Efficacy of Gastrointestinal Decontamination Procedures After Simulated Salicylate Overdose in Man

A thesis presented to the University of Manitoba

In partial fulfillment of the requirements
for the degree of Master of Science

By

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ABSTRACT

The efficacy of whole bowel irrigation (WBI) and activated charcoal/cathartic (ACS) as gastrointestinal decontamination strategies following an acute dose of enteric-coated acetylsalicylic acid (EC-ASA) (9 x 325 mg tablets) was studied in 10 healthy volunteers. The protocol consisted of a three-limbed randomized crossover design with at least one week separating each limb. Four hours post drug ingestion each volunteer was subjected to one of two study interventions, WBI or ACS. Each volunteer served as his own control (CTL).

Peak serum salicylic acid (SA) concentration was reduced by both ACS and WBI ($p<0.001$) and was significantly different among all groups (mean $\pm$ S.D.); CTL=179$\pm$29, ACS=128$\pm$54, WBI=84$\pm$54 mg/l. Also, both treatments reduced the area under the serum concentration versus time curve (AUC) ($p<0.001$) and all groups were significantly different from each other; CTL=51$\pm$24, ACS=22$\pm$16, WBI=12$\pm$11 mg.hr/l.kg ($p<0.01$). Both interventions increased apparent serum SA clearance ($p<0.001$), and all groups were significantly different from each other; CTL=11$\pm$3, ACS=25$\pm$14, WBI=83$\pm$68 ml/kg/hr ($p<0.01$).

Although both ACS and WBI are effective

gastrointestinal decontamination for EC-ASA, these data support WBI as the treatment of choice. It is possible that this intervention strategy may be effectively applied to other modified release pharmaceuticals.

Multiple doses of activated charcoal (AC) were evaluated as a strategy to increase the clearance of absorbed salicylate. This intervention was begun after the absorption of an acute dose of acetylsalicylic acid (ASA) (36 x 80 mg tablets). The protocol consisted of a randomized two-limbed cross-over design with at least one week separating each limb.

There was no apparent difference in the peak serum SA concentration between CTL= 192 $\pm$ 27 and AC= 204 $\pm$ 32 mg/l. Similarly, no difference could be detected in area under the serum concentration versus time curve (AUC) CTL=39 $\pm$ 16 and AC=37 $\pm$ 13 mg.hr/l.kg. However, integrated AUC from 4 hr post drug ingestion to end of the sampling period indicated a modest treatment effect ($p<0.05$). No difference was evident in apparent SA clearance CTL=11 $\pm$ 2 and AC=13 $\pm$ 2 ml/kg/hr.

Multiple doses of AC demonstrated a modest treatment effect on SA elimination.

The safety of concurrent polyethylene glycol electrolyte lavage solution (PEG-ELS) and AC

administration was examined in an in vitro model.

Polyethylene glycol 3350 was mixed with varying concentrations of activated charcoal to determine relative adsorptive capacity of charcoal for polyethylene glycol. These in vitro studies demonstrate that activated charcoal adsorbs polyethylene glycol. Incubation of PEG-ELS and AC mixtures with SA demonstrated decreased SA binding to AC. However, this was minimal at clinically relevant concentrations. The relative safety of co-administration of both of these agents was evaluated in vitro by measurement of supernatant osmolality. No clinically significant change could be demonstrated. These in vitro data support concurrent AC and PEG-ELS administration as a safe and potentially effective intervention.

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AC.....Activated charcoal.

ACS.....Activated charcoal in sorbitol solution.

ANOVA.....Analysis of variance.

ASA.....Acetylsalicylic acid.

AUC.....Area under the serum concentration versus time curve.

CTL.....Control.

EC-ASA.....Enteric-coated acetylsalicylic acid.

HPLC.....High performance liquid chromatography.

PBS.....Phosphate buffered saline.

PEG.....Polyethylene glycol 3350.

PEG-ELS.....Polyethylene glycol-electrolyte lavage solution.

SA.....Salicylic acid.

SUA.....Salicyluric acid.

WBI.....Whole bowel irrigation.

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I. INTRODUCTION

A. General pharmacological properties of acetylsalicylic acid.

Acetylsalicylic acid (ASA, Aspirin®) is a commonly used analgesic, antipyretic and anti-inflammatory agent in North America. The layman relies on ASA as the common household "cure all" for symptomatic relief of low-intensity pain from headache, myalgia, arthralgia and other musculoskeletal disorders. Because this drug is so readily available as an over-the-counter remedy the self medicating patient often underestimates the toxicity of this agent and becomes poisoned (Proudfoot and Brown 1969). Its therapeutic index is quite narrow hence creating a greater risk for toxicity. For example, the optimum salicylate concentration used in treatment of rheumatoid arthritis (serum SA of 250 mg/l) is only slightly below the lower limit of toxicity (serum SA of 300 mg/l). Salicylate intoxication, whether by deliberate or accidental overdose, is a serious problem among pediatric and adult populations with a significant morbidity and mortality (Temple 1981). Patients with significant salicylate poisoning experience tinnitus and deafness (Anderson et al. 1976). Salicylate induced uncoupling of oxidative phosphorylation increases heat

production, basal metabolic rate, oxygen consumption, carbon dioxide production and cardiac output (Glader 1976). The depth and rate of respiration are also increased resulting in respiratory alkalosis. Clearly, ASA in the toxic range can induce several changes in metabolic homeostasis (Gabow et al. 1978).

B. Mechanism of ASA action.

Earlier reports have suggested that autacoid (prostaglandin) production is directly involved in the pathogenesis of fever and inflammation (Vane 1971). ASA has been shown to ameliorate this effect (Flower 1974). The most accepted mechanism by which ASA exhibits its analgesic, antipyretic and anti-inflammatory actions involves inhibition of the cyclooxygenase enzyme through acetylation of a serine residue at the enzyme's active site (Roth and Siok 1978).

C. Pharmacological effects of ASA on organ systems.

a. Respiratory system.

Toxic doses of ASA have both central and peripheral stimulatory actions on the respiratory system and increase

oxygen consumption and carbon dioxide production (Tenney and Miller 1955, Brem et al. 1973). The increased production of carbon dioxide is thought to be a direct result of SA induced uncoupling of oxidative phosphorylation in skeletal muscle. Alveolar ventilation initially compensates for the increased carbon dioxide production such that no apparent change in pCO_2 tension occurs. However, with salicylate poisoning, the depth and rate of respiration are increased resulting in respiratory alkalosis (Glader 1976). Clearly, changes in respiratory function induced by salicylates contribute to the serious acid-base disturbances seen after toxic ingestion (Proudfoot and Brown 1969, Gabow et al. 1978).

b. Acid-base balance.

Toxic doses of ASA induce clinically important changes in acid-base homeostasis (Proudfoot and Brown 1969). The subsequent respiratory alkalosis is partially compensated for by the renal excretion of bicarbonate, sodium and potassium which returns blood pH toward normal. Compensated respiratory alkalosis is commonly seen with adults receiving chronic ASA therapy (Anderson et al. 1976). However, uncompensated respiratory alkalosis occurs with progressive exposure to ASA in the toxic range. This is characterized by an increased blood pH, and

decreased blood pCO_2. Furthermore, adults with mixed acid-base disturbances have been observed (Proudfoot and Brown 1969, Gabow et al. 1978). Metabolic acidosis occurs from the following: 1) SA derivatives at toxic doses dissociate at plasma pH and displace 2 to 3 mEq per liter of plasma bicarbonate. 2) renal function becomes impaired because of dehydration and hypotension (vasomotor depression) with the subsequent accumulation of sulfate and phosphate. 3) organic acids pyruvic acid, lactic acid and acetoacetic acid accumulate secondarily to the salicylate-induced impairment of carbohydrate metabolism (Levy and Tsuchiya 1972).

c. Cardiovascular effects.

Patients receiving therapeutic doses of ASA exhibit no clinically significant cardiovascular effects from this agent. Larger doses however, can produce cardiovascular pathophysiology secondary to acid-base and respiratory disorders (Gabow et al. 1978).

d. Gastrointestinal effects.

The ingestion of ASA may result in epigastric distress, nausea and vomiting. Gastric ulceration and peptic ulcer symptoms (heartburn, dyspepsia),

gastrointestinal hemorrhage and erosive gastritis have all been reported in patients receiving high dose ASA therapy. Salicylate-induced gastric bleeding occurs frequently leading to blood in the stool. The incidence of bleeding is highest with salicylate preparations that dissolve slowly and deposit ASA particles in the gastric mucosal folds (Leonards and Levy 1973). Thus, dosage as well as dosage form, contribute to the gastrointestinal damage induced by ASA. The formulation of enteric-coated tablets (EC-ASA) permits the administration of ASA with reduced incidence of gastrointestinal upset (Hoftiezer and Silvoso 1980). The nature of the enteric-coating prevents tablet disintegration below pH 5, thereby restricting ASA absorption to the small intestine and minimizing gastric irritation (Allen et al. 1983).

e. Hepatorenal effects.

Hepatotoxicity induced by ASA is dose dependent. Benson (1983) has demonstrated that patients receiving ASA for connective tissue disorders and relief of mild peripheral pain may exhibit symptoms of hepatotoxicity. Indications of hepatic damage are elevation of liver enzymes alanine aminotransferase and aspartate aminotransferase. A small percentage of patients experience hepatomegaly, anorexia, nausea and jaundice.

Clearly, salicylates should be used with caution in patients with chronic liver disease (Sbarbaro and Bennett 1977). Additionally, there is concern regarding the use of salicylates in children with chicken pox (varicella virus) or influenza and the development of Reye's Syndrome (Tarlow 1986 , Hurwitz et al.1985).

Chronic use of salicylate alone is rarely associated with nephrotoxicity. However, Clive and Stoff (1984) reported that combination of salicylates and acetaminophen for analgesia can produce papillary necrosis and interstitial nephritis.

f. Metabolic effects.

ASA has been shown to uncouple oxidative phosphorylation in the cellular respiration pathway (Glader 1976). The uncoupling action impairs the production of adenosine triphosphate (ATP) in a manner similar to that seen with the chemical agent 2,4-dinitrophenol. Consequently, cellular oxygen consumption and carbon dioxide production are increased to compensate for the reduction in cellular ATP. Evidence further suggests that toxic concentrations of salicylate compete with pyridine nucleotide coenzymes for their respective dehydrogenases, thereby impairing aerobic metabolism.

In general, salicylates have several different effects on carbohydrate metabolism with salicylate-induced hypogylcemia as the most prevalent. Moreover, hyperglycemia may occur before hypoglycemia through the mobilization of glycogen stores in liver and muscle by SA induced release of norepinephrine (Hill 1973).

D. Pharmacokinetics and Metabolism of ASA.

Several reports have shown that a therapeutic dose of ASA is rapidly hydrolyzed to SA. For the most part, hepatic biotranformation reactions within the endoplasmic reticulum and the mitochondria account for the complete metabolism of SA. SA is metabolized to salicyluric acid (by conjugation with glycine), salicyl phenolic glucuronide, salicyl acyl glucuronide and gentisic acid (Williams 1959). Wilson et al. (1978) identified gentisuric acid, the glycine conjugate of gentisic acid. In contrast to the metabolism of other drugs which follow apparent first-order kinetics, i.e. process in which the rate of drug disappearance is directly proportional to plasma concentration, two reaction processes of SA metabolism follow apparent zero-order (non-linear) kinetics, i.e. process in which the rate of drug elimination is not proportional to plasma concentration

(Levy 1965, Levy and Yaffe 1968, Levy et al.1969). The conversion of SA to SUA and salicyl phenolic glucuronide is capacity-limited at the therapeutic dose range and follows Michaelis-Menten type kinetics (Levy et al.1972). Formation of other SA metabolites follows first order kinetics. This characteristic of SA metabolism implies that the SA half-life is a function of dose i.e half-life increases with increasing dosage. This is important because small changes in a therapeutic dose can alter the SA concentration and renal elimination so drastically, that the patient may become accidentally intoxicated (Anderson et al. 1976).

