Drug Treatment of Disease

VASODILATOR DRUGS FOR PERIPHERAL VASCULAR DISEASE

BY

J. F. GOODWIN, M.D., F.R.C.P.

Consultant Physician, Hammersmith Hospital; Senior Lecturer in Medicine, Postgraduate Medical School, London

INTRODUCTION

The number and complexity of drugs which are capable of producing peripheral vasodilatation are inversely related to their value in the treatment of peripheral vascular disease. More precise knowledge of the disorders of function and of anatomy of the peripheral vascular system has emphasized the importance of reconstructive surgical treatment and outlined the deficiencies in medical methods of treatment. Enthusiasm for vasodilator drugs has waned appreciably, and it has even been suggested that such drugs may actually impair rather than improve the blood flow to ischaemic limbs (Gillespie, 1959). The time is therefore ripe for a critical appraisal of the place and value of vasodilator drugs in the treatment of peripheral vascular disorders.

VASODILATOR DRUGS

Tone is maintained in the peripheral blood vessels, particularly in those of the skin, by adrenergic stimulation. Vasodilatation can be produced by interrupting sympathetic vasoconstrictor nerve impulses or by a local action on the vessel wall.

Thus drugs may act centrally; by ganglion-blockade; by blocking vasoconstrictor impulses; by neutralizing or reversing the action of adrenaline; or by a direct action on the vessel wall. Many substances combine more than one action and are extremely complex in their effects.

Central Action

Drugs in this group exert a sedative and depressant action on the central nervous system, including the vasomotor centre, and produce some central inhibitory effect on sympathetic tone. Reserpine, an ester-alkaloid from the root of certain species of *Rauwolfia*, has a depressant and hypotensive action, but produces only very slight peripheral vasodilatation. Chlorpromazine hydrochloride and promazine hydrochloride are phenothiazine derivatives which produce central nervous depression, and in this way may cause some dilatation of blood vessels. In addition, they also have adrenolytic and antispasmodic actions. In general, however, drugs with a central action have only a very weak peripheral vasodilating effect, and are not used for this purpose.

Ganglion-blocking Action

These drugs interrupt adrenergic impulses at the level of the autonomic ganglia. Their chief use is in the treatment of hypertension, but they also cause peripheral vasodilatation. Examples in this group are hexamethonium, pentolinium, mecamlamine, pempidine, and chlorisondamine. They are, however, unsuitable for routine use because of their hypotensive effects, and because of side actions which are due mainly to associated parasympathetic blockade. Hamilton *et al.* (1954) have shown that an appreciable increase in limb

blood flow can be produced by an injection of hexamethonium.

Adrenergic Blocking Action

These substances produce vasodilatation by preventing or reversing the peripheral effects of adrenaline. The terms adrenergic blocking, adrenolytic, and sympatholytic are often used synonymously. A sympatholytic drug must, of course, be also adrenolytic, though the reverse is not necessarily the case. Drugs in this group are tolazoline (imidazoline, "priscor"), phentolamine ("rogitine"), phenoxymethylamine ("dibenyline") (Wertheimer *et al.*, 1954), azapetine ("ilidar") (Green and DuBose, 1954) and a new substance recently marketed under the name of "vasculit" (Duff, 1959). These drugs act mainly on small peripheral arteries, and thus do not greatly lower blood-pressure.

The new hypotensive agent, bretylium tosylate, has a selective paralytic action on the peripheral adrenergic neurones (Boura *et al.*, 1959). As yet it has been used only for the treatment of hypertension, and the objections to the ganglion-blocking agents also apply to bretylium in the treatment of peripheral vascular disease. Chlorpromazine and promazine, in addition to central depressive effects, also have an adrenolytic action. Dihydroergocornine, a dihydrogenated derivative of ergot, reverses the vasoconstrictor action of adrenaline without producing a direct constrictor effect on the vessel wall. It is also sympatholytic and has a central depressant action. It has been used to lower blood-pressure and also may produce peripheral vasodilatation (Goetz, 1949; Goetz and Katz, 1949).

Direct Action on Blood Vessel Wall

In this group are the nitrites, papaverine, alcohol, β -pyridyl carbinol ("ronicol"), and procaine.

