Mechanism of action of ketanserin: studies on cardiovascular reactivity in essential and diabetes-associated hypertension

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Ketanserin is a selective serotonin-S2 receptor antagonist with α_1-adrenoceptor inhibiting activity. The relative contribution of the latter mechanism to antihypertensive efficacy was studied in a group comprising eight normal subjects, 10 patients with essential hypertension and eight diabetics with arterial hypertension. Ketanserin treatment administered over a period of 8 weeks, decreased arterial pressure in patients with essential hypertension and, to a lesser extent, in diabetics, but not in normal subjects. In all three groups, exchangeable sodium, blood volume, the activity of the adrenergic and renin-angiotensin-aldosterone systems and the pressor responsiveness to norepinephrine (NE) or angiotensin II (Ang II) were unaltered, while the pressor reactivity to phenylephrine showed a significant decrease in normal subjects only. This suggests that the antihypertensive mechanism of ketanserin does not involve a modification of the physiological relationship between endogenous noradrenergic and pressor reactivity to NE. Moreover, ketanserin does not interfere with Ang II-dependent mechanisms.

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Introduction

The piperidine derivative, ketanserin, administered either acutely or chronically, lowers arterial pressure in patients with essential hypertension by causing peripheral vasodilatation [1,2]. The mechanism of action involves both serotonergic and adrenergic pathways. Ketanserin is a selective antagonist of serotonergic S2 receptors [3], which mediate serotonin-induced constriction in vascular smooth muscle cells [4] and could be involved in the amplification of the contractile response to other pressor agents, such as NE or Ang II [4]. On the other hand, ketanserin also exhibits α_1-adrenoceptor inhibiting activity [3]. The relative contribution of this mechanism to antihypertensive potency is still unknown. In acute studies in normal subjects, the pressor reactivity to methoxamine or phenylephrine was found either to be decreased [5] or unchanged [6] after an infusion [5,6] or a 4-day treatment period [7] with ketanserin, while in patients with essential hypertension, a ketanserin infusion failed to alter the pressor effects of phenylephrine [1,8]. Under conditions of stable pharmacological intervention, the pressor reactivity to methoxamine or phenylephrine was found to be decreased in hypertensive patients [9,10]. These pharmacological results do not necessarily demonstrate a role for an adrenergic-dependent mechanism, since ketanserin was also shown to lower blood pressure independently of α-adrenoceptor blockade [1]. Moreover, the effects of ketanserin on the pressor reactivity to endogenous catecholamines is presently unknown.

Essential hypertension is associated with an exaggerated cardiovascular pressor reactivity to NE in the presence of normal endogenous noradrenergic activity [11]. This disturbance is already present at the pre-hypertensive stage [12] and could play an important role in the pathogenesis of essential hypertension [13]. Moreover, the antihypertensive efficacy of certain pharmacological interventions is related, at least partly, to a normalization of the cardiovascular pressor reactivity to NE, with respect to sympathetic activity [14]. Therefore, an evaluation of the effects of ketanserin on these variables could offer an important contribution in the search for a more precise delineation of the antihypertensive mechanism of this compound. Furthermore, in order to obtain a comprehensive assessment of the mechanism of action of ketanserin, a second type of hypertension, namely diabetes-associated hypertension, was included in this

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investigation. This form of hypertension is also associated with an exaggerated cardiovascular pressor reactivity to NE but, in contrast to essential hypertension, has an expanded body sodium [15].

Subjects and methods

The three study groups comprised eight normal subjects (four females and four males), aged 42–55 years [mean age 46 ± 5 (± s.d.) years], 10 patients with essential hypertension (six females and four males), aged 42–58 years (mean age 47 ± 6 years) and eight diabetics with arterial hypertension (three females and five males), aged 45–64 years (mean age 56 ± 8 years). The normal subjects were healthy volunteers without previous episodes of high blood pressure and with a blood pressure consistently <140/90 mmHg throughout the study. The presence of hypertension in the patients was defined by obtaining repeated blood pressure measurements of between 140/90 and 180/115 mmHg taken under outpatient conditions. Secondary forms of hypertension were excluded by the usual tests; no patient had malignant hypertension (hypertensive retinopathy stages III–IV), edema, arrhythmia, renal (serum creatinine >90 μmol/l) or heart failure. In the diabetic patients, the known duration of the diabetes averaged 5 ± 5 years (range 1–15 years). Three diabetics were following diet treatments, two were treated with diet and oral hypoglycaemic agents, and three with diet and insulin. Diabetic retinopathy was present in one patient, no diabetic complications could be found in the other seven. All antihypertensive drugs and potassium supplements were discontinued at least 3 weeks before the study began. None of the women were taking hormonal contraceptives. Informed consent was obtained from all subjects and the study protocol was approved by the ethical committee of our institution.

The subjects were instructed to continue eating a normal diet, avoiding very high or low sodium intakes [16]. A placebo (one tablet twice daily) was given over a period of 3 weeks and was then replaced by a 20-mg dose of active ketanserin, given twice daily. After 4 weeks of treatment, the dose was increased to 80 mg daily and, if diastolic blood pressure was not decreased to 90 mmHg, a further increase to 120 mg daily was introduced after 6 weeks. The duration of the whole treatment was 8 weeks.