SA and its metabolites are excreted from the body by the kidney. The renal elimination of SA and SUA has been studied in man by Gutman et al. (1955) and Schacter and Manis (1958). Studies indicate that urine SA metabolite composition is as follows: free SA (10%), SUA (75%), salicylic phenolic glucuronide (10%), salicylic acyl glucuronide (5%) and gentisic acid (1%). The elimination of SA is pH dependent, because it is a weak acid. Thus in alkaline urine, a greater fraction of free SA will be eliminated by the kidney; in contrast to acidic urine where the fraction of free SA eliminated would be less. SA, a weak acid with a pKa of 3, is ionized at physiological pH (99.996 % at pH 7.4) and is readily

excreted by the kidney in this form (Hill 1973). Thus, changes in urine pH can dramatically affect the distribution (across renal tubular membrane) and elimination of SA by altering the percentage of drug in the ionizable form (Waddel and Butler 1957). If for example the pH of renal tubular fluid was made more acidic, (a reduction in pH, increase in hydrogen ion concentration) the proportion of non-ionizable SA would increase with a tendency for back diffusion across the renal tubule, decreasing renal clearance of SA. It should also be mentioned however, that the conjugates of SA are water-soluble organic acids and do not readily back-diffuse across the renal tubules. They are eliminated primarily by glomerular filtration and proximal tubule secretion (Levy et al. 1972, Bekersky et al.1980). Clearly, any condition (renal pathology) which interferes with either mechanism will affect clearance of SA metabolites.

E. Toxicity of ASA.

More than 200 products containing ASA and 20 billion tablets are consumed by the American public each year (Leist and Banwell 1974). The widespread availability of ASA has made this drug a common source of intentional and accidental overdose (Temple 1981). Several cases of

salicylate intoxication are reported each year with the majority, child related (Litovitz et al. 1985). Clearly, ASA should not be considered a harmless household remedy. Therapeutically, the pediatric dosage of ASA is 10 to 20 mg/kg every 6 hours up to a limit of 60 mg/kg per 24 hours. For adults, the dosage is appropriately titrated to achieve the maximum therapeutic effect without producing toxicity. For example, an initial dose of 1000 mg followed subsequent doses of 650 mg every 4 hours can be considered a safe therapeutic dose for most patients.

Mild to moderate salicylate toxicity in toddlers occurs after the ingestion of 160 to 240 mg/kg. A potentially lethal intoxication is > 480 mg/kg. In adults however, approximately 10 to 30 g of ASA can be fatal. Symptoms of toxicity begin to occur at plasma SA concentrations of 300 mg/l for all ages. These symptoms are dependent upon the serum concentration of SA and may include: headache, vertigo, tinnitus, hyperventilation, respiratory alkalosis and metabolic acidosis, electrolyte disturbances (hyponatremia, hypernatremia, hypokalemia, hypocalcemia), deafness, fatigue, sweating, thirst, vomiting and diarrhea. Central nervous system effects such as nausea irritability, disorientation, convulsions and coma ensue with prolonged exposure to toxic concentrations of SA. Cerebrospinal fluid glucose may be low in the

presence of normogylcemia and contribute to cerebral death (Thurston et al. 1970). Earlier animal studies have demonstrated that a critical brain salicylate concentration is required to cause death in rats (Hill 1973). Salicylate blood concentration associated with lethal brain concentrations ranged from 45 to 195 mg per 100 ml (Hill 1973). The clinical significance of this observation is "poor correlation of serum salicylate concentrations with clinical severity of salicylate intoxication" as described by Done (1960).

The salicylate intoxicated patient requires immediate medical attention. Treatment is generally supportive and usually depends upon the condition of the patient at time of presentation. Depending on type (accidental or intentional) and severity of intoxication, a number of treatment interventions exist which reduce absorption of SA by the gastrointestinal tract. These include chemically induced emesis with syrup of ipecac, orogastric lavage and activated charcoal therapies. Prescott et al. (1983) suggest urine alkalization and forced diuresis to enhance elimination of SA from the body. For example, if a patient presents with metabolic acidosis, the decreased serum pH enhances tissue penetration of SA into the central nervous system. Therefore, an acidosis should be treated aggressively with

the infusion of a bicarbonate solution in sufficient quantity to produce an alkaline diuresis. Similarly, hemodialysis may also be used to enhance clearance of SA from the blood stream. Indications for hemodialysis include cardiac or renal failure, intractable acidosis or severe fluid and electrolyte imbalance (Winchester et al. 1977). The extensiveness of treatment depends upon the patient's status and degree of toxicity at time of presentation.

F. Conventional treatment intervention following a drug overdose.

The primary goal after an acute drug overdose is to reduce morbidity and mortality. This can be achieved by preventing the absorption of the ingested substance. Traditionally, three techniques have been employed to achieve this effect, these include, syrup of ipecac-induced emesis, orogastric lavage and activated charcoal/cathartic administration (Easom and Lovejoy 1979, Cupit and Temple 1984).

a. Ipecac-induced emesis.

Syrup of ipecac is the recommended chemical emetic. Ipecac syrup is derived from the Brazil root

(ipecacuanha). The emetic action is due to the two alkaloids emetine and cephaeline. The alkaloid emetine is cardiotoxic. Both alkaloids induce emesis by local gastric irritation and by central stimulation of the chemoreceptor trigger zone in the floor of the fourth ventricle (Dean and Krenzelok 1984). Once activated, coordinated actions of the stomach and esophagus produce vomiting. The average time for the induction of emesis with ipecac syrup ranges from 12 to 24 minutes (Schofferman 1976, Manoguerra and Krenzelok 1978). However, its use as a gastric emptying procedure has been questioned (Neuvonen et al.1983, Tenenbein 1985, Vale et al. 1986). Recently, in a controlled comparative study, this laboratory demonstrated the limited value of syrup of ipecac in reducing ampicillin bioavailability by 38 % compared to control (Tenenbein et al. 1987a).

b. Orogastric lavage.

Historically, orogastric lavage dates back to 1812 where it was implemented as a gastrointestinal decontamination procedure by Physick of Pennsylvania (Major 1934). Today, gastric lavage remains a principle gastric-emptying procedure for drug overdose. However, its effectiveness is controversial (Comstock et al. 1981,

Tenenbein 1985). Evidence from this laboratory demonstrated that ampicillin bioavailabilty was reduced by 32 % with gastric lavage, in contrast to a 38 % and 57 % reduction with ipecac-induced emesis and activated charcoal/cathartic, respectively (Tenenbein et al. 1987a). Proponents of gastric lavage suggest that in many lavage studies, the lavage was not instituted correctly, or with the proper bore sized tube. Criticisms of this procedure include poor treatment efficacy (Tenenbein 1985, Tenenbein 1987, Tenenbein et al.1987a, Tenenbein et al.1987b) and time required to begin treatment i.e. 30 minutes. Moreover, there are numerous complications which can arise during gastric lavage, for example, laryngeal spasm, cyanosis or cardiac arrest (Reid 1970). Certainly, this procedure can cause morbidity and mortality in its own right. These and other complications as well as its poor results make this technique a controversial gastrointestinal decontamination procedure.

c. Activated charcoal.

Activated charcoal is a universal adsorbent and is a commonly employed intervention strategy following acute overdose. It acts like a sponge soaking up poisons within the gastrointestinal tract, thereby preventing their absorption into the blood stream (Easom and Lovejoy 1979,

Cupit and Temple 1984). Burning of wood and organic residues produces charcoal. Activation of charcoal by steam or chemical treatment increases the available surface area for toxin adsorption. Each charcoal particle contains a network of pores. As the toxic material diffuses through the charcoal pores, it subsequently adheres to the internal walls of the pore, thus preventing gastrointestinal absorption. Therefore, the quantity of toxin absorbed to AC, is directly proportional to the total amount of charcoal present, since binding follows the law of mass action (Neuvonen 1982). The adsorptive capacity of AC is also dependent on its total surface area. Commercially, activated charcoal is available as a fine black powder with a surface area in the range of 1000 to 1200 m^2/g. Administered as a suspension in water or sorbitol (70 % w/v), the optimum dose is normally 10 times the ingested substance (Levy and Tsuchiya 1972). This however, is often impractical because the exact amount ingested by a patient is often unknown. Therefore the following dosages have been established as guidelines for charcoal administration following overdose; 25 to 50 g in children less than 5 years and 50 to 100 g in older children and adults (Minocha and Spyker 1986). Large doses of AC are administered, since the presence food and digestive juices may compete with the ingested toxin for adsorption to charcoal. Furthermore, large doses prevent

desorption of toxin from charcoal, prior to its excretion from the body. It should also be mentioned, that a cathartic such as magnesium sulfate, magnesium citrate or sorbitol are often administered with the charcoal to facilitate elimination.

Recently, the administration of multiple doses of activated charcoal (several hours apart) have been used to treat intoxicated patients (Berg et al. 1982). The intent of multiple or pulse dose charcoal administration is to enhance the elimination of toxin from the body in the post-absorptive state. This mechanism has been referred to as gastrointestinal dialysis (Levy 1982). Anecdotal evidence exists to support multiple dose charcoal as an intervention for salicylate poisoning. Reports in the literature demonstrate the efficacy of multiple doses of charcoal in reducing the half-lives of intravenously administered phenobarbital and theophylline. Berg et al. (1982) demonstrated a reduction from 110 to 45 hr for phenobarbital while Berlinger et al. (1983) found a reduction from 6.4 to 3.3 hr for theophylline. To date, no controlled study has been published establishing it as an effective intervention.

Multiple doses of charcoal may enhance the clearance of certain drugs from the body by interfering with the enterohepatic or enterogastric circulation of drugs,

thereby limiting the time in which these substances remain within the body. However, the most accepted mechanism is gastrointestinal dialysis. In this theory, the gastrointestinal epithelium serves as a dialysis membrane. The repetitive dosing and continual presence of AC within the gastrointestinal tract maintain the intestinal intraluminal free toxin concentration near zero, thereby promoting the back-diffusion of toxin from the blood stream across the intestinal epithelium. The drug then binds to the AC present within the intestinal tract and the complex is excreted. Further support for this gastrointestinal mechanism comes from the observations that serum drug concentrations increase after discontinuation of treatment (Lake et al. 1984 , Neuvonen et al. 1985). This can be compared to the rebound effect after conventional dialysis treatment. To this date, no standard treatment protocol has been established. However, 4 hour dosing intervals are often recommended until the absence of toxic signs or symptoms. The cathartic is usually given with the first charcoal dose but not with subsequent charcoal doses because of the risk of fluid and electrolyte loss caused by diarrhea. As a gastrointestinal decontamination strategy for drug overdose, multiple dose charcoal offers several advantages. It not only increases the elimination of certain drugs from the body but is also noninvasive, inexpensive and can be instituted in a

primary care setting.

