**The biphasic action of bethanidine in the human eye**

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Studies with bethanidine in animals and isolated tissue have suggested that, like bretylium (Boura & Green, 1959, 1965) its initial adrenergic blocking action may not be due to catecholamine depletion (Boura & Green, 1963). Acute administration of bethanidine does not reduce the pressor content of cat iris, but chronic dosing reduces noradrenaline levels in heart and spleen (Costa, Kuntzman, Gessa & Brodie, 1962). A similar type of action has been suggested for guanethidine (Cass & Spriggs, 1961).

Studies in which guanethidine (5%) was applied to the human eye have shown it to potentiate the response to directly acting amines whilst inhibiting that to indirectly acting ones (Sneddon & Turner, 1967). Debrisoquin (2%), however, potentiates phenylephrine mydriasis in the presence of an ephedrine response (Sneddon & Turner, 1968).

The effects of bethanidine on the mydriatic response at 30 min to phenylephrine (5%) and ephedrine (2%) were measured in ten subjects of both sexes using a photographic technique previously described (Turner & Sneddon, 1968).

Control mydriases were obtained to the two amines; 48 hr later bethanidine eye-drops (10%) were instilled into both eyes and the mydriatic response repeated after 2 hr (Table 1). If an ephedrine mydriasis persisted, in the presence of a significant potentiation of phenylephrine response, chronic treatment (three doses at 2 hr intervals) was instituted and the process repeated. If, in contrast, ephedrine mydriasis was absent the concentration of bethanidine was reduced to 5% or 1%. In each subject it was possible to demonstrate a difference between high and low dose effects, although the necessary concentration range of bethanidine varied between subjects. The low dose produced a significant potentiation of phenylephrine mydriasis ($P<0.01$) without a change in ephedrine response. High concentrations produced potentiations of phenylephrine response ($P<0.001$) and suppression of that to ephedrine ($P<0.001$). These findings, therefore, are consistent with those of Costa *et al.* (1962) on the cat.

TABLE 1. *Mean percentage changes* (+S.E.M.) *in mydriasis* 30 *min after instillation of ephedrine* (2%) *and phenylephrine* (5%) *in ten subjects, and their modification by high and low doses of bethanidine*

| Drug | Control | Bethanidine | |
|---|---|---|---|
| | | Low dose | High dose |
| Ephedrine (2%) | 28·5+4·1 | 32·3±6·0 | 6·95±2·7 |
| Phenylephrine (5%) | 21·3±6·1 | 42·9±8·8 | 63·40±9·2 |

N. A. L. is in receipt of a grant from Ciba Laboratories Ltd. Bethanidine eye-drops were supplied by Burroughs Wellcome and Co.

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## The action of pharmacologically active substances on the flow and composition of cat hind-limb lymph

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It has been shown in cats (Lewis, 1967) and rabbits (Lewis & Westcott, 1968) that during tissue injury there is an increase in the flow of lymph and in the concentration of intracellular enzyme systems as well as protein in the lymph draining the injured area. In the present experiments in anaesthetized cats a modification of the method used by Edery & Lewis (1963) and Sturmer & Cerletti (1967) in dogs has been used to study the effects on the flow and composition of lymph of pharmacologically active substances which might be involved in tissue reactions.

Cats were anaesthetized with pentobarbitone sodium (40 mg/kg intraperitoneally). The central stump of the pudendal artery was cannulated with a polythene cannula for retrograde close arterial infusions into the hind limb using a Palmer continuous infusion pump. Venous outflow from the femoral vein was measured by a photoelectric drop-counter, the blood being returned to the animal via the contralateral femoral vein.

To facilitate the cannulation of one of the femoral lymphatics, the connective tissue surrounding the femoral artery and vein was ligated and the limb was passively flexed to fill the lymphatics. One of the vessels was then dissected free and a polythene cannula inserted, tied and glued with Eastman 910 adhesive. As the lymph flow stops in an immobilized animal the resting flow was maintained by passive movements of the limb, obtained by attaching the foot to a motor-driven eccentric wheel. Intracellular enzymes and protein were measured according to methods described by Lewis (1967).

None of the substances infused into the hind limb—histamine, acetylcholine, bradykinin, 5-hydroxytryptamine or prostaglandin ($PGE_1$ or $PGF_{2\alpha}$)—caused an increase in the concentration of any of the intracellular enzymes in the lymph. Histamine, acetylcholine and bradykinin, however, caused vasodilatation and an increase of lymph flow which was usually accompanied by an increase of protein concentration in the lymph.

Histamine increased blood flow when infused in a concentration of 0.1 $\mu$g/min, acetylcholine in a concentration of 1 $\mu$g/min, and bradykinin 0.05 $\mu$g/min. Both lymph flow and protein concentration increased following infusions of histamine