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EFFECTS OF BRETYLIUM AND GUANETHIDINE ON HUMAN HAND AND FOREARM VESSELS AND ON THEIR SENSITIVITY TO NORADRENALINE

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Infusions of bretylium and guanethidine into the brachial artery of normal subjects caused a fall in forearm and hand blood flow followed by a sustained increase in flow. The constrictor phase was attributed to catechol amine release since it was blocked by phenoxybenzamine. A slight and transient increase in response of the hand vessels to noradrenaline was seen after bretylium in the early constrictor phase before sympathetic block was complete. Guanethidine produced a more definite and sustained increase in the response of the hand vessels to noradrenaline. It is concluded that the phenomenon of tolerance which is conspicuous with bretylium and negligible with guanethidine is unlikely to be due to the rapid onset of hypersensitivity of the peripheral vessels.

The postganglionic sympathetic blocking agents bretylium and guanethidine are commonly used in the treatment of hypertension and are important pharmacological tools in the investigation of autonomic mechanisms. One striking difference in their clinical characteristics is that tolerance develops towards bretylium so that successively increasing doses are required to control the blood pressure (Dollery, Emslie-Smith & McMichael, 1960; Hodge & McPhie, 1960). This problem is not encountered to any significant degree with guanethidine (Boura, Green, McCoubrey, Laurence, Moulton & Rosenheim, 1959; Leishman, Matthews & Smith, 1961).

The development of tolerance was attributed by Green (1961) and by Zaimis (1961) to an increased sensitivity of peripheral vessels to noradrenaline. The noradrenaline might be normally circulating from the adrenal medulla, released by sympathetic nervous activity (since in an ambulant patient on treatment it is impracticable to block completely the sympathetic nerves) or released from a peripheral store by the action of the hypotensive agent itself.

The purpose of this investigation was to determine whether an acute increase in sensitivity to noradrenaline accompanied the sympathetic blocking action of bretylium and guanethidine on the blood vessels of the human hand and forearm. Observations were also made on the direct actions of these drugs on the blood vessels and on sympathetic transmission in these areas.

METHODS

The subjects were healthy adults aged 20 to 35 years who lay supine on a couch for 30 to 60 min before observations began. The blood flow through the forearms or hands was measured three to four times each minute by venous occlusion plethysmography using water-filled, temperature-controlled plethysmographs (Greenfield, 1954). Drugs were infused into one or other brachial artery near the ante-cubital fossa through a 3.5 cm long, 23 gauge, short-bevel needle connected by a length of polyethylene tubing to a mechanically-driven syringe which delivered 4 ml. of solution per min. 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.

To follow the time course of the sympathetic block resulting from intra-arterial infusion of bretylium or guanethidine ice was applied to the neck of the subject for 30 sec at intervals before and after infusion, and the resulting vasoconstriction in both hands was recorded. This procedure proved a potent sympathetic stimulus and both hands responded with an equally intense vasoconstriction if the sympathetic nerves were intact. The relationship of the response of the treated side to that of the control side was expressed as the ratio between the percentage falls in flow induced by ice in the injected and control hands respectively multiplied by 100. Thus, if the flow on both sides fell equally the result would be expressed as 100% response; if after injection of the sympathetic blocking drug the control side showed an 80% fall and the injected side a 40% fall, then the result would be expressed as a 50% response.

To test for sensitivity to noradrenaline, two or three different doses of noradrenaline bitartrate (Levophed, Winthrop) were infused before and after the introduction of bretylium or guanethidine. In this way the dose/response relationships in the two periods could be compared. In other experiments the same dose of noradrenaline was given at intervals before and after the introduction of the sympathetic blocking agent. The mean of the flow values in the 2 min preceding the infusion was compared with that in the last 2 min of the 3 min infusion period. Where appropriate, account was taken of general spontaneous changes in limb blood flow by reference to the control side and the method of Duff (1952) used to apply a correction.