G. New approaches for the management of acute drug overdose.

The well accepted interventions for acute drug overdose include ipecac-induced emesis, orogastric lavage and activated charcoal/cathartic administration (Easom and Lovejoy 1979, Cupit and Temple 1984). However, the adequacy of ipecac-induced emesis and orogastric lavage has been questioned (Comstock et al. 1981, Neuvonen et al. 1983, Tenenbein 1985, Vale et al. 1986). Recently, single dose activated charcoal/cathartic administration has been advocated (Fane et al. 1971, Chin 1972, Curtis et al. 1984, Kulig et al. 1985, Tenenbein et al 1987a). Unfortunately, circumstances exist in which all three interventions may be less than optimal in treating the poisoned patient. These are: (1) late presentation after ingestion, (2) ingestion of very large amounts of toxic substance (many times the lethal dose) because following a routine gastrointestinal decontamination procedure the residual drug remaining may still be present in toxic amounts, (3) ingestion of a substance which does not adsorb to activated charcoal (eg. iron), (4) The ingestion of a modified release pharmaceutical such as EC-ASA, theophylline, iron etc. These agents remain within the

gastrointestinal tract and beyond the pylorus for excessive periods and are inaccessible to the conventional gastrointestinal interventions. Clearly, newer innovative strategies are required for patient management in the above situation.

A recent advancement in clinical toxicology is the use of whole bowel irrigation (WBI). WBI is a safe routine preparatory procedure for colonoscopy and large bowel surgery (Davis et al. 1980, Goldman et al. 1982, Thomas et al. 1982, DiPalma et al. 1984). It involves the rapid enteral administration of large volumes of a specially formulated lavage fluid. In contrast to the hydroelectric solutions previously used by Hewitt et al. (1973), this special irrigating fluid known generically as polyethylene glycol electrolyte lavage solution (PEG-ELS) was designed by Davis et al.(1980) to specifically prevent the net absorption or secretion of fluid or electrolyte across the the gastrointestinal epithelium. The composiion of PEG-ELS is shown on Table 1. Sodium sulfate and not sodium chloride was chosen as the predominant salt in this preparation because sulfate is not significantly absorbed, thus in turn limiting the sodium absorption. PEG with a mean molecular weight of 3350 is also not absorbed and was added to the preparation to make the lavage fluid iso-osmotic. Non-absorption was confirmed by

Brady et al.(1986) and DiPiro et al (1986). Safety of WBI with PEG-ELS as a preparative procedure for colonoscopy, large bowel surgery and barium enema has been studied in a numerous patients (Ambrose et al. 1983, Ambrose and Keighley 1983, DiPalma et al. 1984, Lubowski et al. 1985, Fitzsimons et al. 1987).

Until recently, there were only sporadic anecdotal case reports indicating the use of WBI as a treatment intervention following drug overdose. The first human controlled study evaluating the efficacy of WBI after a simulated drug overdose was reported by Tenenbein et al (1987b). Large doses of ampicillin (5 g) served as an overdose model for nine human participants. Serial serum ampicillin samples were used to calculate the appropriate kinetic parameters. WBI with PEG-ELS reduced the area under the serum concentration versus time curve (AUC) by 67 % compared to control. In a previous study, again using the same overdose model, Tenenbein et al. (1987a) compared the efficacy of the traditional interventions following drug overdose. Ampicillin bioavailability was reduced by 32 %, 38 % and 57 % by ipecac-induced emesis, orogastric lavage and activated charcoal/cathartic administration respectively. Additionally, the value of WBI has been demonstrated in the treatment of iron overdose (Tenenbein 1987). Since conventional gastric-emptying procedures are not effective and iron does not adsorb to AC, it appears

Table 1. Composition of polyethylene glycol electrolyte lavage solution (Davis et al. 1980).

Constituent	g/l
Polyethylene glycol 3350	60.0
Sodium chloride	1.46
Potassium chloride	0.75
Sodium bicarbonate	1.68
Sodium sulfate	5.68
Water	to 1 l

that WBI may be the intervention of choice following iron overdose. However, further studies are required to confirm this indication.

WBI mechanically cleanses the bowel of its contents thereby preventing absorption of the ingested toxin. The disadvantage of the traditional gastrointestinal decontamination strategies is their inability to act beyond the pylorus, as toxins within the small or large bowel are inaccessible to these techniques. However, unlike conventional therapies, WBI continues to acts beyond the pylorus, which is imperative for the complete removal of ingested toxin.

It has been proposed that WBI not only prevents the absorption of the ingestant but also speeds its elimination from the body. The mechanism here is similar to the gastrointestinal dialysis theory of Levy (1982) for multiple dose charcoal. The large volumes of fluid within the intestinal tract keep the intraluminal toxin concentration low, thereby promoting back diffusion of drug from the blood stream. Lenz et al.(1983) demonstrated that following a subcutaneous injection of phenobarbital bowel irrigated rats had rectal effluents which contained injected drug. It is also possible that bowel irrigation may accelerate the elimination of certain drugs by interrupting their enterohepatic or enterogastric

circulations.

There are several indications for the use of WBI as a gastrointestinal decontamination strategy, one being the treatment of an acute drug overdose with a modified release pharmaceutical. Several delayed release preparations (EC-ASA, theophylline and iron) are frequently prescribed. Their pharmaceutical design (enteric-coating, honeycombed matrix) delays absorption and prolongs the time in which these agents remain within the gastrointestinal tract (Montgomery and Sitar 1986). In general all modified release preparations have an increased interval of time between ingestion and the appearance within the blood. Consequently, following overdose, peak concentration and toxic effects may not be evident until several hours post drug ingestion. Minocha and Spyker (1986) recommend AC and cathartic administration as the intervention of choice for overdose with a modified release pharmaceutical. However, no data are presented with their proposal and examples exist which demonstrate lack of efficacy of their approach (Henry 1983). Goldberg et al.(1987) reported charcoal plus cathartic is more advantageous than charcoal alone after the ingestion of delayed release theophylline. However, none of these investigations (Minocha and Spyker 1986, Henry 1983, Goldberg et al. 1987) consider WBI as a

potential gastrointestinal decontamination strategy after overdose with a modified release pharmaceutical. Clearly, objective data are needed to establish the most effective and safe gastrointestinal decontamination procedure after overdose with a modified release pharmaceutical.

Additionally, the potential of both AC and WBI as consecutive treatments following acute drug overdose requires evaluation. The effectiveness and safety of this approach should be addressed, since any significant change in PEG-ELS osmolality may expose the patient to a potential iatrogenic effect.

H. Dissertation objectives.

1. to evaluate the comparative efficacy of WBI and ACS following the ingestion of a modified release pharmaceutical by determining the kinetic disposition of EC-ASA after institution of these interventions.

2. to determine if multiple dosing with AC can enhance the elimination of salicylate in the postabsorptive state by determining the kinetic disposition of salicylate after multiple dosing with AC.

3. to determine the relative efficacy and safety of concurrent administration of AC and PEG-ELS for gastrointestinal decontamination using an *in vitro* model.

II. METHODS

A. Inclusion criteria for volunteers accepted into both whole bowel irrigation-activated charcoal/cathartic and multiple dose charcoal studies.

Study approval was granted by the University of Manitoba Faculty Committee on the Use of Human Subjects in Research. Informed signed consent was obtained from each participant.

Volunteer acceptance into both studies required good physical health, freedom from chronic diseases, and no history of asthma, ulcers, gastritis, bleeding disorders or salicylate allergy. The volunteer must not be pregnant, lactating or receiving any type of medication. Additionally, for the WBI/ACS study, each volunteer was asked to complete a detailed questionnaire regarding their tolerance to each study limb. Questions asked included the occurrence of abdominal cramping, dizziness and diarrhea. The questionnaire also included a section for each participant to report additional symptoms they experienced. All responses were then ranked on a scale of 1-4 for severity of symptoms ; a ranked score of 1 indicated no symptoms, whereas a ranked score of 4 indicated a maximum severity of symptoms. Each questionnaire was evaluated for the most commonly reported

complaint in both studies. Furthermore, one week after completion of the whole bowel irrigation-activated charcoal/cathartic study, all volunteers were asked the following: "If you overdosed on enteric-coated acetylsalicylic acid and you were offered the choice between bowel irrigation and activated charcoal/cathartic, which would you pick ?"

B. Demographics of healthy volunteers

Demographics of the ten healthy study subjects who participated in each whole bowel irrigation-activated charcoal/cathartic and multiple dose charcoal studies are reported in detail in Tables 2 and 3 respectively.

C. Experimental protocols

a) Whole bowel irrigation-activated charcoal/ cathartic study.

The protocol for this investigation was a randomized, three-limbed cross-over design, with at last one week separating each limb. In all three limbs, each subject ingested 2925 mg (9 tablets each containing 325 mg) of enteric-coated acetylsalicylic acid (EC-ASA, Entrophen^{R}) orally with 250 ml water. All volunteers were

Table 2 Demographics of the ten study subjects who participated in the whole bowel irrigation-activated charcoal/cathartic study after the ingestion of 16.25 mmol (2925 mg) of EC-ASA. All data are reported as mean ± S.D.

SUBJECT	AGE (yr)	SEX	WEIGHT (kg)	HEIGHT (cm)	DOSE (mg/kg)
A	28	M	82	186	37
B	20	F	53	161	57
C	37	M	65	169	46
D	23	M	58	176	52
E	25	M	76	176	40
F	21	F	60	163	50
G	24	M	98	175	31
H	41	M	74	170	41
I	38	F	66	161	46
J	25	F	63	162	48
mean ± S.D.	28±8		70±13	170±8	44±7

Table 3 Demographics of the ten study subjects who participated in the multiple dose activated charcoal study after the ingestion of 15.8 mmol (2880 mg) of (ASA). All data are reported as mean ± S.D.

SUBJECT	AGE (yr)	SEX	WEIGHT (kg)	HEIGHT (cm)	DOSE (mg/kg)
K	37	F	65	169	57
L	28	M	82	186	37
M	37	M	49	166	46
N	27	M	70	173	43
O	25	M	76	176	39
P	24	M	90	185	33
Q	41	M	74	170	40
R	24	M	98	175	30
S	28	F	59	168	51
T	37	F	63	164	48
mean ± S.D.	31 ± 6		73 ± 15	173 ± 7	42 ± 8

fasted 8 hr prior to and for 9 hr after the EC-ASA ingestion except for apple juice (250 ml) provided at the third hr. One limb served as control, while the other two were for treatment interventions. Four hr post EC-ASA dose, each subject submitted to one of the two study interventions, whole bowel irrigation (WBI) or activated charcoal/sorbitol (ACS). Each volunteer was subjected to both interventions in a mutually exclusive fashion and each served as his or her own control (CTL). All dietary restrictions were removed after the twelfth hr post EC-ASA ingestion.

i. Whole bowel irrigation limb.

In this study limb, a 14-French nasogastric tube was passed three hr and fifty minutes post EC-ASA ingestion. The specialized lavage fluid, polyethylene glycol-electrolyte lavage solution (Colyte®), was infused through the tube by gravity at a flow rate between 1.5 - 2.0 l/hr. Treatment was terminated when the rectal effluent was visibly similar to the infusate, with a minimum of 3 and a maximum of 5 hr of infusion.

ii. Activated charcoal/cathartic limb.

During this limb of the study, each subject ingested 50 g activated charcoal in 70 % w/v sorbitol (Charcodote^{R}) in a final volume of 250 ml. Ten minutes was allowed for each subject to consume the ACS preparation.

b) Multiple dose charcoal study.

This protocol consisted of a randomized two-limbed cross-over design with at least one week separating each limb. One limb served as control, and the other for treatment intervention. In both limbs each volunteer consumed a suspension containing 2880 mg (36 tablets each containing 80 mg) of powdered acetylsalicylic acid, (ASA,Baby Aspirin Bayer^{R}) in 250 ml cold water (5 ^{o}C). All volunteers were fasted 8 hr prior to the ASA dose and remained fasted until 12 hr post ingestion. Each volunteer was provided with apple juice (250 ml) at the third and ninth hr after drug ingestion. All dietary restrictions were removed after the twelfth hr post ASA ingestion. This study was designed with the intent of beginning the charcoal intervention in the post absorptive state. Thus the ASA was administered as a suspension in very cold water to fasted volunteers and 4 hr were allowed to pass

prior to the first charcoal dose.

i. Multiple dose charcoal limb.

