Prowse Prize

THE USE OF
PRISCOLINE (2 BENZYL IMIDAZOLINE HYDROCHLORIDE)
AS A PREOPERATIVE TEST IN OCCLUSIVE VASCULAR DISEASE

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Prowse

By

Reuben M. Cherniack

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Introduction.

Smithwick (14) has recently drawn attention to a group of patients with occlusive peripheral arterial disease, who respond poorly to vasodilatation tests but nevertheless benefit remarkably from sympathectomy. It is obvious that for such cases some new diagnostic test is desirable. The simplest and most reliable tests in modern day use are the reflex thermal test and spinal anaesthesia. Any new test, therefore, in order to be of some aid in the diagnosis of peripheral vascular disorders, must be superior to either of these tests. Currently, a number of new drugs are under investigation as to their effect on the peripheral circulation.

In 1945, Acheson and Moe (1) described the paralytic effect of tetra-ethyl ammonium salts on the ganglia of the autonomic nervous system, and in 1947, Coller et al (4) claimed that the use of one of these, "Etamon", was superior to any other method of vasodilatation. However, Boyd et al (2) contributed evidence that the injection of Etamon was not a favorable test, while Farr and Doupe (6) later showed that it did not compare to reflex thermal stimulation.

Priscoline, which belongs to the group of phenyl substituted alkyl imidazolines, has been reported by Hendrix et al (8) to be adrenolytic and sympatholytic. Nickerson (9) in a recent review agrees with this conclusion. This substance has been used by Grimson et al (7) and Rogers (11) as a vasodilating agent in the treatment of peripheral vascular diseases.

It was therefore decided to study the efficacy of Priscoline as a vasodilator, and to compare its action to the effects of the reflex thermal test, spinal anaesthesia and sympathectomy.

Methods and Apparatus

The subjects were the nineteen patients shown in Table I, who were referred for an assessment of the value of sympathectomy. In their examination, careful note was made of the presence or absence of peripheral sensory disturbance. Those cases in which the examiner had difficulty in estimating sensory loss were classified as questionable.

Skin temperatures were used as an index of vasodilatation and rate of blood flow through the skin. Temperatures were measured by means of copper-constantan (gauge 34) thermocouples, held in contact with the pads of exposed digits by narrow strips of adhesive tape on the dorsum of the second phalanx. Temperatures were recorded from two digits of each foot and from the right index finger, and read to 0.1°C. Rectal temperature was recorded by a thermocouple and read to 0.01°C. Room temperature was kept constant at 19-21°C. and measured by a thermocouple suspended several feet above the parts under observation. All tests were performed under similar conditions, on successive days, in the constant temperature room.

Subjects reclined in the constant temperature room, clad only in a hospital gown. To provide a base line, recordings were made for ten to thirty minutes before a test. Skin temperatures were recorded at two to four minute intervals during each test. The Gibbon-Landis test was performed by

immersing the left arm in water at 44°C., and by covering the trunk and proximal parts of the extremities with blankets. When, after prolonged heating, a definite plateau of maximum skin temperature was attained in the toes and the control finger, the blankets were removed and the left arm placed in cold water at 18°C. This stimulated reflex vasoconstriction, thereby testing the integrity of the sympathetic nerves. On another day, each subject received 75 mgm. Priscoline intramuscularly, and the effect was observed for one and one-half to two hours. Blood pressure, recorded at five minute intervals, was barely affected.

Five subjects received 100 mgm. Novocaine intrathecally. In all, anaesthesia to pin-prick was achieved at least to the level of the tenth thoracic dermatome.

The effect of sympathectomy on skin temperature was observed two to four weeks after operation, in four subjects.

Results

During each procedure, note was taken of the height to which the skin temperature rose. The type of response to warming and cooling was also noted in the case of the reflex thermal test. Dilatation in response to warming, and constriction in response to cold, was considered normal vasomotor behavior.

A comparison of the maximum temperatures attained during the reflex thermal test and the Priscoline test is shown in Figure 1. and Table I. It is seen that in the majority of cases the digits attained a higher temperature with Priscoline than with reflex heating.

Figure 2. shows that in the 20 digits tested the effect of Priscoline was greater than reflex heating or spinal anaesthesia.

The preoperative and postoperative results in the four subjects who were sympathectomized are shown in Table II. The average error of the reflex thermal test in the prediction of the operative result was 4.2°C. The average error in the prediction of the operative result with Priscoline was 2.2°C.