During ketanserin therapy, subjects had their blood pressure, and heart rate measured every 2 weeks after 10 min rest in the supine position and after 2 min in the upright position. During the 4 four days of the placebo and ketanserin treatment phases, the following measurements were obtained. A 24-h urine collection was carried out to determine sodium, potassium, glucose, and creatinine excretion rates. Blood pressure (standard cuff and sphygmomanometer; each value was the mean of three readings), heart rate, exchangeable sodium, blood volume, and plasma sodium, potassium, creatinine, glucose, renin activity, aldosterone, NE, and epinephrine levels were determined the morning after an overnight fast and after 1 h of rest in the supine position (subjects took only the usual morning dose of placebo or ketanserin). Blood pressure, heart rate, plasma renin activity, aldosterone, NE and epinephrine levels were measured again after the subjects had spent 30 min walking. After emptying the bladder, subjects rested in the supine position for 60 min, while a 5% dextrose solution was infused at a constant rate (6 ml/h by constant infusion pump). Basal blood pressure and heart rate were then determined (mean of at least 10 recordings obtained with a cuff and the automated recorder Dynamap 845 XT (Critikon, Tampa, USA). The dextrose solution was then replaced by a solution of phenylephrine (Neo-Synephrine HCl, Winthrop-Breon Laboratories, New York, USA) in 5% dextrose, which was infused at stepwise increasing dose rates of 200, 400, 1000 and 2000 ng/kg per min, lasting 15 min each. If the phenylephrine-induced increase in mean blood pressure failed to reach 20 mmHg, a fifth infusion step with 4000 ng/kg per min was added. During the last 10 min of each infusion step, blood pressure and heart rate were measured at 1-min intervals.

In order to test the subjects' pressor or aldosterone responsiveness, NE and Ang II were infused i.v. 1–3 days after the phenylephrine pressor test. After overnight fasting, subjects took the usual morning dose of placebo or ketanserin. After a 60-min equilibration period with slow i.v. infusion of 5% dextrose and with subjects resting in the supine position(6 ml/h by constant infusion pump), basal blood pressure and heart rate measurements were obtained (at least 10 measurements with a cuff and the automated recorder Dynamap XT 805). Blood samples were obtained from the contralateral arm to determine plasma NE and epinephrine levels. The dextrose solution was then replaced by a solution of l-NE bitartrate in 5% dextrose, infused at stepwise increasing dose rates of 20, 40, 100 and 200 ng/kg per min, each lasting 16 min. When the NE-induced increase of mean blood pressure failed to reach 20 mmHg, a fifth infusion step with 400 ng/kg per min was added. During the last 10 min of each infusion step, blood pressure and heart rate were recorded at 1-min intervals. At the end of each infusion step, plasma NE and epinephrine levels were measured. The NE solution was then replaced by 5% dextrose, infused for 60 min at a constant rate of 6 ml/h. At the end of this second equilibration period, basal blood pressure, heart rate, plasma renin activity, Ang II and aldosterone levels were determined. The dextrose infusion was replaced by a solution of Ang II (Hypertensin, Ciba-Geigy, Basle, Switzerland) in 5% dextrose, which was infused at increasing dose rates of 2, 4, 10 and 20 ng/kg per min, each lasting 20 min. Blood pressure and heart rate were monitored as described previously, and plasma Ang II and aldosterone levels were determined at the end of each Ang II infusion step.

Concentrations of plasma and urinary sodium were measured by flame photometry. Creatinine concentration was measured by autoanalyzer, glucose by the hexokinase method. Plasma renin activity, aldosterone, and Ang II were determined by radio-immunoassay [17–19], and plasma NE and epinephrine concentrations were obtained using a radio-enzymatic method [20], as reported elsewhere [16,21]. Exchangeable sodium and

blood volume were measured by isotope dilution technique using ^{24}Na and ^{125}I-human serum albumin, respectively [22].

Cardiovascular reactivity was analyzed as follows: dose–response curves were calculated by relating the increases in mean (phenylephrine and NE infusions) or diastolic (Ang II infusion) arterial pressure to infused dose rates [23,24]. A regression analysis was calculated using the data points lying on the steep part of the dose–response curve and pressor doses were derived as the phenylephrine, NE or Ang II dose rates required to elevate arterial pressure by 20 mmHg while threshold doses were derived as the dose rates causing zero changes in blood pressure [23,24]. Moreover, concentration–response curves were derived for NE and Ang II infusions by relating the increases in mean (NE infusion) or diastolic (Ang II infusion) arterial pressure to the blood levels of NE or Ang II, respectively [24].

Since logarithmic transformation rather than absolute values followed a Gaussian distribution, the natural logarithmic transformation of plasma renin activity, doses of infused phenylephrine, NE and Ang II, and pressor or threshold doses of phenylephrine, NE and Ang II were used for statistical analysis. Statistical analysis included the paired Student's two-tailed t-test and the Wilcoxon test (comparison of paired values within groups), regression analysis, analysis of variance (comparison of values among the three groups) and covariance (comparison of dose–response curves).

