"PRISCOL" IN TREATMENT OF PERIPHERAL VASCULAR DISEASE

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The pharmacology of 2-benzyl-4,5-imidazoline hydrochloride ("priscol") has been fully worked out in animals (Ahlquist *et al.*, 1947). It has complex actions, consisting of effects resembling the sympathicomimetic amines, histamine and acetylcholine-like properties, and sympatholytic effects. These workers found that priscol produced peripheral vasodilatation, cardiac stimulation, and increased cardiac output in cats and dogs. Coronary vasoconstriction, bradycardia, increase in blood pressure, and stimulation of the gut were produced in rabbits. The last effect could be prevented by atropine. In addition, the administration of adrenaline after priscol caused general vasodilatation, suggesting reversal of adrenaline action.

Grimson *et al.* (1948a) conducted clinical trials with priscol on 43 patients with peripheral vascular disease, including 6 with Raynaud's disease, 15 with atherosclerosis obliterans, and 6 with thrombo-angiitis obliterans. The results in Raynaud's disease were satisfactory and improvement was effected in the atherosclerotic and thrombo-angiitis groups. The peripheral skin temperature of the lower extremities was increased five minutes after intravenous and 45 minutes after oral administration. Definite cutaneous vasodilatation resulted even after oral priscol, but in five cases oscillographic readings were not altered. Eleven patients with hypertension were treated, but the blood pressure fell in only four. In three patients cardiac output was measured, but the results were equivocal. In another series, 17 hypertensive patients were treated, 12 showing a fall in blood pressure (Grimson *et al.*, 1948b).

Rogers (1949a), using skin temperature and oscillographic methods of assessment, obtained similar results in 27 patients suffering from various forms of peripheral vascular disease, using 100 mg. of priscol daily by mouth. In a further observation of 15 arteriosclerotic patients between the ages of 46 and 79 years, Rogers (1949b) reported subjective and objective improvement with oral priscol. He noted that the blood pressure may increase.

Douthwaite and Finnegan (1950) found priscol to have a more lasting vasodilator effect than the commonly used vasodilators, and noted a selective affinity for the smaller arteries of the hands and toes. In nine patients with Raynaud's disease they obtained excellent results, and produced improvement in 24 patients who had claudication of arteriosclerotic origin. Side-effects were particularly common, even with oral administration. Lynn (1950) found that priscol acted mainly on the skin vessels, producing vasodilatation. After intravenous injections of 50 mg. the blood flow was increased in the hands and feet in 11 cases of Raynaud's pheno-

menon and in the feet in 17 cases with occlusive vascular disease. In the sympathectomized limb intravenous injection had no effect, but when priscol was given intra-arterially the blood flow increased locally, suggesting a direct action on the arterial wall. Intra-arterial injection also doubled the calf flow in the non-sympathectomized limb. The results of oral treatment in the spastic group were good, but little or no improvement was noted in the occlusive group with claudication.

Side-effects have been reported, particularly after parenteral administration. These include faintness, vertigo, headache, sweating, and "goose-flesh." The blood pressure may rise, fall, or remain unaltered. Two of Grimson's patients had myocardial infarcts while taking the drug.

Present Investigation

In view of the lack of effective therapeutic agents for the ambulant treatment of patients with peripheral vascular disease, we decided to investigate the effects of oral priscol. The advantages of an effective oral preparation are obvious, particularly as other medical treatment has often very little to offer.

Twelve patients between the ages of 47 and 75 years with obliterative vascular disease were studied. The series included seven patients with hypertension, three of whom had previously suffered from coronary occlusion, which in two cases had probably resulted in aortic "saddle" emboli. Another hypertensive patient had mitral stenosis, auricular fibrillation, and multiple femoro-popliteal emboli.

The effect of priscol was assessed objectively by means of skin temperature readings, reflex heating tests, and measurement of circulation rate using sodium fluorescein. Arteriography was performed on suitable cases.