During the course of the experiments it was observed in certain cases that the vasomotor behavior of the digits was abnormal. This abnormality ordinarily consisted of a failure of the vessels of the toes to constrict in response to cold although the vessels of the control finger showed a good vasoconstrictor response. In a smaller number of cases, the vasomotor behavior was judged to be abnormal because there was an absolute absence of any vasodilatation in response to prolonged heating. That the failure to increase the blood flow was not due to arterial disorder in this group of cases was shown by the ability of other procedures such as Priscoline to produce vasodilatation. These abnormal vascular reactions resemble those reported by Doupe (5) and Richards (10) in individuals with peripheral nerve lesions. This and the abnormality of sensation found in some cases of peripheral occlusive arterial disease would suggest the possibility of a neurological lesion.

It was therefore of interest to observe whether the efficacy of Priscoline could be related to any evidence of this hypothesised nerve lesion. Table III shows that, in contrast to those with normal

innervation, the cases in which there was sensory loss or abnormal vasomotor behavior showed a higher proportion of digits in which the response to Priscoline was greater than the response to the reflex thermal test. Results within 2°C. of each other were considered equal.

Discussion.

It is apparent from the above results that Priscoline had a greater vasodilating effect than either reflex heating or spinal anaesthesia in cases with symptoms suggesting occlusive peripheral vascular disease. In a limited series of cases it was further found, in agreement with Smithwick (14), that the reflex thermal test tended to underestimate the effect of sympathectomy. In contrast to this the results of the injection of Priscoline were nearly identical to those obtained by sympathectomy.

The explanation for the superiority of Priscoline in certain cases may perhaps depend on the existence of a state of hypersensitivity to adrenaline. It has been established by Cannon (3) that sympathetic denervation greatly increases the sensitivity of vessels to adrenaline, and there is evidence of a peripheral nerve lesion in many cases of occlusive arterial disease. Shumacker (13) noted a defect in vasoconstrictor ability in cases of arteriosclerosis and Buerger's disease, while Rundle (12) has reported a similar condition associated with minimal sensory changes in diabetics. In the present series similar evidence indicative of a peripheral nerve lesion was found. It was further found that it was particularly in these cases that Priscoline was superior to the reflex thermal test. Priscoline, being adrenolytic as well as sympatholytic, would therefore be expected to be more potent than sympathetic inhibition or block alone.

It appears paradoxical that sympathectomy should increase the blood flow to digits already denervated, though this has been shown to occur in cases of proven traumatic nerve lesions (5). The explanation for this and for the unsatisfactory results of procedures which consist of the temporary inhibition or blocking of sympathetic fibres may depend on the following considerations. It has been found (5) that the blood flow through denervated digits is dependent on three factors - the environmental temperature, the amount of circulating adrenaline and the temperature of the surrounding parts. Sympathetic blocking tests are usually performed at low environmental temperatures, and it is probable that the procedures frequently increase the amount of circulating adrenaline. Sympathectomy on the other hand, being a chronic state, would not be associated with an increased amount of circulating adrenaline, and furthermore, it would prevent, in partially denervated areas, the liberation of adrenaline from endings adjacent to those which are hypersensitive. It has also been found (5) that the thermal influence on denervated digits of relaxing the blood vessels of adjacent areas, may not be apparent for several hours. Thus it would appear that the sympathetic blocking tests in present day use are not sufficiently prolonged to duplicate the effect of sympathectomy.

Whatever the explanation, Priscoline appears to be a more potent vasodilator than either the reflex thermal test or spinal anaesthesia, and to mimic closely the effects of sympathectomy in producing vasodilatation in the lower extremities.