The treatment limb of the the study consisted of each subject ingesting 25 g of activated charcoal (AC) in 125 ml water at 4,6,8,and 10 hr post ASA ingestion. At the fourth hr, each volunteer received 30 g magnesium sulfate dissolved in 60 ml water along with the charcoal dose. The magnesium sulfate was provided to counteract the constipating effects of the activated charcoal.

c. In vitro polyethylene glycol (PEG) binding studies.

i. PEG/AC binding study.

The design protocol for the in vitro PEG/AC binding study is displayed in Table 4. Powdered PEG and AC were obtained from the (Reed and Carnrick Drug Company (Toronto, Canada) and Pharma Science Inc. (Montreal, Canada) respectively. Various amounts of PEG were dissolved in reagent grade water as per study protocol. The PEG solutions were then mixed with powdered AC in 50 ml Erlenmeyer flasks and incubated in a Dubnoff metabolic shaker at 25 ^{o}C for 30 minutes. Decanted supernatants were

analyzed for PEG concentrations and for osmolality. All PEG/AC combinations and concentrations were chosen to include a simulation for the clinical situation.

ii. PEG-ELS/AC/SA binding study.

The design protocol for the in vitro PEG-ELS/AC/SA binding study is shown in Table 5. The PEG-ELS (Colyte®) was reconstituted to to 4.0 l with reagent grade water (as prescribed by the manufacturer). The PEG-ELS/AC/SA were mixed in 50 ml Erlenmeyer flasks and incubated in a Dubnoff metabolic shaker at 25°C for 30 minutes. Decanted supernatants were analyzed for SA and PEG concentrations and for osmolality. All combinations and concentrations were chosen to simulate an equivalent clinical situation.

D. Sample collection

a. Serum samples for whole bowel irrigation-activated charcoal/cathartic study.

In each of the three study limbs, an intravenous catheter was inserted into a forearm vein of each volunteer prior to the EC-ASA ingestion. The catheter was kept patent with 2 ml of bacteriostatic saline solution

(Shearer 1987). Blood samples were collected at 0, 2, 3, 4, 5, 6, 8, 9, 10, 12 and 14 hr. Before each sample was collected, 2 ml of blood were discarded from the intravenous catheter to ensure that the collected sample was not diluted with saline. The catheter was removed after the fourteenth hr and the final three blood samples 24, 32 and 48 hr drawn by venipuncture. Serum from each sample was immediately separated by centrifugation (1000 x g for 10 minutes) and frozen at -20 ^{o}C for analysis by high performance liquid chromatography (HPLC).

b. Serum samples for multiple dose charcoal study

In both limbs of the study an intravenous catheter was inserted into a forearm vein of each volunteer prior to the ASA ingestion. The catheter was kept patent with 2 ml of bacteriostatic saline solution. Blood samples were collected at 0, .5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hr. Before each sample was collected, 2 ml of blood was discarded from the intravenous catheter to ensure that the sample was not diluted with saline. The intravenous catheter was removed after the 12 hr sample and the final three samples 24,32 and 48 hr drawn by venipuncture. Serum from each sample was separated by centrifugation (1000 x g for 10 minutes) and frozen at -20 ^{o}C for analysis by HPLC.

Table 4 Design protocol for the in vitro PEG/AC binding study. All constituents were mixed to a final volume of 10 ml and incubated at 25 °C for 30 minutes.

Ratio (PEG/AC)	PEG (mg)	AC (mg)
* 2.4:1	530	220
1.2:1	270	220
0.6:1	130	220

* Clinical simulation.

Table 5 Design protocol for the *in vitro* PEG/AC/SA binding study. All constituents were mixed to a final volume of 30 ml and incubated at 25 °C for 30 minutes.

Ratio (by volume) (PEG-ELS/AC)	SA (ml)	AC (ml)	PEG-ELS (ml)	PBS (ml)
20:1	3.0	1.0	20.0	6.0
10:1	3.0	1.0	10.0	16.0
* 8:1	3.0	1.0	8.0	18.0
4:1	3.0	1.0	4.0	22.0
2:1	3.0	1.0	2.0	24.0
1:1	3.0	1.0	1.0	25.0
CTL	3.0	0	0	27.0
CTL	3.0	0	27.0	0

* Clinical simulation.

AC concentration=200 mg/ml

SA concentration=5000 mg/l

PEG-ELS=Colyte®

Phosphate buffered saline (PBS)=pH 7.4

c. Urine samples for whole bowel irrigation-activated charcoal study.

Each subject was instructed to provide complete urine samples at designated intervals post EC-ASA ingestion 0-4, 4-9, 9-14, 14-24, 24-32 and 32-48 hr. Urine volume was measured and an aliquot frozen for quantitative analyses for total SA equivalents by Trinder's method (Trinder 1954).

d. Urine samples for multiple dose charcoal study.

Each subject was instructed to provide complete urine samples at designated intervals post ASA ingestion 0-6, 6-12, 12-24, 24-32 and 32-48 hr. Urine volume was measured and an aliquot frozen for quantitative analyses for SA equivalents by Trinder's method.

E. Principles of high performance liquid chromatography (HPLC).

HPLC is a technique used to separate the constituents of a chemical mixture. Unlike conventional forms of chromatography, HPLC is more advantageous in separating chemical mixtures because of it's speed, high

resolution, and high sensitivity (Schram 1982).

The essentials of a HPLC system include a pump, injector, column, detector and recorder. Since the stationary phase is packed with micron sized particles, a pump capable of generating high pressures is required to move the mobile phase through the column. Interaction of the injected solute with both the stationary (column) and the mobile (solvent) phases can be manipulated to achieve maximum separation of the injected mixture. As each component elutes from the column, its concentration relative to the other components is measured by a detector. An electrical response generated by the detector to each of the eluted components is displayed on a chart recorder as a chromatogram.

F. Sample analysis.

a. Determination of serum SA concentration by HPLC.

HPLC was used to determine serum SA concentrations by a technique developed in this laboratory by Montgomery and Sitar (1981). The major components of the system included a model 6000A pump, model 710B auto-injector, uBondapak C-18 column and a model 441 absorbance detector set at 313 nm (Waters Scientific Ltd. Mississauga, Ontario). The mobile phase was 20% acetonitrile in

purified double distilled water, pH 2.3 with phosphoric acid. The flow rate of the pump was 1.1 ml/minute. Serial serum samples were prepared for analysis by mixing equal volumes of sample and acetonitrile which contained 16 mg/l o-anisic acid as internal standard. Each sample was mixed and centrifuged at 1000 x g for 10 minutes. The supernatant was removed and 25 ul was injected for determination of serum SA concentrations.

b. Determination of total urinary SA metabolite content by Trinder's method.

Urine samples (0.5 ml) were mixed with reagent grade water (5.0 ml) and Trinder's reagent (5.0 ml) (ferric nitrate, mercuric chloride and hydrochloric acid, Trinder 1954). Urine blanks were prepared from urine (0.5 ml) and mixed with 85 % w/v phosphoric acid (0.5 ml) and Trinder's reagent (4.5 ml). Mixtures were allowed to react for 5.0 minutes before centrifugation (1000 x g for 15 minutes). Absorbance of each sample at 540 nm in a Beckman model DU8 spectrophotometer was used to determine total urinary salicylate content expressed as SA equivalents.

c. Determination of total PEG content in the *vitro* PEG binding studies.

The method utilized to quantify total PEG content was a modification of the turbidimetric method of Hyden (1955). Decanted supernatants were diluted 1:100 with reagent grade water and mixed with 1 ml of each, 0.2 N zinc sulfate, 0.2 N barium hydroxide and 10 % w/v barium chloride. Following a 10 minute centrifugation at 1000 x g filtrate supernatants (2.5 ml) were transferred to rectangular cuvettes and mixed with 4.0 ml of a solution containing 30 % w/v trichloroacetic acid and 5 % w/v barium chloride for 5-6 minutes. Turbidity was measured in a Beckman model DU8 spectrophotometer set at 650 nm. Standard curves were derived from filtrates to which known quantities of PEG had been added. Regression analysis was used to calculate supernatant PEG concentrations from standard curves.

d. Osmolality determination of supernatants from *in vitro* PEG binding studies.

Osmolality of all supernatants was determined with a model 5500 vapor pressure osmometer (Wescor Inc.). After calibration of the osmometer, 10 ul of supernatant was injected into the osmometer for analysis. Osmolality was

then expressed as mmol/kg.

G. Data analyses

a. Determination of serum SA concentration.

Serum SA concentrations were determined by peak height ratio analysis to an internal standard (o-anisic acid) from a standard curve (Montgomery and Sitar 1981). The standard curve was derived from blank sera to which known quantities of SA were added. These samples were prepared and analyzed as previously described.

b. Determination of pharmacokinetic parameters.

Serum data obtained from each of the study limbs was used to calculate the kinetic disposition characteristics of SA. These parameters included peak serum SA concentration, time to peak serum SA concentration, total area under the serum concentration time curve (AUC) and apparent serum SA clearance (Gibaldi and Perrier 1982).

i. Peak SA concentration

Peak SA concentration was determined to be the maximum serum SA concentration measured following the ingestion of the EC-ASA or ASA dose.

ii. Time to peak serum SA concentration

Time to peak serum SA concentration was determined to be that time at which the maximum serum SA concentration was measured following ingestion of the ASA or EC-ASA dose.

iii. Total AUC.

This kinetic parameter was calculated from the integration of all volunteer serum SA concentrations obtained from the beginning of drug administration to the end of the 48 hr protocol against time. The trapezoidal formula was used for this calculation (Gibaldi and Perrier 1982).

iv. Apparent serum SA clearance

Apparent serum SA clearance (ml/kg/hr) was calculated for each volunteer with the formula Cl=dose/AUC (Gibaldi and Perrier 1982). The weight corrected dose of

ASA ingested (mg/kg), (adjusted for change in molecular weight to SA) was divided by the total AUC (mg.hr/l.kg) obtained during each limb of the study.

H. Statistical Analyses.

Data were assessed for treatment effects by repeated measures analysis of variance (ANOVA) in the 3 limb study and by paired t-test for the 2 limb study. Tukey's test of non-additivity was used to test for non-homogeneity of variance (3-limb study); data were log transformed when necessary, i.e. when Tukey's test was significant, indicating non-homogeneity of variance. When a significant treatment effect was indicated by ANOVA, Duncan's multiple range test was used to identify the superior treatment. The minimum level for a significant difference was $p \leq 0.05$. All data are reported as mean $\pm$ S.D. (Wilkinson 1986).

