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References

Vatovec, S., Vodopivec, S., Bohinc, P. (1967). *Zbornik Biotehniške fakulteta, Univerza, Ljubljana*, **11**, 97.
Vodopivec, S. & Vatovec, S. (1967). *III Congress for Veterinary Medicine*, Sarajevo: Mart.

Comparison of tolazoline and thymoxamine on skin temperature in man

SIR,—Tolazoline hydrochloride (Priscol) is an α-adrenergic receptor blocking drug which is used clinically by oral and parenteral administration in the treatment of peripheral vascular disease. Thymoxamine (Opilon), a thymoxyalkylamine derivative, is a more recently discovered α-receptor blocking drug (Birmingham & Szolcsanyi, 1965, Foster, 1966). Its action in man has been demonstrated in the pupil, by prevention of ephedrine and phenylephrine mydriasis and reversal of hydroxyamphetamine mydriasis when applied to the conjunctival sac in the form of eye drops (Turner & Sneddon, 1967).

Variations in skin temperature may be used to measure changes in skin blood flow induced by α-receptor blocking drugs and rubifacients, and an investigation was, therefore, made to compare the effects of tolazoline and thymoxamine on skin temperature in man.

The same 10 subjects (5 men and 5 women, aged from 15 to 48 years) took part in three tests viz. comparisons between the two drugs and between each drug and a placebo.

Both tolazoline and thymoxamine were made up into 10% ointments in a water-free cetomacrogol base, the base alone serving as the control placebo.

TABLE 1. CHANGE IN FOREARM SKIN TEMPERATURE °C INDUCED BY THYMOXAMINE, TOLAZOLINE AND A PLACEBO IN 10 SUBJECTS

Treatment	Skin temperature °C					
	Before	After	Difference between treatments	s.e.	t	P
Thymoxamine .. v Placebo	33·34 33·51	33·85 33·55	0·47	0·152	3·12	<0·02
Tolazoline .. .. v Placebo	33·13 33·02	33·19 33·06	0·02	0·062		n.s.
Thymoxamine .. v Tolazoline	32·23 32·38	32·49 32·49	0·14	0·081	1·72	n.s.

Skin temperatures were measured by means of a copper-constantan thermocouple (voltage output 40 V/°C) fixed to the volar surface of each forearm and connected to Grass polygraph Model 7P1-preamplifiers calibrated within a range of 24–40°. When stable recordings were obtained (usually within 2 min), a thin smear of the respective ointments was applied under the thermocouples but was not rubbed in; the choice of side for active or control preparation was arbitrary. Temperatures were again monitored and a reading taken after 10 min.

Although air-movement in the room was minimized during these tests, they were conducted over a period of some weeks, during which the ambient temperature ranged between 18 and 24·5°; however, this temperature range obtained in tests of both drugs.

Changes in mean forearm temperatures in response to treatments are shown in Table 1. Thymoxamine produced a very significant ($P < 0.02$) increase in skin temperature when compared with the placebo base, but although its effect was greater than tolazoline in a direct comparison this did not reach statistical significance. When tolazoline was compared with the placebo, no significant effect was observed. In one subject, both tolazoline and thymoxamine produced an erythema in the treated area, with an increase of 0·8° with tolazoline and 0·4° with thymoxamine.

The principal nervous control of skin blood flow is mediated through α-adrenergic receptors, stimulation of which leads to cutaneous vasoconstriction. It is reasonable, therefore, that specific α-receptor blockade should lead to a reduction in vasoconstrictor activity with an increase both in cutaneous blood flow and in skin temperature. This investigation has demonstrated that thymoxamine 10% in a cetomacrogol base produces a significant increase in skin temperature compared with inactive base, and also that it appeared more effective than tolazoline 10% prepared in the same base in which preliminary uncontrolled experiments had shown tolazoline to be most effective. However, further investigations might show a better vehicle for its activity.

While it is probable that this effect of thymoxamine is specifically due to α-receptor blockade, other modes of action cannot be excluded. Tolazoline has histamine-like actions in animals, including stimulation of gastric secretion and peripheral vasodilatation (Nickerson, 1949), and it is possible that its cutaneous effects are due to this as well as its α-blocking activity. Further studies including pre-treatment with antihistamine drugs might elucidate this further. Thymoxamine is a weak competitive antagonist of histamine (Birmingham & Szolcsanyi, 1965) and thus it is unlikely that its peripheral vascular action is due to histamine-receptor activity. It is also possible that both drugs, like phentolamine (Taylor, Sutherland, & others, 1965), have direct smooth-muscle relaxing properties unrelated to adrenergic or histamine-receptor activity. Whatever the mechanism of action, however, the increase in skin temperature produced by topical administration of thymoxamine suggests that further studies of this drug are indicated both in normal subjects using different bases to determine the best vehicle for its activity, and in patients with ischaemic disease of the skin to assess its therapeutic value.

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References

Birmingham, A. T. & Szolcsanyi, J. (1965). *J. Pharm. Pharmac.*, **17**, 449–458.
Foster, R. W. (1966). *Ibid.*, **18**, 1–12.
Nickerson, M. (1949). *Pharmac. Rev.*, **1**, 27–101.
Taylor, S. H., Sutherland, G. R., MacKenzie, G. J., Staunton, H. P. & Donald, K. W. (1965). *Clin. Sci.*, **28**, 265–284.
Turner, P. & Sneddon, J. M. (1967). *Clin. Pharmac. Ther.*, in the press.