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TAE I

Subjects and Results

Case No.	Diagnosis	Age	Sex	Clinical Summary	Digit*	Sensation**	Vasomotor Response**	Maximum Temperature °C		
								Thermal	Priscoline	Difference
1.	Arteriosclerosis	58	M	Pain, numbness left leg for 2 years. Pulsations: L-, R+	LT4	N	N	31.5	24.0	-7.5
					LT1	N	N	30.5	27.5	-3.0
					RT4	N	N	34.5	33.0	-1.5
					RT1	N	N	34.5	33.0	-1.5
2.	Arteriosclerosis	51	M	Pain in both calves and ankles for 4 years. Pulsations: L+, R+	LT4	N	N	31.0	32.0	+1.0
					LT1	N	N	31.5	31.5	0
					RT4	N	N	32.0	32.0	0
					RT1	N	N	30.5	31.0	+0.5
3.	Arteriosclerosis	75	M	Pain in both calves, worse in left, for 1 year. Pulsations: L-, R-	LT4	N	N	26.0	31.5	+5.5
					LT1	N	N	25.5	32.0	+6.5
					RT4	N	N	32.0	33.0	+1.0
					RT1	N	N	32.0	33.0	+1.0
4.	Arteriosclerosis	61	M	Pain in both calves, worse in left, for 3 yesrs. Pulsations: L-, R-	LT5	?	N	30.5	33.0	+2.5
					LT1	?	N	31.0	32.5	+1.5
					RT5	N	N	35.0	34.0	-1.0
					RT1	N	N	34.5	33.5	-1.0
5.	Arteriosclerosis	66	M	Pain in both calves, worse in left,for 4 years. Pulsations: L-, R-	LT4	?	N	24.0	30.5	+6.5
					LT1	?	N	23.5	31.0	+7.5
					RT4	?	N	33.5	33.0	-0.5
					RT1	?	N	33.0	32.5	-0.5
6.	Arteriosclerosis	69	M	Duodenal ulcer. Pain in right calf and cold feet for 2 yrs. Pulsations: L-, R-	LT4	A	N	33.5	33.0	-0.5
					LT1	A	N	34.0	33.0	-1.0
					RT4	A	N	33.0	32.0	-1.0
					RT1	A	N	30.0	32.0	+2.0
7.	Arteriosclerosis	63	M	Pain and numbness left leg for 3 years. Burning left sole for 1 yr. Pulsations: L-, R-	LT4	?	A	26.0	31.5	+5.5
					LT1	?	A	25.0	29.0	+4.0
					RT4	?	N	30.5	32.5	+2.0
					RT1	?	N	29.5	30.5	+1.0
8.	Arteriosclerosis	64	M	Pain in both calves, worse in left, for 4 yrs. Pulsations: L-, R-	LT4	?	A	26.5	31.0	+4.5
					LT1	?	A	24.5	31.0	+6.5
					RT4	?	A	28.0	32.0	+4.0
					RT1	?	A	26.5	32.0	+5.5
9.	Arteriosclerosis	69	M	Pain in both calves for 3 yrs. Numbness & cold feet - 5 mos. Pulsations: L+, R+	LT4	A	A	23.0	33.0	+10.0
					LT1	A	A	22.5	32.0	+9.5
					RT4	A	N	28.0	34.0	+6.0
					RT1	A	N	25.0	33.5	+8.5
10.	Buerger's	40	M	Amputated right leg 2 years. Numbness and pain in left leg for 9 mos. Pulsations: L-	LT4	N	N	31.5	31.5	0
					LT1	N	N	29.5	33.0	+3.5
11.	Buerger's	40	M	Pain in left great toe for 7 mos. Pulsations: L-, R-	LT4	N	N	25.5	25.0	-0.5
					LT1	N	N	26.0	26.5	+0.5
					RT4	N	N	32.5	28.0	-4.5
					RT1	N	N	35.5	23.5	-12.0
12.	Buerger's	30	M	Pain in right thigh and calf on walking for 3 mos. Slight numbness. Pulsations: L+, R-	LT5	N	N	35.0	33.5	-1.5
					LT1	N	N	33.0	33.0	0
					RT5	N	N	22.5	29.0	+6.5
					RT1	N	N	23.5	28.0	+4.5
13.	Buerger's	47	M	Pain in left calf and right foot, numb cold feet for 1 yr. Pulsations: L-, R-	LT4	?	A	33.0	32.0	-1.0
					LT1	?	A	32.0	32.0	0
					RT4	?	A	32.5	30.5	-2.0
					RT1	?	A	31.0	30.5	-0.5
14.	Buerger's	50	M	Pain in both legs and right great toe; worse at night. Pulsations: L-, R-	LT4	A	A	32.0	32.0	0
					LT1	A	A	30.0	31.0	+1.0
					RT3	A	A	24.0	27.0	+3.0
					RT1	A	A	24.0	27.0	+3.0
15.	Diabetes Arteriosclerosis	59	M	Pain in both calves, particularly right for 9 yrs. Cold & numbness, particularly right leg-3 yrs.Pulsations: L-, R-	LT4	A	A	28.0	30.5	+2.5
					LT1	A	A	29.5	30.0	+0.5
					RT4	A	A	28.0	31.5	+3.5
					RT1	A	A	33.0	31.0	-2.0
16.	Diabetes Arteriosclerosis	63	F	Numbness and cold feet for 10 yrs. Ulcers both ankles for 9 mos. Pulsations: L-, R-	LT4	A	A	23.0	31.5	+8.5
					LT1	A	N	26.5	32.0	+5.5
					RT4	A	A	21.5	27.5	+6.0
					RT1	A	A	21.5	29.0	+7.5
17.	Diabetes Arteriosclerosis	66	F	Pain, numbness and cold feet for 3 yrs. Pulsations: L-,R-	LT4	N	N	31.0	30.5	-0.5
					LT1	A	A	26.0	29.5	+3.5
					RT4	A	A	23.5	26.0	+2.5
					RT1	A	A	22.5	24.5	+2.0
18.	Diabetes Arteriosclerosis	48	F	Amputated right leg, 4 yrs. Numbness left leg, 1 yr. Gangrene left great toe. Pulsations: L-	LT4	A	A	29.0	28.5	-0.5
					LT1	A	A	28.0	28.0	0
19.	Diabetes Arteriosclerosis	57	M	Burning feeling in both legs and feet for 2 yrs. Pulsations: L-, R-	LT4	?	A	28.5	31.0	+2.5
					LT1	?	A	27.0	31.0	+4.0
					RT4	?	A	27.0	31.0	+4.0
					RT1	?	A	29.0	31.0	+2.0