III. RESULTS

A. Salicylic acid assay by HPLC.

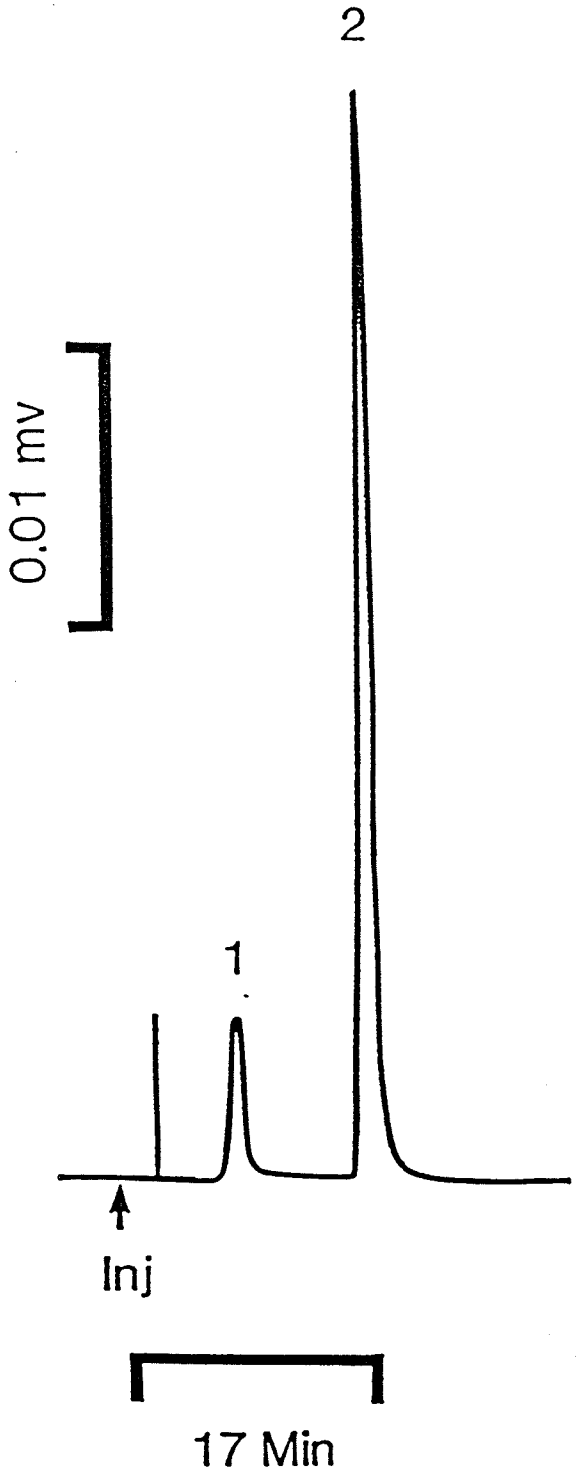
A sample chromatogram is shown in Figure 1. Peak height ratios for SA/internal standard (o-anisic acid) were obtained from standard concentration curves, which ranged from 38 to 300 mg/l. Linearity of all standard curves was accepted with a correlation coefficient $\geq$ 0.99. Retention times for internal standard (o-anisic acid) and SA by HPLC analyses were 8.5 and 16.5 minutes respectively. All samples were analyzed in duplicate with less than 10 % variation between duplicates. The lower limit of SA detection was 0.3 mg/l for all samples.

B. Pharmacokinetic parameters of SA.

a. Whole bowel irrigation-activated charcoal/ cathartic study.

All pharmacokinetic parameters of SA for the whole bowel irrigation-activated charcoal/cathartic study are summarized in Table 6. All volunteers completed each of two study protocols. The maximum peak serum SA concentration was 250 mg/l which is below the lower limit for toxicity i.e. 300 mg/l. Some of the subjects vomited

Figure 1. Representative serum salicylic acid chromatogram by high performance liquid chromatography. Sample injection of o-anisic acid (internal standard) and salicylic acid. Time of sample injection (inj), Peak 1 (internal standard), peak 2 (salicylic acid) are shown.


2
0.01 mv
1
Inj
17 Min

small amounts during the PEG-ELS infusion. Three volunteers demonstrated evidence of clinical dehydration such as dizziness, light headedness, diaphoresis, palor and thirst in the latter stages of the ACS limb. Volunteer questionnaire responses are reported in Table 7. Other symptoms reported by volunteers are shown in Table 8. Additionally, 9 out of the 10 volunteers reported whole bowel irrigation as the choice intervention strategy, following acute overdose with EC-ASA.

i. Peak and time to peak serum SA concentration.

There was no apparent difference between CTL, ACS or WBI interventions prior to the eighth hr post drug ingestion on peak serum SA concentrations (Figure 2). However, at the eighth hr post dose, WBI demonstrated the first significant treatment effect compared to both CTL and ACS ($p<0.01$). The WBI intervention remained the superior treatment for the duration of the sampling interval ($p<0.01$). Following the ninth hr post dose, the ACS treatment was significantly different from CTL ($p<0.01$). Both treatments remained significantly different from each other ($p<0.05$) and CTL ($p<0.001$) until the fourteenth hr post dose, after which no significant difference between treatments could be demonstrated. Similarly, both ACS and WBI demonstrated a significant

Table 6 Drug disposition characteristics for CTL, ACS and WBI study limbs following the acute ingestion of 16.25 mmol (2925 mg EC-ASA). Data are reported as mean ± S.D.

Treatment	Peak serum SA concentration (mg/l)	Time to peak (hr)	AUC (ml/kg/hr)	Apparent clearance (ml/kg/hr)
CTL	179 ± 29	10 ± 22	51 ± 24	11 ± 3
ACS	128 ± 54	7 ± 2	22 ± 16	25 ± 14
WBI	84 ± 54	6 ± 0	12 ± 11	83 ± 68

A treatment effect ($p<0.001$) was demonstrated in all groups. There was a significant difference between treatments ($p<0.05$) for peak SA concentration, AUC and apparent SA clearance.

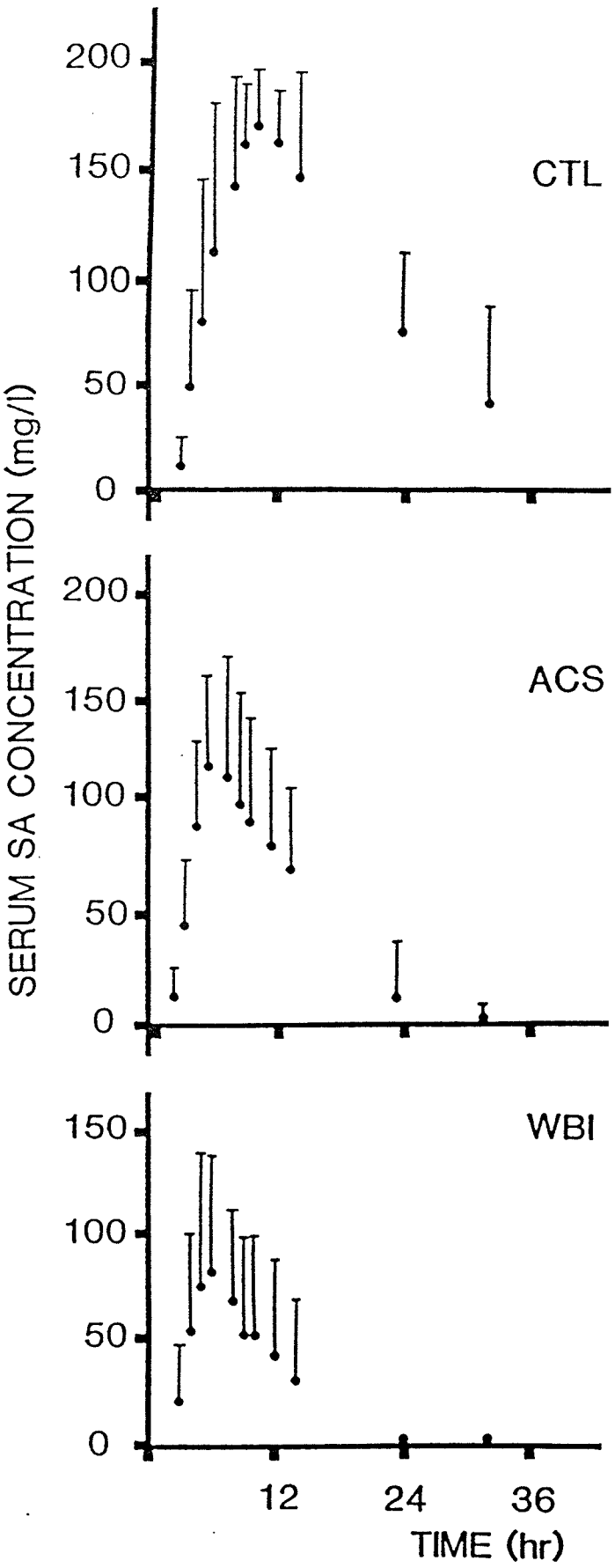
Table 7 Whole bowel irrigation-activated charcoal/ cathartic study volunteer questionnaire responses following completion of each study limb.

Symptom	Number of volunteers		
	CTL	ACS	WBI
Nausea			
None	10	1	3
Mild		2	2
Moderate		3	5
Severe		4	
Vomiting			
None	10	7	1
Mild		1	2
Moderate		2	5
Severe			2
Abdominal cramps			
None	10	1	5
Mild		4	3
Moderate		2	2
Severe		3	
Anal irritation			
None	10	3	4
Mild		5	5
Moderate		1	1
Severe		1	

Table 8 Other symptoms reported by volunteers in whole bowel irrigation-activated charcoal/cathartic study. Each symptom represents its occurrence in one volunteer.

Treatment	Other symptoms
CTL:	headache
	buzzing in ears
	hunger and thirst
	lightheaded
	tired
ACS:	lightheaded
	near syncope with first stool
	headache
WBI:	chills
	"hyperactive stomach"
	sneezing and runny nose
	headache
	headache

Figure 2. Serum salicylic acid concentration versus time curve for whole bowel irrigation-activated charcoal/cathartic study, after the ingestion of 2925 mg of EC-ASA. Individual data are reported with mean (——) ± S.D. (---). A treatment effect was demonstrated ($p<0.001$) and treatments differed from each other ($p<0.05$).


200
150
100
50
0
CTL
200
150
100
50
0
ACS
150
100
50
0
WBI
SERUM SA CONCENTRATION (mg/l)
12
24
36
TIME (hr)

treatment effect on the time to peak SA concentration compared to CTL ($p<0.001$) (Figure 3 and Table 6).

ii. AUC.

Table 6 and Figure 4 show that AUC was significantly reduced following both the ACS and WBI interventions ($p<0.001$) compared to CTL. Moreover, WBI demonstrated its superiority over both CTL ($p<0.01$) and ACS ($p<0.05$) in reducing the AUC of SA in the 14 hr sampling period.

iii. Apparent serum SA clearance.

The final pharmacokinetic parameter used to assess treatment effect was the apparent serum SA clearance. SA clearances for all study limbs are located in Table 6, and in Figure 5. Both ACS and WBI significantly increased ($p<0.001$) the apparent SA clearance compared to CTL. Furthermore, the WBI intervention was superior to both the CTL ($p<0.01$) and ACS limbs ($p<0.05$).

Figure 3. Peak serum SA concentration for whole bowel irrigation activated charcoal/cathartic study, after the ingestion of 16.25 mmol (2925 mg) of EC-ASA. Individual data are reported with mean (——) ± S.D. (---). A treatment effect was demonstrated ($p<0.001$) and treatments differed from each other ($p<0.05$).

