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Comparison of blockade at α-adrenoceptors by thymoxamine and phentolamine in peripheral arteries and veins of man

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Summary

1. The antagonism at α-adrenoceptors by thymoxamine and phentolamine of the response to noradrenaline was investigated in the limb veins and arteries of man.

2. Brachial artery infusions of thymoxamine (40 μg/min) produced rises in resting arterial flow of up to 100%. When infused mixed with noradrenaline, thymoxamine (40 μg/min) attenuated the blood flow response to noradrenaline. Blockade was of a similar degree to that which occurred following a 10 min infusion of phentolamine (40 μg/min).

3. Local intravenous infusion of thymoxamine (400–2,000 ng/min) mixed with noradrenaline attenuated the venoconstrictor response to noradrenaline. The degree of attenuation was similar to that seen after a 10 min infusion of phentolamine (500 ng/min). Blockade after thymoxamine did not last longer than 16 minutes. Neither thymoxamine nor phentolamine altered resting venous compliance.

4. Local intravenous infusions of thymoxamine (500 ng/min) and phentolamine (500 ng/min) abolished the sympathetically mediated venoconstriction produced by overbreathing.

5. Systemic injection of thymoxamine (0·1 mg/kg) did not block the reduction in forearm arterial flow produced by locally infused noradrenaline. In two out of three experiments, however, it produced some antagonism of noradrenaline induced venoconstriction. Systemic phentolamine (5 mg) blocked the effect of noradrenaline in the arterial bed, but antagonized its actions in the veins in only one out of three experiments.

Introduction

Thymoxamine (4-(2-dimethylaminoethoxy)-5-isopropyl-2-methylphenyl acetate, 'Opilon') is a relatively specific competitive antagonist at α-adrenoceptors in isolated tissues of animals (Birmingham & Szolcsanyi, 1965) and of man (Birmingham, Ernest & Newcombe, 1969; Coupar & Turner, 1970), and it is effective in intact animals (Birmingham, Akubue & Szolcsanyi, 1967). Thymoxamine has now been introduced for clinical use, but there is no information concerning its potency as an antagonist in man, nor has its duration of action in human vascular beds been

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studied. We have therefore investigated the effect of thymoxamine in blocking the constrictor response to noradrenaline in forearm arteries and hand veins and also its ability to block venoconstriction mediated through the sympathetic nervous system. The effects of thymoxamine have in each case been compared with those of the established α-adrenoceptor blocking agent phentolamine.

Methods

The subjects were volunteer medical students or doctors, and the nature of the study was explained to them before their consent was obtained. All experiments were carried out with the subjects resting supine and the temperature of the laboratory was maintained in the range of 22–24° C.

Forearm blood flow and superficial hand vein compliance were measured as described in the preceding paper and dose-response curves to noradrenaline were also obtained as detailed there (Collier, Dawnay, Nachev & Robinson, 1972).

Assessment of α-adrenoceptor antagonism in forearm arterial bed

After the recording of a control dose-response curve to noradrenaline, the antagonist under study was given in one of three ways. In some studies the blocking drug was infused into the brachial artery for 10 min at a rate of 40 μg/min, the infusion being completed 5 min before commencing the second dose-response curve. In other studies the blocking drug was infused at the same rate mixed with the second infusion of noradrenaline. The occluding wrist cuff was inflated during all local infusions of drugs. In a third group of studies, the blocking drugs were given systemically, being infused over 30 s into a vein in the opposite arm to that under study; the doses used were those that have been recommended for clinical use (phentolamine 5 mg; thymoxamine 0·1 mg/kg body weight). The second noradrenaline infusion was started 5 min after the antagonist was given.

Assessment of α-adrenoceptor antagonism in hand veins

After recording of the control dose-response curve to noradrenaline, saline was infused until venous distensibility returned to the control level. Either thymoxamine (400–2,000 ng/min) or phentolamine (500 ng/min) was then infused into the vein for 10 minutes. At the end of this infusion, the dose-response curve to noradrenaline was repeated and in some experiments the dose of noradrenaline that had given approximately 50% constriction in the control study was given again, either continuously or intermittently, to determine the duration of the blockade.

In some experiments thymoxamine was infused mixed with the second noradrenaline infusion. Experiments were also performed in which the blocking agent was given systemically, the second noradrenaline infusion being started 5 min after the antagonist had been given.

