Br. J. clin. Pharmac. (1986), **22**, 301–308

Pharmacodynamics and pharmacokinetics of single doses of ketanserin and propranolol alone and in combination in healthy volunteers

FAITH M. WILLIAMS, JENNY E. LEESER & M. D. RAWLINS
Wolfson Unit of Clinical Pharmacology, University of Newcastle upon Tyne, Newcastle upon Tyne

1 The potential interaction between ketanserin and propranolol has been investigated in eight healthy volunteers.

2 Volunteers received single doses of placebo, propranolol (80 mg), ketanserin (20 mg), and propranolol (80 mg) plus ketanserin (20 mg) following a randomised double-blind regimen.

3 A single dose of ketanserin had little effect on resting heart rate and blood pressure and the effects of propranolol and ketanserin in combination were similar to those of propranolol alone.

4 The inhibition of exercise induced tachycardia by propranolol was not affected by ketanserin.

5 The pharmacokinetics of propranolol elimination were not influenced by the concurrent administration of ketanserin, nor the pharmacokinetics of ketanserin by propranolol.

Keywords pharmacodynamics pharmacokinetics ketanserin propranolol interaction

Introduction

Ketanserin (3-[2-[4-fluorobenzoyl)-1-piperidinyl] ethyl]-2,4(*1H, 3H*)-quinazolinedione), a new potent antagonist of 5-hydroxytryptamine has been shown to be an effective antihypertensive agent in patients with essential hypertension (Hedner *et al.*, 1983). Its action appears to be due mainly to serotonin antagonism at peripheral 5-HT_2 receptors resulting in reduced peripheral vascular resistance (Reimann & Frolich, 1983, Zoccali *et al.*, 1983). In clinical practice, however, it is likely that ketanserin would be used in combination with β-adrenoceptor blockers such as propranolol.

Propranolol has been shown to potentiate the 'first dose' postural hypotensive effects of prazosin possibly by preventing reflex tachycardia (Elliot *et al.*, 1981). Propranolol has also been shown to reduce the clearance of a number of drugs such as antipyrine, lignocaine and theophylline which are extensively metabolised by the liver (Bax *et al.*, 1983). This reduced clearance may be due either to direct inhibition of microsomal enzymes by propranolol or the result of a reduction in liver blood flow secondary to the fall in cardiac output (Park, 1984). Ketanserin is extensively metabolised by the liver in man resulting in a 50% bioavailability of an oral dose. The major metabolite, ketanserinol, is formed by a reversible reduction within the liver. Microsomal oxidative *N*-dealkylation of the piperidine nitrogen, and aromatic hydroxylation followed by ether glucuronide formation, are also important metabolic routes (Meuldermans *et al.*, 1983).

Since ketanserin might undergo interaction with propranolol at either a pharmacodynamic or pharmacokinetic level, in this study single

doses of ketanserin and propranolol were administered separately and together to healthy volunteers to assess any interaction.

Methods

Eight healthy volunteers (two females) aged 23–49 years received in a double-blind, randomised, cross-over design single doses of ketanserin (20 mg) plus placebo, propranolol (80 mg) plus placebo, ketanserin (20 mg) plus propranolol (80 mg), and placebo. Prior approval was obtained from Newcastle University Ethics Committee for the study. After giving written informed consent volunteers underwent a pre-study assessment at which the exercise-load (brake power, on a bicycle ergometer) required to achieve a heart rate of 140 beats min^{-1} after 3 min exercise was determined, followed by four visits at not less than 1 week's interval. At each visit subjects attended fasting at 09.00 h, having abstained from alcohol for 24 h. The volunteers denied taking any drugs or medication, including oral contraceptives. The three subjects who were smokers (2M, 1F) abstained during the first 4 h of the study. Blood pressure and radial pulse were recorded at 0, 1, 2, 4 and 6 h both after at least 2 min supine and immediately on standing. Supine blood pressure was taken from duplicate readings using a random zero sphygmomanometer taking diastolic at the fourth Korotkoff sound. Standing blood pressure was a single observation made immediately upon standing. Subjects exercised on a bicycle ergometer for 3 min at 0, 1, 2, 4 and 6 h. Throughout the time on the bicycle, heart rate was monitored using an electrocardiographic recording with precordial leads, and blood pressure was measured at 1 min intervals.

