Br. J. clin. Pharmac. (1990), **30**, 579–584

Effect of UK-52,046, an α_1-adrenoceptor antagonist, on baroreflex function in man

J. P. McKAIGUE & D. W. G. HARRON
Department of Therapeutics and Pharmacology, The Queen's University of Belfast, Northern Ireland

1 In a placebo controlled study (six healthy male subjects), the effects of UK-52,046 (0.4 $\mu g\ kg^{-1}$ i.v.) and prazosin (0.25 mg i.v.) on baroreflex function were compared, at doses which produced antagonism to phenylephrine, but which had no effect on supine blood pressure.

2 Baroreflex function [$\triangle$R-R interval ms mm Hg^{-1} change in SBP] was assessed following increases in systolic blood pressure (SBP) with phenylephrine and during the Valsalva manoeuvre.

3 At these doses neither UK-52,046 nor prazosin had an effect on supine SBP or heart rate; however following prazosin, standing SBPs at 5 s (69.7 ± 7.6 mm Hg) and at 3 min (65.5 ± 11.7 mm Hg) were less than the respective pre-treatment ($P < 0.05$) values (96.0 ± 2.9, 110.3 ± 6.2 mm Hg) and placebo (82.7 ± 5.6, 98.7 ± 11.1 mm Hg). UK-52,046 had no significant effects on standing SBP at 5 s or 3 min. At 5 s, pre- and post-treatment R-R intervals (584 ± 26, 541 ± 27 ms respectively) were not significantly different with prazosin, but at 3 min the post-treatment R-R interval following prazosin (519 ± 17 ms) was less ($P < 0.05$) than the pre-treatment value (658 ± 36 ms).

4 UK-52,046 had no effect on baroreflex sensitivity (12.7 ± 1.3 ms mm Hg^{-1}) compared with placebo (17.9 ± 2.7 ms mm Hg^{-1}). Following prazosin baroreflex sensitivity (9.9 ± 1.5 ms mm Hg^{-1}) was reduced ($P < 0.05$) compared with both the pre-treatment value (16.6 ± 1.8 ms mm Hg^{-1}) and placebo.

5 The results of this study suggest that the different effects of UK-52,046 and prazosin on baroreflex function, standing BP and heart rate may be due to less extensive blockade of peripheral vascular α_1-adrenoceptors by UK-52,046.

Keywords UK-52,046 prazosin baroreflex function α_1-adrenoceptor antagonist phenylephrine

Introduction

UK-52,046 (4-amino-6,7-dimethoxy-2-(1,2,3,4-tetrahydro - 6, 7 - dimethoxyisoquinol - 2 - yl) quinoline methanesulphonate) is an α_1-adrenoceptor antagonist which is being developed to treat cardiac arrhythmias. In a number of experimental adrenaline arrhythmia models, the increased arrhythmic threshold resulting from blockade of myocardial α_1-adrenoceptors was not associated with a marked fall in blood pressure or an increase in heart rate following UK-52,046 (Aubry *et al.*, 1988; Uprichard *et al.*, 1988), in contrast to prazosin, where there were changes in heart rate and blood pressure (Aubry *et al.*, 1988). These results suggest that at anti-

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

arrhythmic doses UK-52,046 had only minimal effects on the peripheral vasculature whereas prazosin was producing significant antagonism of peripheral vascular α_1-adrenoceptors.

In the present study the effects of UK-52, 046 and prazosin on the results of a number of tests of autonomic function (baroreflex sensitivity, Valsalva manoeuvre and 'lying to standing') were investigated. The drugs were compared at doses which produced α_1-adrenoceptor antagonism to increases in blood pressure with phenylephrine, but which had no effect on supine heart rate or blood pressure (Harron *et al.*, 1989; Morganti *et al.*, 1981; Schäfers *et al.*, 1989).

Methods

Six healthy male volunteers age 21.7 ± 0.3 years (mean ± s.e. mean), weight 72.2 ± 3.0 kg gave written informed consent to the study which was approved by the Research Ethics Committee of The Queen's University of Belfast. The study was randomised and double-blind, the volunteers receiving at weekly intervals either UK-52,046 0.4 $\mu g\ kg^{-1}$, prazosin 0.25 mg or placebo.

Following a light breakfast containing no caffeine and having abstained from tobacco for 12 h and alcohol for 48 h the subjects presented themselves in the morning to a temperature controlled laboratory. A constant reference point for the position of the heart was marked on the left lateral chest wall (5th intercostal space, mid-axillary line) so that the pressure transducer could be aligned with the level of the heart for blood pressure readings.