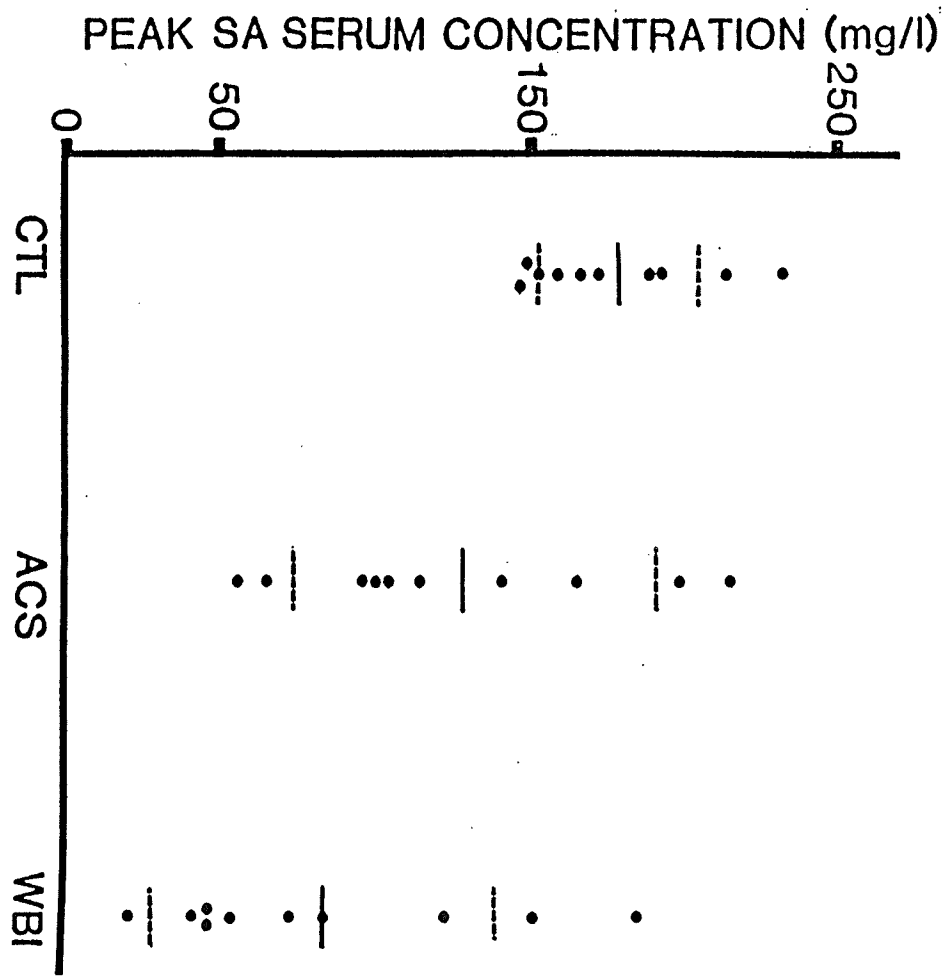

PEAK SA SERUM CONCENTRATION (mg/l)
0
50
150
250
CTL
ACS
WBI

Figure 4. The area under the serum salicylic acid concentration versus time curve for whole bowel irrigation activated charcoal/ cathartic study, after the ingestion of 16.25 mmol (2925 mg) EC-ASA. Individual data are reported with mean (——) ± S.D. (---). A treatment effect was demonstrated ($p<0.001$) and treatments differed from each other ($p<0.05$).

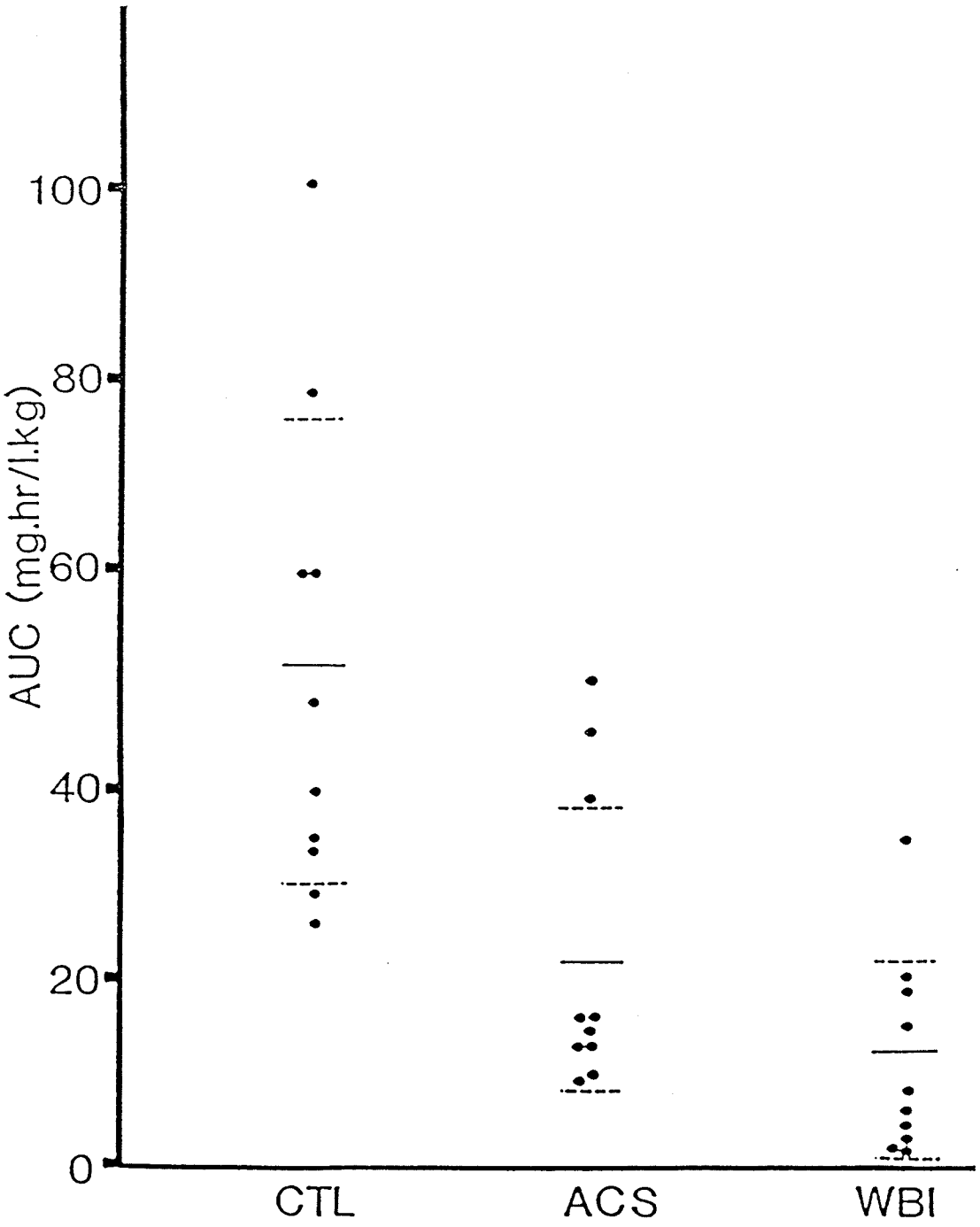
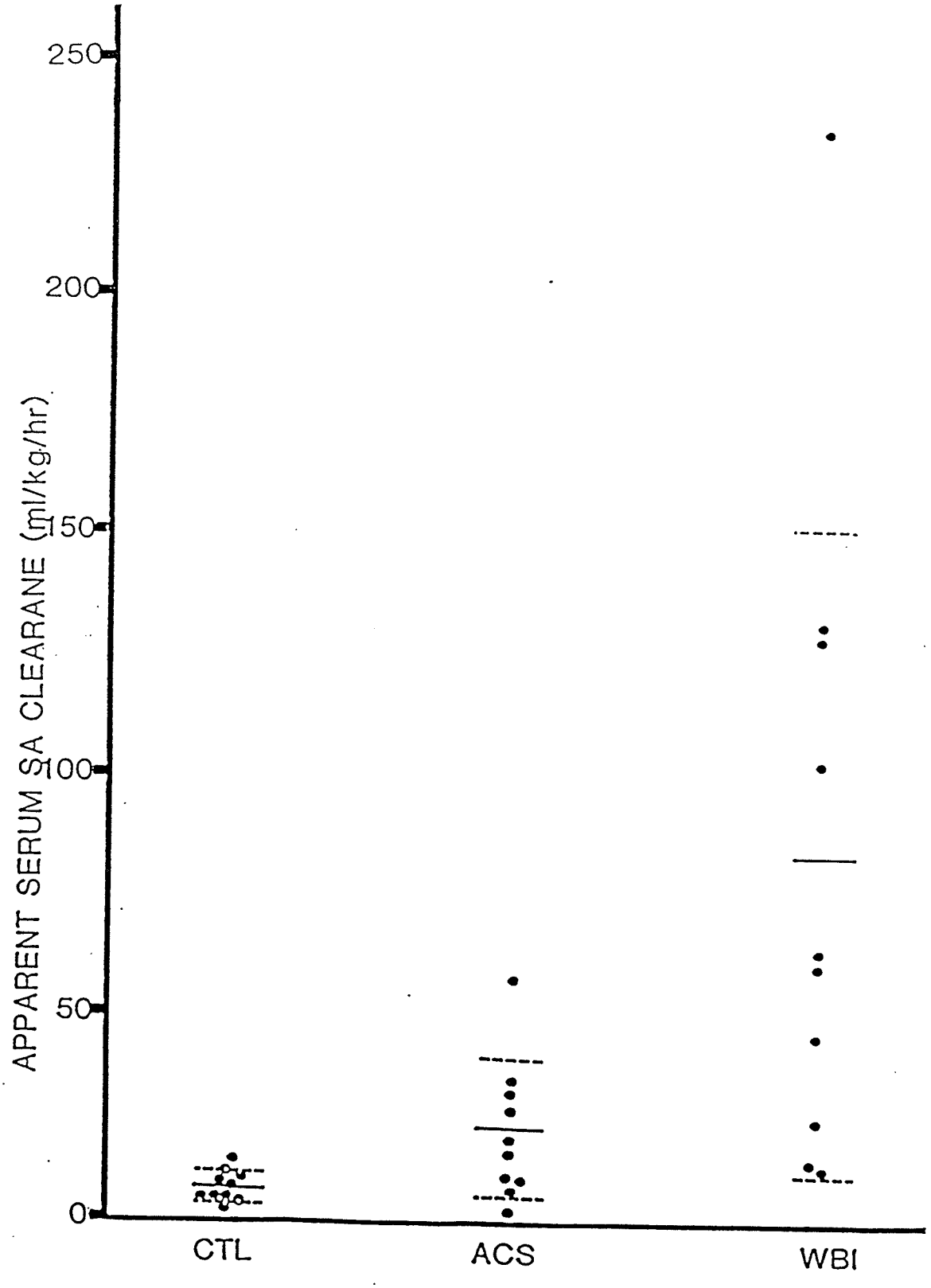

AUC (mg.hr/l.kg)
100
80
60
40
20
0
CTL
ACS
WBI

Figure 5. Apparent serum salicylic acid clearance rates for whole bowel irrigation-activated charcoal/cathartic study, after the ingestion of 16.25 mmol (2925 mg) EC-ASA. Individual data reported with mean (——) ± S.D. (---). A treatment effect was demonstrated ($p<0.001$) and treatments differed from each other ($p<0.05$).


APPARENT SERUM SA CLEARANE (ml/kg/hr)
250
200
150
100
50
0
CTL
ACS
WBI

b. Total urinary SA metabolite content by Trinder's analysis.

Urinary content (Table 9) as measured by total SA equivalents was significantly reduced by ACS and WBI interventions ($p<0.001$) compared to CTL.

c. Multiple dose charcoal study.

All pharmacokinetic parameters for the multiple dose charcoal study are summarized in Table 10.

i. Peak and time to peak serum SA concentration.

There was no significant difference between the CTL and AC limbs on the peak SA serum concentration (Figure 6). Also, there was no significant difference between CTL and AC limbs on the time to peak SA serum concentration (Table 10).

ii. AUC.

When AUC was calculated for the entire sampling interval (Figure 7) there was no apparent difference between the CTL and AC limbs. However, when AUC was calculated to include only those samples following the treatment intervention (i.e. after fourth hr post ASA dose) a significant effect (Table 10) was demonstrated ($p<0.05$).

iii. Apparent serum SA clearance.

The data shown in (Figure 8 and Table 4) indicate that there was no significant difference between the CTL limb and AC intervention.

d. Total urinary SA content by Trinder's method

Urinary content (Table 11) as measured by total SA equivalents was significantly reduced by the charcoal intervention ($p<0.01$) compared to CTL.

Table 9 Urine analysis for total SA equivalents by Trinder's method after the ingestion of 16.25 mmol (2925 mg) of EC-ASA. Data are presented as mean ± S.D.

