An Evaluation of Certain Vasodilator Drugs by a Heat Flow Technic

By B. N. Catchpole, F.R.C.S., and R. P. Jepson, F.R.C.S.

The effects on the skin heat flow, using a copper-tellurium disc technic, of Tolazine (Priscoline), Hydrgine, Regitine and P-9295 when administered parenterally are compared with the results of reflex heat vasodilatation, in normal and atherosclerotic limbs.

There is a great need in clinical practice for an efficient method of increasing the blood flow in the extremities of patients suffering from acute, chronic or intermittent ischemia. A surgical or chemical sympathectomy may be an unsatisfactory or inadequate procedure or be contraindicated by reason of the age or general condition of the patient. Many drugs have been studied in recent years which cause a peripheral vasodilation by their action at various levels in the neuroeffector chain. Some of these have been abandoned following a critical clinical and experimental evaluation because of their inefficiency or their unpleasant and dangerous side effects.1 2

This paper reviews four drugs which have been reported to have vasodilator actions. All have been administered parenterally under controlled conditions to normal subjects and to a group of patients suffering from degenerative arterial disease in the lower extremity. Their action on skin circulation in the digits has been particularly investigated, as a threatened or frank ischemic gangrene in such areas is a frequent cause for the loss of a limb in the atherosclerotic patient.

Methods

One hundred forty studies of the actions of the vasodilator drugs were made in 60 subjects, of whom 21 (61 studies) had atherosclerotic occlusive vascular disease (superficial femoral or popliteal artery thrombosis) of the legs. The major complaint, in this latter group was intermittent claudication. They all had grade 1 nutrition of the feet.3 Patients with ulceration, rest pain or gangrene were omitted from this series. The 79 studies on normal limbs were performed on 39 volunteers. The age groups of the patients are shown in figure 1.

Variations in blood flow through the skin of the digits were estimated by gradient calorimetry utilizing a heat flow disc described by Stafford Hatfield4 and Bonney, Hughes and Janus.5 Heat flow discs consist of tellurium alloy coated on both faces with copper gauze and have diameters varying from 0.5 to 1.0 cm. and thicknesses of 2 to 3 mm. Leads from the copper gauze were connected with a mirror galvanometer (450 ohms). By physical methods it can be shown that there is a linear correlation between the heat exchange across the two faces of the disc and the galvanometer readings. If one surface of the disc is kept at a constant temperature, the potential difference arising from heat loss or gain to the opposing surface allows a direct measurement to be obtained in thermal units per unit area per unit time. The thermolectric constant for any disc varies less than 5 per cent over temperatures ranging from 30 to 200 C.4 Each disc must be separately calibrated.

The lightly clothed subject was rested horizontally on a couch, with the hands and feet uncovered, in a draughtless, temperature-controlled room for at least 45 minutes before the readings were commenced. Precautions were taken to eliminate noise, conversation and other distracting stimuli. The temperature in the room was maintained at 21 C. ± 0.5 C., with a humidity of approximately 50 per cent. Serial blood pressure readings were made before and following the drug injections.

The disc was attached to the pulp skin of a digit by thin cellulose tape. For finger heat flow determinations, the digit and the disc were covered with a fine rubber finger stall and immersed in a continuously stirred water bath maintained at a temperature of 30 C. For lower limb recordings the disc was fixed by tape to the great toe which was then firmly applied to the vertical wall of a copper water bath, the temperature of which was maintained at 30 C. Readings were made from both lower limbs, or a lower limb and a finger. Direct readings from the outer surface of the water bath against which the toe lay were approximately 1 C. lower than the water temperature.

Injections of the drugs were made over a period

From The University Surgical Unit, Manchester Royal Infirmary, England.
of a few seconds either into an antecubital vein (i.v.) or directly into the femoral artery (i.a.) through a 16 gauge needle (outside diameter 0.55 mm.). In a few instances subcutaneous injections (s.c.) were made. The pH of the drugs varied from 3.6 to 6.8 and when they were injected into the artery with active circulation the pH was not believed to modify their effects.