Bretylium tosylate (Darenthin, Burroughs Wellcome) was given in a dose of 10 or 20 mg over a period of 5 min and guanethidine hemisulphate (Ismelin, Ciba) in a dose of 5 mg for the same period. In a number of experiments the effect of phenoxybenzamine hydrochloride (Dibenzyline, Smith, Kline & French, 1.2 or 2 mg in 5 min) on the response of the limb vessels to the above drugs was observed. Doses of the drugs are expressed as weights of the salts.

RESULTS

Effects on limb vessels

The effects of intra-arterial infusions of bretylium (10 or 20 mg) and guanethidine (5 mg) on forearm and hand blood flow were qualitatively similar; vasoconstriction occurred after the administration of the drug, followed by a prolonged vasodilatation (Fig. 1). The vasoconstriction lasted longer after guanethidine than after bretylium, and with each drug was more prolonged in the forearm than in the hand.

In the forearm bretylium caused a transient three- to four-fold increase in flow during its infusion. The hand vessels responded somewhat differently, as only a moderate vasodilatation preceded the vasoconstriction in six of eight subjects, and was more pronounced when the resting flow was low. No such effect was seen with guanethidine, which produced an immediate fall in hand and forearm flow during its infusion (Figs. 1 and 2).

The constrictor effect of bretylium on forearm and hand vessels was abolished by the prior administration of the adrenergic blocking agent phenoxybenzamine.

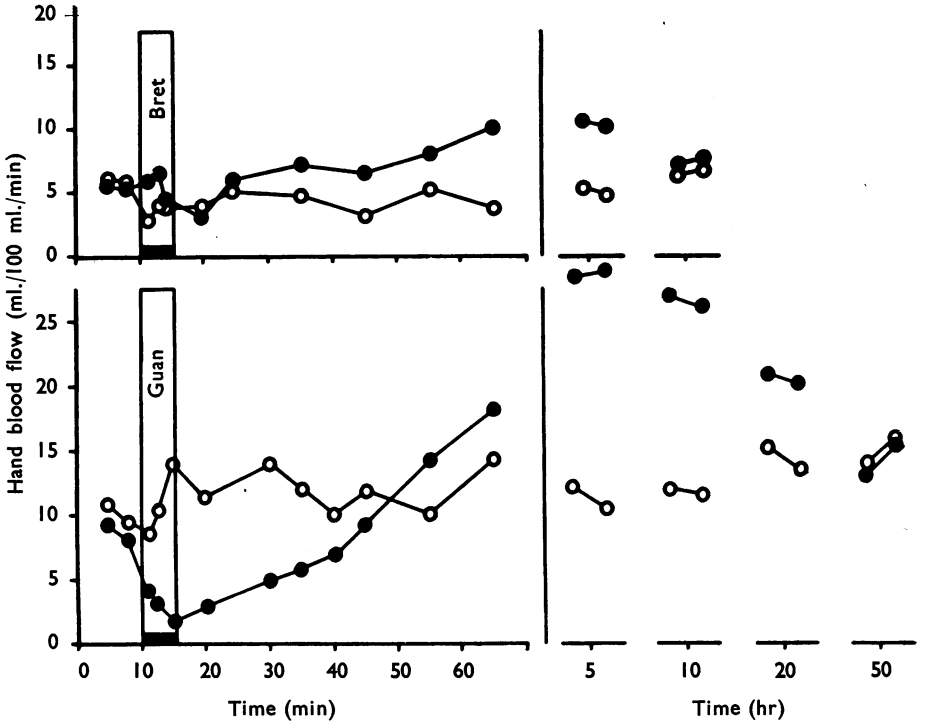

Fig. 1. The response of the blood flow through the hand to infusions of bretylium (20 mg, Bret—upper section) and guanethidine (5 mg, Guan—lower section) into the brachial artery. ●, injected side; ○, control side.

The constrictor effect of guanethidine was not completely abolished, a slight residual fall in flow remaining despite the abolition of the response to noradrenaline (Fig. 2). No change in flow was seen during infusion of the vehicle, and the residual constriction thus appeared to be due to a direct action of the drug on the vessels.