An indwelling venous cannula was inserted before the start of each study, and 10 ml heparinised blood was taken for drug assay at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 10 h. Further samples were taken at 24, 32 and 48 h following the dose. Plasma samples were separated by centrifugation and stored at −20° C until analysis for propranolol and ketanserin.

Adverse effects were noted from clinical observation and from a visual analogue scale (10 cm) of tiredness (not tired to tired), breathlessness (not breathless to breathless) and well-being (very well to unwell).

Plasma concentrations

Plasma propranolol concentrations were measured by a modification of the method of Lo *et al.* (1982). Alkalinised plasma containing methylpropranolol (internal standard) was extracted with ether and then into phosphoric acid for h.p.l.c. on an ODS Bondapak column. Using the mobile phase 28% acetonitrile, 16% methanol in 0.021 M phosphoric acid at a flow rate of 2.5 ml min^{-1}, the retention times of propranolol and methylpropranolol were 3 min and 5 min respectively. Peaks were monitored by a fluorimetric detector at 285 nm (excitation wavelength) and 337 nm (emission wavelength). A calibration curve was constructed over the range 0–200 ng propranolol ml^{-1} plasma and a quality control sample was analysed with each group of plasma samples. The reproducibility of the assay was 5.9% (coefficient of variation) at 70 ng ml^{-1} ($n = 8$).

Plasma samples were also analysed for ketanserin and its major metabolite ketanserinol. Plasma (1 ml) containing metoprolol (as internal standard) plus 1 ml 2 M tris buffer (pH 10.9) was extracted with heptane:diethylether (25:75%), and then into orthophosphoric acid for h.p.l.c. on Novopak R in a Waters Z-module, with the mobile phase, 25% acetonitrile 75% water + triethanolamine and phosphoric acid pH 3.0 at a flow rate of 3.0 ml min^{-1}. Under these conditions the retention times were metoprolol 2.3 min, ketanserinol 4.0 min and ketanserin 6.6 min. Peaks were monitored by a fluorimetric detector at excitation wavelength 220 nm with no emission filter. Coefficients of variation were 5.0% for ketanserin ($n = 10$ at 200 ng ml^{-1}), for ketanserinol 2.7% ($n = 10$ at 200 ng ml^{-1}) and ketanserin 4.0% ($n = 10$ at 2 ng ml^{-1}) and ketanserinol 5.1% ($n = 10$ at 2 ng ml^{-1}).

Pharmacokinetic analysis

The peak plasma concentration (C_{max}) and the time at which it was reached (t_{max}) were calculated for propranolol and ketanserinol. Ketanserin had been absorbed before the 0.5 h sample in most subjects. The terminal phase elimination rate constant (k) was determined by least squares regression analysis of the post absorption and distribution log transformed plasma concentration *vs* time data. The terminal phase elimination half life ($t_{½}$) was calculated from $0.693/k$. The area under the plasma concentration/time curve (AUC) was calculated by the trapezoidal method using the terminal phase rate constant (k) and the last measured plasma concentration to extrapolate to infinity.

Statistical analysis

Pharmacokinetic data were compared by two way analysis of variance. Pharmacodynamic

effects were analysed with respect to treatment and time after dose, by analysis of variance with allowance for repeated measures employing the Greenhouse-Geisser adjustment to account for correlations over time (B.M.D.P. Statistical Software).

Results

Pharmacokinetics

Derived pharmacokinetic parameters for the elimination of ketanserin and ketanserinol alone and in combination with propranolol are summarised in Table 1 and the pharmacokinetic profiles shown in Figure 1. Ketanserin was not detectable at 48 h. Ketanserin (20 mg) was rapidly absorbed and for most subjects the peak plasma level was achieved by 30 min. The terminal half life was 11.2 ± 1.7 h (mean ± s.e. mean) when given alone and 7.5 ± 1.6 h in combination with propranolol; but this difference was not significant. Indeed, there was no significant change in any of the pharmacokinetic parameters of ketanserin when administered with propranolol. There was a six-fold range in terminal half life, and three-fold range in AUC with ketanserin. Following the combination the range in terminal half-life was 10-fold and AUC five-fold.

