*Brit. J. Pharmacol.* (1962), **18**, 331–336.

# EFFECT OF HEXAMETHONIUM ON THE VASCULAR RESPONSE TO NORADRENALINE IN MAN

BY

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(*Received January* 2, 1962)

Intra-arterial infusion of hexamethonium into the brachial artery had no potentiating effect on the constrictor response of the vessels of the forearm or hand to noradrenaline given by the same route. The response of the hand vessels to intravenous infusion of noradrenaline was enhanced after intra-arterial hexamethonium, but this was attributed to entry of the blocking agent into the general circulation resulting in blockade of baroreceptor reflexes since the potentiation was seen to an equal degree on both sides. It is concluded that if increased sensitivity to noradrenaline plays a part in the phenomenon of tolerance to hexamethonium this must be a slowly developing effect.

The development of tolerance is commonly associated with the use of ganglion blocking drugs in the treatment of hypertension, successively increasing doses being required to control the blood pressure.

The mechanism of this tolerance is still a matter of debate. An increase in the pressor response to injected adrenaline and noradrenaline has been demonstrated following ganglion-blocking agents in animals and in man (Page & Taylor, 1947 ; Corcoran & Page, 1947 ; Paton, 1951 ; Gefen & Ross, 1956). While this increased responsiveness has been attributed by some workers solely to blockade of compensatory baroreceptor reflexes (Moe, 1948 ; Page & Taylor, 1950 ; Bartorelli, Carpi & Cavalca, 1954), the findings of others suggest that an increase in the sensitivity of the peripheral vessels to circulating amines also plays a part (St. Clair & Stone, 1951 ; Mantegazza, Tyler & Zaimis, 1958 ; Maengwyn-Davis, Walz & Koppanyi, 1958). The latter proposition has not, however, been supported by the findings on all preparations tested nor for all types of hypotensive agent used (Prado & Carlini, 1959 ; Lum & Rashleigh, 1961 ; Blackman & Laverty, 1961), nor have there been any direct observations made on the development of vascular sensitivity to these drugs in man.

The present investigation was designed to determine whether increased sensitivity to noradrenaline developed in the peripheral vessels of the limbs following hypotensive drug administration in normal human subjects.

## METHODS

The subjects were normal adult males between the ages of 18 and 35 years who lay supine on a couch in a room at a temperature of 21 to 23° C for one-half to one hour before

observations began. The blood flow through the hands or the forearms was measured by the technique of venous occlusion plethysmography using water-filled, temperature-controlled plethysmographs (Greenfield, 1954). Hexamethonium bromide (Vegolysen, May & Baker) in a dose of 10 mg over 5 or 10 min was infused into the forearm or hand through a 3.5 cm (23 s.w.g.) short-bevel needle introduced into the brachial artery at the elbow of one side and connected by way of a length of polythene tubing to a mechanically driven syringe which delivered 4 ml. of solution per min. Saline (0.9% sodium chloride w/v) was infused at a rate of 4 ml./min during control periods. Noradrenaline (Levophed, Bayer) was given intra-arterially in doses ranging from 0.0125 to 0.1 μg/min or intravenously in a dose of 10 or 20 μg/min. The drug was made up in saline containing ascorbic acid 1:50,000 so that the dose per min was contained in 4 ml. Flow records were taken 3 or 4 times per min.

Infusions of noradrenaline were given for 3 or 5 min and the level of flow during the last 2 min of the infusion was expressed both as a net and as a % fall from the previous resting level, determined as the average of all the flow measurements during the preceding 3 to 5 min period. Account was taken of any progressive general drift in blood flow during the experiment by reference to the flow in the opposite control side when this was appropriate, or to the pre- and post-infusion flow in those cases of intravenous administration where both sides were receiving the drug.