Reflex Heating

The patient lay on a couch in a cool room (temperature 19–21° C.), and skin temperature readings were taken with a "Light" multichannel skin thermometer. One channel was attached to the pulp of each great toe and each mid-calf region by means of adhesive plaster. After the resting temperatures had become stabilized, control readings were taken. The patient's trunk was then heated by means of an electric blanket at a temperature of 60° C. for one to one and a half hours, until the skin temperature readings showed no further increase. The room temperature was kept at 19–21° C., for separate observations and during each observation. In all cases the toes were cooler than the calves before heating. After heating, both toe and calf temperatures increased, the former to a greater degree than the latter. Thus reflex heating produced a reduction in the toe-calf temperature difference, or gradient. As a result of the response to reflex heating, the patients were placed in two groups.

Group I (spastic-occlusive) comprised those patients in whom the toe-calf temperature gradient was significantly reduced or abolished by reflex heating, suggesting that they had a considerable number of collateral vessels capable of dilating in addition to vessels grossly narrowed by the pathological process.

Group II (occlusive) was formed by those patients in whom the toe temperatures did not rise enough after reflex heating to reduce the toe-calf gradient so significantly as in *Group I*. These cases, with the possible exception of Case 11, were considered to have a poor collateral blood supply to the lower limbs.

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TABLE I.—Results of Oral Priscol Therapy

Case	Age	Diagnosis	Priscol mg.-day	Duration of Therapy	Arteriogram	% Decrease in Foot- minus-arm Time		Subjective Improvement		
						R	L	Loss of Pain and Paraesthesiae	Increased Warmth	Improve- ment in Claudica- tion
Group I										
1	61	Senile occlusive disease. B.P. 140/68	150	9 weeks	—	50	36	++	++	++
2	51	Multiple bilateral femoro-popliteal arterial emboli. B.P. 190/100. Mitral stenosis. Auricular fibrillation	300 150	10 "	—	14	15	+	+	Not present
3	49	Diffuse occlusive disease. Left femoro-popliteal thrombosis. B.P. 170/100	150	5 "	L. femoro-popliteal thrombosis. Irregular vessels	27	24	++	++	++
4	47	Diffuse occlusive disease	150	12 days	Bilateral femoro-popliteal thrombosis	58	40	Symptoms not present	+	++
5	75	Senile occlusive disease. Ischaemic neuritis. B.P. 240/100	150	5 weeks	—	No decrease		+	++	++
6	60	Senile occlusive disease. Right femoro-popliteal thrombosis. B.P. 154/90	150	4 "	Femoro-popliteal thrombosis (R)	"	"	+	+	+
Group II										
7	60	Senile occlusive disease. B.P. 220/130. ? Old cardiac infarct	150	7 weeks	—	54	36	++	++	+
8	61	Senile occlusive disease. Gangrene right big toe. B.P. 155/95	150	12 "	Normal	53	56	++	++	+
9	66	Senile occlusive disease. ? Aortic saddle embolus. Myocardial infarction 1949. B.P. 126/89. Angina pectoris	150	6 "	—	44	44	++	++	++
10	64	Senile occlusive disease. Right femoro-popliteal thrombosis. Pre-gangrene. B.P. 190/90	150	8 "	—	30	17	+	+	Not known. Bedfast
11	65	Senile occlusive disease. B.P. 200/115. Pulmonary T.B.	150 300	1 week 4 weeks	L. deep femoral artery thrombosis	Nil	38	Nil	Nil	Nil
12	61	Senile occlusive disease. ? Aortic saddle embolus. Myocardial infarction 1943, 1949. Angina pectoris. B.P. 170/100	150	5 "	—	50	24	++	++	+

TABLE II.—Results of Fluorescein Tests (Foot-minus-Arm Time (secs.))

