

## The antihypertensive efficacy of ketanserin in the elderly evaluated by ambulatory blood pressure measurement

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**Summary:** To assess the role of the serotonin antagonist ketanserin in the management of hypertension in the elderly, 12 patients with a mean age of 68 years (range 60–79 years) were treated with ketanserin in a randomised double-blind placebo-controlled cross-over trial. Clinic BP, ambulatory BP, renal function, and pharmacokinetics were assessed. The doses of ketanserin used were 40 mg (ten patients) and 20 mg (two patients) twice daily for 8 weeks. Mean clinic sitting BP was reduced from  $169 \pm 5/98 \pm 2$  on placebo to  $155 \pm 5/88 \pm 3$  mmHg ( $P < 0.05$ / $P < 0.05$ ) and standing pressure from  $168 \pm 6/100 \pm 3$  to  $157 \pm 5/91 \pm 3$  mmHg (NS/ $P < 0.01$ ). Mean ambulatory systolic BP was unaffected by active treatment ( $167 \pm 7$  vs  $164 \pm 5$ ) while diastolic pressure was lowered from  $99 \pm 2$  to  $94 \pm 2$  mmHg ( $P < 0.05$ ). This effect appeared to be mainly confined to the first two hours after drug administration. Renal blood flow was unaltered by treatment. The mean plasma half-life of ketanserin was  $20.9 \pm 5.5$  hours. Side effects were minimal.

In conclusion, while ketanserin may be effective as assessed in the clinic, its efficacy on ambulatory monitoring is substantially less impressive.

### Introduction

The results of both the European Working Party on High Blood Pressure in the Elderly study<sup>1</sup> and the Hypertension Trial in Elderly Patients in Primary Care<sup>2</sup> provide a rational basis for an assertive approach to the management of hypertension in patients aged over 60 years. While data from three major intervention studies support the view that thiazide diuretics are effective BP lowering agents in the elderly,<sup>3</sup> these drugs are associated with a decrease in glucose tolerance, an increase in serum uric acid and creatinine levels<sup>1</sup> and a lowering of glomerular filtration rate<sup>4</sup> in older hypertensive patients. Beta-adrenoceptor blocking drugs, though effective in the elderly,<sup>5</sup> may be contraindicated because of concomitant congestive heart

failure, peripheral vascular disease and chronic obstructive airways disease. Methyldopa causes central nervous system depression<sup>6,7</sup> and is not a suitable drug for many elderly patients.

Because hypertension in elderly patients is characterised in haemodynamic terms by a relatively high total peripheral resistance and a low cardiac output,<sup>8</sup> it would appear logical to use antihypertensive agents in this population to reduce vascular resistance without further lowering cardiac output. Agents acting this way which have been shown to be effective in the elderly include the calcium channel blockers and the angiotensin converting enzyme (ACE) inhibitors.<sup>9–11</sup> The selective  $S_2$ -serotonergic receptor antagonist, ketanserin,<sup>12</sup> which lowers BP mainly by reducing peripheral resistance, while causing a small and transient rise in heart rate and cardiac output<sup>13,14</sup> with an increase in renal blood flow<sup>14</sup> without metabolic disturbance<sup>15,16</sup> seems an attractive choice in the elderly.

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Clinical experience with ketanserin in young and middle-aged patients is sizable.<sup>17,18</sup> Also, the acute antihypertensive effect of ketanserin administered intravenously has been shown to increase with age.<sup>19</sup> Moreover, an age-related increase in diastolic blood pressure (DBP) response rate with ketanserin has been observed.<sup>20</sup> However, there is only one published randomised placebo-controlled study of the antihypertensive efficacy of this drug in the elderly.<sup>21</sup> The present study addresses this issue as well as assessing the duration of antihypertensive effect using ambulatory BP measurement. In addition, the effects of ketanserin on renal haemodynamics and some aspects of the pharmacokinetics of the drug in this population were studied.

#### Patients and methods

Twelve patients (seven females, mean age 68 years, range 60–79 years) with clinic BP greater than 160/90 mmHg entered the study. Patients with BP greater than 240/120 mmHg, secondary hypertension, cardiac conduction defects including sinus bradycardia (< 50 beats per minute), liver impairment (any liver enzyme greater than twice normal) or serum creatinine greater than 220 µmol/l were excluded. The study protocol was approved by the Hospital Ethics Committee and informed consent was obtained.