The following drugs were studied: (a) 2-benzyl-4,5-imidazoline hydrochloride (Tolazoline, B.P. or Priscoline); (b) 2[N-p'-tolyl-N-(m'-hydroxyphenyl)-amino methyl] imidazole (Regitine); (c) the methanesulfonate derivatives of dihydroergocornine dihydroergocristine and dihydroergokryptine (Hydergine); (d) pentamethyl-diethyl-3 azapentane-1,5-diammonium-dibromide (P-9295).

When the changes in digital heat flow following the injection of one of the above drugs had been studied, reflex vasodilatation was obtained in each patient by warming the trunk and the proximal parts of the limbs with an electric blanket until the mouth temperature rose at least 0.3 C. By this technic it was possible to compare the effect of drug injection with the maximal heat flow obtained by reflex vasodilatation. The intraarterial injections were only made in the lower limb. When intravenous or other parenteral injections have been studied, the maximal heat flow response whether in the finger or toe has been recorded.

The following scale has been used:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No change in heat flow</td>
</tr>
<tr>
<td>1</td>
<td>Maximal heat flow increase quantitatively less than a half of that obtained by reflex heating</td>
</tr>
<tr>
<td>2</td>
<td>Heat flow increase more than a half of that obtained by reflex heating</td>
</tr>
<tr>
<td>3</td>
<td>Heat flow increase equal to that obtained by reflex heating</td>
</tr>
<tr>
<td>−1</td>
<td>Diminished heat flow</td>
</tr>
</tbody>
</table>

**Results**

The duration of the response for the whole group of vasodilator drugs ranged as follows: In a grade 1 response, from 3 to 10 minutes; grade 2, from 5 to 30 minutes; grade 3, from 10 to more than 60 minutes. It was apparent that the quantitative response and its duration bore some relationship.

**Fig. 1. Age group distribution of normals and arteriopathic patients.**

**A. 2-benzyl-2-imidazoline hydrochloride (Tolazoline or Priscoline)**

(a) Studies (23) on normal subjects. Intravenous injections of 50 mg. were made in six patients. In three cases no increase in heat flow in the ipsilateral toe was recorded following the injections, although the patient mentioned a feeling of warmth slowly spreading down the leg to the knee or ankle for 60 to 90 seconds after the injection. In the remaining three cases, grade 1, 2 and 3 responses respectively, were obtained.

Fifteen intravenous studies of Tolazoline were made; in five the dose was 25 mg. and in 10, 50 mg. Records were made from the medius of the hand and the great toe. The collective responses are recorded in table 1. In none of the experiments did the heat flow response persist for more than 30 minutes, and it is interesting to note that in two patients a diminished heat flow occurred in the toe disce.

The subcutaneous injection of 50 mg. of Tolazoline resulted in no response in one case and a decrease of heat flow in a second when readings were made from the toe.

(b) Studies (24) in patients suffering from vascular disease. Fifty mg. of Tolazoline was used in every case. Eight intra-arterial injections, recorded from the ipsilateral toe, resulted in an increase of toe heat flow in one patient, no response in five and a decrease in
TABLE 1.—Collective Results of the Parenteral Injections in Normal Patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of Administration</th>
<th>Maximal Response in Toe or Finger, Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolazoline</td>
<td>i.a.*</td>
<td>3 1 1 1</td>
</tr>
<tr>
<td></td>
<td>i.v.*</td>
<td>2 5 3 4</td>
</tr>
<tr>
<td></td>
<td>s.c.*</td>
<td>1 1</td>
</tr>
<tr>
<td>Regitine</td>
<td>i.a.</td>
<td>3 2 2 3</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>2 5 3 3</td>
</tr>
<tr>
<td></td>
<td>s.c.</td>
<td>6 3</td>
</tr>
<tr>
<td>Hydergine</td>
<td>i.a.</td>
<td>3 2 2 1</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>1 2</td>
</tr>
<tr>
<td></td>
<td>s.c.</td>
<td>1 2</td>
</tr>
<tr>
<td>P-9295</td>
<td>i.a.</td>
<td>1 1 2</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>1 2</td>
</tr>
</tbody>
</table>

