Chronic Effect of Ketanserin in Mild to Moderate Essential Hypertension

Arend J.J. Woitiez, Gert J. Wenting, Anton H. van den Meiracker,
Henk J. Ritsema van Eck, Arie J. Man in 't Veld, Frans A. Zantvoort,
and Maarten A.D.H. Schalekamp

SUMMARY Ketanserin, an antagonist highly selective for 5-hydroxytryptamine (serotonin) type 2 (S₂) receptors, was given as monotherapy in a dose of 40 mg b.i.d. to 24 subjects with mild to moderate essential hypertension. Its effects were evaluated in a placebo-controlled double-blind crossover study. The effect on blood pressure in 18 subjects was monitored by 24-hour ambulatory intra-arterial measurements. Systolic and diastolic intra-arterial pressures were significantly lowered by ketanserin both during the day and at night, whereas heart rate was unchanged. Cuff pressure readings (triplicate measurements) with the London School of Hygiene sphygmanomoneter and an automatic device (12 measurements in 1 hour) in the outpatient clinic also showed a significant effect on both supine and standing pressures. No postural hypotension was noted. Ketanserin had no effect on endogenous creatinine clearance, serum cholesterol levels, and the plasma levels of norepinephrine, renin, and aldosterone. The only side effect that was significantly more common with ketanserin than with placebo treatment was an increase in body weight. Ketanserin may have a place in the treatment of mild to moderate essential hypertension. (Hypertension 8: 167–173, 1986)

KEY WORDS • serotonin • blood pressure • ketanserin • ambulatory monitoring

SEROTONIN has been implicated in the regulation of blood pressure and pathogenesis of hypertension for more than 2 decades, but its role is still controversial. Although central serotoninergic neurons are likely to be involved in blood pressure control, surgical and pharmacological manipulations of these central serotoninergic pathways have produced conflicting results. The effect of intravenously administered serotonin on blood pressure is also notoriously variable because activation of vascular serotoninergic receptors can elicit constriction, dilatation, or a biphasic response, depending on the type of blood vessel, its anatomical location, the animal species, and the concentration of the monoamine. The vascular response is also dependent on sympathetic tone. Radioligand binding studies on brain tissue have led to a subdivision of S₁ and S₂-serotonergic receptors. A vascular S₂-receptor has been shown to mediate serotonin-induced constriction. This receptor also appears to be involved in the so-called amplifying effect of serotonin on the pressor responses to norepinephrine and angiotensin II. Ketanserin, a serotonin antagonist that is highly selective for S₂-receptors, is now available for clinical research. Herein, we report on a double-blind placebo-controlled crossover study of the blood pressure lowering effect of ketanserin in 24 subjects with mild to moderate essential hypertension. In 18 of these subjects, the effect was evaluated by 24-hour ambulatory intra-arterial monitoring of blood pressure.

Subjects and Methods

Trial Design

The study comprised 17 men and 7 women, aged 50 ± 3 years (mean ± SEM; range, 24–69 years). A diagnosis of essential hypertension was made after routine screening, which included isotope renography. Antihypertensive treatment, if any, was tapered off 3 weeks before the study began and was replaced by placebo. Hypertension was defined as a cuff measurement of blood pressure in excess of 95 mm Hg diastolic on two or more consecutive visits to the outpatient clinic. After a single-blind placebo run-in period of 4 weeks, the subjects were randomly allocated to receive either placebo or 40 mg of ketanserin...
at 0800 and 1800 for 8 weeks, followed by an identical crossover period. The randomization schedule was kept in the hospital pharmacy, and unmarked formulations were provided by Janssen Pharmaceutica (Beerse, Belgium). Neither the investigator nor the subjects were aware of who was receiving the assigned drug.

Throughout the study the subjects were seen in the outpatient clinic at 2-week intervals between 0900 and 1100. Side effects, both volunteered and elicited by direct questioning, were recorded, and compliance was checked by tablet counting. In the last week of the two treatment periods ambulatory blood pressure was monitored by 24-hour continuous intra-arterial measurement. The recordings were taken while the subjects were hospitalized, which allowed their environmental and living conditions to be relatively well standardized, particularly with regard to physical activity, timing of meals, afternoon nap, and night rest. Apart from these periods, the subjects were free to move around. During the hospital stay, blood was taken, with the subjects in the supine position, 1 to 2 hours after the morning dose of placebo or ketanserin for biochemical determinations, including plasma levels of ketanserin and hormones.