#### Study design

Five patients on diuretic therapy for hypertension (four were on a second agent – three on a beta-blocking drug and one on rauwolfia, one patient was on a third agent – hydralazine) had these medications discontinued over the first two weeks of a three-week run-in placebo phase. Those whose sitting BP remained within the limits 160–220/90–120 mmHg at the end of the run-in phase entered an open titration phase during which the dose of ketanserin was 20 mg twice daily, taken at 0900 and 1800 hours for four weeks, increasing to 40 mg twice daily for the fifth week if sitting clinic BP was greater than 160/90 mmHg.

A randomised double-blind placebo-controlled cross over phase followed using the dose of ketanserin as indicated on titration. During this phase patients were seen after one, two, five and eight weeks in each eight week placebo and treatment period for measurement of clinic BP, heart rate and weight, and documentation of side effects. Ambulatory BP measurement and renal studies were carried out at the end of each treatment period in the double-blind phase.

#### Methods

Clinic BP was measured with the Hawksley random zero sphygmomanometer, Korotkov phase V being taken for diastolic pressure. BP and heart rate recordings were made with the patient sitting after ten minutes' rest and after one minute standing, with the arm supported at heart level.<sup>22</sup> The mean of three readings taken at 1–2 minute intervals was used.

Ambulatory BP and heart rate were measured non invasively at half-hourly intervals using a semi-automated portable recorder, the Remler M2000 (Remler Corp., San Francisco, C.A.).<sup>23</sup> The Remler was operated by the patient from 0900 to 2200 hours. On the day of the ambulatory BP study the patients' medication was administered by a nurse. All Remler tapes were decoded by one operator.

Renal blood flow was estimated using plasma clearance of intravenously injected <sup>125</sup>I hippuran as described elsewhere.<sup>9</sup> Serum creatinine levels were measured using a standard laboratory technique.

The pharmacokinetics of ketanserin and its metabolite ketanserin-ol were studied at the end of the titration phase from blood samples taken before and at intervals after the last dose (30 minutes, 1, 2, 4, 6, 12, 24, 32, and 48 hours). Plasma samples were stored at –20°C prior to assay by high-performance liquid chromatography.<sup>24</sup> The elimination half-lives of ketanserin and ketanserin-ol were calculated from the slope of the line derived by linear least squares regression analysis of the terminal part of the log concentration time curve; the area under the plasma concentration time-curve was calculated by the trapezoidal rule. The values for ketanserin-ol half-life are apparent values as they probably overestimate the elimination half-life due to continuing formation of ketanserin-ol from ketanserin.

Side effects were assessed by asking the patient to report any symptoms experienced during treatment.

Ambulatory BP data were analysed using a computer programme designed to pair half-hourly readings on ketanserin with readings for the same time of day on placebo. Unpaired data were omitted. Mean ambulatory BP was calculated using the mean of each patient's day-time readings on ketanserin and placebo. Student's paired *t*-test was used for all comparisons and the influence of treatment, order and interaction effects were determined by the method appropriate for cross-over trials suggested by Hills and Armitage.<sup>25</sup> It was calculated using the power calculation of Hills and Armitage<sup>25</sup> that nine patients would be required to detect the expected fall in ambulatory BP of

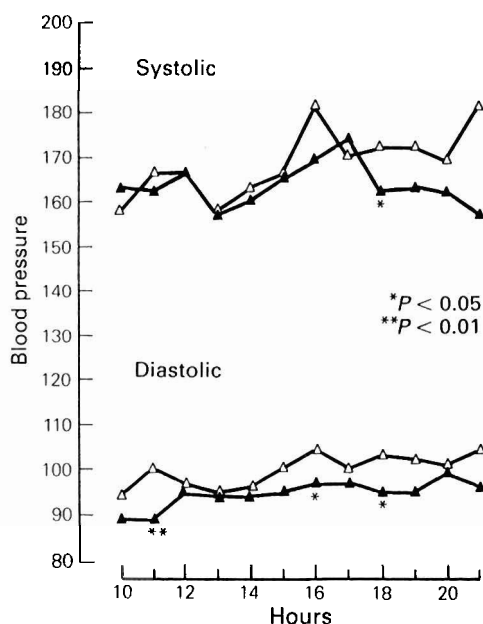
10/5 mmHg. A probability value of less than 5% was taken to be significant.

