux, J.P., and Dupont, P., Comparative study of the peripheral and central effects of terfenadine and cetirizine 2HCl, Annal Allergy, 1987, 59: 235-238

44. De Vos, C., Maleux, M.R., Baltes, E., and Gobert, J., Inhibition of histamine and allergen skin wheal by cetirizine in four animal species, Annal Allergy, 1987, 59: 278-282

45. Snyder, S.H., and Snowman, A.M., Receptor effects of cetirizine, Annal. Allergy, 1987, 59 ( Part 2): 4-8

46. Wood, S.G., John, B.A., Chasseaud, L.F., Yeh, J., and Chung, M., The metabolism and pharmacokinetics of $^{14}$C-cetirizine in humans, Ann. Allergy, 1987, 59 ( Part 2): 31-34

47. Matzke, G.R., Yeh, J., Awni, W.M., Halstenson, C.E., and Chung, M., Pharmacokinetics of cetirizine in the elderly and patients with renal insufficiency, Ann.Allergy,1987, 59 ( Part 2): 25-30

48. Brik, A., Tashkin, D.P., Gong, H., Dauphinee, B., and Lee, E., Effects of cetirizine, a new histamine $H_1$ antagonist, on airway dynamics and responsiveness to inhaled histamine in mild asthma, J. Allergy Clin. Immunol., 1987, 80: 51-56

49. Juhlin, L., de Vos, C., and Rihoux, J.P., Inhibiting effect of cetirizine on histamine-induced and 48/80-induced wheals and flares, experimental dermographism, and cold- induced urticaria, J. Allergy Clin. Immunol., 1987, 80: 599-602

50. Gibaldi, M., and Perrier, D., Pharmacokinetics, 2nd ed., Marcel Dekker : New York, 1982, pp. 1-111, 145-269

51. Rowland, M., Blaschke, T.F., Meffin, P.J., and Williams, R.L., Pharmacokinetics in disease states modifying hepatic and metabolic function, in The effect of disease states on drug pharmacokinetics, Benet, L.Z., ed., American Pharmaceutical Association and Academy of Pharmaceutical Sciences: Washington, D.C., 1976, pp. 53-86

52. Vestal, R.E., Drug use in the elderly: a review of problems and special considerations, Drugs, 1978, 16: 358-382

53. Schmucker, D.L., Aging and drug disposition: an update, Pharmacol. Rev., 1985, 37: 133-148

54. Griffin, J.W., May, J.R., and Dipiro, J.T., Drug interactions: theory versus practice, Am. J. Med., 1984, 77 (suppl.5B): 85-89

55. Mayersohn, M., Special pharmacokinetic considerations in the elderly in Applied pharmacokinetics: principles of therapeutic drug

monitoring, Evans, W.E., Schentag, J.J., and Jusko, W.J., eds., 2nd ed., Applied Therapeutics:Wisconsin, 1986, pp.229-293

56. Smith, C.R., Use of drugs in the aged, Johns Hopkins Med. J., 1979, 145: 61-64

57. Kekki, M., Samloff, I.M., Ihamaki, T., Varis, K., and Siurala, M., Age and sex-related behaviour of gastric acid secretion at the population level, Scand. J. Gastroenterol., 1982, 17: 737-743

58. Bender, A.D., Effect of age on intestinal absorption: implications for drug absorption in the elderly, J.Am.Geratrics Soc., 1968,16: 1331-1339

59. Evans, M.A., Triggs, E.J., Cheung, M., Broe, G,.A., and Creasey, H., Gastric emptying rate in the elderly: implications for drug therapy, J. Am.Gastrics Soc., 1981, 29: 201-205

60. Wilkinson, G.R., and Schenker, S., Drug disposition and liver disease, Drug Metabol. Rev., 1975, 4: 139-175

61. Everitt, D.E., and Avorn, J., Drug prescribing for the elderly, Arch. Intern. Med., 1986, 146: 2393-2396

62. Greenblatt, D.J., Sellers, E.M., and Shader, R.I., Drug disposition in old age, New Engl. J. Med., 1982, 306: 1081-1088

