Effect of acute and chronic oral administration of alfuzosin on baroreflex function and tremor in man

A. H. DEERING, J. G. RIDDELL, D. W. G. HARRON & R. G. SHANKS

Department of Therapeutics and Pharmacology, The Queen's University of Belfast, Belfast BT9 7BL

- 1 The effects of the acute and chronic administration of the α_1 -adrenoceptor antagonist alfuzosin (5 mg twice daily for 7 days) on baroreflex function, physiological tremor and sedation (visual analogue scale) were investigated in six healthy volunteers.
- 2 Phenylephrine-systolic pressure dose-response curves were shifted ($P < 0.05$) to the right by alfuzosin compared with placebo on day 1, and on day 8 prior to the administration of alfuzosin indicating significant α -adrenoceptor blockade over 24 h with 5 mg twice daily administration.
- 3 Baroreflex sensitivity ($\Delta R-R$ ms mmHg⁻¹ systolic arterial pressure) was reduced ($P < 0.05$) by alfuzosin compared with placebo on day 1 (13.8 ± 2.6 vs 20.6 ± 3.6 ms mmHg⁻¹) and on day 8 (13.4 ± 1.7 vs 21.1 ± 2.7 ms mmHg⁻¹).
- 4 Maximum power (μV^2) or frequency (Hz) of physiological tremor did not change 2 h after alfuzosin administration on day 1 ($13.7 \pm 4.4 \mu V^2$, 9.2 ± 0.3 Hz) or day 8 ($11.5 \pm 4.3 \mu V^2$, 10.0 ± 0.4 Hz) compared with placebo on day 1 ($16.9 \pm 7.5 \mu V^2$, 10.0 ± 0.4 Hz) and day 8 ($17.3 \pm 5.7 \mu V^2$, 10.2 ± 0.8 Hz).
- 5 Alfuzosin 5 mg twice daily did not cause sedation on day 1 or day 8.
- 6 In conclusion the reduction in baroreflex sensitivity with the α -adrenoceptor antagonist alfuzosin may contribute to its antihypertensive activity in reducing the reflex tachycardia associated with its hypotensive action.

Keywords alfuzosin baroreflex function physiological tremor sedation

Introduction

Blockade of α -adrenoceptor sites by prazosin and indoramin is effective in reducing blood pressure in man (Royds *et al.*, 1972; Nicholls *et al.*, 1981). These drugs cause vasodilatation which reduces peripheral vascular resistance, and thus act to normalise the major pathophysiological determinant of hypertension. Non-selective α -adrenoceptor blocking drugs such as phenoxybenzamine cause postural hypotension (Nicholls *et al.*, 1984). In addition the hypotensive effect is associated with a marked reflex tachycardia similar to that seen in response to blood pressure reduction with non-specific

vasodilators such as hydralazine (Nicholls *et al.*, 1984). However, the hypotensive effect of selective α_1 -adrenoceptor blocking drugs, such as prazosin and indoramin is not associated with a reflex tachycardia (Sasso & O'Connor, 1982; Nicholls *et al.*, 1984); several mechanisms have been proposed to explain this absence of reflex tachycardia.

Recent studies have shown that prazosin (Sasso & O'Connor, 1982) and indoramin (Deering *et al.*, 1986) reduce baroreflex sensitivity. This may explain, in part, the relative lack of reflex tachycardia associated with their

Correspondence: Dr D. W. G. Harron, Department of Therapeutics and Pharmacology, The Queen's University of Belfast, The Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL, Northern Ireland

hypotensive effect. Clinically, initiation of prazosin therapy requires caution on account of the risks of first-dose postural hypotension (Verbesselt *et al.*, 1976; Graham *et al.*, 1976). Use of indoramin may be limited by the occurrence of sedation (Lewis *et al.*, 1973; Fitzgerald, 1981). Due to the action of α -adrenoceptor blocking drugs on the major pathophysiological determinant of hypertension, and their potential use in reducing afterload in chronic heart failure (Miller *et al.*, 1977; Awan *et al.*, 1978) there is a need for an effective, well tolerated α -adrenoceptor antagonist.