Reduction of ketanserin to ketanserinol occurred very rapidly, and peak levels of the metabolite were detected at 1 h after dose. Levels of ketanserinol exceeded those of the parent drug thereafter with an elimination half-life of 23.5 ± 2.0 h alone and 21.1 ± 0.85 h in combination with propranolol. The mean peak plasma level of ketanserinol was significantly higher (P Δ 0.05) following the combination than after ketanserin alone, but there was no difference in AUC, This observation was the only significant difference in the pharmacokinetic profile of ketanserinol following the combination.

Similarly coadministration of ketanserin had no effect on the pharmacokinetic profile of propranolol (terminal half-life 7.0 ± 0.9 h alone and 6.4 ± 0.8 h in combination). Propranolol pharmacokinetic parameters are shown in Table 1 and the profile in Figure 2. 4-OH propranolol was not measured in this study.

Pharmacodynamics

Supine, standing and exercise blood pressure and heart rate for the four treatment regimens are shown in Figures 3, 4 and 5. The effects of propranolol and ketanserin alone compared to placebo and the possible interaction when administered together were compared by analysis of

Table 1 Pharmacokinetic data of drugs alone and in combination

Parameter	*AUC* ($ng\ ml^{-1}\ h$)	C_{max} ($ng\ ml^{-1}$)	t_{max} (*h*)	*Terminal half-life* (*h*)
Propranolol				
Propranolol alone	726 ± 135 345–1340	106.4 ± 21 39–186	1.7 ± 0.2 1.1–3.0	7.0 ± 0.9 3.5–11.2
Propranolol in combination	835 ± 204 181–1692 NS	107.4 ± 24.3 41–201 NS	1.7 ± 0.2 1.2–2.5 NS	6.4 ± 0.8 4.7–11.2 NS
Ketanserin				
Ketanserin alone	284 ± 39 141–394	62.1 ± 15 15.4–142**	 0.5–2.0*	11.2 ± 1.7 2.9–17.3
Ketanserin in combination	267 ± 43 99–460 NS	65.9 ± 13.5 24.0–139.4** NS	 0.5–1.0* NS	7.5 ± 1.6 1.7–17.1 NS
Ketanserinol				
Ketanserin alone	849 ± 137 392–1567	48.3 ± 6.0 22.2–75.2	1.0 ± 0.14 0.5–2.0	23.5 ± 2.0 16.1–33.0
Ketanserin in combination	827 ± 80 620–1227 NS	69.3 ± 5.8 42–91.8 P Δ 0.05	1.0 ± 0.1 0.5–2.0 NS	21.1 ± 0.85 15.8–23.8 NS

* Absorbed by first sample in most cases

** Maximum measured level

(Results expressed as mean ± s.e. mean (n = 8) (range))