*i.a. = intra-arterial; i.v. = intravenous; s.c. = subcutaneous.

heat flow in two. The maximal duration for which an increased heat flow was recorded in any experiment was 11 minutes. That an increase in heat flow was possible was demonstrated by comparison with the response to reflex heat vasodilatation. Following 11 intravenous injections, a grade 2 response occurred in one patient, a grade 1 in four and no change in heat flow in six (table 2).

TABLE 2.—Collective Results of the Parenteral Injections in Patients Suffering from Occlusive Vascular Disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of Administration</th>
<th>Maximal Response in Toe or Finger, Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolazoline</td>
<td>i.a.</td>
<td>2 5 4 1</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>6 4 1</td>
</tr>
<tr>
<td>Regitine</td>
<td>i.a.</td>
<td>1 6 1</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>1 9 4</td>
</tr>
<tr>
<td>Hydergine</td>
<td>i.a.</td>
<td>3 3</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td></td>
</tr>
<tr>
<td>P-9295</td>
<td>i.a.</td>
<td>1 2</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>1 2</td>
</tr>
<tr>
<td></td>
<td>s.c.</td>
<td>1 1</td>
</tr>
</tbody>
</table>

B. 2[N-p'-tolyl-N-(m'hydroxyphenyl)-amino- methyl] imidazoline (Regitine)

The dose injected in every case was 10 mg. (a) Studies (27) in normal subjects. Intravenous injections were made on five occasions; in three subjects no increase in heat flow resulted and in two a grade 2 response was recorded. No color change or pain was observed in the injected limb although the patient remarked on a "warm or tingling" sensation running down to the foot lasting for a minute or so. A feeling of "flushing" or facial warmth was complained of by two patients.

Thirteen intravenous injections were made. Following the majority of these the patient became aware of a bounding heart action, light headedness and a general sensation of warmth. There was usually a slight depression of the blood pressure in the normotensive patient. An increase in the pulse rate by 20 to 30 a minute and a tachypnea were more frequently recorded. These reactions could be minimized by prolonging the injection over a period of two to three minutes. A considerable fall in blood pressure was recorded especially in one hypertensive patient (not included in this series). (See fig. 2.) Three of the injections resulted in a grade 3 response, three in a grade 2, five in a grade 1 response and two were followed by no change in heat flow in the finger or toe. The response was generally greater in the finger than the toe (fig. 3). Subcutaneous

![Fig. 2. Hypertensive patient, age 40. Horizontal position during reading.](image-url)
injections in nine patients gave a grade 1 response in three instances and no response in six.

(b) Studies (22) in patients suffering from vascular disease. An intra-arterial injection of Regitine was made in eight patients. In six no change in heat flow occurred and in one a decreased reading resulted. A single patient responded by a grade 1 heat flow.

Fourteen intravenous injections were observed and in five cases the finger heat flow was measured together with that of the toe. Following nine injections no change in heat flow was demonstrated, in four a grade 1 increase and in one a decrease.

C. The methanesulfonyl salts of dihydroergokryptine, dihydroergocornine and dihydroergocristine (Hydergine)

Hydergine was injected in a volume of 1 ml. which contained 0.1 mg. of each of the above three compounds.

(a) Studies (16) in normal subjects. Intra-arterial injections were performed in six subjects. In three patients no response, in two a grade 2 response, and in one patient a grade 3 response resulted. The latter persisted for more than 60 minutes. In no instance did an increased heat flow occur in the contralateral leg (fig. 4). Intravenous (seven studies) and subcutaneous injections (three studies) failed to alter the heat flow readings in the toe or finger. The subcutaneous injections were painful.