63. Kim, L.K., Hepatic disorders Part I. adverse effects of drugs on the liver, in Applied therapeutics: the clinical use of drugs, Young, L.Y., and Koda-Kimble, M.A., eds., 4th ed., Applied Therapeutics Inc.: Washington, 1988, pp. 485-500

64. Andreasen, P.B., Ranek, L., Statland, B.E., and Tygstrup, N., Clearance of antipyrine-dependence of quantitative liver function, Eur. J. Clin. Invest., 1974, 4: 129-134

65. Meredith, C.G., Christian, C.D., Johnson, R.F., Madhavan, S.V., and Schenker, S., Diphenhydramine disposition in chronic liver disease, Clin. Pharmacol.Ther., 1984, 35: 474-479

66. Kawasaki, S., Sugiyama, Y., Iga, T., Hanano, M., Beppu, T., Sugiura, M., Sanjo, K., and Idezuki, Y., Hepatic clearances of antipyrine, indocyanine green, and galactose in normal subjects and in patients with chronic liver diseases, Clin. Pharmacol. Ther., 1988, 44: 217-224

67. Siersbæk-Nielsen, Hansen, J.M., Kampmann, J., and Kristensen, M., Rapid evaluation of creatinine clearance, Lancet, 1971, 1: 1133-1134

68. Colli, A., Buccino, G., Cocciolo, M., Parravicini, R., and Scaltrini, G., Disposition of a flow-limited drug (lidocaine) and a metabolic capacity-limited drug (theophylline) in liver cirrhosis, Clin. Pharmacol. Ther., 1988, 44: 642-649

69. Dingell, J.V., and Heimberg, M., The effects of aliphatic halogenated hydrocarbons on hepatic drug metabolism, Biochem. Pharmacol., 1968, 17: 1269-1278

70. Recknagel, R.O., Carbon tetrachloride hepatotoxicity, Pharmacol. Rev., 1967, 19: 145-208

71. Kaka, J.S., Al-khamis, K.I., and Tanira, M.O.M., Effect of hepatic and renal dysfunction on disposition of bupropion in rats, Eur. J. Drug. Metabol. Pharmacokinet., 1988, 13: 149-153

72. Freston, J.W., Cimetidine I: developments, pharmacology and efficacy, Annal. Intern. Med., 1982, 97: 573-580

73. Gerber, M.C., Teiwani, G.A., Gerber, N., and Bianchine, J.R., Drug interactions with cimetidine: an update, Pharmacol. Ther., 1985, 27: 353-370

74. Powell, J.R., and Donn, K.H., Histamine $H_2$ antagonist drug interactions in perspective: mechanistic concepts and clinical implications, Am. J. Med., 1984, 77 (suppl. 5B): 57-84

75. Smith, S.R., and Kendall, M.J., Ranitidine versus cimetidine: a comparison of their potential to cause clinically important drug interactions, Clin. Pharmacokinet., 1988, 15: 44-56

76. Reilly, P.E.B., Carrington, L.E., and Winzor, D.J., The interaction of cimetidine with rat liver microsomes, Biochem. Pharmacol., 1983, 32: 831-835

77. Jensen, J.C., and Gugler, R., Cimetidine interaction with liver microsomes *in vitro* and *in vivo* involvement of an activated complex with cytochrome P-450, Biochem. Pharmacol., 1985, 34: 2141-2146

78. Harvey, R.P., and Schocket, A.L., The effect of $H_1$ and $H_2$ blockade on cutaneous histamine response in man, J. Allergy Clin. Immunol., 1980, 65: 136-139

79. Kaur, S., Greaves, M., and Eftekhari, N., Factitious urticaria (dermographism): treatment by cimetidine and chlorpheniramine in a randomized double-blind study, Br. J. Dermatol., 1981, 104: 185-190

80. Boyle, J., and Mackie, R.M., The use of combined $H_1$ and $H_2$ receptor blockers in urticaria with dermographism, Br. J. Dermatol., 1982, 107: 18-19

