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KETANSERIN, A NOVEL 5-HYDROXYTRYPTAMINE ANTAGONIST: MONOTHERAPY IN ESSENTIAL HYPERTENSION

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1 Blood pressure and heart rate, supine and standing, were studied in patients with essential hypertension during 8 weeks of oral therapy with two dosage schedules of ketanserin, 40 mg once and twice daily.

2 Ketanserin caused significant reductions in both supine and standing blood pressure but no significant alterations in heart rate in both groups of patients.

3 Measurements of blood pressure and heart rate over a 24 h period during steady state conditions revealed that maximal blood pressure reduction was correlated with time to peak plasma concentrations.

4 Steady state plasma concentrations of ketanserin were significantly higher in the patients receiving 40 mg twice daily compared to 40 mg once daily. In the group with once daily treatment, t_{max} was 1.2 ± 0.17 h, C_{ss} 13 ± 4.3 ng/ml, C_{max} 137 ± 19.6 ng/ml and $t_{½,z}$ 9.6 ± 1.27 h.

Keywords ketanserin 5-HT antagonist hypertension

Introduction

5-Hydroxytryptamine (5-HT) is a potent vasoconstrictive substance by itself, and additionally it amplifies the vasoactive properties of e.g. noradrenaline and angiotensin (De La Lande *et al.* 1966; van Neuten *et al.*, 1981). Based on radioligand studies in animals two different forms of 5-HT receptors, designated 5-HT_1 and 5-HT_2, have recently been defined (Leysen *et al.*, 1981). The population of 5-HT receptors causing vascular contraction in rats appears to belong to the designated 5-HT_2 subtype (Cohen *et al.*, 1981; van Neuten *et al.*, 1981). The concept of involvement of 5-HT in hypertension is not new. However, this idea has not retained major interest, mainly due to poor efficacy and disturbing central side effects of previously existing 5-HT receptor blocking drugs (Kuhn *et al.*, 1980).

Ketanserin, 3-[2- 4-4-(fluorobenzoyl)-1-piperidinyl ethyl]-2,4(1H, 3H)-quinazolinedione; R41468, has recently been introduced as a specific 5-HT_2 receptor antagonist (Leysen *et al.*, 1981; van Neuten *et al.*, 1981). The compound lowers blood pressure in animals (van Neuten *et al.*, 1981; Persson *et al.*, 1982). Ketanserin has also been shown to reduce blood pressure in man following acute treatment (DeCree *et al.*, 1981; Wenting *et al.*, 1982). The dose range needed in chronic treatment of essential hypertension in man has not yet been adequately determined. The object of the present study was two-fold: firstly to evaluate the therapeutic efficacy of various doses of ketanserin in essential hypertension and, secondly, to study the pharmacokinetics and relate the plasma concentrations of ketanserin during steady state conditions to its blood pressure lowering effects.

Methods

Subjects

Twenty-eight caucasian patients of both sexes (26 males and two females) aged 33–67 years (mean 58.2 ± 1.8) with mild to moderate uncomplicated essential hypertension were studied. Patients with coronary heart disease, congestive heart failure, symptomatic peripheral atherosclerotic disease, significant renal or hepatic disease or alcohol abuse were excluded. Twenty-five patients were previously treated (mainly with diuretics and/or β-adrenoceptor blocking agents) for periods ranging from 1—15 years, while three patients were previously untreated.

Outline of the study

The study was carried out as a single blind study. After a 1 week washout period and a 2 week placebo period the patients with a supine diastolic blood pressure of 95–115 mm Hg were randomised and treated with ketanserin 40 mg once or twice daily. On an outpatient basis the supine and standing blood pressure as well as heart rate were measured before and at 1, 2, 4, 6, and 8 weeks after the start of active treatment. The measurements were with few exceptions performed in the morning 08.00–10.00 h. Before active treatment after 4 weeks and 8 weeks of active treatment ECG tracings were obtained, the patients weighed and the following blood tests performed: red blood cells and white blood cells, differential blood cell count, platelets, sedimentation rate, haemoglobin, liver transaminases, serum bilirubin, alkaline phosphatases, serum electrolytes, serum creatinine, blood glucose and serum lipids.