An intra-arterial cannula (Abbocath 20 G) was inserted into the non-dominant radial artery under local anaesthetic (lignocaine 2%) and connected to an arterial line monitoring kit incorporating the Intraflo Continuous Flush Device (Sorenson Research 42101–01) which contained 0.9% NaCl and heparin (2500 iu heparin/500 ml saline). An intravenous cannula (Venflon 2 20 G) was inserted into a forearm vein on the same arm and connected to a slow running infusion of 0.9% NaCl, for the administration of phenylephrine. The pressure transducer was a Bell and Howell, Type 4-422-0001-1-B4M5 which was calibrated against a mercury manometer. The signal was amplified (Lectromed 3552) and recorded on a chart recorder (Lectromed Multitrace 4 Type 5041). The heart rate was displayed continuously on an ECG monitor and in addition the ECG was recorded on the chart recorder as described above. Paper speed was 25 $mm\ s^{-1}$.

Phenylephrine responses

After 15 min quiet rest baseline blood pressure and heart rate were recorded. Intravenous injections of phenylephrine ranging from 20 μg through 50, 100, 200, 300, 400 and 600 μg were administered as rapid boluses until systolic blood pressure increases of the order of 25–30 mm Hg were achieved. Between each of the doses of phenylephrine, heart rate and blood pressure were allowed to return to baseline. The earliest initial increase in blood pressure associated with a slowing of the heart rate usually occurred about 20–45 s following the phenylephrine injection. When this point was identified four values for SBP were determined from four consecutive arterial pressure waveforms and the associated R-R intervals were recorded. Linear regression was performed on the pooled SBPs and R-R intervals obtained from injections of phenylephrine which produced a dose dependent increase in BP, to obtain a slope ($\triangle$R-R interval ms mm Hg^{-1} change in systolic blood pressure) and intercept.

Valsalva manoeuvre

Following injections of phenylephrine the Valsalva manoeuvre was then performed. This involved the subjects blowing into a rubber tube connected to a mercury manometer and elevating the mercury level by 30 mm for 25 s. Subjects were instructed to take a deep breath prior to straining and to breathe as smoothly as possible on completion of straining. Baroreflex sensitivity was assessed using the highest systolic pressure at the start of the initial strain and ending with the lowest pressure attained during the strain. Linear regression analysis was performed on the systolic pressure values and corresponding R-R intervals for successive beats between these two values. During the release phase of Valsalva's manoeuvre (Deering & Harron, 1987) baroreflex sensitivity was assessed beginning with the first systolic pressure which was greater than the baseline systolic pressure, recorded just prior to commencement of the Valsalva manoeuvre and ending with the highest pressure attained several beats later (McAloney *et al.*, 1987). Linear regression analysis was performed on the systolic pressure values and corresponding R-R intervals for successive beats between these two values. In addition the Valsalva ratio was also calculated (maximum R-R interval ms during release/minimum R-R interval ms during strain).

After return of the blood pressure to baseline values the subjects were then asked to stand up.

Table 1 Supine blood pressure and heart rate in six healthy subjects, before and 0.25, 0.5, 1.0 and 2.0 h post-treatment with placebo, UK-52,046 0.4 μg kg^{-1} i.v. and prazosin 0.25 mg i.v. Results expressed as mean ± s.e. mean.

		Baseline	*Pre-dose*	*0.25 h*	*0.5 h*	*1.0 h*	*2.0 h*
Supine SBP (mm Hg)	Placebo	106.5 ± 4.6	107.3 ± 4.0	109.2 ± 3.5	111.8 ± 5.4	113.5 ± 5.2	114.2 ± 3.8
	UK-52,046	107.8 ± 4.7	111.2 ± 3.0	109.3 ± 3.6	108.8 ± 3.3	113.5 ± 5.6	112.3 ± 4.2
	Prazosin	106.7 ± 5.4	109.3 ± 5.4	101.2 ± 5.3	105.0 ± 3.8	107.0 ± 4.7	108.0 ± 4.7
Supine DBP (mm Hg)	Placebo	53.5 ± 3.4	54.3 ± 2.1	55.7 ± 3.5	57.0 ± 3.2	58.8 ± 5.0	58.0 ± 3.2
	UK-52,046	53.3 ± 2.5	54.8 ± 1.8	53.5 ± 1.5	52.8 ± 2.2	53.7 ± 2.1	55.3 ± 2.3
	Prazosin	53.8 ± 2.0	54.2 ± 2.4	50.7 ± 2.3	51.3 ± 1.4	51.5 ± 1.5	53.8 ± 2.0
Supine heart rate (beats min^{-1})	Placebo	65.2 ± 3.3	64.5 ± 3.5	63.7 ± 3.7	63.3 ± 3.6	63.3 ± 4.3	63.3 ± 3.9
	UK-52,046	60.0 ± 3.1	59.3 ± 3.2	67.3 ± 4.9	64.0 ± 4.0	61.8 ± 3.9	65.5 ± 3.9
	Prazosin	58.7 ± 4.9	61.2 ± 3.8	68.3 ± 4.5	64.3 ± 4.5	62.8 ± 4.6	63.7 ± 4.8