## RESULTS

Fig. 1 shows the responses of the forearm blood vessels to intra-arterial infusions of noradrenaline in 5 subjects before and immediately after infusion of hexamethonium into the same artery. An interval of 4 or 5 min was allowed to elapse

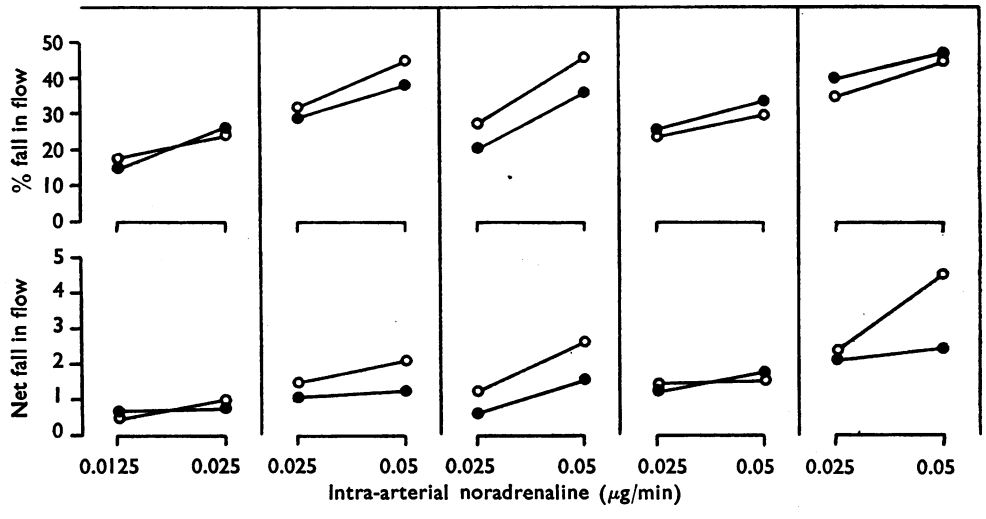


Fig. 1. The constrictor responses of the vessels of the forearm to infusions of noradrenaline into the brachial artery in five subjects before (○——○) and after (●——●) infusion of hexamethonium (10 mg) into the same artery. Upper frames: % fall in flow from resting level; lower frames: net fall in flow in ml./100 ml./min.

between the end of one infusion and the beginning of the next, which was sufficient for the blood flow to return to its previous resting level. The first dose of noradrenaline to be given after the end of the hexamethonium infusion was commenced immediately without any interval. This dose was usually repeated at the end of the series of infusions. The last infusion of noradrenaline was

commenced within 20 to 30 min of the end of the infusion of hexamethonium. While there were variations between the responses before and after hexamethonium, these differences were small and not constant. There was no evidence of an increased sensitivity to noradrenaline after hexamethonium, whether the data were expressed as percentage fall in flow or as a net reduction in ml./100 ml./min.

A similar conclusion was reached from the experiment illustrated in Fig. 2, where a different procedure was adopted. A noradrenaline infusion into the brachial artery was commenced in a dose of 0.025 μg/min. After a period of 4 min, by which time the blood flow had reached its new level, the noradrenaline solution was replaced by one containing noradrenaline 0.025 μg/min and hexamethonium 2 mg/min. This was maintained for 5 min, after which the noradrenaline alone