The protocol was approved by the Hospital Ethical Review Committee. Informed consent was obtained from all subjects.

**Blood Pressure Measurements**

Office readings were made at each visit to the outpatient clinic, with the London School of Hygiene sphygmomanometer. Blood pressure was also recorded for 1 hour in each subject with an automatic device (Accutorr TM1, Datascope, Paramus, NJ, USA). Direct 24-hour intra-arterial ambulatory recordings, using the Oxford system, were made in 18 of the 24 subjects.

Measurements with the London School of Hygiene sphygmomanometer were made after 5 minutes of supine rest. Korotkoff phase V was taken as diastolic pressure. Readings were taken at 1-minute intervals, and the arithmetic mean of three measurements was recorded. Measurements were repeated with the subject in the upright position. Pulse rate was counted for 30 seconds in both positions. Mean arterial pressure was calculated as diastolic pressure plus one third of the pulse pressure.

The Accutorr noninvasive blood pressure monitor has been designed for measuring systolic, mean, and diastolic pressure according to the oscillometric method. The microprocessor computes the displayed variables as follows. The systolic pressure is the preset cuff pressure at which the pressure oscillations begin to increase in amplitude during deflation. The mean pressure is the lowest preset cuff pressure at which the oscillations are maximal. The diastolic pressure is the preset cuff pressure at which the oscillations stop decreasing in amplitude. Twelve consecutive measurements were made at 5-minute intervals with the subject in the supine position. The accuracy of the Accutorr was assessed by comparison with direct intra-arterial measurement. Results are shown in Figure 1. In the pressure range tested, the Accutorr slightly underestimated intra-arterial systolic pressure; the mean difference was 7.5 mm Hg (SD = 7.1). The Accutorr-measured diastolic pressure was consistently higher than the intra-arterial value; the mean difference was 11.7 mm Hg (SD = 6.6). These results are comparable with data obtained with the Dinamap oscillometric device.

![Figure 1](http://hyper.ahajournals.org/)

**Figure 1.** Comparison between blood pressures simultaneously determined by Accutorr and intra-arterial measurement in 24 subjects. Data were analyzed by linear regression; for systolic pressure: $y = 0.98x - 4.77$, $r = 0.95$, $p < 0.01$; for diastolic pressure: $y = 1.04x + 9.14$, $r = 0.92$, $p < 0.01$. 

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**Figure 1**

**Comparison between blood pressures simultaneously determined by Accutorr and intra-arterial measurement in 24 subjects. Data were analyzed by linear regression; for systolic pressure: $y = 0.98x - 4.77$, $r = 0.95$, $p < 0.01$; for diastolic pressure: $y = 1.04x + 9.14$, $r = 0.92$, $p < 0.01$.**
Reproducibility of blood pressure readings obtained with the Accutorr at weekly intervals was assessed by comparing pressures obtained during Weeks 7 and 8 of placebo treatment. The correlation coefficient (linear regression) for 12 consecutive measurements of systolic pressure in individual subjects ranged from an $r$ value of 0.78 to 0.92 (mean, 0.84; SEM = 0.02; $n = 24$; $p < 0.01$). The correlation coefficient for 12 consecutive measurements of diastolic pressure ranged from an $r$ value of 0.64 to 0.78 (mean, 0.72; SEM = 0.03; $n = 24$; $p < 0.01$).

The Oxford system was used for continuous intraarterial ambulatory blood pressure monitoring. Its accuracy and the reproducibility of 24-hour blood pressure profiles have been reported by others. Briefly, a small (1-mm diameter) catheter (Seldicath, Plastimed, Saint-Leu-La Foret, France) was inserted into the nondominant brachial artery after local anesthesia with 2% lidocaine solution and connected to a transducer-perfusion unit suspended in front of the subject's chest. Signals from the transducer and from two thoracic electrocardiographic electrodes were registered on a portable minicassette tape recorder (Medilog 2, Oxford Instruments, Oxford, UK). Calibration was performed before and after registration. The analogue pressure signal was digitized with a sample frequency of 33½ samples per second of real time and fed into a Hewlett-Packard 2113-E computer (Palo Alto, CA, USA). A computer-based program was used to preprocess the signal, which was scrutinized for beat loss, damping, clipping, and movement artifacts, but the final editing of distorted tracings was done after visual inspection. For each 24-hour tracing, the number of beats that had to be excluded from the final analysis was less than 10% of the total. The computer determined systolic, mean, and diastolic pressure and pulse interval and stored this information for each beat. Blood pressure and heart rate obtained during placebo and with ketanserin treatment were examined in two ways: as hourly means and as 6-hour means.