Treatment	SA equivalents (mmol)
CTL	9.8 ± 0.9
ACS	4.5 ± 1.9
WBI	4.2 ± 2.2

Treatment effect among interventions ($p<0.001$).

Table 10 Drug disposition characteristics for CTL and AC study limbs following the acute ingestion of 15.8 mmol SA (2880 mg ASA). Data are reported as mean ± S.D.

Treatment	Peak serum SA concentration (mg/l)	Time to peak (hr)	* AUC (mg.hr/l.kg) (4hr-48hr)	Apparent clearance (ml/kg/hr)
CTL	192 ± 27	4 ± 1	2139 ± 517	11 ± 2
AC	203 ± 32	3 ± 1	1950 ± 456	12 ± 2

There was no significant difference between treatment intervention and CTL.

* AUC calculated from beginning of treatment intervention to end of sampling period was different from CTL ($p<0.05$).

Figure 6. Peak serum salicylic acid concentration data for multiple dose charcoal study, after the ingestion of 15.8 mmol (2880 mg) of ASA. Individual data are reported with mean (——) ± S.D. (---). There was no significant treatment effect.

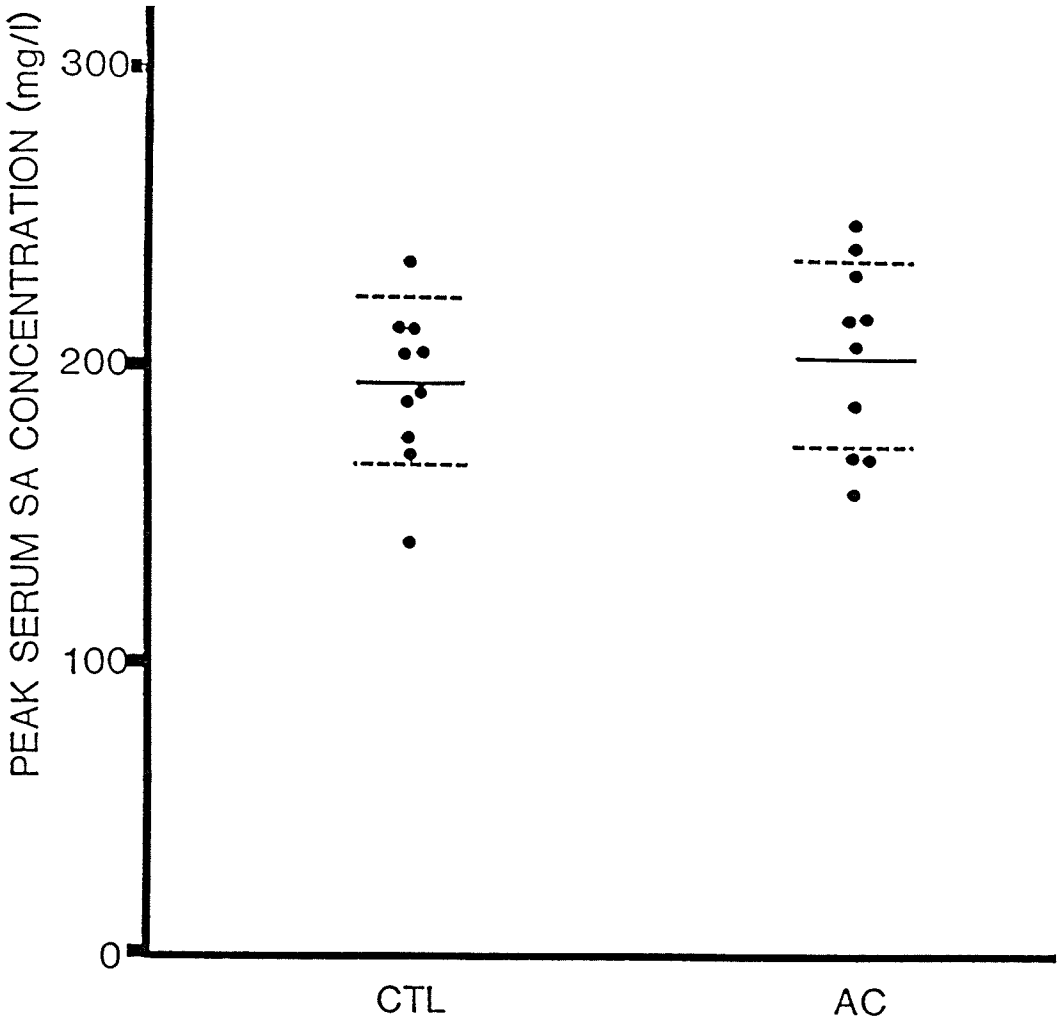
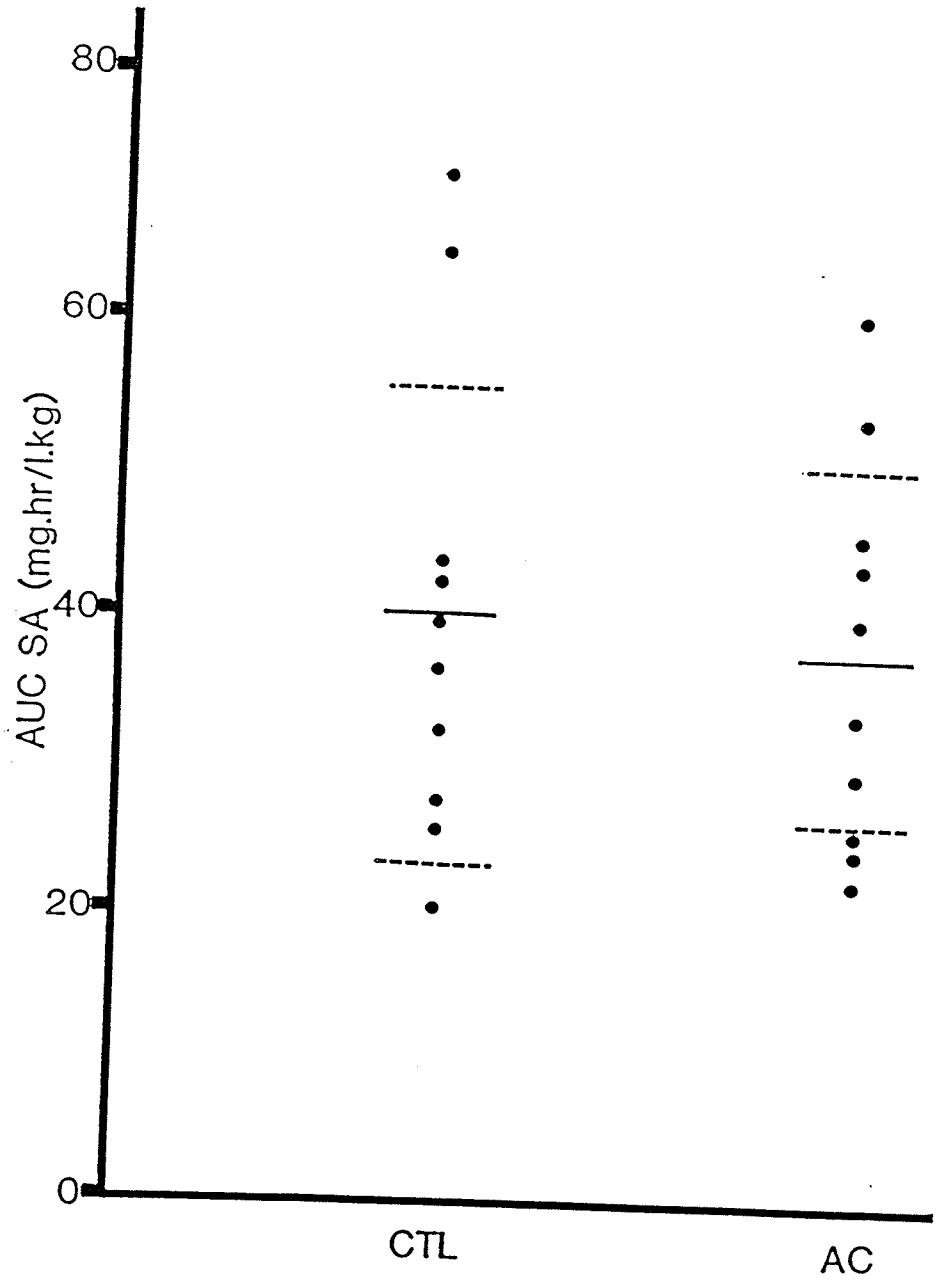

PEAK SERUM SA CONCENTRATION (mg/l)
300
200
100
0
CTL
AC

Figure 7. The area under the serum salicylic acid concentration versus time curve for the multiple dose charcoal study, after ingestion of 15.8 mmol (2880 mg) ASA. Individual data are reported with mean (——) ± S.D.(---) for the entire sampling period. There was no significant treatment effect.


80
60
40
20
0
AUC SA (mg.hr/l.kg)
CTL
AC

C. In vitro PEG binding studies.

i. PEG/AC binding study.

The results of the in vitro PEG/AC binding study are depicted in Table 12. These data demonstrate that PEG adsorbs to AC. However, no clinically significant change in osmolality was demonstrated in any of the supernatants analyzed.

ii. PEG-ELS/AC/SA binding study.

Initial experiments demonstrated that SA is completely bound to AC in absence of PEG-ELS. The results of the in vitro PEG-ELS/AC/SA binding study are shown in Table 13. The data suggest that PEG-ELS interferes with the complete adsorption of SA to AC. The percentage of SA bound to AC decreased as a function of the PEG-ELS to AC ratio. These studies demonstrate interference between PEG-ELS and the adsorption of SA to AC. No clinically significant changes in osmolality were detected in any of the supernatants analyzed.

Figure 8. Apparent serum salicylic acid clearance rates for the multiple dose charcoal study, after the ingestion of 15.8 mmol (2880 mg) ASA. Individual data are reported with mean (——) ± S.D. (---). There was no significant treatment effect.