Alfuzosin is a post-synaptic α -adrenoceptor antagonist which reduces blood pressure in animals (Cavero *et al.*, 1984a, b) and man (Harron *et al.*, 1987). Initial studies in healthy volunteers have indicated that the drug is well tolerated. While standing systolic blood pressure is significantly reduced compared with placebo in healthy volunteers, this hypotensive effect is accompanied by a small but significant reflex tachycardia (Harron *et al.*, 1987).

The aim of the present study was to investigate the effects of alfuzosin on baroreflex sensitivity in normal man following intravenous bolus doses of phenylephrine. As sedation has been reported with indoramin (Lewis *et al.*, 1973; Fitzgerald, 1981; Deering *et al.*, 1986) and as α -adrenoceptor antagonists may influence tremor (Mai & Olsen, 1981), the effects of alfuzosin on sedation and physiological tremor were also investigated.

Methods

Observations were made in six healthy male volunteers aged 21.0 ± 0.9 years, weight 65.6 ± 3.0 kg, who gave written informed consent to the procedures. The protocol of the study had been approved by the Ethical Committee of the Queen's University of Belfast. Subjects were asked to take their normal breakfast on each study day. The study was performed in a quiet temperature-controlled ($23\text{--}25^\circ\text{C}$) laboratory at the same time each day. Having emptied their bladder the subjects lay comfortably with the trunk elevated to 45° and the head and neck supported. A cannula was inserted into the left radial artery and connected, via a monitoring kit (Sorenson Research Co. Inc.), to a disposable dome on a transducer (Bell and Howell) for the measurement of arterial blood pressure. The signal from the pressure transducer was amplified (Lectromed No. 3552), and recorded on a four-channel recorder (Lectromed Multitrace 4, speed 10 mm s^{-1}). A cannula was placed in a

large vein in the left antecubital fossa for administration of drugs. Respiratory movement was monitored continuously from a strain gauge (Electromed 4320) applied around the lower chest wall, and the heart rate from a direct-writing electrocardiograph.

Finger tremor was measured with a piezoelectric accelerometer (Devices Trem 1) taped to the dorsum of the middle phalanx of the right hand. The fingers and hand were outstretched horizontally in the same plane as the right forearm which was comfortably supported, to the wrist, on a wooden rest. The output of the accelerometer was fed directly through a pre-amplifier (Devices 3543) to an Apple IIe micro-computer with a suitable data-acquisition board (McAllister *et al.*, 1983). This board, together with the necessary software performs analogue-to-digital conversion of the signal and in each session records 64 s of signal in 8 s epochs. The data is analysed using fast Fourier transformation on each 4 s of signal and the power spectra calculated. The numerical value of power in each 1 Hz band is printed together with its standard deviation and the frequency power curve plotted.

Following the setting up procedures the subjects rested quietly for 30 min. At this time the subject was asked to mark on a 10 cm visual analogue scale marked from 'Wide awake' to 'Nearly asleep' how he felt 'at this moment'. The subject then outstretched the fingers and hand for 3 min; finger tremor was measured throughout the final 64 s. Five minutes later phenylephrine was administered by graded intravenous bolus (20, 50, 100 and 200 μg) until systolic arterial pressure had increased by approximately 30 mmHg. Between each dose of the pressor drug, blood pressure and heart rate were allowed to return to pre-treatment values.

