THE EFFECTS OF BETHANIDINE ON THE PERIPHERAL CIRCULATION IN MAN

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Bethanidine has been administered intra-arterially and intravenously into normo-tensive subjects and its effects on the limb blood vessels, arterial blood pressure, vascular sensitivity to noradrenaline and the degree and time course of sympathetic nerve blockade have been studied. The drug caused an initial constriction of hand and forearm vessels which is attributed to release of catechol amines since it is abolished by the prior administration of phenoxybenzamine. The constriction was followed by a sustained vasodilatation lasting between 5 and 20 hr. Sympathetic blockade of hand vessels commenced immediately on infusion and was complete within 1 hr of administration. Recovery occurred in about 5 hr. Sensitivity to intra-arterial noradrenaline was increased within 10 to 15 min of infusion and before sympathetic blockade was complete. Intravenous administration caused a slight rise in blood pressure of supine subjects. Baroreceptor reflex responses of heart and of limb vessels elicited by tilting the subject feet downwards were abolished by bethanidine and postural hypotension occurred. Bethanidine is a potent sympathetic blocking agent in man with properties intermediate between those of bretylium and guanethidine.

In the treatment of hypertension a number of drugs are available which block the transmission of impulses at sympathetic nerve terminals without interfering with the action of catechol amines. Two such drugs in clinical use are bretylium and guanethidine. Each, however, has certain disadvantages, tolerance being prominent with the first and the onset and offset of action slow with the second, while undesir-able side-effects commonly occur with each. The search for an ideal hypotensive drug continues and a series of compounds related to bretylium and guanethidine was described by Boura, Copp, Green, Hodson, Ruffell, Sim, Walton & Grivsky (1961), the most potent of these being bethanidine.

Pharmacological studies on animals and isolated preparations have shown this drug to be a potent hypotensive agent resembling guanethidine and bretylium in its action, blocking postganglionic sympathetic nervous transmission, inducing hypersensitivity to catechol amines and possessing a transient sympathomimetic action (Boura & Green, 1963). Clinical trials of the drug in hypertensive patients have shown that it may be a useful alternative to guanethidine and its effects have been ascribed to block of adrenergic neurones (Montuschi & Pickens, 1962 ; Smirk, 1963).

No results are available on the direct action of bethanidine on the blood vessels in man, and the investigation described here was designed to determine the nature and the mechanism of action of the drug on the limb blood vessels in normal human subjects. Intra-arterial and intravenous infusions were given and measurements were made of forearm and hand blood flow, systemic arterial pressure, the degree and time course of block of sympathetic transmission and the development of hypersensitivity to noradrenaline.

METHODS

The subjects were normal adults between the ages of 20 and 35 years who lay supine on a couch in a laboratory, maintained at 23 to 25° C, for 0.5 to 1 hr before observations began. The blood flow through the forearms or hands was measured three- to four-times each minute by the technique of venous occlusion plethysmography using water-filled, temperature-controlled plethysmographs (Greenfield, 1954). Plethysmograph temperatures for forearm and hand were 34 and 32° C respectively. Drugs were infused into one or other brachial artery near the cubital fossa through a 3.5 cm, 23 gauge, short-bevel needle connected by a length of polyethylene tubing to a mechanically-driven syringe which delivered 4 ml./min of solution. Saline (0.9%, w/v) containing ascorbic acid (1:20,000) was used for infusion during control periods and as a vehicle for the drugs. Doses of drugs are expressed as weights of the salts.

Bethanidine was given intra-arterially in a dose of 1 mg/min for 5 min and its effects on the circulation through the hand or forearm recorded. The responses of the vessels to intra-arterial infusion of noradrenaline and to a potent sympathetic stimulus (application of ice to the neck) were observed before and after administration of bethanidine. The blood flow through the opposite hand or forearm was simultaneously measured as a control.

In a number of subjects bethanidine was given intravenously (8 mg/min for 5 min) and its effects on blood pressure, heart rate and forearm blood flow were determined with the subject both horizontal and tilted 45° feet downwards. Blood pressure was recorded from a needle in the brachial artery using an electromanometer and an ultraviolet recorder.