Blood Chemistry

The plasma levels of active renin (normal range, 6–52 µU/ml, unrestricted sodium intake) and aldosterone (normal range, 40–180 pg/ml) were measured by radioimmunoassay. Plasma norepinephrine (normal range, 150–400 pg/ml) was measured by a radioenzymatic technique. The plasma level of ketanserin was measured by high-performance liquid chromatography.

Statistical Analysis

Data are given as means ± SEM. Mean values of renin were calculated after logarithmic transformation. Treatment-order interactions were tested by analysis of variance. The differences between placebo and ketanserin therapy were assessed by the two-tailed paired Student’s $t$ test. Chi-square test was used for calculating differences in the number of subjects having side effects and in the number of subjects who responded to treatment. Subjects, in whom supine diastolic pressure, as measured by the London School of Hygiene sphygmonanometer, fell by more than 10% after 8 weeks of treatment from the last measurement in the placebo run-in period were considered to be responders.

Results

The study began with 29 subjects. During the run-in phase, three subjects appeared to be normotensive and one had to be withdrawn because of concomitant disease (sarcoidosis). Six weeks after randomization one patient withdrew because she moved to another city. Of the remaining 24 subjects, 11 were first treated with ketanserin and 13 were first treated with placebo. Both groups were reasonably matched for blood pressure and age (Table 1).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ketanserin to Placebo</th>
<th>Placebo to Ketanserin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Men/women</td>
<td>6/5</td>
<td>10/3*</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>48 (33–63)</td>
<td>51 (24–69)</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)†</td>
<td>161 ± 10/104 ± 5</td>
<td>174 ± 6/109 ± 4</td>
</tr>
<tr>
<td>Duration of hypertension (mo)</td>
<td>61 (20–200)</td>
<td>74 (15–200)</td>
</tr>
<tr>
<td>Weight (kg)†</td>
<td>72.4 ± 3.1</td>
<td>75.3 ± 2.8</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)†</td>
<td>0.94 ± 0.04</td>
<td>1.08 ± 0.07</td>
</tr>
</tbody>
</table>

Range is given in parentheses. $^*p < 0.05$, compared with ketanserin-to-placebo value. $^†$Values are means ± SEM.

<table>
<thead>
<tr>
<th>Blood Pressure</th>
</tr>
</thead>
</table>
| As shown in Figure 2, supine systolic and diastolic cuff pressures, as measured with the London School of Hygiene sphygmonanometer, were significantly reduced by ketanserin treatment in both groups. Similar results were obtained for standing blood pressures measured with the London School of Hygiene sphygmonanometer and for supine 1-hour blood pressure measurements obtained with the automatic device, Accutorr. Since a significant carryover effect of ketanserin was observed in the first 2 weeks after switching to placebo, the data obtained from the two groups after more than 2 weeks are combined in Table 2. Based on the criterion described in Methods, 11 subjects (46%) were considered to be responders to ketanserin, whereas three subjects (12%) responded to placebo ($p < 0.05$). Ketanserin had no effect on heart rate. None of the subjects showed a more than 10 mm Hg drop in systolic or diastolic pressure on standing. Eighteen subjects (3 women), aged 49 ± 3 years, were studied by using continuous 24-hour intra-arterial measurement of pressure. Ketanserin lowered systolic pressure, as measured by the London School of Hygiene sphygmonanometer, fell by more than 10% after 8 weeks of treatment from the last measurement in the placebo run-in period were considered to be responders.
and diastolic pressure both at night and during the day (Figure 3, opposite). The effect on intra-arterial pressure in the late morning was comparable to the effect on cuff pressure measured at about the same time of day in the outpatient clinic (Tables 2 and 3). The blood pressure patterns in our subjects showed a dip between 1300 and 1500 that corresponded with the time of the afternoon nap.

**Humoral and Biochemical Parameters**

Ketanserin had no effect on the serum levels of urea, uric acid, and cholesterol. Endogenous creatinine clearance and the plasma levels of norepinephrine, renin, and aldosterone were unchanged (Table 4). Sodium excretion on the day that blood samples for hormone measurements were taken was 133 ± 13 mEq/24 hr during placebo treatment and 144 ± 15 mEq/24 hr during ketanserin treatment; the difference was not statistically significant. The values for serum electrolytes, bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, glutamic-oxaloacetic transaminase and lactate dehydrogenase, and white blood cell and platelet counts were also unchanged.