After the intravenous injection of phenylephrine, baroreflex sensitivity was assessed by measuring the systolic pressure for each heart beat and the corresponding R-R interval of the next beat during expiration. Baroreflex sensitivity was defined as the change in R-R interval in ms mmHg^{-1} change in systolic pressure (i.e. the slope of the linear regression line). Phenylephrine had a pharmacological effect between 20 to 30 s after administration; the systolic pressure and R-R intervals measured were those preceding and including the maximum change in systolic pressure. A single oral dose of placebo, or alfuzosin 5 mg, with 50 ml of water was then administered to the subjects. Two hours later sedation, tremor and the baroreflex sensitivity were measured as previously described. Twelve hours after the first dose the subjects took a second dose of placebo or alfuzosin and continued

to take placebo or alfuzosin 5 mg twice daily for a further 6 days (7 days total). On the eighth day sedation, tremor and baroreflex sensitivity were measured as described above, the last dose of placebo or alfuzosin 5 mg administered and the procedures repeated. Alfuzosin and placebo were administered double-blind at weekly intervals, in random order. Comparisons were made between placebo and active drug values, and between pre- and post-treatment values using Friedman's non-parametric analysis of variance and Wilcoxon's signed-rank test for matched-pairs. The regression lines were compared using analysis of covariance. A *P* value of less than 0.05 was regarded as significant.

Results

The effects of placebo and acute and chronic administration of alfuzosin 5 mg on supine intra-arterial blood pressure and R-R interval are shown in Table 1. No changes occurred in supine systolic pressure after placebo or alfuzosin on day 1 and day 8. However, significant α -adrenoceptor blockade occurred after alfuzosin as the phenylephrine dose-response curve was shifted significantly ($P < 0.05$) to the right on day 1, compared with placebo and pre-treatment (Figure 1). Prior to the final administration of alfuzosin on day 8, the dose-response curve was still significantly shifted to the right compared with placebo, and was unchanged 2 h after alfuzosin (Figure 2). The R-R interval was unchanged after placebo on day 1 and day 8, and after alfuzosin on day 1, but was significantly less than placebo prior to the last dose of alfuzosin

on day 8 (881 ± 44 vs 1015 ± 21 ms). No further reduction was seen 2 h after dosing. For equivalent rises in systolic blood pressure with phenylephrine the increases in R-R interval before and after administration of placebo on day 1 and day 8, and alfuzosin on day 1 were not significantly different (Table 1). There was a significantly smaller ($P < 0.05$) increase in R-R interval after alfuzosin on day 8 than after placebo (260 ± 41 vs 435 ± 48 ms).

Baroreflex sensitivity (change in R-R interval in ms mmHg⁻¹ systolic arterial pressure) before and after placebo and alfuzosin on day 1 and day 8 is shown in Figures 3a and 3b. No significant change occurred in baroreflex sensitivity after placebo on day 1 (18.3 ± 1.9 to 20.7 ± 3.6 ms mmHg⁻¹) or on day 8 (19.9 ± 4.6 to 21.1 ± 2.7 ms mmHg⁻¹). A significant reduction ($P < 0.05$) occurred on day 1 after alfuzosin 5 mg compared with both placebo (13.8 ± 2.6 vs 20.7 ± 3.6 ms mmHg⁻¹) and pre-treatment values (13.8 ± 2.6 vs 25.1 ± 3.5 ms mmHg⁻¹). Prior to the final administration of alfuzosin on day 8 baroreflex sensitivity was still significantly less compared with placebo (14.0 ± 2.0 vs 19.9 ± 4.6 ms mmHg⁻¹) and to pre-treatment values of alfuzosin on day 1 (14.0 ± 2.0 vs 25.1 ± 3.5 ms mmHg⁻¹). Two hours after alfuzosin on day 8 baroreflex sensitivity was unchanged compared with pre-treatment (13.4 ± 1.7 vs 14.0 ± 2.0 ms mmHg⁻¹), but was significantly less ($P < 0.05$) compared with placebo on day 8 (13.4 ± 1.7 vs 21.1 ± 2.7 ms mmHg⁻¹) and to pre-treatment with alfuzosin on day 1 (13.4 ± 1.7 vs 25.1 ± 3.5 ms mmHg⁻¹).