At steady state conditions (following at least 8 weeks of active treatment) plasma concentrations of ketanserin and blood pressure were determined during a 24 h period in a subpopulation of the study group (15 patients; 40 mg × 1, $n = 5$, 40 mg × 2, $n = 10$). The patients came fasting to the hypertension clinic at 08.00 h. Supine and standing blood pressure measurements, followed immediately by blood sampling for plasma concentrations of ketanserin, were performed before tablet intake and subsequently at 0.25, 0.5, 1, 2, 4, 6, 12 and 24 h after tablet intake. Those patients on ketanserin twice daily took their second tablet at 20.00 h. One hour after the first tablet intake a standardized hospital breakfast was served.

Plasma samples containing ketanserin were separated by centrifugation within minutes of collection and stored at -20°C until assay by a high performance liquid chromatography method (Woestenborghs *et al.*, in preparation).

Blood pressure recordings

Apart from the washout period, the blood pressure and heart rate were recorded blindly by an automatic manometer (Auto-Manometer, Southern Computers Ltd, New Zealand) (Nyberg, 1977) by no more than two different observers throughout the study. Disappearance of the sounds (Korotkoff V) was taken as the diastolic value. Values were registered after 5 min in supine and 2 min in standing position. The lower value of two successive measurements in each position was recorded.

Data analysis

Mean ± s.e. mean results were calculated by standard methods for the group of 25 patients completing the study. The three patients who dropped out due to side effects during the study period were analysed separately.

Statistical significances of differences from values obtained at placebo treatment (Figure 1) or at steady state conditions (Figure 2) were calculated by analysis of variance with two independent criteria for classification followed by Student's *t*-test (Davies, 1949). Regression analysis was performed by the method of least squares (Davies, 1949).

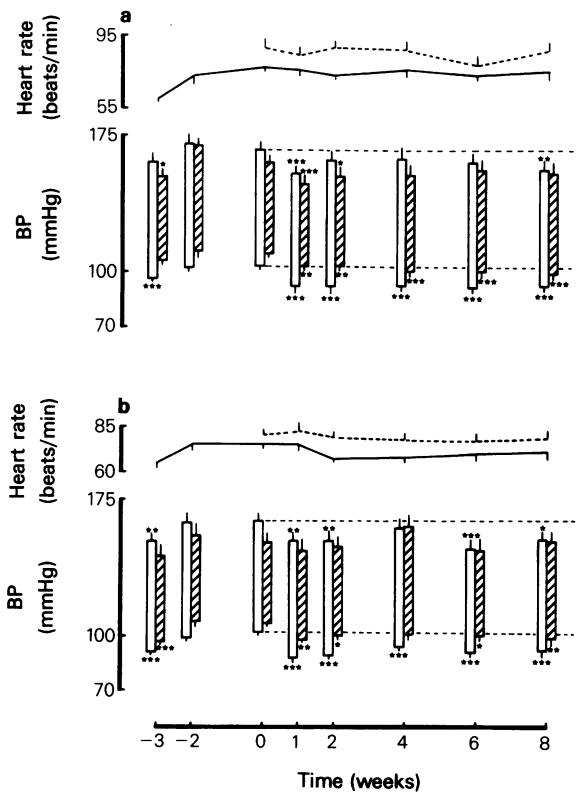

Figure 1 Supine (□) and standing (▨) blood pressure (BP, mm Hg, mean ± s.e. mean) as well as supine (——) and standing (---) heart rate (beats/min, mean ± s.e. mean) during treatment with previous therapy (time −3), placebo (time −2–0) and ketanserin in monotherapy (time 0–8 weeks). Number of patients were 12 in the **(a)** 40 mg × 2 group and 13 in the **(b)** 40 mg × 1 group. Asterisks denote significant differences from placebo values (time 0). $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

Results

Blood pressure and heart rate

Blood pressures and heart rates in the supine and standing positions at various times of the study are shown in Figure 1. The antihypertensive response to