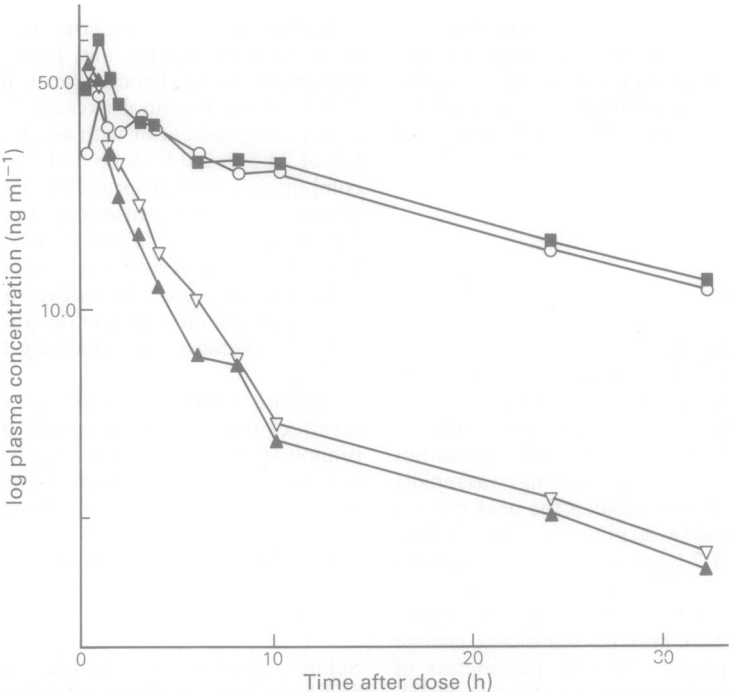

Figure 1 Plasma ketanserin and ketanserinol concentrations after 20 mg ketanserin alone and with 80 mg propranolol. Plasma ketanserin concentrations after ketanserin alone (▽) and with propranolol (▲); plasma ketanserinol concentrations after ketanserin alone (○) and with propranolol (■). Curves were obtained from mean data at each time point.

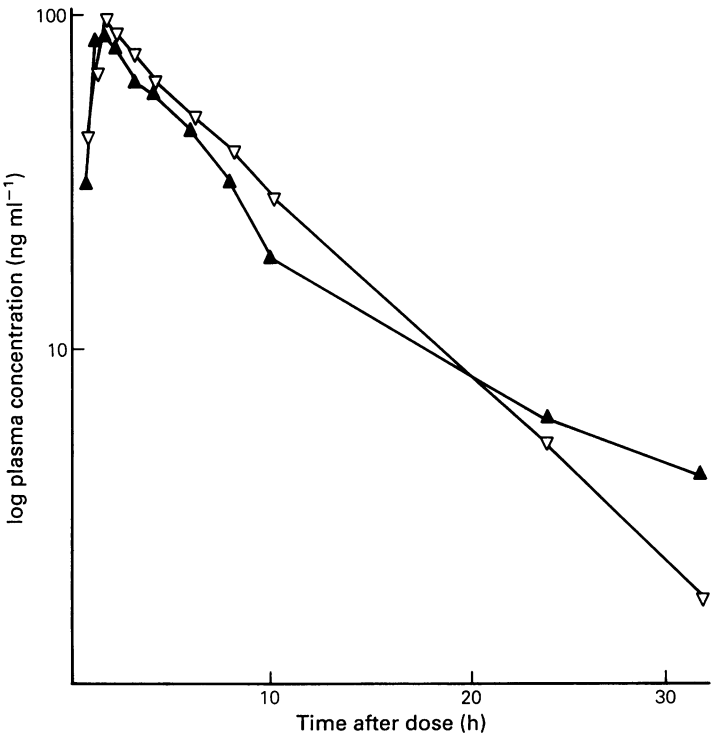

Figure 2 Mean plasma propranolol concentrations after 80 mg propranolol given alone (▲) and with 20 mg ketanserin (▽).