The stimulus used to produce sympathetically mediated venoconstriction was hyperventilation; subjects were asked to take deep breaths for 40 s at a rate of thirty-six/min in time with a metronome. A cuff around the upper arm was inflated to 45 mmHg (1 mmHg≡1·333 mbar) before the overbreathing was commenced and the hand vein allowed to fill. The subject then hyperventilated and the microscope

was adjusted to keep the dot in focus. At the end of the hyperventilation the position of the microscope was noted, the cuff deflated and the venous distensibility recorded. Two measurements were obtained while saline was being infused, and then a third study was performed while the saline was replaced by one or other of the blocking drugs ; 10 min later a fourth measurement was obtained during infusion of saline. Both blocking drugs were infused at 500 ng/minute.

Drugs

The drugs used were noradrenaline acid tartrate ('Levophed' Bayer), phentolamine mesylate ('Rogitine' Ciba) and thymoxamine hydrochloride ('Opilon' Warner). Drugs were made up in physiological saline (0·9% w/v) containing ascorbic acid (approximately 5–10 μg/ml) to prevent oxidation of noradrenaline. Doses of noradrenaline are expressed as the base and those of the other agents as the salt.

Results

Effect of thymoxamine and phentolamine on forearm arterial bed

Resting flow. Intra-arterial thymoxamine (40 μg/min) caused an increase in forearm flow of 50–100% over that recorded during the control period (four experiments in four subjects). Phentolamine in the same dose caused increases of 200–250% (two experiments in two subjects). Flow usually remained elevated for about 25 min after the administration of the drug, but in one subject who had received thymoxamine it had returned to control levels by the second minute.

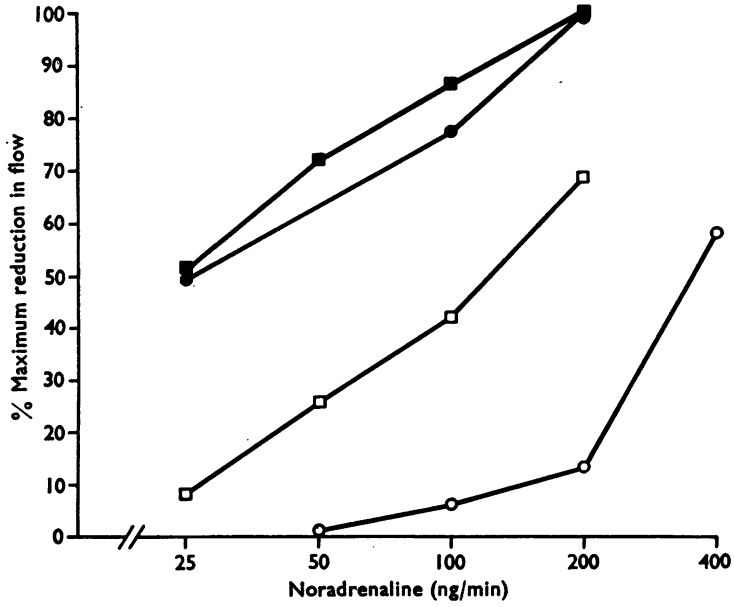

FIG. 1. Effect of intra-arterial thymoxamine and phentolamine on response to noradrenaline in forearm arterial bed in one subject. Thymoxamine was given at 40 μg/min mixed with noradrenaline (○——○) while phentolamine was given at 40 μg/min for 10 min before noradrenaline (□——□). The control responses to noradrenaline are shown by the corresponding closed symbols.

Blockade of noradrenaline. There was no clear evidence of attenuation of the constrictor response to noradrenaline when the agonist was given after infusion of thymoxamine (40 μg/min ; four experiments in four subjects) ; following the same dose of phentolamine, however, there was a parallel shift to the right of the log dose-response curve. When thymoxamine was given mixed with the agonist it blocked the constrictor response (Fig. 1).

The two blocking drugs were each given in turn to three subjects intravenously. After administration of thymoxamine, there was no evidence of any attenuation of the response to intra-arterial noradrenaline. After phentolamine, however, there was a shift to the right of the log dose-response curve to noradrenaline in each experiment (Fig. 2).

Effect of thymoxamine and phentolamine on superficial hand veins

Effect on resting compliance. In twenty-five experiments in five subjects, neither thymoxamine (nineteen experiments) nor phentolamine (six experiments) produced any change of venous compliance in the resting subject.