RESULTS

Effects on limb vessels

Fig. 1, *a*, illustrates a typical response of the vessels of the hand to an infusion of 5 mg of bethanidine into the brachial artery of one side. An initial transient fall in flow was followed by a sustained vasodilatation which persisted for more than 5 hr. When re-examined 20 hr after the infusion the flow had returned to
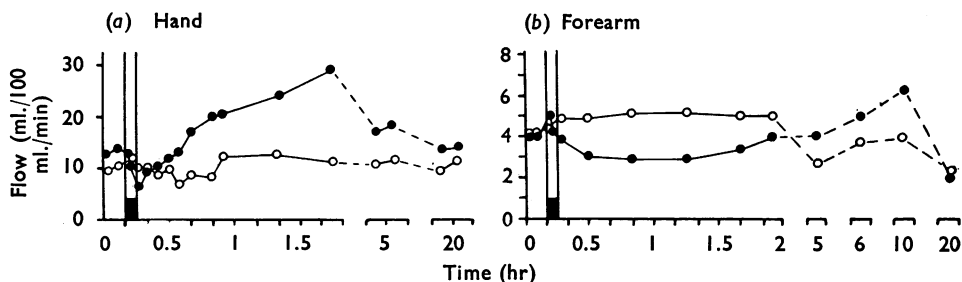

Fig. 1. Response of the blood vessels of the hand (*a*) and the forearm (*b*) to infusion of bethanidine (1 mg/min for 5 min during the vertical columns) into the brachial artery of one side. ● , infused side; ○, control side. Ordinate, blood flow in ml./100 ml./min; abscissa, time (note the changes of time scale).

about the resting value. This pattern of response of the hand vessels to bethanidine was observed in seven other experiments in six subjects.

The effect of intra-arterial bethanidine on the vessels of the forearm differed from that on the hand vessels in that the initial constrictor effect was much more prolonged, lasting up to 2 hr. The subsequent dilatation was less marked than in the hand, and had subsided at some time between 10 and 20 hr after the infusion. Fig. 1, *b*, illustrates one of four such experiments on the forearm. The influence of phenoxybenzamine given into the brachial artery in a dose of 3 mg in 5 min on the subsequent response of the forearm vessels to bethanidine is shown in Fig. 2. An infusion of noradrenaline (0.05 µg/min for 3 min) was given before
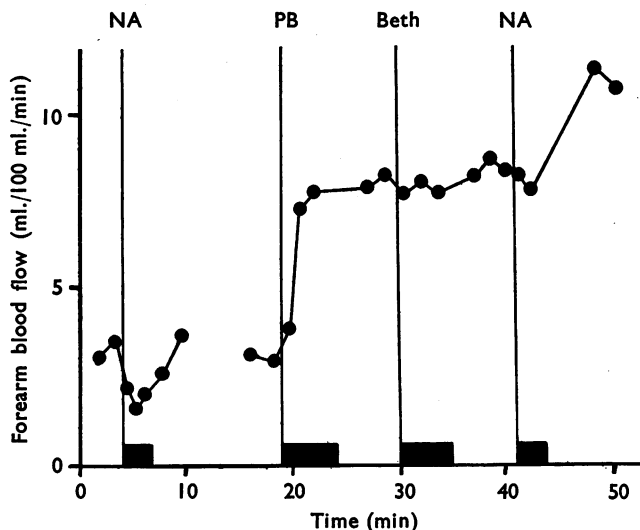

Fig. 2. The effect of phenoxybenzamine on the response of the forearm vessels to bethanidine. Forearm blood flow (ordinate) is expressed in ml./100 ml./min. NA, infusion of noradrenaline (0.05 µg/min for 3 min) into the brachial artery; PB, infusion of phenoxybenzamine (0.6 mg/min for 5 min); Beth, infusion of bethanidine (1 mg/min for 5 min).

and after the phenoxybenzamine to demonstrate that drugs given by this route were reaching the vascular bed being studied, and as a control for the adrenergic blocking action of the phenoxybenzamine. Infusion of phenoxybenzamine resulted in a rise in forearm blood flow presumably as a consequence of block of sympathetic constrictor tone. When the new level of flow had become stabilized, bethanidine was infused. Little or no fall in flow was now seen, in contrast to the responses illustrated in Fig. 1, *b*. The constrictor effect of bethanidine on hand blood vessels was also abolished by the prior administration of phenoxybenzamine.