During this procedure the blood pressure and R-R interval after standing erect for 5 s were calculated from a single arterial pressure waveform trace and the ECG respectively. At 3 min standing the blood pressure and R-R interval were calculated from the mean of 10 arterial pressure waveform traces and 10 R-R intervals respectively.

Treatment was then administered intravenously over 2 min and the tests were repeated, commencing 30 min after injection. Blood pressure was measured invasively for 2 h after administration of treatment and thereafter using a Hawksley random zero sphygmomanometer at 3, 4 and 24 h. Results were compared using the Friedman 2-way ANOVA and Student's *t*-test. A P value < 0.05 was regarded as significant. Results are expressed as mean ± s.e. mean.

Results

Both active treatments were well tolerated by the subjects without any serious side effects.

Effects on blood pressure and heart rate

There were no significant differences between the treatments and their effects on supine blood pressure and heart rate (Table 1). At 30 min post-treatment supine SBP for UK-52,046, prazosin and placebo were respectively (108.8 ± 3.3, 105.0 ± 3.8, 111.8 ± 5.4 mm Hg) and corresponding heart rates were (64.0 ± 4.0, 64.3 ± 4.5, 63.3 ± 3.6 beats min^{-1}).

The blood pressures immediately after standing (on average 75 min post-treatment) were reduced ($P < 0.05$) compared with the pre-treatment values by prazosin: SBP (Figure 1) and DBP at 5 s were (69.7 ± 7.6, 40.5 ± 3.7 mm Hg) and the corresponding pre-treatment values (96.0 ± 2.9, 56.3 ± 2.8 mm Hg); corresponding values for UK-52,046 were (84.2 ± 7.7, 48.7 ± 4.9 mm Hg) and (97.8 ± 1.4, 58.2 ± 2.0 mm Hg); and for placebo (82.7 ± 5.6, 48.3 ± 3.9 mm Hg) and (92.5 ± 4.7, 49.8 ± 3.1 mm Hg). There were no significant differences in the R-R intervals between the treatments (Figure 1).

At 3 min standing, SBP (Figure 1) and DBP following prazosin (65.5 ± 11.7, 42.7 ± 6.0 mm Hg) were less ($P < 0.05$) than the pre-treatment values (110.3 ± 6.2, 67.0 ± 3.2 mm Hg) and less ($P < 0.05$) than the post-treatment UK-52,046 values (103.3 ± 6.8, 63.0 ± 3.9 mm Hg), pre-treatment (108.2 ± 6.0, 64.2 ± 4.0 mm Hg); the corresponding values for placebo were (98.7 ± 11.1, 58.5 ± 8.4 mm Hg) and (112.7 ± 7.7, 66.3 ± 4.9 mm Hg). The R-R

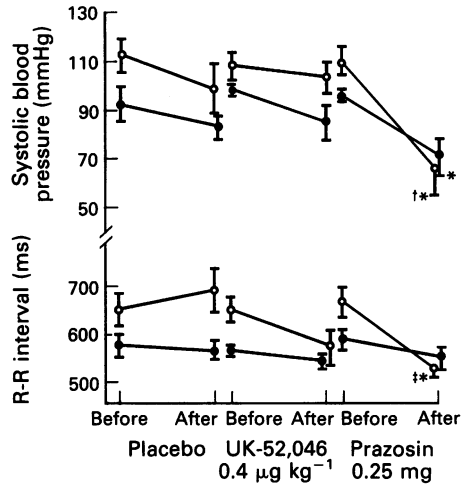

Figure 1 Systolic blood pressure and R-R interval at 5 s (●) and 3 min (○) after assuming the standing position in six healthy subjects, before and after treatment with placebo, UK-52,046 0.4 μg kg^{-1} i.v. and prazosin 0.25 mg i.v. Results displayed as mean ± s.e. mean.