Blockade of noradrenaline. After a 10 min infusion of thymoxamine (500–2,000 ng/min) there was a variable attenuation of the constrictor response to noradrenaline, but this never persisted for more than 16 min (seven experiments in three subjects). After infusion of phentolamine (500 ng/min) there was clear evidence of blockade in all subjects, and this lasted about 40 min (five experiments in five subjects). When thymoxamine (400–2,000 ng/min) was given mixed with noradrenaline (nine experiments in three subjects) there was a shift to the right of the log dose-response curve similar in degree to that seen after phentolamine (500 ng/min) (Fig. 3). It was not possible to demonstrate a clear difference in the blockade produced by simultaneously infused thymoxamine at the two dose levels of 400 and 2,000 ng/minute.

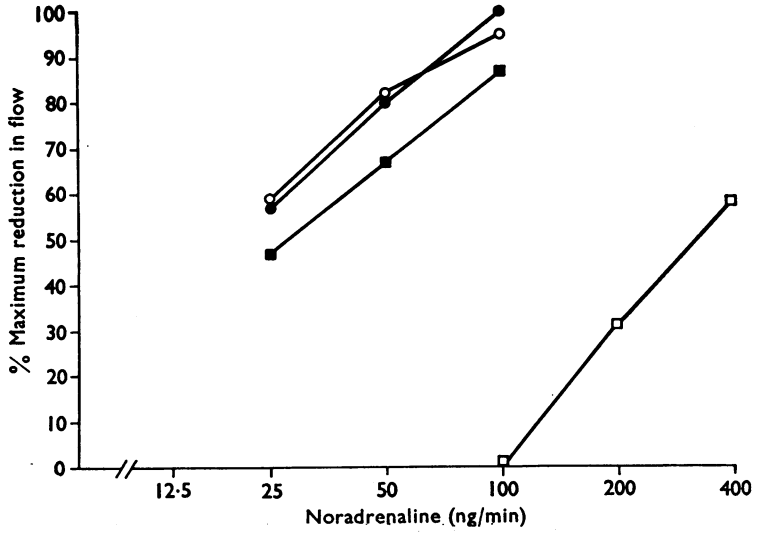

FIG. 2. Effect of systemic administration of thymoxamine and phentolamine on response to noradrenaline in forearm arterial bed in one subject. Thymoxamine 0·1 mg/kg (○——○) and phentolamine 5 mg (□——□) were given 5 min before commencing intra-arterial noradrenaline. The control responses to noradrenaline are shown by the corresponding closed symbols.

After systemic administration of thymoxamine (three subjects) attenuation of the venoconstrictor response to noradrenaline was shown by a parallel shift to the right of the log dose-response curve in two subjects but no change was seen in the third. After systemic administration of phentolamine (three subjects), evidence of blockade was obtained in only one.

Both drugs produced similar subjective symptoms on systemic administration: within a minute or so of the injection there was a feeling of warmth and pulsation in the face and forehead together with nasal stuffiness. The first two symptoms passed off in 4–5 min, but the nasal stuffiness persisted for at least 30 minutes. Blood pressure was recorded by sphygmomanometer at the fifth minute after injection and showed no difference from the control after either drug.

Blockade of neurogenic venoconstriction

In all six experiments in five subjects, hyperventilation produced a reproducible constriction in the control studies. During the infusion of either thymoxamine or phentolamine (three experiments with each) the venoconstrictor effect of hyperventilation was abolished. When challenged 10 min after completion of the infusion, the venoconstrictor response was found to be fully restored in all subjects who had received thymoxamine, but some blockade persisted in two of the three who had received phentolamine.

Discussion

Thymoxamine has previously been shown to be a relatively specific competitive α-adrenoceptor blocking agent in tissues from both animals (Birmingham & Szolcsanyi, 1965) and man (Birmingham, *et al.*, 1969; Coupar & Turner, 1970). Our experiments indicate that thymoxamine antagonizes the constrictor effect of