The effects of placebo and alfuzosin on sedation are shown in Figure 4 and Table 2. No significant changes occurred after placebo or alfuzosin administration on day 1 and day 8. No

Table 1 Supine systolic arterial pressure; the maximum increase in systolic arterial pressure following phenylephrine; the R-R interval and the change in R-R interval following phenylephrine before and 2 h after oral administration of placebo and alfuzosin 5 mg to healthy male subjects on day 1 and day 8. Placebo and alfuzosin (5 mg) were administered twice daily from day 1 to day 7 and once on day 8. Results are expressed as mean $\pm$ s.e. mean ($n = 6$).

		Systolic pressure (mmHg)	Increase in systolic pressure (mmHg)	R-R interval (ms)	Increase in R-R interval (ms)
Placebo	Before	119.2 $\pm$ 6.1	22.9 $\pm$ 3.4	875.7 $\pm$ 18.5	582.2 $\pm$ 47.6
Day 1	After	120.7 $\pm$ 5.4	20.6 $\pm$ 3.6	933.5 $\pm$ 35.4	491.9 $\pm$ 97.2
Placebo	Before	112.5 $\pm$ 6.1	26.4 $\pm$ 2.5	1014.8 $\pm$ 21.0	467.3 $\pm$ 77.7
Day 8	After	115.2 $\pm$ 4.9	23.9 $\pm$ 2.6	1012.3 $\pm$ 17.3	434.8 $\pm$ 47.8
Alfuzosin 5 mg	Before	113.8 $\pm$ 6.0	22.0 $\pm$ 2.5	921.7 $\pm$ 36.0	573.8 $\pm$ 77.2
Day 1	After	116.7 $\pm$ 3.1	21.5 $\pm$ 4.7	896.5 $\pm$ 28.2	390.0 $\pm$ 58.2
Alfuzosin 5 mg	Before	114.8 $\pm$ 1.0	21.3 $\pm$ 3.1	881.0 $\pm$ 43.6*	413.9 $\pm$ 66.5
Day 8	After	116.8 $\pm$ 3.8	21.0 $\pm$ 1.7	917.3 $\pm$ 37.0	260.0 $\pm$ 41.2*

* $P < 0.05$ vs placebo

Figure 1 Effects of increasing doses of phenylephrine on supine systolic blood pressure before (○) and 2 h after (●) oral administration of alfuzosin (5 mg) and before (Δ) and 2 h after (▲) placebo to healthy male subjects. Results are expressed as mean ($n = 6$).

significant changes in physiological tremor occurred after administration of placebo or alfuzosin on day 1 and day 8 (Table 2).

Discussion

Alfuzosin, a selective α_1 -adrenoceptor blocking drug, reduces blood pressure in normal man. In the present study the α -adrenoceptor blocking activity of the drug following oral dosing was demonstrated as the dose-response curve relating the increase in supine systolic blood pressure to dose of phenylephrine was significantly shifted to the right on day 1. Following twice daily administration of alfuzosin 5 mg for 7 days, the dose-response curve was still significantly shifted to the right prior to the final administration of the drug on day 8. No change occurred 2 h after dosing. This suggests that significant α -adrenoceptor blockade is maintained throughout the day with twice daily administration of the drug.

Administration of alfuzosin did not cause a fall in supine systolic blood pressure which is in agreement with studies on prazosin (Nicholls *et al.*, 1981) and indoramin (Nicholls *et al.*, 1981; Deering *et al.*, 1986). However, administration of alfuzosin has previously been shown to reduce standing blood pressure (Harron *et al.*, 1987). In contrast to indoramin and prazosin, the hypotensive effect of alfuzosin is accompanied by reflex tachycardia (Harron *et al.*, 1987).