**Results**

All 12 patients completed the study. Mean sitting BP at the end of the three-week run-in phase on placebo was  $174 \pm 4/101 \pm 2$  mmHg. The doses of ketanserin used were 20 mg twice daily (in two patients) for eight weeks and 40 mg twice daily (in ten patients) for seven weeks. The mean ( $\pm$  SD) number of paired ambulatory BP readings per patient was  $14.5 \pm 3.7$ .

Ketanserin reduced clinic sitting and standing BP to a similar extent (Table I) although the difference between placebo and active treatment was not statistically significant for standing systolic pressure (SBP). Mean sitting DBP after treatment was reduced to 90 mmHg or less in only five patients (42%) and SBP to 160 mmHg or less in eight patients (67%). The correlation between entry BP and response to treatment was not significant. For standing BP the corresponding values were four and nine patients for DBP and SBP respectively. Heart rate and weight were not significantly affected with treatment.

Mean ambulatory DBP (Figure 1) was reduced with active treatment from 98.7 to 94.1 mmHg (treatment difference, 4.6 mmHg; 95% confidence interval, 0.8:8.4;  $P < 0.05$ ) with the effect being greatest at 1100 hours. However, there was no significant reduction in mean ambulatory SBP on active treatment (from 166.7 to 164.3 mmHg; treatment difference, 2.5 mmHg; 95% confidence



**Figure 1** Curves derived from the means of hourly values of ambulatory systolic and diastolic blood pressures on placebo ( $\Delta$ ) and ketanserin ( $\blacktriangle$ ) after eight weeks' treatment ( $n = 12$ ).

interval, -6.2:11.2). There were no order or interaction effects.

Renal blood flow on placebo was  $608.8 \pm 47.0$  ml/minute and on active treatment  $607 \pm 58.4$  ml/minute. Similarly plasma creatinine levels were unchanged ( $87.2 \pm 6.4$  vs.  $88.2 \pm 5.9$   $\mu\text{mol/l}$ ).

**Table I** Clinic blood pressure, heart rate and weight on placebo or ketanserin

	Placebo	Ketanserin	Treatment difference	95% Confidence interval	Significance
Sitting BP, mmHg					
Systolic	$169.2 \pm 4.8$	$155.4 \pm 5.4$	$13.8 \pm 5.7$	1.1:26.4	$P < 0.05$
Diastolic	$98.0 \pm 1.9$	$87.8 \pm 3.3$	$10.2 \pm 3.7$	1.9:18.4	$P < 0.05$
Standing BP, mmHg					
Systolic	$168.2 \pm 5.5$	$157.4 \pm 4.6$	$10.8 \pm 6.1$	-2.8:27.3	NS
Diastolic	$100.4 \pm 2.7$	$91.2 \pm 2.5$	$9.2 \pm 2.2$	4.4:14.1	$P < 0.01$
Heart rate, beats/min					
Sitting	$78.6 \pm 3.0$	$75.2 \pm 2.5$	$3.4 \pm 2.4$	-1.9: 8.7	NS
Standing	$79.2 \pm 3.7$	$76.3 \pm 3.6$	$2.8 \pm 3.2$	-4.3: 9.9	NS
Weight, Kg	$73.2 \pm 3.6$	$75.6 \pm 3.6$	$-2.4 \pm 2.0$	-6.9: 2.2	NS

Dose of ketanserin was 20 mg twice daily in two patients and 40 mg twice daily in ten patients. Values are mean  $\pm$  SEM;  $n = 12$ .

Table II summarises the pharmacokinetic findings. The mean ( $\pm$  SD) elimination half-life for ketanserin was  $20.9 \pm 5.5$  hours. Pre-dose and maximum post-dose concentrations ( $C_{\max}$ ) of ketanserin increased with increasing doses of the drug. Times to  $C_{\max}$  did not differ substantially between doses. Data for ketanserin-ol were similar in trend.