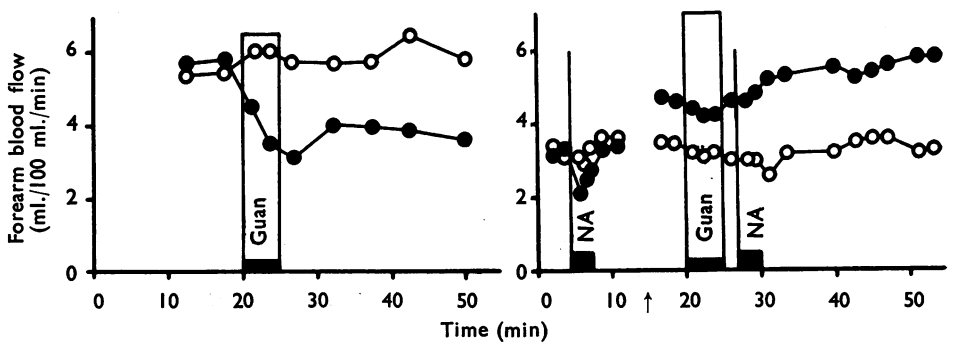

Fig. 2. Right-hand section: the effect of phenoxybenzamine infused (at arrow) into the brachial artery on the response of the forearm vessels to guanethidine (Guan). ●, injected side; ○, control side. At NA, noradrenaline (0.025 μg/min for 3 min) was infused intra-arterially to check the efficacy of the block by phenoxybenzamine. The left-hand section shows the response of the forearm flow to guanethidine (Guan) alone in the same subject on a previous occasion.

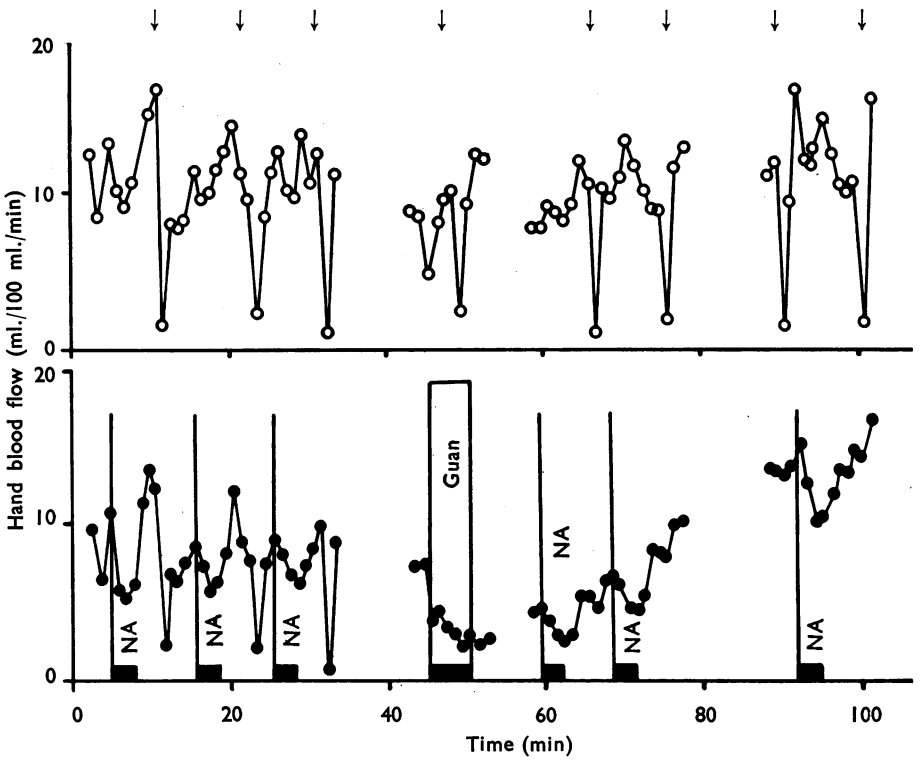

Fig. 3. The response of the hand blood flow to application of ice to the neck (at arrows) and to intra-arterial infusions of noradrenaline (NA) at intervals before and after intra-arterial infusion of guanethidine (Guan). ●, infused side; ○, control side.