**Table 3. Effect of Ketanserin on Ambulatory Intra-arterial Pressure in 18 Subjects**

<table>
<thead>
<tr>
<th>Blood pressure (mm Hg)</th>
<th>Time of day</th>
<th>Placebo</th>
<th>Ketanserin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td>0600-1200</td>
<td>149 ± 2</td>
<td>145 ± 3*</td>
</tr>
<tr>
<td></td>
<td>1200-1800</td>
<td>153 ± 3</td>
<td>150 ± 2</td>
</tr>
<tr>
<td></td>
<td>1800-2400</td>
<td>155 ± 3</td>
<td>145 ± 3†</td>
</tr>
<tr>
<td></td>
<td>06000-0600</td>
<td>132 ± 1</td>
<td>123 ± 2†</td>
</tr>
<tr>
<td>Diastolic</td>
<td>0600-1200</td>
<td>98 ± 2</td>
<td>91 ± 2†</td>
</tr>
<tr>
<td></td>
<td>1200-1800</td>
<td>99 ± 2</td>
<td>94 ± 1†</td>
</tr>
<tr>
<td></td>
<td>1800-2400</td>
<td>99 ± 3</td>
<td>90 ± 2†</td>
</tr>
<tr>
<td></td>
<td>0600-0600</td>
<td>81 ± 1</td>
<td>75 ± 1†</td>
</tr>
</tbody>
</table>

Values are means ± SEM. *p < 0.05, †p < 0.01, ‡p < 0.001, compared with placebo value.

**Table 2. Effect of Ketanserin on Cuff Blood Pressure in 24 Subjects**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Run in (4 wk)</th>
<th>Placebo</th>
<th>Ketanserin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 wk</td>
<td>6 wk</td>
<td>8 wk</td>
</tr>
<tr>
<td>LSH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>168 ± 5</td>
<td>164 ± 6</td>
<td>162 ± 5</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>107 ± 3</td>
<td>104 ± 3</td>
<td>101 ± 2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>72 ± 2</td>
<td>74 ± 2</td>
<td>71 ± 2</td>
</tr>
<tr>
<td>Standing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>160 ± 5</td>
<td>160 ± 5</td>
<td>156 ± 5</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>109 ± 3</td>
<td>107 ± 4</td>
<td>104 ± 3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>82 ± 2</td>
<td>81 ± 2</td>
<td>81 ± 2</td>
</tr>
<tr>
<td>Accutorr (1-hr measurement)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>149 ± 4</td>
<td>152 ± 4</td>
<td>152 ± 4</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>101 ± 3</td>
<td>102 ± 3</td>
<td>100 ± 2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>74 ± 2</td>
<td>74 ± 2</td>
<td>73 ± 2</td>
</tr>
</tbody>
</table>

Values are means ± SEM. LSH = London School of Hygiene sphygmomanometer; BP = blood pressure. *p < 0.05, †p < 0.01, ‡p < 0.001, as compared with 8-week placebo value.
KETANSERIN AND 24-HOUR BLOOD PRESSURE/ Woittiez et al.

Subject Compliance and Side Effects

Subject compliance was excellent. Less than 5% of the tablets to be taken were returned. Also, the plasma level of ketanserin was 71.9 ± 7.1 ng/ml, which is in the upper therapeutic range.\(^15,16\) Ketanserin caused an increase in body weight, and this effect was sustained for the full 8 weeks of treatment (see Table 4). Drowsiness was reported by 50% of the subjects at some time during the active treatment period and by 25% of the subjects receiving placebo (Figure 4). The difference was not statistically significant. Other side effects also were not significantly more common with ketanserin than with placebo treatment.

Discussion

Long-term oral treatment with ketanserin, 40 mg b.i.d., significantly reduced blood pressure. Intra-arterial 24-hour measurements showed a 5% fall in mean arterial pressure as compared with results of placebo treatment. Since these measurements were made in the hospital, they might not have been representative for daily practice; however, the effect on intra-arterial pressure in the hospital was comparable to the effect on the office cuff pressure readings (see Tables 2 and 3).