Significance *$P < 0.05$ before *vs* after, † $P < 0.05$ *vs* UK-52,046, ‡ $P < 0.05$ *vs* placebo.

interval following prazosin (519 ± 17 ms) was less ($P < 0.05$) than the pre-treatment value (658 ± 36 ms) and placebo (687 ± 49 ms) (Figure 1), the corresponding value for UK-52,046 (564 ± 42 ms) was not different from pre-treatment or prazosin.

Thereafter standing blood pressure and heart rates measured at 3, 4 and 24 h were not significantly different between the treatments (Table 2). At 3 h post-treatment standing SBP for UK-52,046, prazosin and placebo were respectively (105.3 ± 3.4, 105.0 ± 4.1, 108.3 ± 2.0 mm Hg) and corresponding heart rates were (98.2 ± 3.9, 101.5 ± 6.4, 95.2 ± 4.0 beats min^{-1}).

Effects on baroreflex function

Using phenylephrine to produce a rise in systolic blood pressure of 25–30 mm Hg to activate the baroreceptors, baroreflex sensitivity (Table 3) was reduced ($P < 0.05$) following prazosin (9.9 ± 1.5 ms mm Hg^{-1}) compared with the pre-treatment value (16.6 ± 1.8 ms mm Hg^{-1}) and placebo (17.9 ± 2.7 ms mm Hg^{-1}), the corresponding value for UK-52,046 was 12.7 ± 1.3 ms mm Hg^{-1}. Neither UK-52,046 nor prazosin had an effect on baroreflex function during both the strain and release phases of the Valsalva manoeuvre or the Valsalva ratio (Table 3).

Discussion

In this study the effects of the α_1-adrenoceptor antagonist, UK-52,046, on the results of a number of tests of autonomic function, were compared with those of prazosin. The drugs were compared at doses which produced significant α_1-adrenoceptor antagonism to increases in blood pressure with phenylephrine, but which had no effect on supine heart rate or blood pressure (Harron *et al.*, 1989; Morganti *et al.*, 1981; Schäfers *et al.*, 1989).

From the results of this study it is apparent that the dose of prazosin used blocked peripheral α_1-adrenoceptors, the effects of which were only unmasked on standing; no effects on supine heart rate or blood pressure were observed. This is in contrast to UK-52,046 which produced no significant effects on heart rate and blood pressure on change of posture. This disparity may be explained on the basis that the pressor response to phenylephrine is mediated through both stimulation of the myocardial α_1-adrenoceptor, resulting in an increase in inotropy (Govier, 1967; Schümann *et al.*, 1978; Wagner *et al.*, 1980; Wenzel & Su, 1966) as well as a peripheral effect

Table 2 Standing blood pressure and heart rate in six healthy subjects, at 3, 4 and 24 h following treatment with placebo, UK-52,046 0.4 μg kg^{-1} i.v. and prazosin 0.25 mg i.v. Results expressed as mean ± s.e. mean

		3 h	*4 h*	*24 h*
Standing SBP (mm Hg)	Placebo	108.3 ± 2.0	105.3 ± 1.9	109.0 ± 4.4
	UK-52,046	105.3 ± 3.4	103.7 ± 5.6	107.7 ± 3.2
	Prazosin	105.0 ± 4.1	102.3 ± 3.7	111.3 ± 3.9
Standing DBP (mm Hg)	Placebo	78.7 ± 3.0	75.0 ± 4.0	82.3 ± 3.9
	UK-52,046	68.3 ± 3.1	71.3 ± 4.6	75.0 ± 2.6
	Prazosin	74.3 ± 2.8	75.3 ± 4.0	77.0 ± 3.4
Standing heart rate (beats min^{-1})	Placebo	95.2 ± 4.0	95.2 ± 4.0	91.2 ± 4.6
	UK-52,046	98.2 ± 3.9	105.5 ± 4.1	93.3 ± 5.3
	Prazosin	101.5 ± 6.4	100.8 ± 5.7	98.8 ± 4.1

Table 3 Slopes (ΔR-R interval ms mm Hg^{-1} change in systolic blood pressure) (baroreflex sensitivity) and intercepts of linear regression lines following stimulation of the baroreceptor with phenylephrine and during the Valsalva manoeuvre in six healthy subjects, before and after treatment with placebo, UK-52,046 0.4 μg kg^{-1} i.v. and prazosin 0.25 mg i.v. Results expressed as mean ± s.e. mean

