Antagonism of phenylephrine-evoked sweating by trazodone and amitriptyline in humans *in vivo*

Human eccrine sweat glands are innervated by cholinergic sympathetic fibres and they readily respond to intradermal injections of cholinomimetic drugs (Dobson & Sato, 1972). There is evidence, however, that sweat glands may also possess α -adrenoceptors since they can be activated by α -adrenoceptor stimulants such as adrenaline and phenylephrine (Szabadi *et al.*, 1980). Since phenylephrine is a selective α_1 -adrenoceptor stimulant, antagonism of phenylephrine-evoked sweating can be used as a measure of α -adrenoceptor blockade by systemically administered drugs. Indeed, we have found that amitriptyline and binodaline, antidepressants with α -adrenoceptor blocking properties, reduce phenylephrine-evoked sweating (Longmore *et al.*, 1985).

In the present study we have compared the effects of single oral doses of trazodone, a novel antidepressant drug (Georgotas *et al.*, 1982) with those of amitriptyline and placebo. Trazodone was used in two formulations: conventional (Molipaxin) and a recently developed controlled-release formulation (Roussel Laboratories).

Eight healthy, drug-free male volunteers (aged 18–30 years, weighing 63–77 kg) participated in the study, which was approved by the Ethics Committee of Withington Hospital, Manchester. Each subject participated in four experimental sessions, separated by weekly intervals. In each session the responses of sweat glands to intradermally injected phenylephrine were assessed (see Maple *et al.*, 1982) 4 h after ingestion of one of the following drugs: trazodone chloride (conventional formulation, 100 mg),

trazodone chloride (controlled-release formulation, 100 mg), amitriptyline hydrochloride (50 mg) and lactose placebo. The drugs were administered in double-blind fashion according to a balanced crossover design. The data were analyzed using two-factor analysis of variance with repeated measures on both factors. The two factors were drug treatment and dose of intradermally injected phenylephrine.

Table 1 shows the effects of the four drug treatments on phenylephrine-evoked sweating. Analysis of variance revealed significant main effects of drug treatment ($F[3,21] = 5.42$; $P < 0.01$) and of dose of intradermally injected phenylephrine ($F[3,35] = 29.95$; $P < 0.001$). The interaction effect was not significant ($F[15,105] = 1.02$; $P > 0.05$). Individual comparisons of the three active drugs with placebo (using Student's *t*-test with Dunnett's correction for multiple comparisons) showed significant effects of trazodone (conventional formulation: $P < 0.05$; controlled-release formulation: $P < 0.005$) and amitriptyline ($P < 0.001$).

Phenylephrine-evoked sweating was reduced by both amitriptyline and trazodone; the observation with amitriptyline is in agreement with our previous finding (Longmore *et al.*, 1985). The effect of the antidepressants is likely to reflect the blockade α_1 -adrenoceptors (see above). The α_1 -adrenoceptor blocking property of amitriptyline is well-documented both in experimental animals and in human subjects *in vivo* (for review see Szabadi & Bradshaw, 1986), and it has been reported that trazodone also has affinity for α_1 -adrenoceptors in binding experi-

Table 1 Phenylephrine-evoked sweating: number of sweat glands activated (mean $\pm$ s.e. mean)

Dose of phenylephrine injected (μ M)	Placebo	Amitriptyline***	Trazodone* (conventional)	Trazodone** (controlled-release)
1000	25.4 $\pm$ 3.8	21.9 $\pm$ 2.7	19.1 $\pm$ 2.8	18.4 $\pm$ 1.9
500	22.1 $\pm$ 4.4	12.4 $\pm$ 2.4	13.6 $\pm$ 2.0	12.3 $\pm$ 1.9
100	19.1 $\pm$ 2.8	9.1 $\pm$ 2.0	12.8 $\pm$ 1.9	9.4 $\pm$ 0.9
50	15.4 $\pm$ 2.7	9.4 $\pm$ 1.7	10.9 $\pm$ 1.8	9.4 $\pm$ 1.4
10	13.0 $\pm$ 2.8	6.5 $\pm$ 0.6	8.5 $\pm$ 1.4	5.8 $\pm$ 1.7
5	7.0 $\pm$ 2.5	4.9 $\pm$ 0.6	6.1 $\pm$ 1.6	3.3 $\pm$ 1.4

* $P < 0.05$, ** $P < 0.005$, *** $P < 0.001$ (for statistical analysis see text)

ments (Richelson, 1984). The present results show that trazodone can antagonize α_1 -adrenoceptor mediated tissue responses in humans when administered in therapeutically used single doses. The blockade of α_1 -adrenoceptors by trazodone may be responsible for some of the side-effects of the drug, such as sedation and orthostatic hypotension resulting in dizziness (Georgotas *et al.*, 1982).

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Effect of posture on glyceryl trinitrate plasma concentrations following transdermal application

Curry & Kwon (1985) reported that sublingual application of glyceryl trinitrate (GTN) to supine subjects resulted in plasma concentrations which were three-fold higher than for subjects in the sitting position. This observation is of considerable clinical interest since if an increase in steady state plasma concentrations also occurs during prolonged nitrate therapy then the dose of nitrate for supine patients would need to be adjusted accordingly. We have therefore examined the effect of posture on the plasma concentrations of GTN during 12 h application of a nitroplaster.

The investigation consisted of a randomised crossover application of a transdermal GTN

plaster (Nitroderm TTS 10, Ciba-Pharma) releasing 10 mg GTN over 24 h to a contact area of 20 cm² in eight healthy subjects aged 21–46 years. The plaster was applied to the chest above the left musculus pectoralis major with subjects in either the supine position or standing position following a stabilising period of at least 15 min. Subjects in the supine position remained so for 12 h. Standing subjects were allowed to pursue their normal daily activities. A light standard breakfast was taken at 2 h post dose and lunch 6 h post dose but the consumption of coffee, tea, alcohol and smoking were not permitted during the study. Drug applications were separated by an interval of at least 7 days. Plasma GTN con-