Sensitivity to noradrenaline

In Fig. 3 is illustrated an experiment in which the sensitivity of the vessels of one hand to a dose of 0.05 μg/min of noradrenaline was determined at intervals before and after intra-arterial infusion of guanethidine. The reflex constrictor responses of the vessels of both hands to ice applied to the neck are also shown. The results from this and from seven other such experiments are summarized in Fig. 4. In every experiment within 5 to 10 min of infusion of guanethidine the percentage reduction in flow caused by noradrenaline was greater than before the infusion. At this time the blocking action of the drug was incomplete as judged by the proportion of the sympathetic response (elicited by application of ice) which survived the block. At 30 min, when block was complete and blood flow levels had returned to or had risen above control values, the response to noradrenaline was still increased in six of the eight subjects.

The results of six similar experiments with bretylium are illustrated in Fig. 5. In four subjects there was an increase in the percentage fall in flow with noradrenaline within 5 min of the end of the infusion of bretylium at a time when sympathetic block was minimal and the vasoconstrictor action of the drug was most marked.

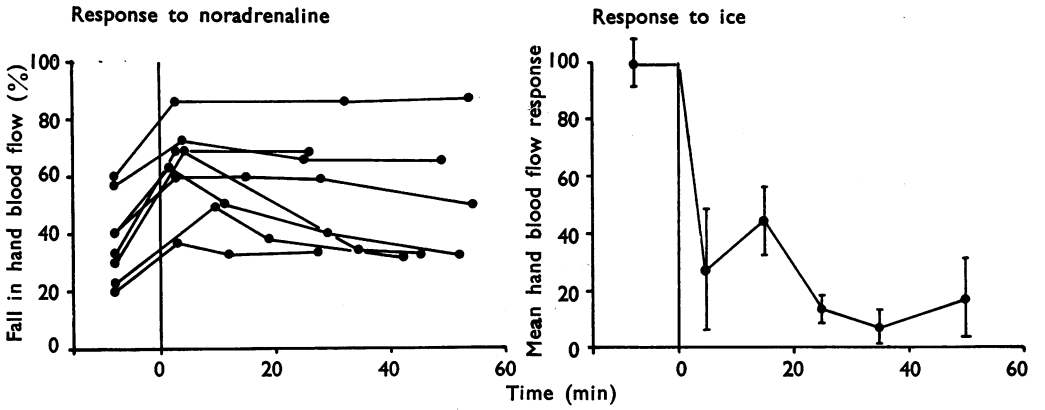

Fig. 4. Left-hand section: the percentage fall in hand blood flow in eight subjects in response to intra-arterial infusions of noradrenaline (0.05 μg/min) before and at intervals after intra-arterial administration of guanethidine at time zero. Right-hand section: pooled data of the responses of the hand blood flow to ice applied to the neck in the above subjects. The response (ordinate) is expressed as the ratio of the falls in blood flow on the infused and control sides respectively, times 100. Each point represents the mean of all observations in the appropriate 10 min period, and the vertical line through each point represents the standard deviation.

By the time sympathetic block was complete (30 to 35 min after bretylium) the blood flow level was restored and the responses to noradrenaline had returned to pre-infusion levels in all but one subject in whom a 10% increase persisted.

With the forearms the time course of the blocking action of the drugs was not defined since the response of the forearm vessels to the application of ice was inconsistent. The dose/response curves of the forearm blood vessels to noradrenaline obtained before and after administration of bretylium or guanethidine did not