The mechanism of absence of reflex tachycardia with indoramin is likely to be multifactorial. Studies in animals have demonstrated membrane stabilizing activity (Algate *et al.*, 1981), prolongation of repolarization time (Harron *et al.*, 1984a), reduction in sympathetic nerve activity (Ramage, 1984) and reduction in baroreflex sensitivity (Harron *et al.*, 1984b). Studies with indoramin in man indicate selective α_1 -adrenoceptor blockade (Nicholls *et al.*, 1984), prolongation of repolarization time (Harron *et al.*, 1985) and reduction in baroreflex sensitivity (Deering *et al.*, 1986). Similarly prazosin causes reduction in baroreflex sensitivity (Sasso & O'Connor, 1982).

Figure 2 Effects of increasing doses of phenylephrine on supine systolic blood pressure before (○) and 2 h after (●) oral administration of alfuzosin (5 mg) and before (Δ) and 2 h after (▲) placebo twice daily for 7 days and once on day 8 to healthy male subjects. Results are expressed as mean ($n = 6$).

In the present study alfuzosin reduced baroreflex sensitivity. However, the hypotensive effect of this drug is associated with reflex tachycardia (Harron *et al.*, 1987). This would suggest that factors other than reduced baroreflex sensitivity are important in explaining the lack of reflex tachycardia with indoramin and prazosin.

The change in baroreflex sensitivity seen with α -adrenoceptor antagonists may be due to effects of the drugs on afferent, central and efferent components of the baroreflex arc. Baroreceptors are stretch receptors which supply the afferent input to the central nervous system. The walls of the baroreceptor regions contain smooth muscle in both animals and man. The presence of α -adrenoceptor blockade may thus conceivably increase distensibility and compliance of the baroreceptor wall resulting in increased deformation of the baroreceptors and thus increased baroreceptor sensitivity. However, smooth muscle fibres are scant in human carotid sinus, and seemingly unable to induce baroreceptor activation when contracted by

topical application of adrenaline or stimulation of the cervical sympathetic trunk (Carlsten *et al.*, 1958).

Intracerebroventricular administration of α -adrenoceptor antagonists has been shown to cause depression of baroreflex sensitivity in animals (Abraham *et al.*, 1970). Several studies have shown that indoramin causes sedation (Lewis *et al.*, 1973; Fitzgerald, 1981; Deering *et al.*, 1986), this being a central effect. However, in the present study alfuzosin reduced baroreflex sensitivity without causing sedation. There are no reports of sedation with prazosin.

Indoramin reduces sympathetic nerve activity (Ramage, 1984) and does not cause a rise in plasma noradrenaline (Nicholls *et al.*, 1984). In addition, chronic administration of prazosin does not result in elevated plasma noradrenaline levels (Sasso & O'Connor, 1982). However, chronic administration of alfuzosin is associated with elevated plasma noradrenaline levels (Harron *et al.*, 1987) suggesting enhanced sympathetic tone. It is more likely that the different effects of indoramin, prazosin and

Figure 3 a) Baroreceptor sensitivity (change in R-R interval ms mmHg⁻¹ change in systolic blood pressure) following intravenous administration of phenylephrine (20, 50, 100 and 200 μ g). * $P < 0.05$ vs placebo, $\dagger P < 0.05$ vs pre-treatment. b) Baroreceptor sensitivity (change in R-R interval ms mmHg⁻¹ change in systolic blood pressure) following intravenous administration of phenylephrine (20, 50, 100 and 200 μ g). * $P < 0.05$ vs placebo. (●—●) represents the baroreflex sensitivity for each healthy male subject before and 2 h after administration of placebo and alfuzosin (5 mg) twice daily for 7 days and once on day 8. (●-----●) represents the mean + s.e. mean for the six subjects.

Figure 4 A visual analogue scale for sedation. The healthy male subjects were asked to mark how they felt between 'Wide awake' and 'Nearly asleep' 'at this moment'. Measurements were made before and 2 h after administration of placebo and alfuzosin (5 mg) twice daily for 7 days, and once on day 8. Results are expressed as the mean $\pm$ s.e. mean ($n = 6$).

* $P < 0.05$ vs placebo.