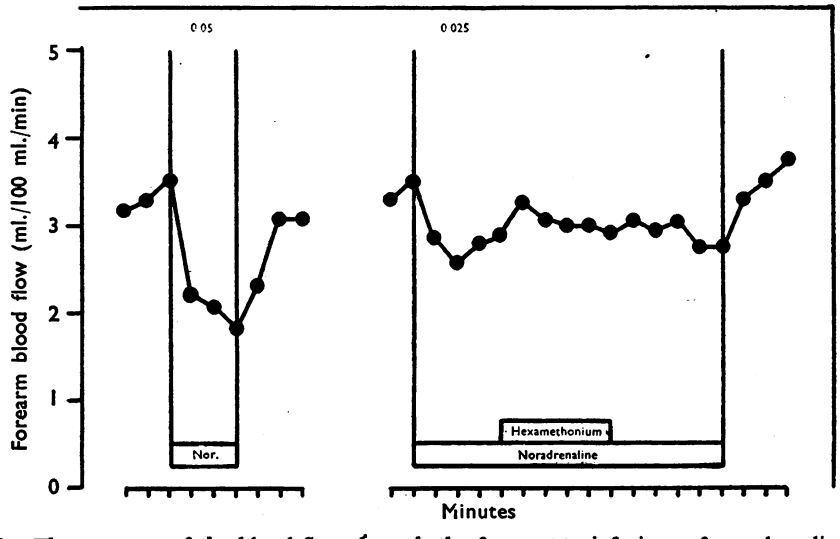


Fig. 2. The response of the blood flow through the forearm to infusions of noradrenaline (0.05 and 0.025 μg/min) into the brachial artery. Hexamethonium 2 mg/min was given for 5 min during the second infusion of noradrenaline. Each point represents the average of the four flow records taken in each min.

was continued for a further 5 min. The addition of hexamethonium to the noradrenaline infusion did not result in any further reduction in blood flow. That the vessels were capable of further constriction is demonstrated by the greater response to a dose of 0.05 μg/min of noradrenaline given previously.

One of each of the above types of experiment was carried out on the hands with the same result.

In 3 subjects hexamethonium was given into the brachial artery of one side (10 mg in 10 min). Test doses of noradrenaline (2.5 μg/min for 5 min) were given intravenously before, during and after the blocking agent, and hand blood flow measured on both sides. There was an increased constrictor response both during and after the hexamethonium infusion in 2 of the subjects which was manifest in both hands and to an equal degree (Fig. 3).

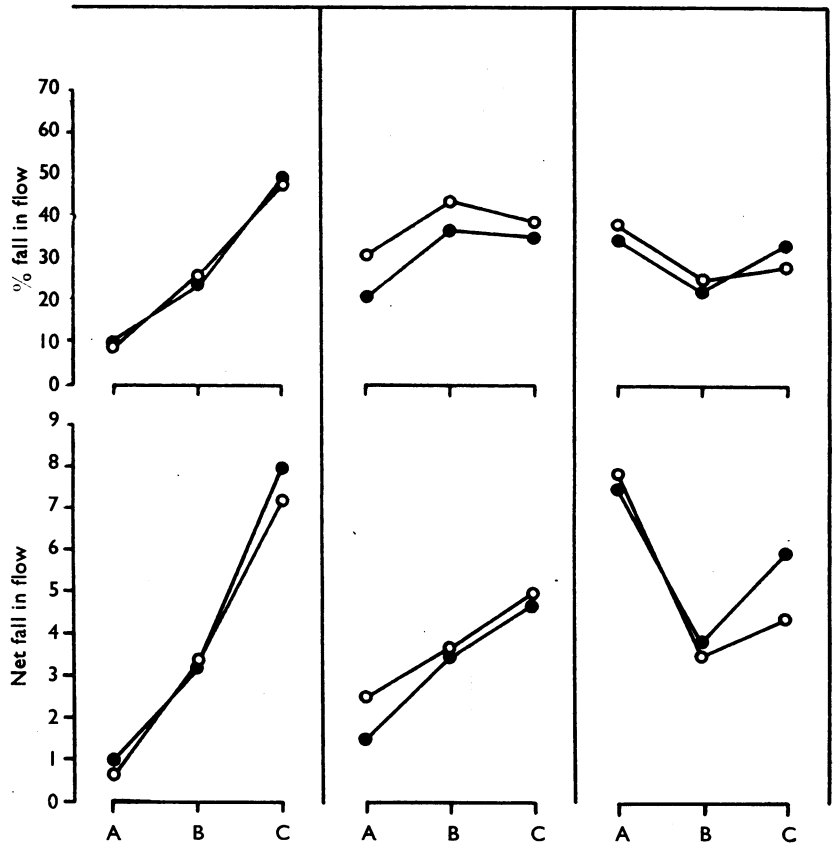


Fig. 3. The response of the blood flow through the right (○) and left (●) hands to intravenous infusions of noradrenaline (2.5 μg/min) in three subjects before (A), during (B) and after (C) infusion of hexamethonium (10 mg) into the brachial artery of the left side. Upper frames: % fall in flow from the resting level; lower frames: net fall in flow in ml./100 ml./min.