Case No.	Age	Diagnosis	Pre-treatment	During Treatment. After Reflex Heating	During Treatment. No Heating	Max. % Decrease During Treatment	Control
<i>Group I</i>							
1	61	Senile occlusive disease. B.P. 140/68	R 10 L 11	5 7	5 7	50 36	9 9
2	51	Mitral stenosis with auricular fibrillation. Bilateral femoro-popliteal emboli. B.P. 190/100	R 14 L 15	12 13	10 11	29 27	— —
3	49	Diffuse occlusive disease. Left femoro-popliteal thrombosis. B.P. 170/100	R 15 L 17	11 13	11 14	27 24	11 17
4	47	Diffuse occlusive disease. Bilateral femoro-popliteal thrombosis. B.P. 140/90	R 14 L 10	6 6	— —	58 40	— —
5	75	Senile occlusive disease. Ischaemic neuritis. B.P. 240/100	R 9 L 6	7 19	7 17	22 0	13 11
6	60	Senile occlusive disease. Right femoro-popliteal thrombosis. B.P. 154/90	R 6 L 6	9 7	9 8	0 0	— —
<i>Group II</i>							
7	60	Senile occlusive disease. B.P. 220/130. ? Old antero-lateral infarct	R 15 L 14	7 9	10 10	54 36	11 18
8	61	Senile occlusive disease. Gangrene right big toe. B.P. 155/95	R 17 L 18	10 8	8 10	53 56	12 15
9	66	Senile occlusive disease. ? Aortic saddle embolus. Myocardial infarction 1949. B.P. 126/89. Angina pectoris	R 16 L 16	9 9	10 10	44 44	8 8
10	64	Senile occlusive disease. Right femoro-popliteal thrombosis. Pre-gangrene. B.P. 190/90	R 17 L 12	14 10	12 10	30 17	— —
11	65	Senile occlusive disease. B.P. 200/115. Pulmonary T.B.	R 7 L 16	9 14	8 10	0 38	— —
12	61	Senile occlusive disease. ? Aortic saddle embolus. Myocardial infarction 1943, 1949. Angina pectoris. B.P. 170/100	R 18 L 17	12 13	9 16	50 24	8 16

FIG. 1.—Group I. Case 1. Shows high resting calf-toe temperature gradient ($10^{\circ}\text{C}.$) before treatment, reduction of gradient during treatment, and return of gradient to $9^{\circ}\text{C}.$ after withdrawal of drug. Improved response of left great toe to reflex heating during treatment persists in some measure after withdrawal of priscol.

Prior to treatment the resting toe temperature before heating did not exceed $26.5^{\circ}\text{C}.$ (Case 5), with the exception of Cases 3 ($33^{\circ}\text{C}.$) and 11 ($31^{\circ}\text{C}.$). In Case 1 the temperature was as low as $19^{\circ}\text{C}.$ The small toe-calf gradient before heating in Cases 2, 3, and 11 may be explained by the presence of dilated collateral skin vessels (Pickering, 1933). The test was repeated after the patients had been taking priscol for seven to fourteen days, and in seven cases two to four weeks after the drug had been withdrawn.

Fluorescein Circulation Rate

The objective measurement of the circulation rate using skin fluorescence under ultra-violet light after the intravenous injection of fluorescein has been utilized by several workers (Lange and Boyd, 1942; Fishback *et al.*, 1942; Sicher, 1943; Winsor *et al.*, 1947).

We have used the technique of MacGregor and Wayne (1951), which one of us (J. F. G.), working in association with these authors, found entirely satisfactory.

With a solution of 1:1,000 histamine acid phosphate and 2% procaine, intradermal weals 0.5 to 0.75 mm. in diameter are raised on the left antecubital fossa, just below both knees, and on the dorsal surfaces of both feet. Then 4 ml. of a solution of 20% sodium fluorescein and 2% sodium bicarbonate is injected rapidly into a vein in the right antecubital fossa with the room in darkness. The interval between the first appearance of fluorescence in the weals and the beginning of the injection is measured with a stop-watch, the skin being illuminated by an ultra-violet lamp (Mercra 125 watt MBW/V, Range 3,130 Å–4,070 Å, 95% radiation concentrated at 3,650 Å). By this method a sharp end-point is obtained, the normal values being as follows:

	Arm-to-arm Time (Secs.)	Arm-to-Foot Time (Secs.)	Foot-minus- arm Time (Secs.)
Range:			
MacGregor and Wayne (1951)	9–25	21–35	8–13
Winsor <i>et al.</i> (1947)	15–25	25–35	9–11.2 (rarely 14)
Mean:			
MacGregor and Wayne (1951)	16.6	27.2	10.6
Winsor <i>et al.</i> (1947)	18.6	28.1	9.5

The foot-minus-arm time, which is obtained by subtracting the arm-to-arm time from the arm-to-foot time, measures the circulation rate in the lower extremities.