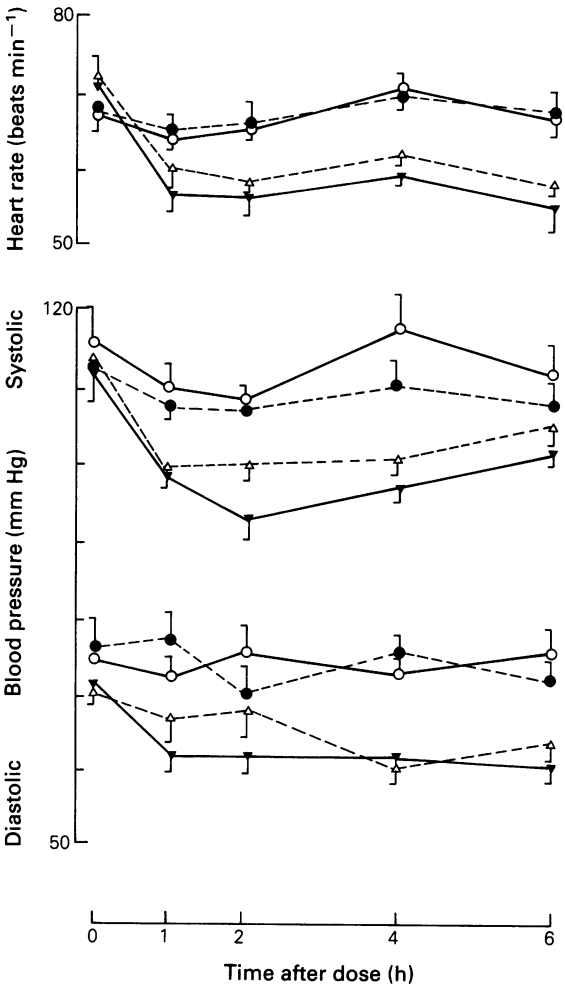

Figure 3 Comparison of the effects (mean ± s.e. mean) of 80 mg propranolol (△), 20 mg ketanserin (●), placebo (○) and propranolol plus ketanserin (▼) on supine heart rate, systolic and diastolic blood pressure.

variance between treatments and taking into account repeated measures with respect to time. Table 2 shows the probabilities, which were regarded as significant if less than 0.05. Ketanserin (20 mg) did not produce a significant reduction in supine blood pressure or heart rate when compared to placebo. Propranolol (80 mg) alone reduced supine heart rate, and systolic and diastolic blood pressure, but there was no significant interaction when the drugs were given in combination.

Ketanserin alone did not alter standing systolic blood pressure or heart rate, but significantly reduced standing diastolic pressure ($P < 0.05$). Ketanserin was without effect on heart rate and blood pressure after 3 min exercise at fixed work load, whereas propranolol significantly reduced the heart rate and blood pressure responses to exercise.

Adverse effects

The visual analogue scales did not reveal significant effects of any treatment on tiredness, breathlessness or well being. Four subjects complained of a dry mouth after propranolol alone, and two after propranolol plus ketanserin. Three subjects felt 'odd and detached' after ketanserin alone.

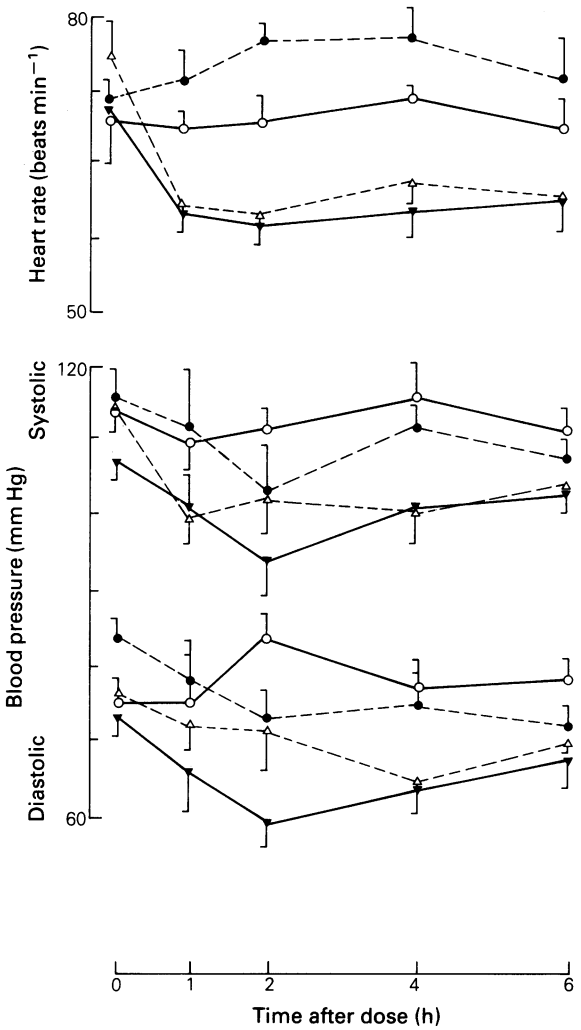

Figure 4 Comparison of the effects (mean ± s.e. mean) of 80 mg propranolol (△), 20 mg ketanserin (●), placebo (○) and propranolol plus ketanserin (▼), on standing heart rate, systolic and diastolic blood pressure.

Discussion

This study designed to investigate possible interactions between ketanserin and propranolol was carried out using single oral doses of drugs in healthy volunteers. In these subjects 20 mg ketanserin, a dose selected to avoid postural hypotension, had no effect on blood pressure or heart rate except standing diastolic blood pressure and this is similar to the effects observed in normotensive individuals by others (Fagard *et al.*, 1984). In the same subjects 80 mg propranolol produced the typical effects of a β-adrenoceptor antagonist on supine and standing heart rate and blood pressure both at rest and after exercise. There was no detectable interaction when ketanserin and propranolol were administered together in single doses; the effect of the combination being similar to the effects of propranolol alone.