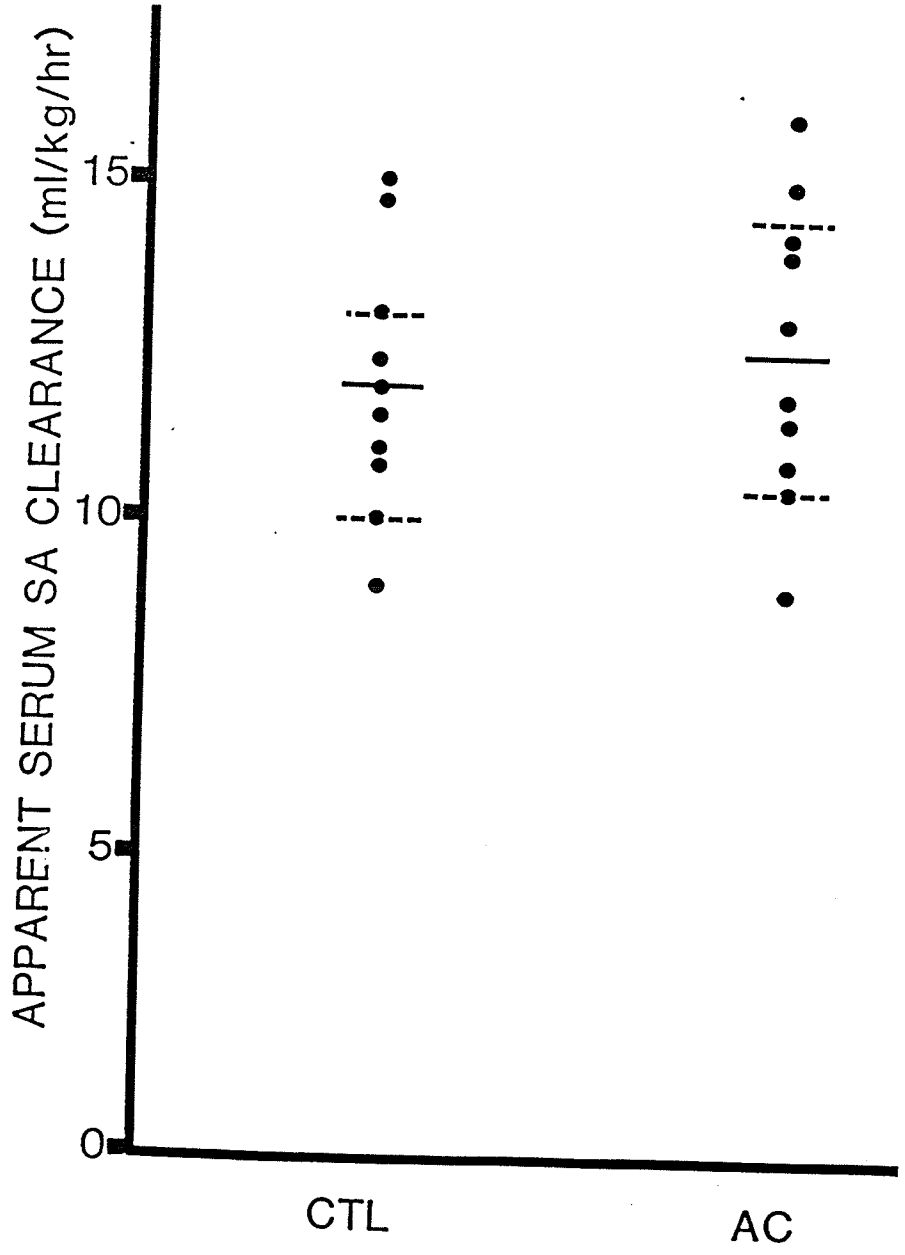

APPARENT SERUM SA CLEARANCE (ml/kg/hr)
15
10
5
0
CTL
AC

Table 11 Urinary analysis for total SA equivalents by Trinder's method after the ingestion of 15.8 mmol (2880 mg) of ASA. Data are presented as mean ± S.D.

Treatment	SA equivalents (mmol)
CTL	9.1 ± 1.5
AC	7.5 ± 1.2

There was a significant difference between groups ($p<0.01$).

Table 12 Results from *in vitro* PEG/AC binding study, following incubation at 25°C for 30 minutes. Supernatants were analyzed for PEG content and osmolality.

	Ratio PEG/AC	PEG concentration (mg/ml)	% PEG bound to AC	Osmolality predicted (mosmol)	Osmolality observed (mosmol)
*	2.4:1	43	16	66	67
	1.2:1	17	32	62	65
	0.6:1	8	38	59	65

* Clinical simulation.

Table 13 Results from the in vitro PEG/AC/SA binding study, following incubation at 25 °C for 30 minutes. Supernatants were analyzed for PEG and SA content and for osmolality. See Table 5 for design protocol.

Ratio PEG-ELS/AC (by volume)	SA conc. (mg/l)	PEG conc. (mg/l)	Osmolality predicted (mosmol)	Osmolality observed (mosmol)
CTL[1]	504	-	271	270
CTL[2]	473	50	272	276
1:1	235	5	262	261
2:1	353	5	262	261
4:1	380	7	262	260
8:1	390	13	262	257
10:1	386	17	263	257
20:1	330	30	264	257

[1] CTL PBS

[2] CTL PEG

IV. DISCUSSION

A. Pharmacokinetic parameters of SA.

a. Whole bowel irrigation-activated charcoal/ cathartic study.

This was the first human study which evaluated the comparative efficacies of ACS and WBI interventions following a simulated drug overdose with a modified release pharmaceutical.

EC-ASA was chosen as our overdose model because its relative toxicity is less than other modified release agents such as theophylline, thereby permitting the administration of larger quantities to simulate the overdose situation. Also a salicylate preparation was chosen because of the demonstrated expertise by this laboratory in its measurement (Montgomery and Sitar 1986).

Acute overdose with a modified release pharmaceutical presents unique problems for health care providers. The absorption lag time of modified release preparations is longer than for conventional preparations. Consequently, after overdose, peak drug concentration and toxic effects are not evident until several hours post

ingestion. Thus, gastrointestinal decontamination is imperative at the initial stages of overdose to prevent drug absorption and toxicity. The traditional gastrointestinal decontamination procedures previously described (ipecac-induced emesis, orogastric lavage and activated charcoal/cathartic) may be less than optimal following overdose with such agents. Until now, there has been no human controlled study evaluating the comparative efficacies of WBI and ACS following acute overdose with a modified release pharmaceutical.

The kinetic disposition of SA was assessed for treatment effect by the conventional pharmacokinetic parameters. Both interventions significantly reduced the time to peak. This was expected and consistent with other data previously reported by Montgomery and Sitar (1986) and Martio and Kahela (1983). Similarly, both interventions significantly reduced the peak serum SA concentration from CTL (Table 6, Figure 2). The first significant treatment effect was demonstrated by the WBI intervention (Figure 2) at the eighth hr post ingestion. This effect was significantly different from both CTL and ACS interventions and remained the superior treatment for the duration of the sampling interval. Furthermore, ACS did not demonstrate a significant treatment effect until the ninth hr post dose. Both interventions remained

significantly different from CTL and from each other until the fourteenth hr post dose, after which no difference between treatments existed.

The AUC was significantly reduced by 55 % and 71 % from CTL by ACS and WBI respectively (Figure 4). The only other controlled human study in the literature examining the role of WBI after overdose was reported by this laboratory (Tenenbein et al. 1987b). In this study WBI reduced the bioavailability of ampicillin following a simulated overdose by 67 % compared to CTL. Thus this study corroborates the previous one establishing WBI as an effective gastrointestinal decontamination procedure.

Both ACS and WBI significantly increased the apparent SA clearance from CTL, with WBI the superior intervention (Figure 5). Moreover, the urinary data support this interpretation as indicated by the significant treatment effect that both ACS and WBI had on total SA equivalents recovered. Both treatments reduced the total urinary recoverable SA equivalents compared to CTL. Since each intervention accelerates SA elimination through a non-renal mechanism, i.e. gastrointestinal tract, it is reasonable to expect a reduced renal excretion of SA equivalents. Clearly, both sera and urinary data reflect the superiority of the WBI

intervention to CTL and ACS.

It should also be mentioned that in the previous study (Tenenbein et al.1987b), WBI was begun one hour post dose compared to four hours post dose in this present study. This further strengthened our overdose model since there is an average delay of 3.3 hr for adults to present for treatment following acute overdose (Kulig et al. 1985). Goldberg et al. (1987) recently reported that bioavailability of delayed release theophylline could be reduced by approximately 70% following treatment with multiple doses of activated charcoal plus sorbitol. However, 3 subjects in our study and 2 in Goldberg's study experienced symptoms of clinical dehydration possibly from the sorbitol.

WBI mechanically cleanses the bowel of its contents thereby preventing absorption of the ingested toxin. It acts beyond the pylorus and is superior to traditional gastrointestinal decontamination procedures (Tenenbein et al. 1987a, Tenenbein et al. 1987b). In all instances, WBI was superior to CTL and ACS without the adverse effects observed and previously reported (Goldberg et al. 1987) for the ACS intervention. These data support WBI for gastrointestinal decontamination after overdose of EC-ASA.

b. Multiple dose charcoal study.

Recently, multiple doses of AC have been suggested for the the management of the poisoned patient (Minocha and Spyker 1986). Unlike the conventional single dose charcoal therapy, multiple doses of charcoal have been shown to enhance the elimination of absorbed toxin from the body (Berg et al. 1982, Berlinger et al. 1983). The proposed mechanism of action has been termed gastrointestinal dialysis (Levy 1982). The gastrointestinal epithelium serves as a dialysis membrane as drug diffuses into the intestine from the blood stream. The enhanced elimination of phenobarbital (Berg et al.1982) and theophylline (Berlinger et al. 1983) has been previously studied. Until this present study salicylates had not been evaluated in a controlled manner.

Conventional pharmacokinetic parameters were used to assess treatment efficacy of treatment Table 10. The peak serum SA concentrations are displayed in Figure 6, total AUC in Figure 7, and apparent SA clearance in Figure 8. The integration of AUC from the beginning of treatment intervention, 4 hr post ingestion of ASA, to the end of the sampling period, demonstrated a modest reduction in AUC compared to CTL ($p<0.05$). This effect was also reflected by a reduction in the total Trinder urinary SA

equivalents recovered in charcoal treated subjects (Table 11). However, these findings should be interpreted with caution since Trinder analysis is less sensitive for SA metabolites i.e. salicyluric acid and gentisic acid (Montgomery and Sitar 1981). Consequently, interference from these metabolites may grossly underestimate total SA content by Trinder analysis. Thus, validity of total urinary SA equivalents by Trinder's colorimetric method is less rigorous than the serum SA data by HPLC.

B. In vitro PEG binding studies.

Activated charcoal/cathartic administration had been advocated by Curtis et al. (1984), Kulig et al.(1985) and Tenenbein et al. (1987a) as the intervention of choice following acute overdose. Tenenbein et al. (1987b) demonstrated the efficacy of WBI. Both interventions have potential benefit, and it is postulated that their co-administration, may have synergistic effects. PEG-ELS solution was specifically designed to prevent a net secretion or absorption of fluid or electrolyte across the gastrointestinal epithelium (Davis et al. 1980). AC does not bind simple electrolytes but it may bind PEG. It is therefore possible that the physical nature of the PEG-ELS may become altered if consecutively administered with AC. If this occurred tonicity of the lavage fluid

would decrease, resulting in fluid shift from the gastriontestinal lumen into the intravascular space. This could expose the patient to a potential iatrogenic effect.

a. PEG/AC binding study.

The *in vitro* PEG/AC study indicated that PEG does bind to AC. Moreover, as the PEG to AC ratio was reduced the percent binding of PEG to AC increased. This effect was expected and consistent with the *in vivo* observation by Levy and Tsuchiya (1972) that efficacy of AC increases with increasing dose (adsorption follows the law of mass action). No clinically significant change in osmolality could be detected.

b. PEG-ELS/AC/SA binding study.

The interaction between AC, PEG-ELS and SA was quantified. Earlier studies demonstrated that PEG does interfere with the complete adsorption of SA to AC. However, the extent of interference following a toxic ingestion was not known. This experiment was designed to simulate a relevant clinical situation following overdose with a toxic amount of SA. Clearly, as the ratio of PEG-ELS/AC was increased the free SA concentration also increased. Similarly, as the ratio of PEG-ELS/AC was

decreased the free drug concentration decreased. These data indicate that PEG-ELS interferes with the adsorption of SA to AC at higher PEG-ELS/AC ratios. However, this interference was minimal at clinically relevant concentrations. In all experimental combinations there was no clinically significant change in osmolality, suggesting that the concurrent use of AC and PEG-ELS may be employed without iatrogenic complications. In vivo data are required to demonstrate synergism of these two interventions.

V. CONCLUSION

WBI is superior to single dose ACS following the acute ingestion of a EC-ASA for gastrointestinal decomtamination.

These data suggest the potential efficacy of WBI for treatment of acute drug overdose with other modified release pharmaceuticals.

Our model demonstrated only a modest effect for the enhanced elimination of absorbed salicylate by multiple doses of activated charcoal.

Although the in vitro PEG binding studies demonstrated that PEG does adsorb to AC and PEG-ELS interferes with binding of SA to AC at high PEG-ELS/AC ratios no clinically significant changes in osmolality could be detected. These data suggest concurrent administration of both AC and PEG-ELS is likely to be safe. However, further evaluation is required.

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