Times within the normal range are occasionally obtained in cases with definite organic disease, probably as a result of dilatation of collateral vessels. A difference in time between two legs is always abnormal.

A total of 46 fluorescein circulation estimations were carried out. All patients with occlusive disease were so investigated immediately after reflex heating, both before and during therapy. In 11 patients circulation rates were also estimated during treatment without previous reflex heating. Seven patients acted as their own controls, reflex heating and circulation rate estimations being carried out two to four weeks after withdrawal of priscol. No toxic effects were noted from the injection of fluorescein, except nausea in one case and

vomiting in another. During treatment and investigation all patients, except Case 10 (early gangrene of toe), were ambulant, and were attending as out-patients in order to assess improvement under normal conditions. As the object of the investigation was to assess the long-term therapeutic value of priscol, tests were deliberately performed at random time intervals in relation to daily dosage. No other treatment was given, although patients were advised to avoid smoking.

Dosage and Duration of Treatment (Table I)

Initially 50 mg., thrice daily, was administered to all patients. In two patients (Cases 2 and 11) this was increased to 100 mg. thrice daily. The higher dosage was tolerated in Case 11 but not in Case 2. The duration of treatment varied from 12 days to 12 weeks, investigations usually being carried out one to two weeks after starting therapy.

FIG. 2.—Resting calf-toe temperature gradient before treatment, during treatment, and two to four weeks after withdrawal of drug (control) in Group I. Shows abolition of gradient while on priscol, and return of gradient after withdrawal.

Toxic Effects

All patients noticed flushing of the whole body, mainly the lower extremity, headache, and "gooseflesh." These symptoms were seldom severe, and tended to wear off after two or three days' treatment. Case 6, a nervous patient with mitral stenosis and auricular fibrillation, found them disabling when on 300 mg. a day, but was able to take 150 mg. a day without ill effects. During treatment another patient (Case 12) developed epigastric pain and vomiting possibly due to stimulation of gastric secretion by the drug. The symptoms rapidly disappeared on withdrawal of priscol and on the administration of atropine. Subsequent priscol did not cause a recurrence of symptoms.

Results

Group I (Spastic Occlusive).—Fig. 1 shows the response to reflex heating before, during, and after termination of priscol therapy (control). Changes of this order were found in all cases in this group, both calf and toe temperatures being increased and the resting toe-calf temperature gradient being greatly reduced or even reversed while on treatment. In Cases 1, 3, and 5 (who acted as their own controls) the gradient was restored two to four weeks after stopping the drug (Fig. 2). Fig. 3 shows the effect of priscol on the toe-calf gradient in all cases in this group.

Group II (Occlusive).—Fig. 4 illustrates the responses to reflex heating in Case 12. The increase in temperature and the reduction in gradient are less marked, as is the response to priscol. In this group the results were much more variable, though the skin temperature of the toes was increased in every case while on priscol. Cases 7, 8, 9, and 12 acted as their own controls, and showed an increase in toe-calf gradient after

FIG. 3

FIG. 4

FIG. 5

FIG. 3.—Group I. Effect of priscol on the calf-toe temperature gradient change after reflex heating. Case 1 initially shows a gradient of 10 in right leg before heating, reduced to 1.5 after heating. During treatment, the gradient before heating is only 0.5 and after heating becomes reversed (−0.5)—that is, before treatment and without heating the right big toe is 10° cooler than right calf—after heating, temperature increases 8.5°. When on priscol the resting toe temperature is 9.5° higher and the gradient only 0.5. After heating, the toe becomes warmer than the calf, and the gradient is actually reversed. All cases in Group I show changes of same order.

FIG. 4.—Group II. Case 12. Shows elevation of toe temperature during treatment, and fall when treatment was stopped. Effect of priscol on calf-toe temperature gradient is very slight, though both calf and toe temperatures are elevated during therapy. Reflex heating does not alter the gradient appreciably, indicating absence of spasm and mainly occlusive changes in vessels.