Block of sympathetic transmission

Fig. 3 shows the pooled results from eight experiments on six subjects in whom the reflex vasoconstrictor response of the hand vessels to ice applied to the neck for 15 sec was recorded before and at intervals after infusion of bethanidine into the brachial artery of one side. The application of ice is a potent sympathetic stimulus
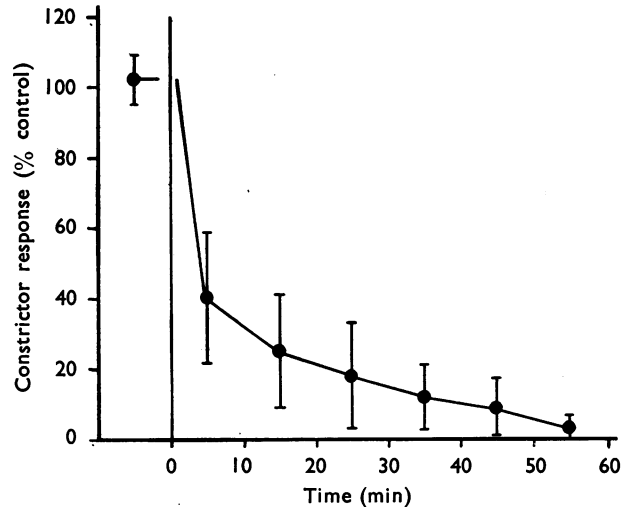
Fig. 3. Sympathetic block of the hand blood vessels following bethanidine (1 mg/min for 5 min) given into the brachial artery at zero time. The constrictor response of the hand vessels to ice applied to the neck is expressed as the percentage of the control response (see text). Each point represents the mean of observations on four subjects and the vertical line through each point represents the standard deviation of the individual values from the mean.

to which both hands respond with an equally intense vasoconstriction if the sympathetic nerves and transmission are intact. The relationship of the response of the treated side to that of the control side was expressed as a percentage by applying the formula $I/C \times 100$ where I and C were the percentage falls in flow (induced by ice) in the injected and control hands respectively. Block was complete in less than 1 hr, and in three subjects who were followed for a sufficient time recovery to 75 to 80% of the control side had occurred by 5 hr.

Sensitivity to noradrenaline

In four subjects noradrenaline (0.05, 0.1 or 0.2 μg/min) was infused for 3 min into the brachial artery of one side before and at intervals after infusion of bethanidine (Fig. 4). The average of the hand blood flows recorded in the last 2 min of each noradrenaline infusion was compared with that of the flows in the 2 min immediately preceding the onset of the infusion. Where appropriate, account was taken of general spontaneous changes in limb blood flow by reference to the control side, and a correction was made. An increase in sensitivity occurred within 10 to 15 min of the end of the infusion of bethanidine in all subjects and in three of the subjects this persisted until the experiments were terminated 35, 45 and 55 min after infusion. In the fourth subject the response had returned by the end of 30 min to below the control value.

Intravenous infusion

Block of the baroreceptor reflex responses to tilting was seen within 20 min of intravenous infusion of 40 mg of bethanidine over 5 min in two subjects. In neither subject was a fall in supine blood pressure below the pre-infusion level seen
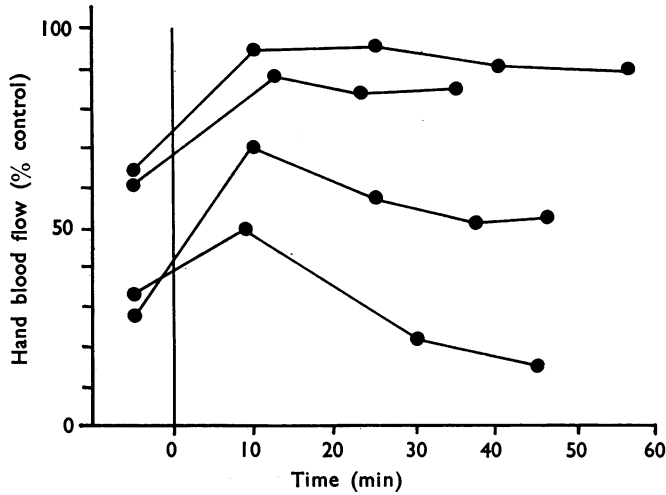
Fig. 4. The response of the hand blood vessels to repeated doses of noradrenaline before and at
intervals after bethanidine (1 mg/min for 5 min at zero time) in four subjects. The constrictor
effect of noradrenaline is expressed as the percentage fall in flow from the control value. Drugs
were given by the intra-arterial route.

at any stage of the experiment. On the contrary, a rise of 9 and 11 mm Hg in
mean pressure occurred towards the end of the intravenous infusion of bethanidine.