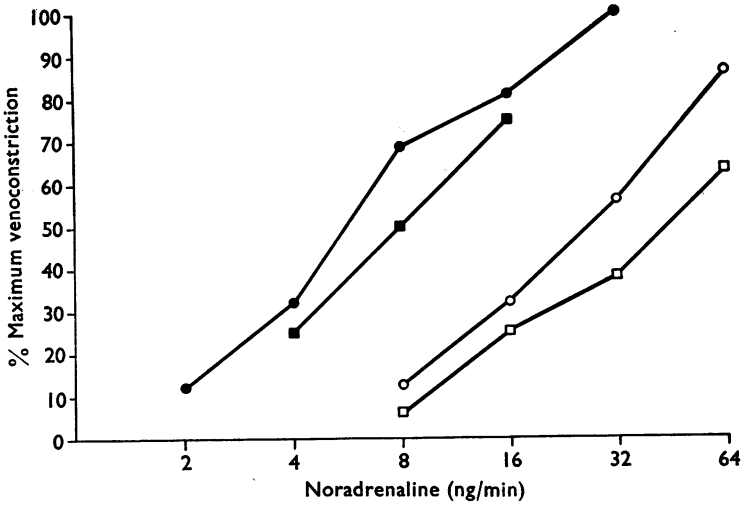

FIG. 3. Effect of local intravenous infusion of thymoxamine and phentolamine on response to noradrenaline in a superficial hand vein in one subject. Thymoxamine was given at 500 ng/min mixed with noradrenaline (○——○) while phentolamine was given at 500 ng/min for 10 min before noradrenaline (□——□). The control responses to noradrenaline are shown by the corresponding closed symbols.

noradrenaline in the forearm arterial bed and hand veins of man *in vivo*, and the results are compatible with the drug acting as a competitive blocker. Thymoxamine and phentolamine have been shown to be of approximately equal potency as α-adrenoceptor blockers in isolated tissues (Coupar & Turner, 1970; Birmingham, personal communication). The two drugs also appeared of equal potency in our studies on peripheral vessels, but this finding is difficult to interpret as phentolamine was given before the agonist while thymoxamine had to be infused simultaneously.

The difference in duration of action of the two drugs when infused locally presumably reflects a difference in the time for which they are retained in the tissues. The factors determining the duration of action after systemic administration are, of course, usually quite different to those concerned after local administration. The finding that a drug acts only for a short time when given locally does not, therefore, imply that it will necessarily be short-acting when given systemically.

Both thymoxamine and phentolamine caused a rise in forearm blood flow when given intra-arterially; this was presumably due, at least in part, to release of sympathetic constrictor tone, although a direct smooth muscle relaxant effect has also been thought to contribute in the case of phentolamine. The ability of both thymoxamine and phentolamine to antagonize low levels of neurogenic venoconstriction has been demonstrated by our experiments. The absence of effect on resting venous compliance is not unexpected since we have never observed any response to dilator drugs in the basal vein, and our observations suggest that there is not normally any resting venoconstrictor tone. This finding is at variance with that of Burki & Guz (1970) who noted an increase in forearm venous compliance in two subjects after sympathetic blockade; possibly the difference reflects the extent to which the subjects were relaxed during the control observations.

The effects of thymoxamine and phentolamine differed when they were given systemically in doses commonly used clinically. Thymoxamine produced a moderate degree of α-adrenoceptor blockade in the hand vein in two out of three subjects, but no blockade could be demonstrated in the arteries. Phentolamine produced detectable blockade in the veins of only one out of three subjects, but it always produced a significant degree of blockade in the forearm arterial bed. The finding that phentolamine is much more effective than thymoxamine in producing blockade of the forearm arteries could be accounted for if a large proportion of the dose was retained in the arterial bed on the first circulation. The long duration of action of phentolamine after local infusion is compatible with this hypothesis. The observation that 5 mg phentolamine intravenously results in effective blockade of the forearm arterial bed is in keeping with the established use of the drug in this dose as a test for the presence of a catecholamine secreting tumour. Thymoxamine has been tried in the management of this condition (Richards, Adamson & MacDonald, 1969), but our results suggest that it would need to be given in higher doses than phentolamine to achieve a comparable effect.

It is important that the effectiveness of new drugs in producing blockade should be assessed in man in specific tissues after systemic administration. The fact that a substance can be shown to be an effective blocking agent in studies of isolated tissues and in animals does not prove that it will be equally effective in man. Even when differences in absorption are removed by parenteral administration, variations in distribution, metabolism and excretion may still result in significant differences in effectiveness. As our results have shown, two drugs may be of approximately

similar potency as blocking agents in specific tissues when given locally, but their actions may differ when given systemically. Direct studies of the action of drugs on specific tissues *in vivo* are therefore required if their clinical action is to be understood.

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