		Phenylephrine		*Valsalva manoeuvre*			
				Strain		*Release*	
		Slope	*Intercept*	*Slope*	*Intercept*	*Slope*	*Intercept*
Placebo	Before	13.4 ± 2.2	−492 ± 294	5.5 ± 1.3	80 ± 175	12.6 ± 2.6	−961 ± 271
	After	17.9[a] ± 2.7	−882[a] ± 184	5.2 ± 1.2	206 ± 148	13.0 ± 2.8	−1006 ± 345
UK-52,046	Before	13.5[a] ± 3.1	−349[a] ± 378	5.3 ± 0.8	105 ± 105	13.6 ± 1.6	−1164 ± 172
	After	12.7[b] ± 1.3	−414[b] ± 170	4.0 ± 0.9	301 ± 108	12.7 ± 1.8	−1155 ± 207
Prazosin	Before	16.6 ± 1.8	−663 ± 193	4.6 ± 1.1	266 ± 130	15.3 ± 3.7	−1299 ± 471
	After	9.9†* ± 1.5	−541* ± 184	3.7 ± 0.8	431 ± 25	19.5 ± 6.0	−1849 ± 666

[a] $n = 4$, [b] $n = 5$
† $P < 0.05$ *vs* placebo, * $P < 0.05$ before *vs* after

causing vasoconstriction. UK-52,046 therefore, while having minimal peripheral vascular effects, may still antagonise the pressor response to phenylephrine, due to blockade of myocardial α_1-adrenoceptors. In another study (Tomlinson *et al.*, 1989) where UK-52,046 and prazosin were compared at doses which had similar effects on a phenylephrine systolic pressor response, UK-52,046 appeared to show less inhibition of the diastolic pressor response and less orthostatic effects than prazosin, the authors concluding that there was less inhibition of peripheral α_1-adrenoceptors at equal levels of cardiac α_1-adrenoceptor antagonism. In the present study, diastolic blood pressure fell with prazosin but not with UK-52,046, on first being asked to stand up. These observations suggest that at this dose UK-52,046 has more effects on the myocardial than the peripheral α_1-adrenoceptor compared with prazosin. This is in agreement with the results of other workers (Aubry *et al.*, 1988) who showed that anti-arrhythmic doses of UK-52,046 were not associated with significant changes in heart rate or blood pressure whereas similarly effective doses of prazosin caused significant falls in blood pressure.

Concerning the possibility of an association between extent of peripheral blockade of vascular α_1-adrenoceptors and the effects of a drug on baroreflex sensitivity, the findings are not conclusive proof of a cause and effect relationship. However evidence is accumulating that sinoaortic baroreceptor nerve endings contain α_1-adrenoceptors and that baroreflex function may be modulated by agonist interactions with these receptors (Goldman & Saum, 1984; Munch & Brown, 1987; Munch *et al.*, 1987; Tomomatsu & Nishi, 1981). It is possible therefore that prazosin is exerting its effects by binding to the baroreceptor nerve endings and antagonising the excitatory effect which locally released noradrenaline from sympathetic efferent neurones is known to exert on baroreceptor activity. Similarly prazosin may inhibit a direct excitatory effect of phenylephrine on the baroreceptor. Possible differences may also exist in selectivity or affinity for prazosin, between vascular and baroreceptor α_1-adrenoceptors, which could then result in decreases in the slope of the linear regression line relating changes in systolic blood pressure to changes in R-R interval. The decrease in baroreflex sensitivity with prazosin, as assessed using phenylephrine, is similar to the findings of other workers (Sasso & O'Connor, 1982) and the effects of other α_1-adrenoceptor antagonists indoramin and alfuzosin (Deering *et al.*, 1988a, b).

In conclusion, the results of this study suggest that the different effects of UK-52,046 and prazosin on baroreflex function may be related to relative differences in blockade of peripheral vascular α_1-adrenoceptors.

We would like to thank Dr J. G. Riddell and Professor R. G. Shanks for their help and advice during the study.

References

Aubry, M. L., Davey, M. J. & Petch, B. (1988). UK-52,046 a novel α_1-adrenoceptor antagonist with antidysrhythmic activity. *Br. J. Pharmac.*, **95**, 752P.