On tilting 45° feet downwards, after administration of bethanidine, a profound
fall in blood pressure rapidly developed and with one subject the supine position
had to be restored after 2.75 min because of impending syncope, whereas before
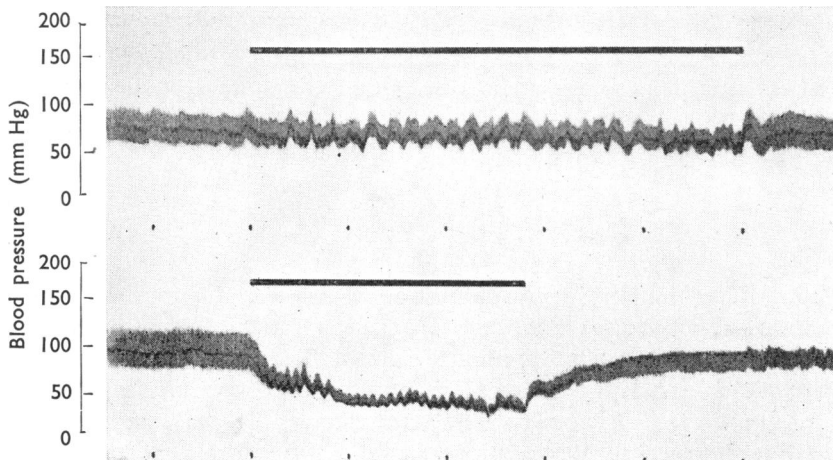bethanidine a tilt of 5 min was tolerated without a fall in blood pressure (Fig. 5).

Fig. 5. The effect of tilting 45° feet downwards from the supine position on the brachial arterial
blood pressure in one subject before (upper record) and 20 min after (lower record) intravenous
infusion of bethanidine (8 mg/min for 5 min). The horizontal bar represents the duration of the
tilt in each instance. Time signals are at minute intervals.

The blood pressure, heart rate, forearm vascular resistance and blood flow responses to tilting in the same subject are shown in Fig. 6. The normal compensatory increase in pulse rate and in forearm vascular resistance seen during tilting before bethanidine was modified or abolished after the drug. Thus, an initial small increase in pulse rate occurred which was not maintained and, by the end of the tilt, when fainting was imminent, the rate had fallen below the resting level. No increase in forearm vascular resistance occurred during the tilt after the drug. The fall in forearm blood flow at this time must therefore have been due solely to the reduced perfusion pressure.
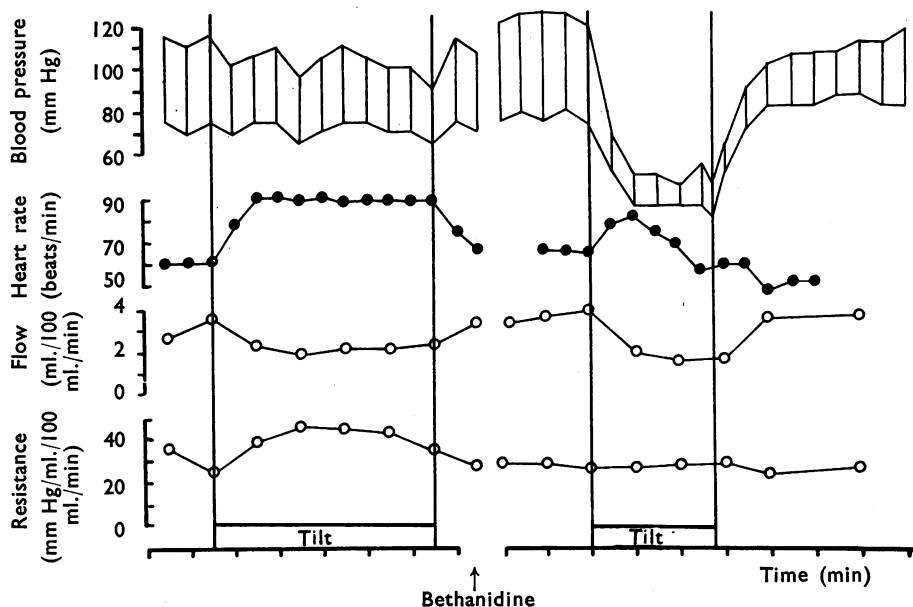

Fig. 6. The effects of tilting on the arterial blood pressure, heart rate, forearm blood flow and calculated forearm vascular resistance before (lefthand graphs) and 20 min after (righthand graphs) intravenous infusion of bethanidine (8 mg/min for 5 min). Same subject as in Fig. 5. Abscissal scale in minutes.