THE VASODILATOR PARADOX

The object of using any vasodilator drug or medical method in the treatment of peripheral vascular disease is to produce selective and sustained vasodilatation in an ischaemic limb. This effect must not be achieved at the expense of producing generalized vasodilatation throughout the body, which would lower blood-pressure and might actually reduce the perfusion to the affected limb. If this occurs, then it might be argued that the blood flow to the ischaemic part would actually fall rather than increase. The ideal vasodilator drug would be one which produces a marked vasodilating effect restricted to the ischaemic part. Such a drug should produce an effect similar to selective sympathectomy, which is the best method (other than arterial reconstruction) of increasing the blood flow to an ischaemic limb. There is, however, no drug which will restrict its effects merely to one limb, and therefore the more effective the vasodilator the more widespread and marked will be the vasodilatation and the less the effect in the ischaemic part. It is this difficulty which is mainly

responsible for the failure of vasodilators in peripheral vascular disease, for there is no doubt that many drugs will significantly increase the blood flow in a normal limb.

It is the practical experience of most workers in the field of peripheral vascular disease that vasodilator drugs are of only very limited value. Gillespie (1959) has produced evidence to suggest that these drugs are actually harmful, for by measuring blood flow to the limb by venous-occlusion plethysmography he showed that in the healthy limb a blood flow of up to 500% could be obtained after the intravenous injection of a vasodilator drug. However, in the abnormal limb, blood flow could actually fall for the reasons which have already been outlined. His conclusions that vasodilators have no place in the treatment of acute or chronic arterial occlusion are perhaps too sweeping, however, for there is evidence that vasodilating drugs, by mouth or by injection, are capable of producing increased blood flow in diseased limbs, when measured objectively.

Grimson *et al.* (1948) produced an increase in skin temperature in the affected extremities of patients suffering from Raynaud's phenomenon and thromboangiitis obliterans by the administration of tolazoline by mouth. Lynn (1950) noted that tolazoline acted mainly on the skin vessels, producing an increase in blood flow to the hands and feet in patients with Raynaud's phenomenon and with occlusive arterial disease. He also showed that intravenous injection had no effect on the sympathectomized limb, whereas intra-arterial injection almost doubled the calf blood flow to that limb, indicating that tolazoline also had a dilator effect on the vessel wall in addition to its adrenergic blocking action. Goodwin and Kaplan (1951) showed that tolazoline by mouth increased the skin blood flow to ischaemic limbs, the flow returning to pre-treatment level after discontinuing the drug. Similar results have been reported with phentolamine, phenoxybenzamine, and azapetine. Many of the reports, however, are difficult to assess owing to lack of quantitative objective evidence of improvement in the circulation.

Improvement in the circulation after a long period of time is often due to the development of collateral vessels rather than to any drug, and it is exceptional for any vasodilator drug to have any very distinct and lasting effect in occlusive peripheral vascular disease. In Goodwin and Kaplan's (1951) series the objective evidence of increase in blood flow as a result of tolazoline was convincing, but the amount of improvement gained by the patients was limited, presumably owing to the progressive nature of the occlusive disease. It is now recognized that in patients with signs of ischaemia of a limb with or without intermittent claudication an arterial block is almost invariably present. This situation is likely to limit the effects of vasodilator drugs, and focuses attention on the importance of reconstructive surgery to restore an adequate blood supply to the limb.

INDICATIONS FOR TREATMENT WITH VASODILATOR DRUGS

Vasospastic Disorders

Conditions characterized by episodic hypertonus of digital blood vessels, such as Raynaud's disease, are commonly treated with vasodilator drugs, but with only moderate success. In primary Raynaud's disease the

digital arteries are unduly sensitive to cold and develop acute spasm on exposure to low temperatures. Treatment with one of the adrenergic blocking drugs such as tolazoline, phentolamine, or phenoxybenzamine is rational, especially in the winter. It should be combined with measures to keep the hands and feet warm by wrapping them up well and avoiding exposure to cold so far as possible.