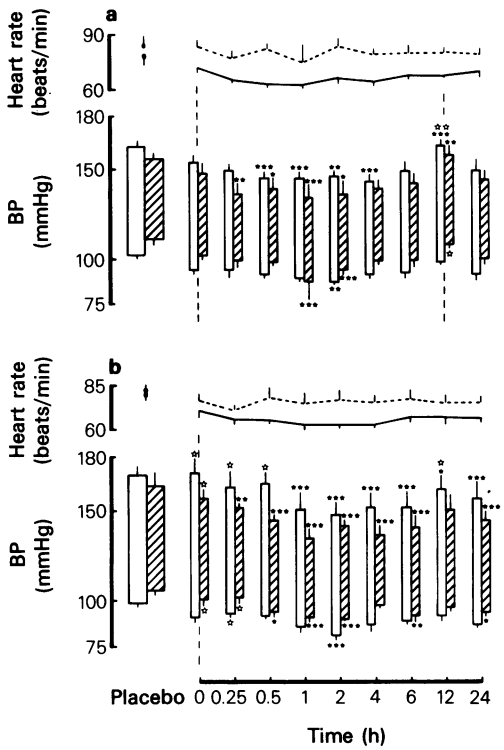

Figure 2 Supine (□) and standing (▨) blood pressure (BP, mm Hg, mean ± s.e. mean) as well as supine (——) and standing (---) heart rate (beats/min, mean ± s.e. mean) followed for 24 h during treatment with ketanserin **(a)** 40 mg × 2, $n = 10$ or **(b)** 40 mg × 1, $n = 5$) at steady state conditions, 2 months after initiation of therapy. Tablets were taken at time 0 and at time 12 (only 40 mg × 2). Thicker staples to the left represent values obtained during placebo from 2 months earlier. Filled asterisks denote significant differences from values at time 0 (i.e. before tablet intake). Open asterisks indicate that values are *not* significantly (at $P < 0.05$ level) lower than placebo values (staples to the left). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

ketanserin was similar whether the patients were treated with 40 mg once or twice daily. Obtaining maximal efficacy within 1 week of treatment both dosages caused comparable and significant decreases in systolic and diastolic blood pressure in supine as well as upright positions. Placebo supine mean pressures (122 ±2 mm Hg in 40 mg × 1 group and 124 ± 2 mm Hg in 40 mg × 2 group) were reduced by 7–11% and 7–10%, respectively, at the various times of the study. Heart rate was but slightly affected.

The response of individual patients varied. When defining a 'no response' as that with a less than 10% reduction of placebo supine diastolic blood pressure on at least three (of five) occasions after start of active treatment five out of 12 patients in the 40 mg once daily group (placebo supine blood pressures were 164 ± 8/101 ± 1 mm Hg for nonresponders and 166 ± 4/102 ± 27 mm Hg for responders) and five out of 13 patients in the 40 mg twice daily group (placebo supine blood pressures were 167 ± 5/106 ± 3 mm Hg for nonresponders and 166 ± 5/100 ± mm Hg for responders, respectively) did not respond. There was no correlation between initial level of blood pressure and degree of subsequent blood pressure reduction to ketanserin but patients who were definitely not well controlled on previous medication (supine diastolic value about 110 mm Hg) responded poorly also to ketanserin.

In Figure 2 are shown blood pressure levels during 24 h after tablet intake. Maximal blood pressure reductions were obtained 0.5–2 h after tablet intake, i.e. correlated well in time with maximal plasma concentrations of ketanserin. There were no significant correlations between the maximal plasma concentrations and blood pressure reductions (from placebo) during the 24 h measurements in the individual patients (data not shown). However, steady state plasma concentrations of ketanserin i.e. at 0 h in the 40 mg × 1 and 40 mg × 2 groups correlated significantly to the reduction in SBP (from placebo BP) at eight weeks after the initiation of therapy (Figure 3).