DISCUSSION

The intra-arterial route of drug administration was used for most of the experiments reported here because an effective local concentration of drug can be achieved in the limb by this means, but dilution to subthreshold levels when it reaches the general circulation avoids drug-induced changes in blood pressure or general vasomotor tone. Correction for spontaneous changes in vasomotor tone can be made by reference to the control side. In the assessment of changes in sensitivity of the limb vessels to noradrenaline after bethanidine, the intra-arterial route of administration was again used, since the response of the hand or forearm vessels to intravenous noradrenaline is a complex one, being the resultant of the direct action of noradrenaline on the vessels and the reflex dilator responses which

occur as a consequence of the rise in arterial and venous pressures (Barcroft, Gaskell, Shepherd & Whelan, 1954). After general block of the baroreceptor reflex mechanism noradrenaline will not only cause an increased blood pressure rise because of the absence of the normal compensatory reflexes, but will also cause an increased constriction of the peripheral vessels since central reflex activity no longer opposes the direct action of the drug. This effect represents an increased response of the vessels but cannot be construed as an increased sensitivity of the vascular smooth muscle. Only by direct arterial infusion of noradrenaline into the limb can a valid assessment of sensitivity be made.

The effects of bethanidine on the forearm and hand vessels, when given intra-arterially, are intermediate between those previously observed with bretylium and guanethidine given by the same route (Blair, Glover, Kidd & Roddie, 1960 ; French & Matthews, 1961 ; Cooper, Fewings, Hodge & Whelan, 1963). The initial vaso-constriction, of shorter duration than after guanethidine, was abolished by phenoxybenzamine and is probably due to release of catechol amines. The subsequent dilatation is associated with the increasing block of sympathetic transmission. If used in appropriate dosage, bethanidine, like bretylium and guanethidine, can produce virtually complete sympathetic block of the hand vessels.

The increase in sensitivity of the hand vessels to noradrenaline after infusion of bethanidine into the arm commenced with 20 min, before sympathetic block was complete, and persisted in three of the four subjects for the remainder of the experiments. A similar effect has been demonstrated with bretylium and guanethidine, but was very transient with the former, having disappeared by the time sympathetic block was complete (Cooper *et al.*, 1963). Bethanidine resembles guanethidine in the persistence of the increased sensitivity. As previously suggested for bretylium and guanethidine (Cooper *et al.*, 1963), this acute sensitivity may be related to release of catechol amines, a phenomenon observed by Innes (1960) and Nakamura & Shimamoto (1960) in animal tissues. The fact that the size of the increase in sensitivity with bethanidine is intermediate between that with guanethidine and that with bretylium accords with its catechol amine releasing potency, which is also intermediate between those of the two latter drugs.

It has been suggested that increased sensitivity of the peripheral vessels to circulating noradrenaline after administration of sympathetic blocking agents may be a factor in the development of clinical tolerance to these substances (Zaimis, 1961). However, the increased sensitivity to noradrenaline observed after bethanidine in the present study is not necessarily an indication that tolerance will occur in clinical use since guanethidine, in the use of which tolerance is not a feature, produced a sustained hypersensitivity while bretylium, to which tolerance is conspicuous, increased the sensitivity to noradrenaline only transiently (Cooper *et al.*, 1963). Studies of patients on long-term oral drug administration will be necessary to investigate the possible development of chronic hypersensitivity to noradrenaline and its relationship to tolerance.

The intravenous dose of bethanidine necessary to block the baroreceptor reflex mechanism to a degree sufficient to cause severe hypotension on tilting is larger than might be expected from published results on oral administration in hypertensive

patients. This difference may have been due to the fact that the present study was carried out on normotensive subjects.

The slight increase in blood pressure seen during and shortly after infusion of bethanidine is probably due to the vasoconstrictor action of catechol amines released from tissues. This initial pressor effect suggests that, used alone, bethanidine should not be administered intravenously in hypertensive emergencies.

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