Raynaud's phenomenon, however, is often a sign of more serious organic disease of the vessels, and may be a feature of thromboangiitis obliterans, scleroderma, or systemic lupus. Furthermore, it may be produced by local conditions such as a cervical rib or thoracic-inlet syndrome, or be associated with cold agglutinins or cryoglobulins. It is therefore important to make sure that no underlying condition requiring other treatment is present. Secondary Raynaud's phenomenon may be associated with digital thrombosis, and this may account for some failures with vasodilator drugs.

Vasodilators may be of some value in the treatment of chilblains, though this is somewhat questionable.

Chronic Occlusive Arterial Disease

In these cases vasodilator drugs should be given only in addition to surgical treatment or when surgical treatment is impossible because of generalized vascular or other disease. One or more of the adrenergic blocking drugs may be combined with reflex heating in patients with chronic gangrene or with threatened gangrene. The dosage of the various drugs is indicated in Table I. In general the intramuscular or intravenous routes have little superiority over the oral route, which is of course much simpler. Repeated intra-arterial injections have been advocated but are now losing favour. Edwards *et al.* (1952) reported on the results of repeated intra-arterial injections into ischaemic limbs of tolazoline, papaverine, alcohol, acetylcholine, and histamine. Nine patients were apparently considerably improved after several arterial injections of one or other of these substances. However, Catchpole and Jepson (1954) reported that the increase in blood flow produced by intra-arterial injection was disappointingly transient, and were sceptical of the value of such treatment.

If vasodilator drugs are to be given orally they should be given in the maximum tolerated doses. It is possible to combine more than one drug, though evidence of synergism is lacking. Patients, however, may tolerate one drug rather than another and so it is worth trying several until the most satisfactory one has been found.

One of the most satisfactory vasodilators is alcohol. One or two ounces of whisky or brandy last thing at night will produce not only gentle vasodilatation but also satisfactory sleep. This is a valuable form of treatment in elderly patients with occlusive vascular disease and should not be neglected in favour of esoteric modern drugs.

The most distressing feature of severe peripheral vascular disease is ischaemic pain at rest, which is often an indication for amputation, and many patients endure great misery before this is carried out. Vasodilators are of little value in the relief of this pain, but some improvement may sometimes be obtained by raising the head of the bed at night, and by giving alcohol and a sedative such as promazine, which perhaps has some

TABLE I.—*Some Drugs Other Than Alcohol Which May Be Used for the Induction of Peripheral Vasodilatation*

Drug	Site of Action	Hypotensive Effect	Side-effects	Usual Daily Oral Dose (mg.)	
				Initial	Maximum
Tolazoline (prisol)	Sympatholytic and local. Mainly acts on digital vessels	Slight or absent, except in high dosage	Palpitation, goose-flesh, dyspepsia, headache	75	400
Phentolamine (rogitine)	" " "	" " "	" " "	75	400
Phenoxybenzamine (dibenyline)	Adrenergic blockade	" " "	Nasal congestion, miosis, drowsiness, tachycardia, dry mouth, wheezing	20	120
Azapetine (ilidar)	Adrenergic blockade and local action	" " "	Dyspepsia, weakness, dry mouth, nasal congestion, headache, palpitation	75	300
" Vasculit "	Sympatholytic	? Absent	Possibly less than other related drugs	25	100
β -Pyridyl carbinol (ronicol)	Local	Negligible	Flushing	200	400

vasodilating action in addition to its tranquillizing effects. Alternatively, methylpentynol ("oblivon") or trifluoperazine ("stelazine") may be of value, and are safer. Methylpentynol, one of the higher alcohols, may be given in a dose of 1 g. at night, or as the carbamate 200 mg. 2-5 times daily. But often stronger drugs are required and morphine or pethidine may be necessary. The risks of addiction from opiates and of serious toxic effects from promazine or chlorpromazine, such as bone-marrow depression or liver damage, may have to be run in order to relieve the intolerable pain. Misplaced faith in vasodilating drugs should not delay reconstructive surgery or amputation.

Peripheral Arterial Embolism

Embolism to a major artery is a medical emergency. The most important therapeutic measures are the relief of pain, the use of heparin to prevent spread of the embolus, and the control of cardiac arrhythmia and congestive heart failure if present. Early consultation should be held with the vascular surgeon lest embolectomy be required. Vasodilatation in the ischaemic limb is encouraged by exposing the limb to the air and warming the trunk.