This study has failed to detect any difference in ketanserin elimination profile when propranolol is coadministered to normotensive volunteers. A single dose of propranolol does

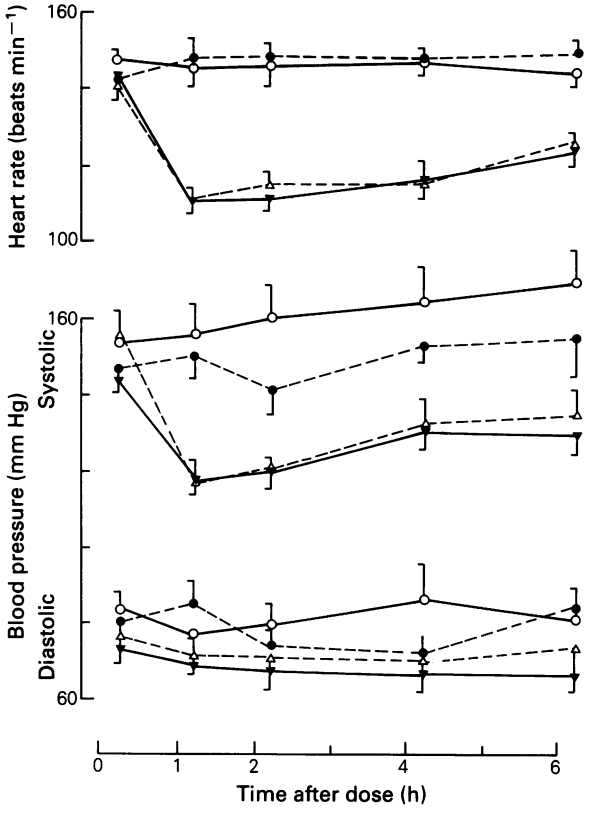

Figure 5 Comparison of the effects (mean ± s.e. mean) of 80 mg propranolol (△), 20 mg ketanserin (●), placebo (○) and propranolol plus placebo (▼) on exercise (3 min) heart rate, systolic blood pressure, diastolic blood pressure.

not therefore appear to inhibit significantly ketanserin reduction to ketanserinol nor ketanserin metabolism by liver monooxygenases.

Propranolol lowers cardiac output by 20–30% in man at rest and this is accompanied by a corresponding fall in hepatic blood flow (Trap-Jansen *et al.*, 1976). Although ketanserin is readily extracted by the liver as indicated by the 50% bioavailability after oral dosing compared to intravenous dosing, reduction in hepatic blood flow by propranolol did not affect the overall elimination of ketanserin or conversion to ketanserinol when propranolol and ketanserin were administered together in single doses.

Table 2 Analysis of variance of pharmacodynamic parameters

		Treatment effect		*Overall effect*		*Treatment interaction*
Parameter		*Ketanserin*	*Propranolol*	*Ketanserin*	*Propranolol*	*Ketanserin + Propranolol*
Supine	Systolic BP	NS	$P < 0.001$	NS	$P < 0.05$	NS
	Diastolic BP	NS	$P < 0.01$	$P < 0.05$	NS	NS
	Heart rate	NS	$P = 0.01$	NS	$P < 0.05$	NS
Standing	Systolic BP	NS	$P < 0.05$	NS	NS	NS
	Diastolic BP	$P < 0.05$	$P < 0.01$	NS	NS	NS
	Heart rate	NS	$P < 0.0001$	NS	NS	NS
Exercise	Systolic BP	NS	$P < 0.01$	NS	$P < 0.001$	NS
	Diastolic BP	NS	$P < 0.001$	NS	NS	NS
	Heart rate	NS	$P < 0.0001$	NS	$P < 0.001$	NS

All statistical values are compared to placebo
BP Blood pressure

Visual analogue scales failed to elicit any significant effects of propranolol or ketanserin on tiredness, breathlessness or wellbeing. The subjective side effects of ketanserin were no greater when coadminstered with propranolol—side effects after the first dose of ketanserin have previously been reported in normotensive volunteers (Amery *et al.*, 1985).