81. Phanuphak, P., Schocket, A., and Kohler, P.F., Treatment of chronic idiopathic urticaria with combined $H_1$ and $H_2$ blockers, Clin. allergy, 1978, 8: 429-433

82. Paul, E., and Bodeker, R.H., Treatment of chronic urticaria with terfenadine and ranitidine: a randomized double-blind study in 45 patients, Eur. J. Clin. Pharmacol., 1986, 31: 277-280

83. Mansfield, L.E., Smith, J.A., and Nelson, H.S., Greater inhibition of dermographia with a combination of $H_1$ and $H_2$ antagonists, Ann. Allergy, 1983, 50: 264-265

84. Bleehen, S.S., Thomas, S.E., Greaves, M.W., Newton, J., Kennedy, C.T.C., Hindley, F., Marks, R., Hazell, M., Rowell, N.R., Fairiss, G.M., Cartwright, P.H., Glenny, H.P., and Howland, K., Cimetidine and chlorpheniramine in the treatment of chronic idiopathic urticaria: a multi-centre randomized double-blind study, Br. J. Dermatol., 1987, 117: 81-88

85. Commens, C.A., and Greaves, M.W., Cimetidine in chronic idiopathic urticaria: a randomized double-blind study, Br. J. Dermatol., 1978, 89: 675-679

86. Monroe, W., Cohen, S.H., Kalbfleisch, J., and Schulz, C.I., Combined $H_1$ and $H_2$ antihistamine therapy in chronic urticaria, Arch Dermatol., 1981, 117: 404-407

87. Salo, O.P., Kauppinen, K., and Mannisto, P.T., Cimetidine increases the plasma concentration of hydroxyzine, Acta. Derm. Venereol., 1986, 66: 349-350

88. Fox, R.R., The rabbit as a research subject, The Physiologist, 1984, 27: 393-401

89. Shumaker, R.C., PKCALC: an interactive computer program for statistical and pharmacokinetic analysis of data, Drug Metabol. Rev., 1986, 17: 331-348

90. Don Brown, R., and Manno, J.E., ESTRIP: a BASIC computer program for obtaining initial polyexponential parameter estimates, J.Pharm.Sci., 1978, 67:1687-1691

91. Waters chromatography division, Waters sourcebook for chromatography columns and supplies, 1985, pp. 6-18

92. Simons, K.J., And Simons, F.E.R., The effect of chronic administration of hydroxyzine on hydroxyzine pharmacokinetics in dogs, J. Allergy Clin. Immunol., 1987, 79: 928-932

93. Pang, K.S., A review of metabolic kinetics, J. Pharmacokinet. Biopharm., 1985, 13: 633-662

94. Unpublished data from previous studies, see Ref. 33 and 34.

95. Rihoux, J.P., and Polderman, J., The effect of clemastine and hydroxyzine on cutaneous histamine response in man, J. Int. Med. Res., 1982, 10: 383-385

96.Gibaldi, M., Measurement and interpretation of certain biopharmaceutic and pharmacodynamic parameters, Chemotherapy, 1968, 13: 1-15

97. van Rossum, J.M., and Burgers, J.P.T., Quantitative relationships between dynamics and kinetics of drugs: a systems dynamics approach, Drug Metabol. Rev., 1984, 15: 365-382

98. Schwinghammer, T.L., and Kroboth, P.D., Basic concepts in pharmacodynamic modeling, J. Clin. Pharmacol., 1988, 28: 388-394

99. Tallarida, R.J., Receptor theories and quantitative effect versus dose-concentration relationship, Drug Metabol. Rev., 1984, 15: 345-363

100. Dingemanse, J., Danhof, M., and Breimer, D.D., Pharmacokinetic-pharmacodynamic modeling of CNS drug effects: an overview, Pharmacol.Ther., 1988, 38: 1-52

101. Oosterhuis, B., and van Boxtel, C.J., Kinetics of drug effects in man, Ther.Drug Monitoring, 1988, 10: 121-132

102. Cheng, H.C., and Woodward, J.K., Antihistaminic effect of terfenadine: a new piperidine-type antihistamine, Drug Develop. Res., 1982, 2:181-196