Vasodilator drugs have only a small part to play in the treatment of embolism. The injection of a vasodilator substance into the artery proximal to the obstruction is sometimes practised and may have some limited value in certain cases, though enthusiasm for its use is now waning. If it is desired to give an intra-arterial injection—for example, into the femoral artery—tolazoline is probably the most satisfactory drug to use; 25-50 mg. diluted in 10 ml. of saline may be slowly injected into the artery. Firm pressure over the artery must be applied for at least five minutes after the puncture to prevent a haematoma. This is particularly important if the heparin has already been given, lest a very large haematoma result.

It is doubtful whether the effects of intra-arterial injection are sufficiently sustained to be of much value, but tolazoline or other drugs of the same group may be given by intramuscular injection or by mouth (Table I). However, perhaps the best vasodilator in these circumstances is alcohol by mouth.

Procaine paravertebral nerve block to simulate the effects of sympathectomy has little to recommend it. On no account should protracted treatment with vasodilators delay embolectomy in cases where this operation is necessary. The results of treatment of serious arterial embolism are poor (Martin, 1959;

Jacobs, 1959). They are likely to become even worse if those patients whose limbs might be saved by operation are denied this because of misdirected "vasodilator" treatment.

Intermittent Claudication

The increased blood flow to skeletal muscles which normally occurs on exercise is due to the accumulation of local metabolites which are powerful vasodilators. Such vasodilatation is not apparently under the control of the autonomic nervous system. It is therefore improbable that any vasodilator drug will be capable of increasing blood supply to claudicating muscles sufficiently to relieve pain. This in fact is the case.

Hamilton and Wilson (1952) in a carefully controlled trial showed that none of the vasodilating drugs had any significant effect upon intermittent claudication. The same, of course, applies to sympathectomy, which does not increase blood flow to muscles. Although there is good experimental evidence that adrenaline will increase blood flow to muscles (Barcroft and Swan, 1953), Hamilton and Wilson (1952) did not find that subcutaneous injections of adrenaline had any effect on the duration or severity of intermittent claudication. The assessment of severity of intermittent claudication based on exercise tests at different times is notoriously fallacious. Improvement after certain drugs is probably due to the natural improvement in the disease or reduction in pain sensitivity which commonly occurs without any treatment at all.

At the present time there is no drug treatment for intermittent claudication other than the administration of haematinic substances to correct anaemia if present. Persistent indulgence in expensive vasodilators is to be deprecated, for the treatment of intermittent claudication due to arterial obstruction is essentially surgical. This is not to say that patients with intermittent claudication should never be treated with vasodilators. Many of them have ischaemia of the skin, which may be improved to some extent by the use of certain vasodilating drugs, but it should be clearly understood that these drugs are given to improve blood flow to the skin and not claudication.

CHOICE OF VASODILATOR DRUG

Table I lists the drugs which may be used for producing peripheral vasodilatation. Personal experience suggests that the most useful are tolazoline, phentolamine and phenoxybenzamine. These and azopetine are best given by mouth. The dosages are set out in Table I. Their duration of action is 4-6 hours,

with the exception of phenoxybenzamine, which acts for up to 12 hours, and need be given only twice a day; there may also be a delay of up to two weeks before it produces any definite effect. If necessary administration by mouth may be supplemented by intramuscular injection, but in general this does not seem to have great superiority. There is little point in giving the drugs intravenously, unless a very rapid action is desired. The initial dose by injection should not exceed 25 mg. of tolazoline or phentolamine. "Vasculit" can produce appreciable vasodilatation without hypotension when given by injection (Duff, 1959).

β -Pyridyl carbinol is the alcohol of nicotinic acid. Its action on blood vessels is purely local and it is of little clinical value, though it may be used to enhance the action of a sympatholytic drug. Papaverine has no appreciable vasodilator action except when applied directly to the arterial wall. Alcohol has already been mentioned as a useful vasodilator. The nitrites are of no value in producing peripheral vasodilatation.