(b) Studies (6) in patients suffering from vascular disease. In patients suffering from occlusive vascular disease, three intra-arterial and three intravenous injections of Hydergine resulted in no increase in the heat flow measurements in the finger or the toe. No toxic manifestations were recorded following the injection of Hydergine in the normal or the atherosclerotic patients.

D. Pentamethyl-diethyl-3-azapentane-1, 5-diammonium dibromide (P-9295)

The dose injected in every case was 100 mgm.

(a) Studies (8) in normal subjects. Following four intra-arterial injections, a grade 2 response was recorded in two studies, a grade 1 in one and no response in another. The greatest duration of response was 45 minutes, and in every case the initial increase, occurring simultaneously and to the same degree in the ipsi- and contralateral limbs, was delayed for 90 to 120 seconds following the injection of P-9295. Four intravenous injections gave a grade 2 response in two cases and a grade 1 in two cases.

(b) Studies (6) in patients suffering from arterial disease. A grade 2 response was obtained in two patients following intra-arterial P-9295. Three studies made following the intravenous introduction of P-9295 showed a grade 2 response on two occasions and no change on one. A single subcutaneous injection caused a grade 1 response. The maximum duration of increased heat flow following the in-
TABLE 3.—Collective Results of Parenteral Administration in Patients with Occlusive Vascular Disease Who Had Been Subjected to Lumbar Sympathectomy Several Months Previously

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of Administration</th>
<th>Maximal Response in Toe or Finger, Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolazoline</td>
<td>i.a.</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>2</td>
</tr>
<tr>
<td>Regitine</td>
<td>i.a.</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>2</td>
</tr>
</tbody>
</table>

TABLE 4.—Collective Results of Parenteral Administration in Patients with Normal Arterial Circulation Who Had Been Subjected to a Lumbar Sympathectomy Some Months Previously

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of Administration</th>
<th>Maximal Response in Toe or Finger, Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolazoline</td>
<td>i.a.</td>
<td>1</td>
</tr>
<tr>
<td>Hydergine</td>
<td>i.a.</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>1</td>
</tr>
<tr>
<td>P-9295</td>
<td>i.a.</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>1</td>
</tr>
</tbody>
</table>

Injection of P-9295 by any route in both normals and patients with vascular disease was 40 minutes. No toxic or unpleasant side effects were noted following the administration of P-9295 to the resting patient, although several patients developed a hypotension and tachycardia. A postural hypotension could be demonstrated for hours after the injections.

A limited number of additional studies were made using the vasodilator drugs in patients who had been subjected to a lumbar sympathectomy 3 to 12 months previously. (See tables 3 and 4.) In these patients the response was a minimal, or absent, change in heat flow.

**Discussion**

The technic of disc calorimetry has proved satisfactory for this type of investigation. The heat flow is proportional to the skin temperature if the external disc face is maintained at constant temperature. It is not supposed that a linear relationship exists between digital skin blood flow and heat flow recordings, nor is the method suitable for registering the upper limits of vasodilatation. For the higher levels of digital blood flow "vacuum" calorimetry or venous occlusive plethysmography are required. As the response to the vasodilator drugs was generally below that following reflex vasodilatation, these more elaborate methods were not used.

Disc calorimetry is remarkably sensitive to changes of blood flow at the intermediate and lower levels of peripheral vasodilatation and vasoconstriction. Psychic stimuli, smoking and arterial occlusion by a pneumatic cuff cause rapid changes in the galvanometer readings, and minute-to-minute fluctuations in finger and toe blood flow under standard conditions can be assessed. It would appear to have distinct advantages over the copper-constantan thermocouple in its rapidity of response.

The importance of a standard and controlled room temperature must be emphasized. If this is above 23 C. release of peripheral vascular tone is greatly facilitated and is maintained. Should the room temperature fall below 19 C., it is difficult to produce a peripheral vasodilatation even with body heating. The optimal temperature would appear to be 21 C. ± 0.5 C. Certainly any comparison of vasodilator drugs in which the conditions are not controlled is valueless.