103. Cheng, H.C., Reavis, O.K., Jr., Munro, N.L., and Woodward, J.K., Cutaneous vascular histamine $H_1$ and $H_2$ receptors in the guinea pig: the histamine skin wheal as a cutaneous vascular model, Arch. Int. Pharmacodyn. Ther., 1979, 240: 214-219

104. Harvey, R.P., Wegs, J., and Schoket, A.L., A controlled trial of therapy in chronic urticaria, J. Allergy Clin. Immunol., 1981, 68: 262-266

105. Chipman, P., and Glover, W.E., Histamine $H_2$-receptors in the human peripheral circulation, Br. J. Pharmacol., 1976, 56: 494-496

106. Davies, M.G., and Greaves, M.W., The current status of histamine receptors in human skin: therapeutic implications, Br.J.Dermatol., 1981, 104: 601-606

107. Dixon, W.J., Brown, M.B., Engelman, C., Frane, J.W., Hill, M.A., Jennrich, R.I., and Topprek, J.D., BMDP statistical software 1985 Printing, University of Calfornia Press: Berkely, 1985, pp.289-344

108. Ghys, L., and Rihoux, J.P., Pharmacological modulation of cutaneous reactivity to histamine: a double-blind acute comparative study between cetirizine, terfenadine and astemizole, J.Int.Med.Res., 1989, 17: 24-27

109. Dale, H.H., The action and uses of the antihistamine drugs as applied to dermatology, Br.J.Dermatol., 1950, 62: 151-157

110. Marks, R., and Greaves, M.W., Vascular reactions to histamine and compound 48/80 in human skin: suppression by an histamine $H_2$-receptor blocking agent, Br.J.Clin.Pharmacol., 1977, 4: 367-369

111. Robertson, I., and Greaves, M.W., Responses of human skin blood vessels to synthetic histamine analogues, Br.J.Clin.Pharmacol., 1978, 5: 319-322

112. Fikry, J., and Aboul-Wafa, M., Intestinal absorption in the old, Gerontol.Clin., 1965, 7: 171-178

113. Stevenson, I., Salem, S., and Shepherd, A., Studies on drug absorption and metabolism in the elderly, in Drugs and the Elderly, Crook, J., and Stevenson, I., eds., University Park Press: Baltimore, 1979, pp. 51-63

114. Warren, P.M., Pepperman, M.A., and Montgomery, R.D., Age-related changes in small-intestinal mucosa, Lancet, 1978, 2: 848-859

115. Lefebvre, R.A., Rosseel, M.T., Bernheim, J., Single dose pharmacokinetics of cetirizine in young and elderly volunteers, Int.J.Clin.Pharm.Res., 1988, 8: 463-470

116. SAS Institute Inc., SAS user's guide:statistics, Version 5 edition, SAS Institute Inc.:Cary, NC, 1985, pp.113-137

117. Atkinson, A.J., and Strong, J.M., Effect of active drug metabolites on plasma-level response correlations, J. Pharmacokinet. Biopharm., 1977, 5: 95-109

118. Bilzer, W., Gundert-Remy, U., and Weber, E., Relationship between antihistamic activity and plasma level of diphenhydramine, Eur.J.Clin.Pharmacol., 1974, 7: 393-395

119. Carruthers, S.G., Shoeman, D.W., Hignite, C.E., and Azarnoff, D.L., Correlation between plasma diphenhydramine level and sedative and antihistamine effects, Clin.Pharmacol.Ther., 1978, 23: 375-382

120. Sheiner, L.B., Stanski, D.R., Vozeh, S., Miller, R.D., and Ham, J., Simultaneous modeling of pharmacokinetics and pharmacodynamics: application to d-tubocurarine, Clin.Pharmacol.Ther., 1979, 25: 358-371

121. Colburn, W.A., Simultaneous pharmacokinetic and pharmacodynamic modeling, J.Pharmacokinet.Biopharm., 1981, 9: 367-388