## DISCUSSION

The intra-arterial route of administration of noradrenaline and hexamethonium was chosen for a number of reasons. The dose of noradrenaline given in this way is such that no effective amount enters the general circulation and there is no change in blood pressure or in blood flow in the opposite hand. Any central action of hexamethonium due to its entry into the general circulation will therefore not influence the response of the vessels of the limb to the locally applied noradrenaline. The administration of the hexamethonium by the intra-arterial route ensures a high local concentration in the blood vessels of the part under study. With a resting level of flow in the forearm of 5 ml./100 ml./min, a forearm volume of 500 to 1,000 ml., infusion of hexamethonium 20 mg/min results in a local concentration of the order of 0.4 to 0.8 g/l. during the 10 min period of infusion. This is much greater than the blood concentration likely to be attained during oral or intravenous administra-

tion of the drug in hypertensive therapy where the highest recommended initial intravenous dose is 50 mg or 10 mg/l. of circulating blood volume. Hexamethonium itself given intra-arterially had no direct effect on the limb vessels.

No evidence of an increase in the constrictor response to noradrenaline was obtained either in the vessels of the hand or of the forearm whether the noradrenaline was given after hexamethonium or the hexamethonium was administered during infusion of noradrenaline when its constrictor effect had been established. This finding was obtained irrespective of whether the constrictor response to noradrenaline was expressed as % fall from the resting level or as net reduction in flow.

The evidence in the literature for changes in sensitivity to pressor amines after ganglion blocking agents is conflicting. Evaluation is made difficult by the different preparations, techniques and ganglion blocking agents used. One important feature that emerges from studies using blood-pressure responses of cats and dogs is that apparent sensitization by ganglion blocking drugs can occur as long as any cardiovascular baroreceptor reflexes remain intact, and that to abolish these completely, animals must be pithed and vagotomized. Page & Taylor (1950) found total abolition of augmented responses in vagotomized, lumbodorsally-sympathectomized animals only after cord destruction below C6 and inactivation of the carotid sinus mechanism. Bartorelli, Carpi & Cavalca (1954) found potentiation to noradrenaline after hexamethonium in vagotomized animals with spinal section, but this was abolished by pithing. Moe (1948) used pithed cats and found that the pressor responses to noradrenaline were not altered in the presence of a ganglion blocking agent. Lum & Rashleigh (1961) found no potentiation of vasoactive substances by hexamethonium in vagotomized pithed cats or in cat carotid arterial strips.

Mantegazza, Tyler & Zaimis (1958) reported an increased blood pressure and fall in venous outflow from the hind-limb of the cat on intra-arterial and intravenous infusions of noradrenaline following hexamethonium, and infer an increase in vascular sensitivity. However, the possible influence of a reduced perfusion pressure and increased vascular tone on the responses to intra-arterial noradrenaline has not been completely excluded. Blockade of baroreceptor reflexes could have been responsible for the increased effect of intravenous noradrenaline.

In the present experiments the apparent increases in sensitivity of the hand vessels seen on intravenous infusion of noradrenaline in two subjects may be accounted for by the ganglion blocking action of the hexamethonium on reaching the general circulation, even though administered intra-arterially. If the response of the hand vessels to intravenous noradrenaline represents a balance between the direct constrictor effect of the drug on the vessels and an indirect reflex dilatation as a consequence of the rise in blood pressure or some other central action, then blocking of this reflex effect by hexamethonium would now result in the direct action of noradrenaline being unopposed and therefore more marked. The fact that both hands behaved similarly though one received a very much higher concentration of hexamethonium than the other further supports this interpretation.

It is concluded that hexamethonium has no immediate local sensitizing effect on the vessels of the upper limb in man, and, if sensitization to circulating amines plays a part in the occurrence of tolerance to the drug, this must be a slowly

developing effect. The immediate increase in responsiveness of the limb vessels to circulating noradrenaline can be accounted for by blockade of baroreceptor reflexes.

We wish to express our thanks to Dr I. S. de la Lande for helpful advice and to Mr C. Jennings and Miss C. Appelbee for technical assistance. We are grateful to our students and colleagues who volunteered to be subjects.

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