It is also important that the effects of the vasodilator drugs should be compared with some known effective peripheral vasodilatation technic. In all our cases an increase of heat flow has been demonstrated by reflex heating. The quantitative response has been greater in the normal group than in the atherosclerotic patients, but even in the latter a definite increase of heat flow from the basal readings has been readily demonstrated.

The pharmacologic actions of Tolazoline (Priscoline) have been reviewed by Nickerson and Ahlquist, Huggins and Woodbury and its clinical application by Lynn, Grimson and coworkers and White, Smithwick and Simeone. This synthetic imidazoline, which is chemically related to pilocarpine and histamine, has many of their actions. It is also a powerful adrenergic blocking agent and has
in addition a blocking action at the neuromuscular junction. It is suggested that its peripheral vasodilatation action is dependent on its histamine-like, or its adrenergic-blocking activities.

In 1950 Lynn demonstrated the marked vasodilator effect of Tolazoline following an injection into the brachial artery. In our experience with six normal subjects, the introduction of the drug into the femoral artery resulted in no increase in heat flow in three subjects and a varying response of relatively short duration in the remainder. It is possible that the lower limb responds less well than the upper to the vasodilator properties of Tolazoline. The heat flow response was even less pronounced in patients with occlusive vascular disease. In eight studies, five patients gave no response to intra-arterial administration, one showed a short lived increase and two a decrease in heat flow. It is interesting to note that shrinkage of the paw and diminution in the paw pulse wave is sometimes seen in anesthetized dogs following the intra-arterial introduction of Tolazoline.

On one occasion an intra-arterial injection of Tolazoline in a normal subject was followed by a more prolonged and greater rise in heat flow in the ipsilateral than the contralateral limb. This observation together with the rapidity of response and the vasodilatation following intra-arterial Tolazoline in sympathectomized limbs suggests that the drug is active at the effector level. Patients often complained of a sense of warmth in the leg when no change in heat flow could be demonstrated, and it was noted that a similar sensation may be experienced by the patient if isotonic saline (2 ml.) is likewise introduced intra-arterially.

Regitine is a synthetic imidazoline. Unlike Tolazoline, however, it has no cholinergic effects such as myotropic contractile activity in the experimental animal, and by reason of its adrenergic blocking properties it has been used in the diagnosis and treatment of pheochromocytoma of the adrenal gland. Its clinical application has been investigated by Longino and associates and Green and Grimesley. In our experience its action when administered intra-arterially was comparable to that of Tolazoline, in that, peripheral increase in heat flow was absent in many of the normal patients and in the majority of the patients suffering from peripheral vascular disease. In one normal patient its action following intra-arterial injection was more persistent in the ipsilateral than in the contralateral limb. Although intravenous injections in normal subjects caused an increase in heat flow in the toe or the finger in 11 out of 13 studies, its administration by this route caused considerable distress to the patient. Tachycardia, tachypnea and a fall in blood pressure were frequently demonstrated. In patients with occlusive arterial disease, four developed a grade 1 response following its intravenous injection and 10 showed no response or demonstrated a decrease of heat flow. One hypertensive patient (not included in this series) developed a severe fall of blood pressure. In the experimental animal the blood pressure may remain depressed for two hours following a single dose of Regitine.

Hydergine is a mixture of three hydrogenated ergot alkaloids and following intra-arterial injection has a greater quantitative effect in the ipsilateral than the contralateral limb of normal subjects. In three of our six studies in normal subjects no change in heat flow followed its intra-arterial introduction. In the three studies in which Hydergine was injected into the femoral artery in patients suffering from occlusive vascular disease, no increase in heat flow could be detected and in one case a diminution resulted. In both groups of patients, subcutaneous or intravenous injection of the dihydrogenated ergot alkaloids failed to produce an increase in heat flow in the toe. Its intra-arterial or intravenous injection was painless and unassociated with any systemic disturbance except for a slight lowering of the blood pressure, although Goertz has reported toxic effects following its use. Barcroft, Kouzett and Swan have shown that Hydergine has a dual action by central inhibition and by a peripheral adrenergic blockade, and that when the alkaloids were given intra-arterially to sympathectomized subjects they tended to cause a vasoconstriction in the hands and feet.
Intravenous infusions of Hydergine, they found, caused little change in calf blood flow although the hand and foot flow increased in 10 normal patients.