Pharmacokinetics

The mean steady state plasma concentration curves of ketanserin orally 40 mg once and twice daily are show in Figure 4. The mean values of the pharmacokinetic parameters studied in five patients after an oral dose of 40 mg ketanserin during steady state are given in Table 1. Steady state plasma concentrations were significantly higher in the 40 mg twice daily compared to the 40 mg once only daily group (30 ± 3.8 *vs* 13 ± 4.3 ng/ml, respectively, $P < 0.025$). Mean peak plasma concentrations occurred 1 h after oral intake (Figure 4). The peak concentrations did not differ between the two dosage schedules. The terminal half life, $t_{½,z}$ for ketanserin after a single oral dose was calculated on the 6, 12 and 24 h values for four patients and on the 12 and 24 h interval for one patients. Thus, a mean value of 9.6 ± 1.27 h (range 7.06–14.42 h) was obtained.

Adverse reactions

No serious side effects were experienced during the study. After active questioning, five patients in the once daily treatment group and two in the twice daily treatment group at one point reported symptoms of dizziness, fatigue and light headedness. These symptoms occurred 1–2 h after tablet intake and tended to subside with continued treatment. They were accepted as mild by most patients. One patient, however, dropped out due to these particular symp-

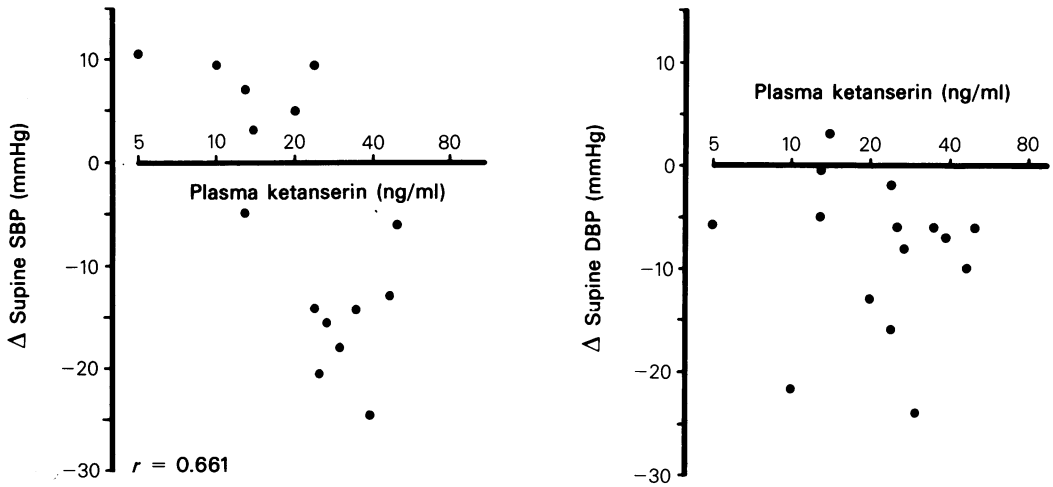

Figure 3 Changes in systolic and diastolic blood pressures (from placebo values) at steady state (just before next tablet intake, i.e. at 0 h in the 40 mg × 1 and the 40 mg × 2 group; see Figures 2 and 4) plotted against steady state ketanserin plasma concentrations (C_{ss}) in patients with essential hypertension receiving 40 mg once daily and 40 mg twice daily, 2 months after initiation of treatment. Regression analysis by method of least squares.

toms. One patient reported increased appetite and two others increased voiding. Finally, two other patients dropped out because of headache, in one instance possibly related to poor blood pressure control. No other side effects were reported.

Analysis of ECG tracings revealed no change after ketanserin treatment. Likewise haematological and biochemical data did not show any drug related alterations. The weight was not significantly altered during the study.