TOXIC EFFECTS AND DANGERS

The adrenergic blocking agents are complex substances capable of producing unpleasant side-effects. Most of these are due either to hypotension or to adrenergic blockade. Thus faintness, vertigo, headache, sweating, and "goose-flesh" may all result, particularly from parenteral administration. These side-effects may limit the use of the drug. More serious consequences of adrenergic blockade may be peptic ulceration, or perforation of an existing ulcer. Vomiting or diarrhoea may occasionally occur. The gastric effects, however, can usually be minimized by giving at the same time a non-absorbable antacid such as aluminium hydroxide. If it is considered desirable to administer tolazoline to a patient with a history of dyspepsia, an antacid should always be given in addition.

Cardiac infarction has been reported in patients taking tolazoline, but there is no certain evidence that the drug has been responsible for this complication, the infarction probably resulting from the associated occlusive coronary artery disease which so commonly complicates peripheral vascular disease. However, it should be remembered that tolazoline has extremely complex actions in animals, consisting of histamine- and acetylcholine-like properties as well as sympatholytic and local actions on blood vessels. Thus coronary vasoconstriction, bradycardia, and stimulation of the gut have been reported in rabbits receiving the drug (Ahlquist *et al.*, 1947).

The administration of adrenergic blocking drugs to patients subject to asthma may precipitate an attack of bronchospasm, and this possibility should always be borne in mind before administering one of them. In practice, however, the side-effects from the usual dosage are seldom serious.

CONCLUSION

There is a limited place for the use of vasodilator drugs in the treatment of vasospastic disorders such as Raynaud's phenomenon and to supplement other methods of medical treatment such as reflex heating, sedation, and anticoagulant therapy in acute and chronic occlusive arterial disease. When reconstructive arterial surgery is not practicable,

sympathectomy is the best method of producing a sustained increase in blood flow to the skin of the ischaemic limb. Once again it should be emphasized that correct surgical treatment should never be denied because of unrealistic faith in vasodilator drugs.

REFERENCES

- Ahlquist, R. P., Huggins, R. A., and Woodbury, R. A. (1947). *J. Pharmacol.*, **89**, 271.
 Barcroft, H., and Swan, H. J. C. (1953). *Sympathetic Control of Human Blood Vessels*. Arnold, London.
 Boura, A. L. A., Green, A. F., McCoubrey, A., Laurence, D. R., Moulton, R., and Rosenheim, M. L. (1959). *Lancet*, **2**, 17.
 Catchpole, B. N., and Jepson, R. P. (1954). *Circulation*, **9**, 408.
 Duff, R. S. (1959). *Brit. med. J.*, **1**, 1007.
 Edwards, J. W. L., Jones, N. B., McConnell, R. B., Pemberton, H. S., and Watson, D. C. (1952). *Ibid.*, **2**, 808.
 Gillespie, J. A. (1959). *Lancet*, **2**, 995.
 Goetz, R. H. (1949). *Ibid.*, **1**, 510.
 — and Katz, A. (1949). *Ibid.*, **1**, 560.
 Goodwin, J. F., and Kaplan, S. (1951). *Brit. med. J.*, **1**, 1102.
 Green, H. D., and DuBose, H. H. (1954). *Circulation*, **10**, 374.
 Grimson, K. S., Reardon, M. J., Marzoni, F. A., and Hendrix, J. P. (1948). *Ann. Surg.*, **127**, 968.
 Hamilton, M., Henley, K. S., and Morrison, B. (1954). *Clin. Sci.*, **13**, 225.
 — and Wilson, G. M. (1952). *Quart. J. Med.*, **21**, 169.
 Jacobs, A. L. (1959). *Proc. roy. Soc. Med.*, **52**, 159.
 Lynn, R. B. (1950). *Lancet*, **2**, 676.
 Martin, P. (1959). *Proc. roy. Soc. Med.*, **52**, 165.
 Wertheimer, L., Redisch, W., and Steel, J. M. (1954). *Circulation*, **10**, 366.

SIR HENRY DALE, O.M., 85

Doctors the world over will wish to join with us in extending affectionate greetings to Sir Henry Dale on the occasion of his 85th birthday, celebrated on June 9. The photograph reproduced here was taken at his home a week or two ago. It is the portrait of a man who, as Lord Adrian wrote in this journal five years ago, has "helped to guide the whole course of scientific work in Great Britain" as head of the National Institute for Medical Research and President of the Royal Society.

[Allan Chappelow, London, N.W.]