The drug P-9295 whose chemical structure resembles hexamethonium, has been investigated by Lynn, Sancetta and Simeone. By reason of its delayed action when injected intra-arterially and the equal quantitative response in both lower limbs, its action is thought to be at the autonomic ganglion level. It has been shown to have a blocking action at the neuromuscular junction in dogs. Following 14 parenteral injections in normal and atherosclerotic patients no augmentation of heat flow was recorded of more than 30 minutes duration. Its central and general action would appear to be major objections to its clinical use.

Conclusion

Although of great pharmacologic interest, the general usefulness of ganglionic blocking agents such as tetraethylammonium bromide and hexamethonium is limited. They are incomplete, nonselective and transient in their actions, producing a general blockade of the autonomic system with resultant unpleasant and possibly dangerous side effects such as hypotension. Furthermore their action is more pronounced in the normal than in the atherosclerotic limb. P-9295 would appear to have the failings of this class of drug.

There is nevertheless a need for a drug which will produce a selective vasodilatation in a limb without general or central effects. Such a drug would supply an alternative or supplementary method of treatment to those already available in surgical and chemical sympathectomy. Tolazoline, Hydergine and possibly Regitine can in some instances produce such a selective action at the neuroeffector level although, even in normal subjects, this is capricious in occurrence, of short duration and unlikely to be of therapeutic value.

From our experience we would agree with White, Smithwick and Simeone that the action of vasodilator drugs on the blood flow to limbs of patients suffering from occlusive arterial disease is quantitatively less than in normal subjects, and we believe that their effectiveness does not justify repeated arterial puncture. Indeed, in the hypertensive patient, the fall in blood pressure which is often induced may cause an additional embarrassment to the ischemic limb. When possible, reflex vasodilatation and sympathetic nerve interruption would in every way appear to be more satisfactory and efficient methods of increasing peripheral skin blood flow. Although the observations on sympathectomized limbs are limited, our results indicate that the blood flow to the normal or diseased lower limb does not increase significantly with the parenteral administration of any of the four drugs investigated.

Summary

1. A technic for the measurement of changes in heat flow from skin is described, using a copper-tellurium disc.
2. The effects on the skin heat flow of Tolazoline (Priscoline), Hydergine, Regitine and P-9295 when administered parenterally are compared with the results of reflex heat vasodilatation, in normal and atherosclerotic limbs.
3. In normal and particularly in atherosclerotic limbs the drugs, when injected into the femoral artery, are capricious in their action and effective only for short periods.
4. It is concluded that the effectiveness of the drugs does not justify repeated arterial puncture.

Acknowledgments

Professor A. M. Boyd kindly provided us with all the facilities required for this investigation, and we wish to thank Ciba Limited, and Sandoz Limited for supplying the drugs and Mr. J. Cronin for his willing help.

Sumario Español

1. Una técnica para la determinación de los cambios en temperatura cutánea usando un disco de cobre y telurio se describe.
2. Los efectos del cambio en temperatura cutánea del Tolazoline (Priscoline), Hydergine, Regitine y P-9295 cuando son administrados parenteralmente se comparan con los resultados de la vasodilatación refleja al calor en extremidades normales y ateroescleróticas.
3. En las extremidades normales y particularmente en las ateroescleróticas, las drogas cuando fueron inyectadas en la arteria femoral sus acciones fueron caprichosas y efectivas solamente por cortos períodos.
4. Se concluye que la efectividad de estas drogas no justifica la puncion arterial repetida.

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