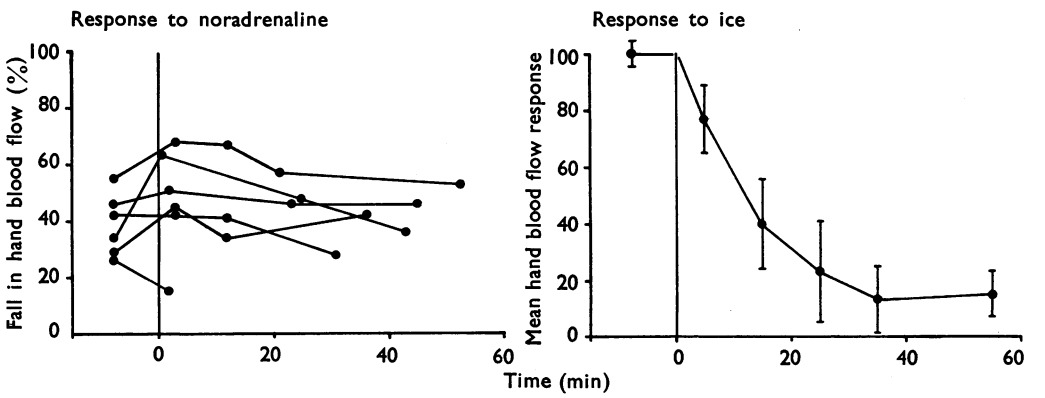

Fig. 5. Left-hand section: the percentage fall in hand blood flow in six subjects in response to intra-arterial infusions of noradrenaline (0.05 μg/min) before and at intervals after intra-arterial administration of bretylium at time zero. Right-hand section: pooled data of the responses of the hand blood flow to ice applied to the neck in the above subjects, calculated as for Fig. 4.

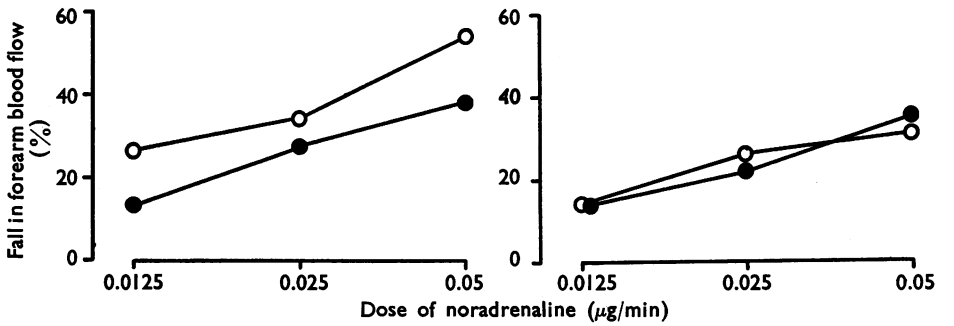

Fig. 6. The responses of the forearm blood vessels to three doses of noradrenaline given into the brachial artery before (○) and after (●) intra-arterial infusion of bretylium (left section) and guanethidine (right section).

demonstrate any increase in vascular sensitivity (Fig. 6). The dilatation of the forearm vessels in response to mental arithmetic, which is mainly due to cholinergic nerve activity (Blair, Glover, Greenfield & Roddie, 1959), was not affected by either bretylium or guanethidine.

DISCUSSION

The response of the vessels to bretylium and guanethidine

The effects of bretylium on the blood flow in the forearm and hand in the present study are similar to those described by Blair, Glover, Kidd & Roddie (1960), and by French & Matthews (1961). The initial transient vasodilatation in the forearm was attributed by Blair *et al.* (1960) to a direct action of the drug on the vessels since it occurs in the nerve-blocked limb. The constriction of hand and forearm vessels by bretylium appears to be adrenergic and is probably due to local release of catechol amines from the tissue since we found it was abolished by phenoxybenzamine. Animal experiments have also demonstrated that this drug releases catechol amines (Gaffney, 1961 ; Gillis & Nash, 1961 ; Gilmore & Siegel, 1962).

The pattern of response of the blood vessels of the hand and forearm to guanethidine (5 mg) differed from that to bretylium (10 to 20 mg) in that no initial vasodilatation was observed. The constrictor phase became evident during the period of infusion and both it and the subsequent dilatation persisted for longer periods than after bretylium. Most of the constrictor effect can be attributed to release of catechol amines, but a small residual fall in flow occurred after treatment with phenoxybenzamine which was presumably due to a direct action of the drug on the vessels. These actions of guanethidine are consistent with those observed in animals and isolated tissues which demonstrate that it causes a much greater release of catechol amines than does bretylium (Gillis & Nash, 1961), and accord with clinical observations that its hypotensive action is more prolonged (Page & Dustan, 1959).