122. Fuseau, E., and Sheiner, L.B., Simultaneous modeling of pharmacokinetics and pharmacodynamics with a nonparametric pharmacodynamic model, Clin.Pharmacol.Ther., 1984, 35: 733-741

123. Unadkat, J.D., Bartha, F., and Sheiner, L.B., Simultaneous modeling of pharmacokinetics and pharmacodynamics with nonparametric kinetic and dynamic models, Clin.Pharmacol.Ther., 1986, 40: 86-93

124. Brandes, L.J., Bogdanovic, R.P., Cawker, M.D., and LaBella, F.S., Histamine and growth: interaction of antiestrogen binding site ligands with a novel histamine site that may be assoicated with calcium channels, Cancer Res., 1897, 47: 4025-4031

125. Saxena, S.P., Brandes, L.J., Becker, A.B., Simons, K.J., and LaBella, F.S., Histamine is an intracellular messenger mediating platelet aggregation, Science, 1989, 243: 1596-1599

126. Togias, A.G., Naclerio, R.M., Waner, J., Proud, D., Kagey-Sobotka, A., Nimmagadda, I., Norman, P.S., and Lichtenstein, L.W., Demonstration of inhibition of mediator release from human mast cells by azatadine base, JAMA, 1986, 255: 225-229

127. Simons, F.E.R., $H_1$-receptor antagonists: clinical pharmacology and therapeutics, J.Allergy Clin. Immunol., 1989, 84: 845-861

128. Sheiner, L., and Rowland, M., The seventh one-week workshop on advanced methods in pharmacokinetics/pharmacodynamics, University of California, San Francisco, 1990, pp.130-136

129. Ariens, E.J., and Simonis, A.M., A molecular basis for drug action, J. Pharm. Pharmacol., 1964, 16: 137-157

130. Chen, X., The evaluation of the rabbit as an animal model in determining the bioavailability of controlled-release chlorpheniramine dosage forms, M.Sc. thesis, University of Manitoba, Winnipeg, 1988

# Appendix I Derivation of Eq.(10)

Since hydroxyzine and cetirizine are both $H_1$-receptor antagonists, it can be assumed that hydroxyzine and cetirizine act competitively on the same $H_1$-receptors. The effect produced by hydroxyzine in the presence of cetirizine is then given by (see Ref.129):

$$E = \frac{E^H_{max} \times C_H}{EC^H_{50}(1+\frac{C_c}{EC^c_{50}}) + C_H} + \frac{E^c_{max} \times C_c}{EC^c_{50}(1+\frac{C_H}{EC^H_{50}}) + C_c} \qquad (1)$$

where E is the effect produced by hydroxyzine and cetirizine, $E^H_{max}$ is the maximum possible response that can be attributed to hydroxyzine, and $E^C_{max}$ is the maximum possible response that can be attributed to cetirizine. $EC^H_{50}$ is the hydroxyzine concentration that produces 50% $E^H_{max}$, and $EC^C_{50}$ is the cetirizine concentration that produces 50% $E^C_{max}$.

From *in vitro* studies, it is known that hydroxyzine is four times more potent than cetirizine is (45), so it is proposed that the following relationship holds:

$$EC^C_{50} = 4 \times EC^H_{50} \qquad (2)$$

By substituting Eq.(2) into Eq.(1), Eq.(1) can be simplified to:

$$E = \frac{E^H_{max} \times C_H + E^C_{max} \times \frac{C_C}{4}}{EC^H_{50} + C_H + \frac{C_C}{4}} \qquad (3)$$

If it is further assumed that the maximum responses produced by hydroxyzine and cetirizine are the same, thus,

$$E^{H}_{max} = E^{C}_{max} \qquad (4)$$

Substituting Eq.(4) into Eq.(3) and rearranging yield:

$$E = \frac{E_{max} \times (C_H + \frac{C_C}{4})}{EC^{H}_{50} + (C_H + \frac{C_C}{4})} \qquad (5)$$