A reduction of approximately 10% in cuff pressure has been reported in a double-blind placebo-controlled study of 10 patients using ketanserin, 20 mg t.i.d.,\(^16\) in a similar study of 8 patients using ketanserin, 40 mg b.i.d.,\(^17\) in a dose-finding study of 16 patients using ketanserin in an average daily dosage of 91 mg,\(^18\) and in a single-blind study of 13 patients receiving 40 mg once daily and 12 patients receiving 40 mg b.i.d.\(^19\) A somewhat lower pressure reduction has been observed in a double-blind placebo-controlled crossover study of 14 patients receiving ketanserin, 40 mg t.i.d.; systolic and diastolic pressures fell by 6%,\(^20\) which agrees with our findings. We chose a dosage of 40 mg b.i.d. because the terminal plasma half-life of ketanserin has been reported to be approximately 10 hours.\(^16\) Although this fixed dose may not have been optimal in all subjects, the continuous blood pressure measurements showed an effect that lasted for a large proportion of the 24-hour period, if not for the full period.

About half of the subjects receiving ketanserin showed a more than 10% decrease in diastolic pressure

| Table 4. Effect of Ketanserin on Body Weight, Biochemical Variables, and Renal Function in 24 Subjects |
|-------------------------------------------------|----------------------------------|---------------------------------|----------------------------------|
| Variable                                        | Run in (4 wk)                   | Placebo (8 wk)                  | Ketanserin (8 wk)                |
| Weight (kg)                                     | 76.8 ± 2.3                      | 76.7 ± 2.4                      | 78.0 ± 2.4*                     |
| Plasma                                          |                                 |                                 |                                 |
| Norepinephrine (pg/ml)                          | 340 ± 34                        | 284 ± 25                        | 314 ± 23                        |
| Renin (µU/ml)                                   | 10.5 (8.9–12.4)                 | 9.8 (8.2–11.6)                  | 9.2 (7.8–10.8)                  |
| Aldosterone (pg/ml)                             | 115 ± 11                        | 110 ± 16                        | 103 ± 13                        |
| Ketanserin (ng/ml)                              | 0                               | 0                               | 71.9 ± 13                       |
| Serum                                           |                                 |                                 |                                 |
| Urea (mg/dl)                                    | 31.8 ± 1.8                      | 33.0 ± 2.4                      | 32.4 ± 1.8                      |
| Uric acid (mg/dl)                               | 6.0 ± 0.3                       | 6.0 ± 0.3                       | 5.9 ± 0.3                       |
| Cholesterol (mg/dl)                             | 205 ± 8                         | 213 ± 8                         | 205 ± 12                        |
| Endogenous creatinine clearance (ml/min)        | 136 ± 14                        | 112 ± 13                        | 118 ± 17                        |

Values are means ± SEM. Range is given in parentheses. *p < 0.01, compared with placebo value.
as compared with the pressure at the end of the placebo run-in period. A similar response rate has been observed with thiazide diuretic or β-adrenergic receptor antagonist treatment. In our series, the responders could not be distinguished from the nonresponders with respect to age or initial blood pressure.

Ketanserin did not modify the circadian blood pressure pattern, since the blood pressure lowering action of the drug was at least as strong during the night as during the day. It is difficult to draw conclusions from these observations as to ketanserin's mechanism of action. Various drugs, such as diuretics, β-adrenergic antagonists, α1-adrenergic receptor antagonists, and calcium entry blockers, have also been found to exert little influence on the circadian blood pressure variations.

Heart rate and plasma norepinephrine levels were not altered by ketanserin, and these findings certainly contrast with the reduction in these parameters that occurs during treatment with a centrally acting drug, such as clonidine. Animal experiments, in which ketanserin was injected into the cerebral ventricles, have provided evidence that the drug does not lower blood pressure by a central action.

Previous studies have shown that the fall in blood pressure after an intravenous injection of 10 mg of ketanserin is associated with a small and transient rise in heart rate and plasma norepinephrine levels. No such changes were observed in the present study, possibly because the effect on blood pressure was more gradual, thereby allowing the baroreflex to be reset.

The pharmacological evidence now available indicates that ketanserin selectively antagonizes the S2-mediated peripheral pressor action of serotonin but is not fully specific for S2-receptors. It also has some affinity for α2-adrenergic receptors. Intravenous ketanserin, however, appears to be capable of lowering blood pressure in hypertensive subjects independently of α2-adrenergic receptor blockade. Steady state plasma levels of ketanserin in these intravenous studies were about 80 ng/ml, which is comparable to the peak levels measured after oral intake in the present study.

Ketanserin did not cause postural hypotension in our subjects. Body weight had increased by 1.3 kg after both 4 and 8 weeks of ketanserin treatment. This increase may have been caused by renal sodium and water retention, as is often seen during treatment with vasodilator drugs, but we did not perform balance studies to prove this possibility. Among other minor side effects, none were significantly more frequent with ketanserin than with placebo treatment.

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