Tolerance and hypersensitivity

Hypersensitivity of the cat nictitating membrane to noradrenaline has been reported both after bretylium and after guanethidine (Green, 1962), although tolerance in

clinical use, which is usually ascribed to vascular hypersensitivity, is prominent only with bretylium. Much of the evidence for vascular hypersensitivity comes from studies on intact animals or humans, and is more difficult to interpret than results from isolated tissues. Thus in acute experiments, Abboud, Eckstein & Wendling (1962) found an increased pressor response to noradrenaline infusions in dogs and man 30 min after intravenous administration of guanethidine and demonstrated an increased constriction of the forearm vessels in man, which was attributed to hypersensitivity of the vessels. However, inhibition of the baroreceptor reflexes, whether by an action of the drug on the baroreceptors or centrally, or by interruption of the efferent pathways, will result in an exaggerated response of the limb vessels to noradrenaline, on account of the absence of the usual reflex dilatation which tends to oppose the direct vasoconstrictor action of the drug (Barcroft, Gaskell, Shepherd & Whelan, 1954). The increased responsiveness may enhance the pressor effect of noradrenaline, but this is not necessarily evidence of true hypersensitivity of the vascular smooth muscle. For example, hexamethonium, which blocks the baroreceptor reflex pathway, produces no increase in vascular sensitivity to intra-arterial injection of noradrenaline at a time when the responses to intravenous administration are considerably increased (Hodge & Whelan, 1962).

In the present study the intra-arterial route of administration was used so that a high concentration of bretylium and guanethidine could be applied to the vessels, while the amount entering the systemic circulation would be insufficient to have any general effect. Noradrenaline was also given intra-arterially to avoid the complex reflex responses which result from blood pressure changes. A small increase in the percentage fall in hand blood flow with noradrenaline was found in four of six subjects given bretylium, but in only one did this persist for more than 30 min. It is doubtful whether the observed increase in response to noradrenaline represented a genuine increase in sensitivity since it was only apparent when the blood flow level was considerably reduced, so that the assessment of constrictor responses was difficult. The more definite and prolonged increase in sensitivity to noradrenaline after injection of guanethidine occurred before sympathetic block was complete and thus appeared to be unrelated to the blocking action. The interesting possibility remains that the increased sensitivity may depend on the ability of guanethidine to release catechol amines. A similar phenomenon has been reported in animal tissues immediately after treatment with reserpine by Innes (1960) and by Nakamura & Shimamoto (1960).

With the forearm vessels no increase in sensitivity to noradrenaline was observed either after bretylium or after guanethidine. This absence of an increase in total forearm blood flow response to noradrenaline, however, does not altogether exclude the possibility of a change in sensitivity of one or other of the vascular beds which together make up the forearm circulation, and which cannot be differentiated by the plethysmographic method of flow measurement. For example, Skinner & Whelan (1962) have demonstrated that adrenaline constricts forearm skin vessels and dilates the underlying muscle vessels. The direction of change in total forearm blood flow produced by adrenaline depends on the initial level of skin blood flow. If this is high, the constrictor effect of adrenaline on the skin vessels will predominate

and a fall in total forearm blood flow results; when skin blood flow is low the reverse occurs (Whelan & de la Lande, 1963). It is not known whether the effect of noradrenaline is greater on forearm skin or on muscle vessels, nor are there any observations to indicate whether the forearm blood flow changes following bretylium and guanethidine are due to effects on skin or muscle vessels or both. These uncertainties make it impossible to be sure that a change in sensitivity to noradrenaline did not occur in one of the vascular beds of the forearm, but it can be concluded that if any such change did occur it was not sufficiently great to alter the change in overall forearm vascular resistance produced by noradrenaline.

The slight transient increase in sensitivity of the hand vessels to noradrenaline after bretylium (to which tolerance is marked), the more sustained increase in sensitivity with guanethidine (to which tolerance is negligible) and the absence of any increase in overall forearm vascular sensitivity all suggest that it is unlikely that the development of sensitivity to catechol amines as a consequence of its blocking action can account for the phenomenon of tolerance to bretylium.

It is possible that a more pronounced and widespread increase in vascular sensitivity to catechol amines may develop with the use of these drugs in therapy, but longer-term studies on patients undergoing treatment will be necessary before this point can be elucidated.

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