* LT4 means left fourth toe, RT1, right first toe, etc.

** N indicates normal, A, abnormal and ? questionable sensation or vasomotor response.

TABLE II.

The Effect of Preoperative Tests and Sympathectomy on Skin Temperature.

(Temperatures given in °C. above Room Temperature)

Case No.	Digit	Thermal	Priscoline	Sympathectomy
5	LT4	3.0	9.5	5.5
	LT1	2.5	10.0	8.0
10	LT4	10.5	10.5	12.0
	LT1	8.5	12.0	12.5
12	RT5	1.5	8.0	10.5
	RT1	2.5	7.0	9.0
18	LT4	8.0	7.5	10.0
	LT1	7.0	7.0	10.0

TABLE III.

The Effect of Denervation on the Relative Efficacy of the Injection of Priscoline and the Reflex Thermal Test.

Evidence of Denervation	Total Number of Digits	Number of Digits		
		Priscoline Less than Reflex	Priscoline Equal to Reflex	Priscoline Greater than Reflex
No Sensory Loss	26	4	16	6
Questionable Sensory Loss	22	0	9	13
Definite Sensory Loss	24	0	11	13
Normal Vasomotor Behavior	40	4	25	11
Abnormal Vasomotor Behavior	32	0	11	21

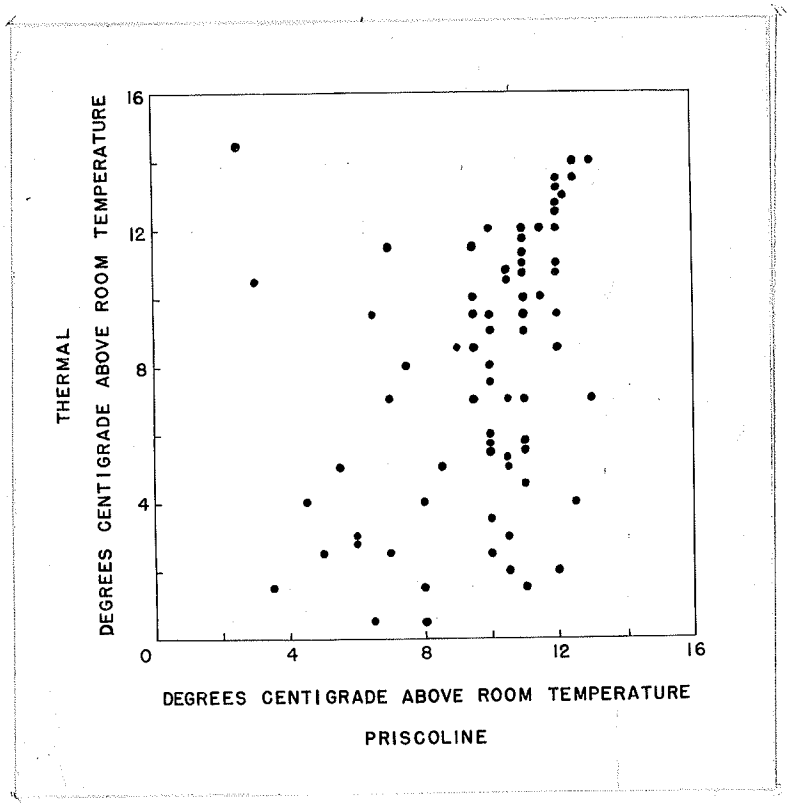

Fig.1. A comparison of the maximum temperatures attained with the reflex thermal test and the intramuscular injection of 75 mgm. of Priscoline.

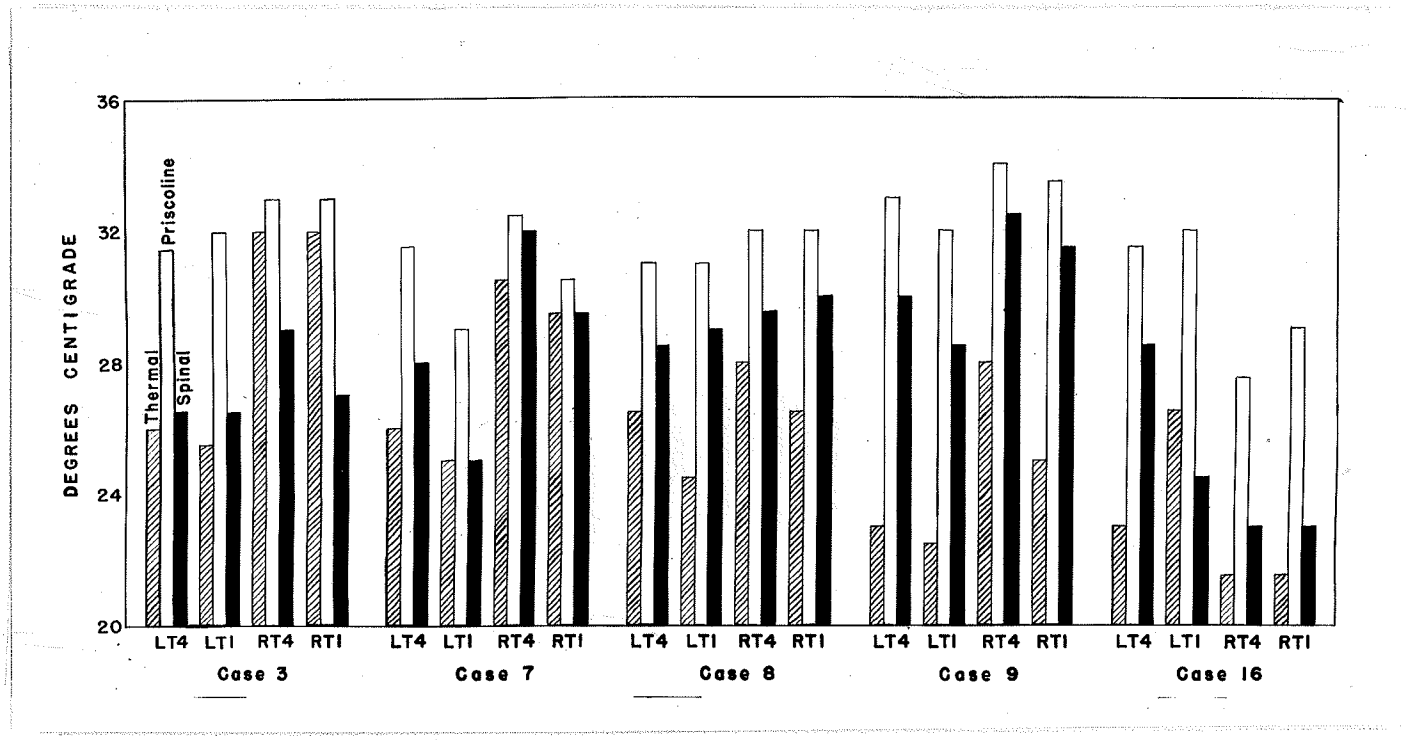

Fig. 2. A comparison of the maximum temperatures attained in toes with the reflex thermal test, intramuscular Priscoline and spinal anaesthesia.