FIG. 5.—Resting toe-calf temperature gradient before, during, and after treatment. Showing an increase in gradient after withdrawal of therapy.

withdrawal of therapy (Fig. 5). Fig. 6 shows the toe-calf gradients before and after priscol in Cases 7 to 12.

Effect on Fluorescein Circulation Rate

Table II shows the fluorescein times before treatment, during treatment (with and without previous reflex heating), and, in seven cases (1, 3, 5, 7, 8, 9, and 12), after

the drug had been withdrawn. Maximum shortening of the foot-minus-arm time has been expressed as % decrease for each leg. In all cases except 5 (left leg), 6 (both legs), and 11 (right leg) an appreciable reduction occurred in the affected leg, varying from 17% to 56%, with an average of 38.7%. In 12 legs the foot-minus-arm time was reduced from an abnormal figure to one within the normal range. The average decrease was greater in Group II (43%) than in Group I (34.5%). These results are comparable with those obtained by MacGregor and Wayne (1951) in sympathectomized legs.

Case 5 shows prolonged times in the left leg, and Case 6 in both legs, during treatment. The explanation of this is not clear, but in Case 5 at the time of the test the temperature of the left toe was high (35° C.), indicating dilatation of the arteriovenous anastomoses in the skin. It is possible that the local circulation was shunted through the anastomoses, by-passing the skin capillaries, and delaying the onset of fluorescence. Harpuder *et al.* (1940) have shown that the efficiency of the peripheral circulation in the presence of vascular disease depends upon the capillary circulation, and Popoff (1934) found that patent arteriovenous skin anastomoses may be present in patients with organic occlusive peripheral vascular disease.

Case 6 shows normal times throughout, possibly owing to the opening up of adequate collateral vessels, but abolition of calf-toe gradient and considerable symptomatic improvement occurred during treatment. Arteriography revealed occlusion of the right femoropopliteal artery (Table I). MacGregor and Wayne (1951) found that normal foot-minus-arm times could occasionally occur after reflex heating in patients with occlusive disease. Pickering (1933) also noted that normal skin temperatures were sometimes found in patients with organic disease. Case 9 showed no appreciable increase in gradient or lengthening of the foot-minus-arm time one month after withdrawal of priscol, indicating that a good collateral circulation was being maintained. Shortening of the right-foot-minus-arm time also persisted after withdrawal of the drug in Case 12.

Fig. 7 shows the relation of toe temperature to foot-minus-arm time in each limb, and it will be seen that, in the main, the length of the foot-minus-arm time varies inversely with the skin temperature, indicating that this circulation time is greatly influenced by skin blood flow. During treatment the majority of limbs show a high toe temperature and rapid foot-minus-arm times, suggesting that oral priscol increases the blood flow to the skin.

FIG. 6.—Shows that the effects of reflex heating and priscol on calf-toe temperature gradient are inconstant in patients with predominantly occlusive disease, but that there is a general tendency for the gradient to be reduced.

FIG. 7.—Skin temperature of toes at time of fluorescein test plotted against foot-minus-arm time before and during treatment. Each dot represents one leg. Apart from some scatter of points, the results before treatment show that the foot-minus-arm time tends to be short when toe temperature is high, and vice versa. During treatment most cases show high toe temperatures and short foot-minus-arm times.

Subjective Changes During Treatment

All cases, except Case 11, experienced improvement in symptoms. Pain due to ischaemic neuritis, paraesthesiae, and numbness disappeared or was greatly reduced. The patients said that the legs felt warmer. No attempt was made to assess improvement in claudication accurately owing to the extreme difficulty in obtaining reliable results, even with graded exercise tests. Lynn (1950) found claudication to be unchanged by priscol, so that it was surprising to find that, out of ten of our patients who complained of claudication, nine said that they could walk further without pain and that the pain was less severe when it did occur. Case 11, however, who showed definite objective signs of improvement, persistently denied any subjective improvement whatever. He refused, however, to reduce his very large consumption of tobacco. Case 7 proved a disappointment. After obtaining great symptomatic and objective improvement for seven weeks, his condition suddenly deteriorated and he complained of a return of severe claudication in both legs, numbness, and rest pain. Although there was no great change in the physical signs, it was thought that further occlusion had occurred in the absence of adequate collateral vessels. In Case 9 amelioration of symptoms persisted even after priscol had been discontinued for one month.