**Table II** Ketanserin and ketanserin-ol pharmacokinetics

Parameter	Ketanserin	Ketanserin-ol
$t_{1/2}$ B, hr	$20.8 \pm 6.0$	$22.9 \pm 5.7$
AUC 0–12 ng/ml/hr	$753.0 \pm 260.0$	$2723.0 \pm 840.9$
$C_{\min}$ ng/ml	$33.4 \pm 17.9$	$180.5 \pm 52.0$
$C_{\max}$ ng/ml	$123.0 \pm 38.1$	$324.4 \pm 121.9$
$t_{\max}$ hr	$2.2 \pm 1.4$	$2.8 \pm 1.3$

Data are mean  $\pm$  SD; Dose of ketanserin, 40 mg twice daily;  $n = 10$ ;  $t_{1/2}$  B = elimination half-life; AUC 0–12 = area under plasma concentration-time curve during a dosing interval;  $C_{\min}$  = pre-dose drug plasma concentration;  $C_{\max}$  = peak drug plasma concentration;  $t_{\max}$  = time to  $C_{\max}$ .

Side effects in the open titration phase included headache (3 patients), insomnia (2 patients), lightheadedness (1), facial flushing (1) and gastric fullness (1). Patients on ketanserin in the double-blind phase complained of dizziness (2), lightheadedness (1), headache (1), insomnia (1), irritability (1) and constipation (1). There were complaints of fatigue (1), paraesthesiae (1), unsteady gait (1) and headache (1) on placebo in the double-blind phase. Side effects were transient and did not necessitate stopping therapy.

## Discussion

The present study shows that while ketanserin as monotherapy was effective in reducing clinic DBP, the effect on SBP, especially in the standing position, was less impressive. These findings are in agreement with most other placebo-controlled studies<sup>26–31</sup> in younger patients where BP was measured in the standing position, though Amery and colleagues found a significant fall in both standing SBP and DBP.<sup>32</sup> Similarly, in a randomised placebo-controlled study of ketanserin in elderly hypertensive patients only the reduction in DBP was significant.<sup>21</sup>

The lack of effect on SBP with ambulatory

measurement is possibly due to the fact that these measurements were made during normal daily activity when the patients were in the upright position for much of the time. The fact that SBP was unaffected by active treatment from 1000 until 1800 hours (Figure 1), a time when patients were likely to be in the upright position and ambulant, tends to confirm this observation. In an intra-arterial ambulatory BP assessment carried out in 18 patients by Woittiez and colleagues,<sup>28</sup> mean 24 hour SBPs and DBPs were reduced compared to placebo. However, hourly means for SBP were not significantly reduced on active treatment when patients were more likely to be in the upright position and ambulant, namely from 0600 to 2000 hours.

From the ambulatory data in the present study it is evident that ketanserin had its maximal effects on DBP at 1100 hours (Figure 1), two hours after the morning dose was administered by the nurse who fitted the BP recorder. It is of interest to note that in the study in which clinic standing SBP was significantly reduced, the measurements were taken two hours after the morning dose.<sup>32</sup> Clinic measurement was carried out between 1000 and 1200 hours in the present study, and if only these measurements had been relied upon to assess drug efficacy, ketanserin would have been adjudged an effective BP lowering agent. These findings further emphasise the importance of performing ambulatory BP measurement in efficacy studies of anti-hypertensive drugs.<sup>33</sup>

Renal blood flow was unchanged on treatment with ketanserin in keeping with the findings of a similar study of slightly younger patients (mean age 57 years)<sup>31</sup> but in contrast to an intravenous study in younger patients where renal blood flow was increased.<sup>14</sup> It is possible that nephrosclerosis, which is commoner in older hypertensive patients,<sup>8</sup> attenuates possible effects of ketanserin on renal vascular tone. Although the number of patients observed in the present study was small, the maintenance of renal function in the face of a fall in DBP with ketanserin in elderly hypertensive patients who might be expected to have decreased renal perfusion<sup>34,35</sup> is reassuring.

The elimination half-life for ketanserin of 20.9 hours is longer than that of 14.3 hours reported in similar studies of younger patients.<sup>36</sup> During chronic oral treatment, steady-state levels for the 40 mg twice daily dosing regimen fluctuate between 40 ng/ml (pre-dose drug plasma concentration) and 100 to 140 ng/ml (peak drug plasma concentration) within two hours of dosing<sup>36</sup> which are similar to our findings.

In conclusion these findings suggest that while ketanserin may be effective as monotherapy as

assessed in the clinic, its efficacy, by ambulatory BP monitoring in the elderly group of patients studied, is substantially less impressive. On the basis of the evidence from the present study, this drug cannot be recommended as monotherapy in elderly hypertension.

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