Deering, A. H. & Harron, D. W. G. (1987). Valsalva's manoeuvre. *Int. Pharm. J.*, **1**, 48–52.

Deering, A. H., Riddell, J. G., Harron, D. W. G. & Shanks, R. G. (1988a). Effect of acute and chronic indoramin administration on baroreflex function and tremor in humans. *J. cardiovasc. Pharmac.*, **11**, 284–290.

Deering, A. H., Riddell, J. G., Harron, D. W. G. & Shanks, R. G. (1988b). Effect of acute and chronic oral administration of alfuzosin on baroreflex function and tremor in man. *Br. J. clin. Pharmac.*, **25**, 417–424.

Goldman, W. F. & Saum, W. R. (1984). A direct excitatory action of catecholamines on rat aortic baroreceptors *in vitro*. *Circulation Res.*, **55**, 18–30.

Govier, W. C. (1967). A positive inotropic effect of phenylephrine mediated through alpha adrenergic receptors. *Life Sci.*, **6**, 1361–1365.

Harron, D. W. G., McKaigue, J. P., Burke, M. T., Riddell, J. G. & Shanks, R. G. (1989). Effects of intravenous and oral UK-52,046, an α_1-adrenoceptor antagonist, on heart rate and blood pressure in man. *Br. J. clin. Pharmac.*, **27**, 680P–681P.

McAloney, R., Mitchell, H., Deering, A. H., Shanks, R. G. & Harron, D. W. G. (1987). Computerized evaluation of Valsalva's manoeuvre before and during α-adrenoceptor blockade with alfuzosin. *J. pharmac. Methods*, **18**, 163–177.

Morganti, A., Sala, C., Palermo, A., Turolo, L. & Zanchetti, A. (1981). α_1-adrenoceptor blockade: dissociation of its effects on renin release and arterial blood pressure in man. *Clin. Sci.*, **61**, 307s–309s.

Munch, P. A. & Brown, A. M. (1987). Sympathetic modulation of rabbit aortic baroreceptors *in vitro*. *Am. J. Physiol.*, **253**, H1106–H1111.

Munch, P. A., Thoren, P. N. & Brown, A. M. (1987). Dual effects of norepinephrine and mechanisms of baroreceptor stimulation. *Circulation Res.*, **61**, 409–419.

Sasso, E. H. & O'Connor, D. T. (1982). Prazosin depression of baroreflex function in hypertensive man. *Eur. J. clin. Pharmac.*, **22**, 7–14.

Schäfers, R. F., Elliott, H. L., Howie, C. A. & Reid, J. L. (1989). Preliminary clinical pharmacological studies with the novel α_1-adrenoceptor antagonist UK-52,046. *Br. J. clin. Pharmac.*, **27**, 102P–103P.

Schümann, H. J., Wagner, J., Knorr, A., Reidemeister, J. C., Sadony, V. & Schramm, G. (1978). Demonstration in human atrial preparations of α-adrenoceptors mediating positive inotropic effects. *Naunyn-Schmiedeberg's Arch. Pharmac.*, **302**, 333–336.

Tomlinson, B., Renondin, J-C., Graham, B. R. & Prichard, B. N. C. (1989). α_1-adrenoceptor antagonism and haemodynamic effects of UK-52,046 compared with prazosin. *Br. J. clin. Pharmac.*, **27**, 686P–687P.

Tomomatsu, E. & Nishi, K. (1981). Increased activity of carotid sinus baroreceptors by sympathetic stimulation and norepinephrine. *Am. J. Physiol.*, **240**, H650–H658.

Uprichard, A. G. C., Harron, D. W. G., Wilson, R. & Shanks, R. G. (1988). Effects of the myocardial-selective α_1-adrenoceptor antagonist UK-52046 and atenolol, alone and in combination, on experimental cardiac arrhythmias in dogs. *Br. J. Pharmac.*, **95**, 1241–1254.

Wagner, J., Schümann, H. J., Knorr, A., Rohm, N. & Reidemeister, J. C. (1980). Stimulation by adrenaline and dopamine but not by noradrenaline of myocardial α-adrenoceptors mediating positive inotropic effects in human atrial preparations. *Naunyn-Schmiedeberg's Arch. Pharmac.*, **312**, 99–102.

Wenzel, D. G. & Su, J. L. (1966). Interactions between sympathomimetic amines and blocking agents on the rat ventricle strip. *Arch. int. Pharmacodyn.*, **160**, 379–389.

(Received 31 January 1990, accepted 30 May 1990)