Therefore this study has failed to detect differences in ketanserin elimination or pharmacodynamic effects when a single dose of propranolol (80 mg) is coadministered with 20 mg ketanserin in healthy volunteers.

In patients with essential hypertension undergoing treatment with propranolol, the addition of ketanserin has been shown to produce a further reduction in blood pressure at plasma ketanserin levels similar to those observed in patients taking the latter drug alone (Hedner & Persson, 1985).

Plasma ketanserin and ketanserinol concentrations were measured by Dr G. Tucker, Department of Therapeutics, Sheffield. This study was supported by Janssen Pharmaceuticals. We are grateful to J. Simpson, Department of Medical Statistics for statistical assistance.

References

Avery, A., Fagard, R., Fiocchi, R., Lijnen, P., Staessen, J. & Vanhees, L. (1985). Ketanserin: a new hypotensive drug? *J. cardiovasc. Pharmac.*, **7**, Suppl. 7, S176–182.

Bax, N. D. S., Lennard, M. S., Al-Asady, S., Deacon, C. S., Tucker, G. T. & Woods, H. F. (1983). Inhibition of drug metabolism by beta adrenoceptor antagonists. *Drugs*, **25**, Suppl. 2, 121–126.

Elliot, H. L., McLean, K., Sumner, D. T., Meredith, P. A. & Reid, J. L. (1981). Immediate cardiovascular responses to oral prazosin—effect of concurrent beta blockers. *Clin. Pharmac. Ther.*, **29**, 303–309.

Fagard, R., Cattaert, A., Lijnen, P., Staessen, J., Vanhees, L., Moerman, E. & Amery, A. (1984). Responses of the systemic circulation and of the renin-angiotensin-aldosterone system to ketanserin at rest and exercise in normal man. *Clin. Sci.*, **66**, 17–25.

Hedner, T., Persson, B. & Berglund, G. (1983). Ketanserin, a novel 5-hydroxytryptamine antagonist: monotherapy in essential hypertension. *Br. J. clin. Pharmac.*, **16**, 121–125.

Hedner, T. & Persson, B. (1985). Antihypertensive properties of ketanserin in combination with beta-adrenergic blocking agents. *J. cardiovasc. Pharmac.*, **7**, Suppl. 7, S161–S163.

Lo, Man-Wai, Silber, B. & Riegelman, S. (1982). An automated HPLC method for the assay of propranolol and its basic metabolites in plasma and urine. *J. Chromatog. Sci.*, **20**, 126–131.

Meuldermaus, W., Henderick, J., Hurkmans, R., Swysen, E., Prinsen, P., Woestenborghs, R., Lauwers, W., Van Peer, A., De Cree, J. & Heykants, J. (1983). *Absorption, excretion and metabolism of ketanserin in volunteers after oral and intravenous administration*. Janssen Clinical Research Report.

Park, B. K. (1984). Prediction of metabolic drug interactions involving β-adrenoceptor blocking drugs. *Br. J. clin. Pharmac.*, **17**, 3S–11S.

Reimann, I. W. & Frölich, J. C. (1983). Mechanism of antihypertensive action of ketanserin in man. *Br. med. J.*, **287**, 381–383.

Trap-Jensen, J., Clausen, J. P., Noer, I., Larsen, O. A., Krogsgaard, A. R. & Christensen, N. J. (1976). The effects of beta-adrenoceptor blockers on cardiac output, liver blood flow and skeletal muscle blood flow in hypertensive patients. *Acta Physiol. Scand.*, **30** (Suppl. 440), 27.

Zoccali, C., Zabludowski, J. R., Isles, C. G., Murray, G. D., Inglis, G. C., Robertson, J. I. S., Fraser, R. & Ball, S. G. (1983). The effect of a 5-HT antagonist, ketanserin, on blood pressure, the renin-angiotensin system and sympatho-adrenal function in normal man. *Br. J. clin. Pharmac.*, **16**, 305–311.

(Received 18 July 1985, accepted 20 May 1986)