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).

This work was supported by the Sir Jules Thorn Charitable Trust and Roussel Laboratories.

References

- Dobson, R. L. & Sato, K. (1972). The stimulation of eccrine sweating by pharmacological agents. In *Advances in Biology of Skin*, Vol. XII eds, Montagne, W., Stoughton, R. B. & van Scott, E. J., pp. 447–475. New York: Appleton-Century-Crofts.
- Georgotas, A., Forsell, T. L., Mann, J. J., Kira, M. & Gershon, S. (1982). Trazodone hydrochloride: a wide spectrum antidepressant with a unique pharmacological profile. A review of its neurochemical effects, pharmacology, clinical efficacy, and toxicology. *Pharmacother.*, **2**, 255–265.
- Longmore, J., Szabadi, E. & Bradshaw, C. M. (1985). Comparison of the effects of binodoline and amitriptyline on peripheral autonomic functions in healthy volunteers. *Br. J. clin. Pharmac.*, **19**, 295–300.
- Maple, S., Bradshaw, C. M. & Szabadi, E. (1982). Pharmacological responsiveness of sweat glands in anxious patients and healthy volunteers. *Br. J. Psychiat.*, **141**, 154–161.
- Richelson, E. (1984). The newer antidepressants: structures, pharmacokinetics, pharmacodynamics and proposed mechanism of action. *Psychopharmac. Bull.*, **20**, 213–223.
- Szabadi, E. & Bradshaw, C. M. (1986). Antidepressant drugs and the autonomic nervous system. In *The Biology of Depression*, ed. Deakin, J. F. W., pp. 190–220. London: Gaskell.
- Szabadi, E., Gaszner, P. & Bradshaw, C. M. (1980). Comparison of the effects of adrenoceptor and cholinergic agonists on sweat gland activity in man. *Br. J. clin. Pharmac.*, **10**, 301–303.

Received 3 September 1986,
accepted 30 September 1986

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-

Figure 1 Effect of posture on plasma concentrations of glyceryl trinitrate following transdermal application of glyceryl trinitrate in eight healthy subjects using nitroplasters delivering 10 mg day^{-1} . — standing/ambulant, supine.

centrations were determined according to the method of Heidemann *et al.* (1985) using gas chromatography on capillary columns with electron capture detection. The calibration range was $0.22\text{--}2.64 \text{ nm}$ plasma with a coefficient of variation over this range of below 10%.

Plasma GTN concentrations measured pre-dose and at 2 hourly intervals over the 12 h observation period are shown for individual subjects in Figure 1. The mean GTN plasma concentrations for the six time points between 2 h and 12 h post-dose ranged from 0.85 to 1.80 nm for subjects in the supine position and from 0.52 to 1.45 nm for standing/ambulant subjects. AUC ranged from 2.65 to 27.55 nm h for the supine subjects and from 1.68 to 23.38 nm h for the standing/ambulant subjects. A Wilcoxon paired rank test and Student's paired *t*-test, carried out after the Wilk-Shapiro test for a normal distribution of the data, showed that there was no significant difference in AUC ($P > 0.1$) between transdermal GTN applied in the supine position and the standing/ambulant position. These results therefore do not support the view that posture can produce major changes in GTN-plasma concentrations. The effects observed by Curry & Kwon therefore appear to be due either to a short-lived change in GTN disposition and con-

finied to the first 30 min post-dose or to an artifact because of the small number of subjects examined and failure to use a crossover design. In the study of Curry & Kwon (1985) the between subject variation in AUC and C_{max} were so large that only standard error of the means could be shown on their figure and the three-fold difference in the means was significant only at the 5% level. If, in the present study, we had compared subjects 3, 4, 7, 8 (standing) with subjects 1, 2, 5, 6 (supine) without a crossover design we would also have obtained a three-fold or even greater difference in AUC.

Until further evidence is obtained to the contrary we are of the opinion that posture has only a minor effect, if any, on GTN plasma concentrations of GTN absorbed by parenteral routes and that adjustments in the maintenance dose of nitrates for supine patients is not necessary.

RAPHAELA HEIDEMANN, CHRISTEL BECKENBAUER & B. G. WOODCOCK
Department of Clinical Pharmacology, University Clinic Frankfurt, Theodor-Stern-Kai 7, D-6000 Frankfurt am Main, Federal Republic of Germany

Received 23 July 1986,
accepted 3 September 1986

References

- Curry, S. H. & Kwon, H.-R. (1985). Influence of posture on plasma nitroglycerin. *Br. J. clin. Pharmac.*, **19**, 403–404.
- Heidemann, R., Menke, G., Letzel, H. & Rietbrock, N. (1985). Serumkonzentration von Glyceroltrinitrat (GTN) bei transdermaler Applikation von GTN-Pflastern unterschiedlicher Provenienz. *Dtsch. med. Wschr.*, **110**, 1568–1572.

trat (GTN) bei transdermaler Applikation von GTN-Pflastern unterschiedlicher Provenienz. *Dtsch. med. Wschr.*, **110**, 1568–1572.