The two patients suffering from Raynaud's disease showed normal reflex heating responses and normal fluorescein foot-minus-arm times after reflex heating before treatment, as was expected. The calf-toe and finger-to-arm temperature gradients were abolished and attacks did not occur during therapy.

Conclusions

The results obtained suggest that priscol is an effective vasodilator when administered orally to patients with occlusive arteritis. The most satisfactory results are seen in patients in whom vasodilatation of collateral vessels is possible. Definite, though limited, objective and subjective improvement can also occur in patients with advanced occlusive disease. In patients with mild degrees of disease priscol may be expected to afford considerable or even complete relief of symptoms, and may even delay the onset of more severe ischaemic changes. Priscol cannot be said to replace sympathectomy, but it may constitute a valuable alternative in patients unsuitable for or unwilling to undergo operation, and in early mild cases. In patients with acute occlusive ischaemic changes it may be of value as interim therapy while the extent of the disease and the suitability of the patient for operation are being assessed. It may well prove to be the treatment of choice in uncomplicated Raynaud's disease. Our results do not warrant any definite conclusion on the value of priscol in relieving the pain of intermittent claudication, but it must be remembered that even sympathectomy not infrequently fails to relieve this symptom.

The ease of administration and lack of serious toxic effects when given orally warrant its further trial in occlusive vascular disease. A long-term study of a large number of cases is necessary to assess fully the value of the drug.

Summary

Twelve patients with occlusive vascular disease and two patients with Raynaud's disease were treated with 2-benzyl-

4,5-imidazoline hydrochloride (priscol) in a dosage of 75-300 mg. a day by mouth for periods of up to three months. Objective criteria of improvement were obtained in cases of occlusive disease, using the fluorescein circulation rate and reflex heating tests. Varying degrees of subjective improvement occurred in all except one case. Improvement in intermittent claudication was claimed by nine out of ten patients with this symptom. In the two cases with Raynaud's disease the attacks were completely prevented by priscol. Toxic effects were slight.

It is concluded that priscol is of some value in the treatment of ambulant cases of occlusive vascular disease, in patients unsuitable for sympathectomy, as an interim treatment in cases with acute ischaemia, and in patients with Raynaud's disease. Priscol is unlikely to replace sympathectomy, but further work is necessary to evaluate fully its place in the treatment of peripheral vascular disease.

We wish to thank Professor J. McMichael for his help and advice. The arteriograms were kindly carried out by Mr. Peter Martin and Mr. R. B. Lynn, of the department of vascular surgery.

ADDENDUM.—Since this paper was submitted for publication one of the patients with Raynaud's disease has suffered a return of the attacks with the onset of winter. These attacks are much less frequent and less severe than before starting treatment, and do not seriously inconvenience the patient.

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The Mecca pilgrimage, which annually draws thousands of pilgrims to the holy land of Hedjaz, in Saudi Arabia, will from now on be protected through a new set of health rules drafted by a special committee of the World Health Organization. These rules will become a part of the W.H.O. International Sanitary Regulations governing health aspects of all international travel by land, sea, and air, and have already been approved by a special committee. They were submitted to the fourth World Health Assembly, which opened in Geneva on May 7, and are intended to come into force in the middle of 1952. These special provisions will be inserted as addenda to the main regulations, and will replace the pilgrimage clauses of the 1926 International Sanitary Conventions established in Paris. The main modifications include for the first time provisions for the sanitary control of pilgrim aircraft. Two vaccinations only—against cholera and against smallpox—are obligatory for all pilgrims, whatever their country of origin or its sanitary condition, and if they come from a yellow-fever area they must be vaccinated against yellow fever. The quarantine station at Kamaran will no longer be used. This island in the Red Sea off Eritrea was an obligatory port of call for all pilgrim ships coming from the south on their way to Hedjaz. Adequate facilities will soon be provided at Jeddah, the main port of Saudi Arabia, which receives pilgrims from all parts of the world.