Eq.(5) can be further simplified by substituting C for $(C_H + C_C/4)$:

$$E = \frac{E_{max} \times C}{EC^{H}_{50} + C} \qquad (6)$$

# Appendix II Derivation of Eqs.(15) and (16)

A hypothetical effect-compartment similar to that of Sheiner *et al* (128) was postulated. The effect-compartment is connected to the central compartment by a link model. The effect compartment has an in/out plasma flow of Qe, and a volume of distribution of Ve. The rate of change of the amount of hydroxyzine in the effect-compartment can then be expressed as:

$$V_e\frac{dC_e}{dt} = Q_e \cdot C - Q_e\frac{C_e}{k_{pe}} \qquad (1)$$

where $k_{pe}$ is a partition coefficient, $k_{pe}=(Ce)ss/Css$ with Css being the steady-state plasma concentration, and (Ce)ss being the steady-state effect-compartment concentration. Since Ce cannot be determined directly, its units can be assigned arbitrary. Ce is chosen so that

$$(C_e)_{ss} = C_{ss} \qquad (2)$$

and

$$k_{pe} = 1 \qquad (3)$$

Substituting Eq.(3) into Eq.(1), and rearranging yield:

$$\frac{dC_e}{dt} = K_{eo} \cdot (C - C_e) \qquad (4)$$

where Keo = Qe/Ve.

The Laplace transform of Eq.(4) is given by:

$$s\overline{C_e} = K_{eo} \cdot (\overline{C} - \overline{C_e}) \qquad (5)$$

On rearranging Eq.(5), it is obtained:

$$\overline{C_e} = \frac{K_{eo}}{s + K_{eo}} \cdot \overline{C} \qquad (6)$$

By using the same method, the Laplace transform of the cetirizine concentration in the effect-compartment is given by Eq.(7):

$$\overline{C_e'} = \frac{K_{eo}'}{s + K_{eo}'} \cdot \overline{C'} \qquad (7)$$

Since hydroxyzine displays two-comparment model characteristics, the Laplace transform of its concentration in the central compartment after an intravenous bolus injection is thus given by (50):

$$\overline{C} = \frac{X_0(s + K_{21})}{V_1 (s+\alpha)(s+\beta)} \qquad (8)$$

where Xo is the amount of hydroxyzine given intravenously, $V_1$ is the apparent volume of distribution of the central compartment. s is the Laplace operator. $\alpha$ and $\beta$ are the roots of the equation $r^2 + (K_{10} + K_{12} + K_{21})r + K_{21} \cdot K_{10} = 0$.

Substituting Eq.(8) into Eq.(6) yields:

$$\overline{C_e} = \frac{X_0 K_{eo}(s + K_{21})}{V_1 (s+\alpha)(s+\beta)(s+K_{eo})} \qquad (9)$$

Solving Eq.(9) for Ce gives:

$$C_e = \frac{X_0 K_{eo}}{V_1}\left(\frac{K_{21} - \alpha}{(\beta - \alpha)(K_{eo} - \alpha)} e^{-\alpha t} + \frac{K_{21} - \beta}{(\alpha - \beta)(K_{eo} - \beta)} e^{-\beta t} + \frac{K_{21} - K_{eo}}{(\alpha - K_{eo})(\beta - K_{eo})} e^{-K_{eo} t}\right)$$

For cetirizine formed from hydroxyzine after an intravenous dose of hydroxyzine, its plasma concentrations can be described by a one-compartment model with a first-order formation rate constant $K_m$ and an elimination rate constant of K. The Laplace transform of the cetirizine plasma concentration is:

$$\overline{C'} = \frac{X_0' K_m}{V'(s+K)(s+K_m)} \qquad (11)$$

where Xo' is the amount of cetirizine formed from hydroxyzine, and V' is the volume of distribution of cetirizine.

Substituting Eq.(11) into Eq.(7), and solving for Ce' yield:

$$C_e' = \frac{X_0' K_m K_{eo}'}{V} \left( \frac{e^{-K_m t}}{(K-K_m)(K_{eo}'-K_m)} + \frac{e^{-Kt}}{(K_m-K)(K_{eo}'-K)} + \frac{e^{-K_{eo}' t}}{(K_m-K_{eo}')(K-K_{eo}')} \right)$$