Table 2 Tremor (maximum power and frequency) and sedation measured before and 2 h after oral administration of placebo and alfuzosin 5 mg to healthy male subjects on day 1 and day 8. Placebo and alfuzosin (5 mg) were administered twice daily from day 1 to day 7 and once on day 8. Results expressed as the mean $\pm$ s.e. mean ($n = 6$).

		Tremor		Sedation
		Maximum power (μV^2)	Frequency (Hz)	(mm from 'Wide awake')
Day 1	Before	24.1 $\pm$ 12.2	9.5 $\pm$ 0.2	30.3 $\pm$ 4.0
	After	16.9 $\pm$ 7.5	10.0 $\pm$ 0.4	34.7 $\pm$ 10.3
Day 8	Before	14.8 $\pm$ 4.9	9.7 $\pm$ 0.2	43.7 $\pm$ 10.0
	After	17.3 $\pm$ 5.7	10.2 $\pm$ 0.8	30.3 $\pm$ 7.1
Day 1	Before	11.4 $\pm$ 5.8	8.3 $\pm$ 0.4	31.5 $\pm$ 6.4
	After	13.7 $\pm$ 4.4	9.2 $\pm$ 0.3	33.9 $\pm$ 13.8
Day 8	Before	18.3 $\pm$ 11.0	9.8 $\pm$ 0.8	34.7 $\pm$ 5.9
	After	11.5 $\pm$ 4.3	10.0 $\pm$ 0.4	39.7 $\pm$ 8.1

alfuzosin on sympathetic tone reflect differences in their selectivity for post-synaptic α_1 -adrenoceptors than differences in the effect on the efferent pathway of the baroreflex arc. From the available evidence it is not possible to deduce whether the mechanism of action of alfuzosin on baroreflex sensitivity is afferent, central or efferent.

Blockade of α -adrenoceptor sites has been associated with depression of physiological tremor (Mai & Olsen, 1981). In the present study tremor was not changed following acute and chronic administration of alfuzosin. There

was large inter-individual and day-to-day variation although inter-day variation was small. A similar effect of indoramin on tremor has been reported (Deering *et al.*, 1986).

Alfuzosin is an effective α -adrenoceptor antagonist. It reduces baroreflex sensitivity on acute and chronic administration, but does not affect physiological tremor or cause sedation.

We would like to thank L.E.R.S.-Synthelabo for the supply of alfuzosin and for financial support. Dr A. H. Deering is the holder of a Fellowship from the Department of Health and Social Services (N.I.).