Discussion

The present study shows that ketanserin on a 40 mg schedule reduces blood pressure in a large number of patients with essential hypertension. Judging from the chronic study, treatment with 40 mg twice daily was not superior to treatment with 40 mg once daily in this respect. However, in this part of the study blood pressure measurements were performed in the morning, i.e. 2–4 h after tablet intake. Since, as was re-

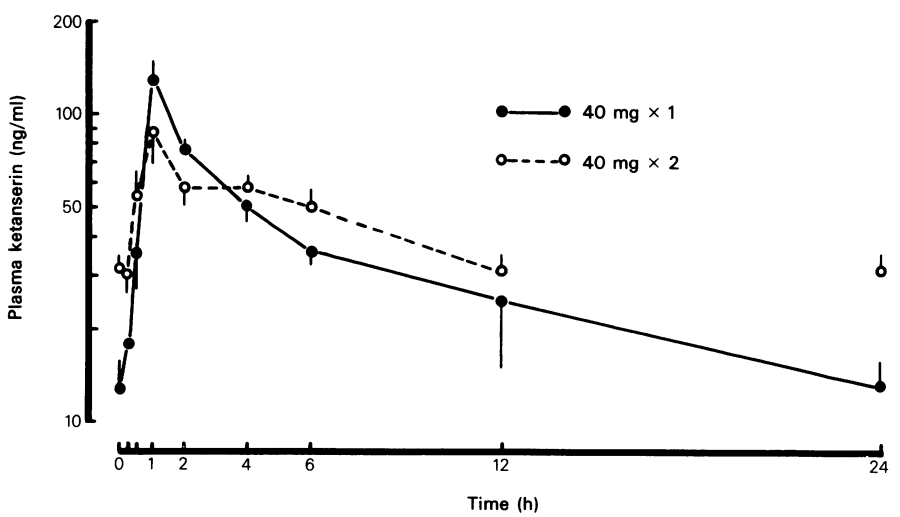

Figure 4 Mean plasma ketanserin concentrations (ng/ml) during 24 h at steady state after 2 months of therapy in patients with essential hypertension. Shown are means ± s.e. mean of five patients receiving 40 mg × 1 (tablet intake at time 0, ●—●) and patients receiving 40 mg × 2 (tablet intakes at time 0 and 12, O---O)

Table 1 Pharmacokinetic data after oral administration of ketanserin, 40 mg, during steady state.

C_{ss}	13 ± 4.3 ng/ml
C_{max}	137 ± 19.6 ng/ml
t_{max}	1.2 ± 0.17 h
$t_{½,z}$	9.6 ± 1.27 h

Shown are mean ± s.e. mean of steady state plasma concentrations (C_{ss}), maximal plasma concentration (C_{max}), the time for maximal plasma concentration (t_{max}) and terminal elimination half-life ($t_{½,z}$) from five patients receiving ketanserin 40 mg once daily.

vealed in the 24 h experiment, the blood pressure reduction correlated well in time with plasma concentrations and varied accordingly during the day, our results may not adequately reflect blood pressure control during the whole day. From this point of view, as was further observed in the 24 h experiment, the blood pressure levels were significantly lower than placebo values during a larger part of the day in the 40 mg twice daily than in the 40 mg once daily treatment group.

During steady state conditions in the morning (i.e. 12 and 24 h after last tablet intake in the 40 mg × 2 and 40 mg × 1 treatment groups, respectively) blood pressure measurement revealed that blood pressure control was adequate only with the twice daily regimen. At this time interval supine blood pressure reductions correlated significantly with plasma ketanserin concentrations during steady state. Due to the disparate number of patients completing the 24 h experiments, no firm conclusions can be drawn from these results but available data including the calculated plasma half life of 10 h for ketanserin in hypertensive patients would indicate that ketanserin in clinical practice will have to be administered twice daily.

With the 40 mg schedule used in this study the slight side effects were well tolerated. Since the only common adverse effect, a transient dizziness, correlated in time with peak plasma concentrations of ketanserin, this particular side effect is probably related to the dose per intake rather than the total daily dose. In our study, if anything there were fewer side effects in the 40 mg twice daily than the 40 mg once daily group. A dose schedule with 60 or 80 mg tablets has been reported to be associated with an unacceptably high incidence of side effects (Hansson *et al.*, personal communication).

In summary, ketanserin on a 40 mg schedule reduces blood pressure in essential hypertension. A dose of 40 mg twice daily does not cause more adverse reactions than 40 mg once daily but seems to offer a better blood pressure control. Ketanserin on a twice daily regimen will probably be preferred in clinical use.

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