References

- Abraham, G. J. S., Ahmed, S. S. & Verghese, K. G. (1970). Effects of cerebroventricular perfusion of alpha and beta adrenergic blocking agents on carotid occlusion response. *Arch. int. Pharmacodyn. Ther.*, **188**, 105–111.
- Algate, D. R., Rashid, S. & Waterfall, J. F. (1981). Cardioregulatory properties of indoramin in the rat. *J. Pharm. Pharmacol.*, **33**, 236–239.
- Awan, N. A., Miller, R. R., Miller, M. P., Vera, K. S. Z. & Mason, D. T. (1978). Clinical pharmacology and therapeutic application of prazosin in acute and chronic refractory congestive heart failure. *Am. J. Med.*, **65**, 146–154.
- Carlsten, A., Folkow, B., Grimby, G., Hamberger, C. A. & Thulesius, O. (1958). Cardiovascular effects of direct stimulation of the carotid sinus nerves in man. *Acta physiol. Scand.*, **44**, 138–145.
- Cavero, I., Galzin, A. M., Langer, S. Z., Lefevre-Borg, F., Manoury, P. H. & Pimoule, C. (1984a). Alfuzosin (SL 77.499), a new antihypertensive agent with a peripheral site of action. II. *In vitro* pharmacological studies. *Br. J. Pharmacol.*, **81**, 14P.
- Cavero, I., Lefevre-Borg, F. & Manoury, P. H. (1984b). Alfuzosin (SL 77.499), a new antihypertensive agent with a peripheral site of action. I. *In vivo* pharmacological studies. *Br. J. Pharmacol.*, **81**, 13P.
- Deering, A. H., Riddell, J. G., Harron, D. W. G. & Shanks, R. G. (1986). Effect of acute and chronic administration of indoramin on baroreceptor function in man. *Br. J. clin. Pharmacol.*, **22**, 231P.
- Fitzgerald, M. V. T. (1981). A longterm open evaluation of indoramin in hypertension. *Br. J. clin. Pharmacol.*, **12**, 117S–123S.
- Graham, R. M., Thornell, I. R., Gain, J. M., Bagnoli, C., Oates, H. F. & Stokes, G. S. (1976). Prazosin: the first-dose phenomenon. *Br. med. J.*, **2**, 1293.
- Harron, D. W. G., Kerr, M. J. & Shanks, R. G. (1984b). Investigation into the mechanism of lack of reflex tachycardia in response to the hypotensive action of indoramin in dogs. *J. cardiovasc. Pharmacol.*, **6**, 596–600.
- Harron, D. W. G., Lillie, C. & Kobinger, W. (1984a). Indoramin: bradycardia due to prolongation of repolarization time. *Br. J. Pharmacol.*, **82**, 312P.
- Harron, D. W. G., Nicholls, D. P. & Shanks, R. G. (1985). Indoramin – prolongation of repolarization time, a mechanism of bradycardia in man. *Br. J. clin. Pharmacol.*, **19**, 266–271.
- Harron, D. W. G., Scott, M. G., Deering, A. H., McMahon, M. & Shanks, R. G. (1987). Alfuzosin: clinical pharmacology. *Proceedings of the Xth International Congress of Pharmacology*, Sydney, Australia, 675.
- Lewis, P. J., George, C. F. & Dollery, C. T. (1973). Clinical evaluation of indoramin, a new antihypertensive agent. *Eur. J. clin. Pharmacol.*, **6**, 211–216.
- McAllister, H. G., Armstrong, G. A., McClelland, R. J. & Lingard, R. (1983). Data acquisition in neurophysiology. *Br. J. Audiology*, **17**, 275–277.
- Mai, J. & Olsen, R. B. (1981). Depression of essential tremor by α -adrenergic blockade. *J. Neurology, Neurosurgery & Psychiatry*, **44**, P.1171.
- Miller, R. R., Awan, N. A., Maxwell, K. S. & Mason, D. T. (1977). Sustained reduction of cardiac impedance and preload in congestive heart failure with the anti-hypertensive vasodilator prazosin. *New Engl. J. Med.*, **297**, 303–307.
- Nicholls, D. P., Harron, D. W. G. & Shanks, R. G. (1981). Acute and chronic cardiovascular effects of indoramin and prazosin in normal man. *Br. J. clin. Pharmacol.*, **12**, 61S–66S.
- Nicholls, D. P., O'Connor, P. C., Harron, D. W. G., Leahey, W. J. & Shanks, R. G. (1984). Differential blockade of α -adrenoceptors by indoramin. *Br. J. clin. Pharmacol.*, **17**, 719–728.
- Ramage, A. G. (1984). The effect of prazosin, indoramin and phentolamine on sympathetic nerve activity. *Eur. J. Pharmacol.*, **106**, 507–513.
- Royds, R. B., Coltart, D. J. & Lockhart, J. D. F. (1972). Pharmacologic studies of indoramin in man. *Clin. Pharmacol. Ther.*, **13**, 380–392.
- Sasso, E. H. & O'Connor, D. T. (1982). Prazosin depression of baroreflex function in hypertensive man. *Eur. J. clin. Pharmacol.*, **22**, 7–14.
- Verbesselt, R., Mullie, A., Tjandramage, T. B., DeSchepper, P. J. & Dessain, P. (1976). The effect of food intake on the plasma kinetics and toleration of prazosin. *Acta Ther.*, **2**, 27–39.

(Received 16 March 1987,
accepted 27 November 1987)