Results

At the end of the placebo phase, none of the three study groups differed significantly (analysis of variance) in mean body weight, total exchangeable sodium and blood volume, heart rate, creatinine clearance and urinary excretion rates of sodium and potassium (Table 1). Exchangeable sodium and blood volume, expressed in relation to body surface area [22], averaged 96.1 ± 9.7% and 92.6 ± 14.6% in normal subjects, 103.5 ± 9.6% and 96 ± 11.8% in patients with essential hypertension and 111.2 ± 16.6% and 96.8 ± 12.2% in diabetes associated hypertension, respectively.

For two of the normal subjects, the dosage of ketanserin had to be reduced to a daily dose of 60 mg during treatment weeks 4–8 because of dizziness; the maximal dose of 80 mg could be maintained without side effects in the other six volunteers. The dose of ketanserin given to patients with essential hypertension or diabetes-associated hypertension ranged between 80 and 120 mg daily, averaging 86 ± 28 mg and 90 ± 18 mg, respectively. One of the patients with essential hypertension complained of tiredness during the treatment phase with the highest dose; no relevant side effects were noted in the other patients.

When compared to the placebo phase, ketanserin did not modify arterial pressure in normal subjects and caused a significant decrease of both supine and upright arterial pressure in patients with essential hypertension and a slight but not significant decrement in hypertensive diabetics (Table 1). Ketanserin did not modify heart rate, but tended to increase body weight in normal subjects and diabetics. Exchangeable sodium and blood volume, however, did not change significantly in any of the three groups (Table 1). Plasma levels of sodium, potassium, calcium or glucose, supine and upright plasma renin activity, aldosterone, NE and epinephrine levels and creatinine clearance were also unchanged after ketanserin treatment in all three study groups (Table 1). In hypertensive diabetics, the urinary excretion rates of glucose and the haemoglobin Alc concentration were comparable after placebo and after ketanserin (10.5 ± 14.9 versus 13.2 ± 17.1 g/24 h and 7.4 ± 1.9 versus 7.7 ± 2.5%).

The response of arterial pressure to phenylephrine was judged by the calculated threshold and pressor doses or by dose–response curves. The two first variables tended to increase after ketanserin as compared with placebo conditions in all three study groups (Table 2). When all study participants were combined, the ketanserin-induced increments were significant (threshold dose from 476 ± 242 to 769 ± 381 ng/kg per min; $P < 0.01$ and pressor dose from 1497 ± 581 to 2016 ± 930 ng/kg per min; $P < 0.02$; $P < 0.05$ by Wilcoxon test). The slope of the pressor–response curve was unchanged (Table 2). Under placebo conditions, the increase in mean blood pressure during phenylephrine infusion at the dose rate of 2000–4000 ng/kg per min (+24 ± 7 mmHg in normal subjects, +28 ± 8 mmHg in patients with essential hypertension and +22 ± 5 mmHg in diabetics with hypertension) was associated with a significant decrease ($P < 0.01$) of heart rate (−19 ± 8, −16 ± 8 and −16 ± 15 beats/min). Similar changes were observed after treatment with ketanserin (+28 ± 6, +31 ± 9 and +33 ± 8 mmHg, −22 ± 9, −13 ± 5 and −16 ± 9 beats/min). Moreover, the relationship between phenylephrine-induced increments of mean blood pressure and decrements of heart rate did not differ between placebo and ketanserin conditions in the three groups (F = 0.26, 0.89 and 0.06, respectively). The dose–response curve of arterial pressure and phenylephrine dose rates was significantly displaced to the right after ketanserin treatment as compared to placebo conditions in normal subjects (F = 8.01; $P < 0.05$; Fig. 1); it was slightly but not significantly shifted in patients with essential hypertension (F = 3.04; NS) and unchanged in hypertensive diabetics (F = 0.06; NS; Fig. 1) or in the entire study population (F = 3.21; NS).

When compared with placebo conditions, mean preinfusion plasma NE and the calculated threshold and pressor doses of infused NE did not change after ketanserin treatment in normal subjects and patients with essential or diabetes-associated hypertension. Under placebo conditions, the increase in mean blood pressure during NE infusion at the dose rate of 200 ng/kg per min (+18 ± 8 mmHg in normal subjects, +21 ± 10 mmHg in patients with essential hypertension and +17 ± 7 mmHg in hypertensive diabetics) was associated with a significant ($P < 0.05$) decrease in heart rate (−15 ± 9, −5 ± 4 and −11 ± 7 beats/min, respectively). After ketanserin, the NE-induced increase in mean arterial pressure (+19 ± 5, +22 ± 12 and +17 ± 6 mmHg) was associated with a somewhat smaller decrement in heart rate (−11 ± 11, +1 ± 6 and −8 ± 6 beats/min). The rela-

Table 1. Clinical and biochemical findings before and after ketanserin treatment in normal subjects and hypertensive patients.

	Normal subjects		Essential hypertension		Diabetes-associated hypertension	
	Placebo	Ketanserin	Placebo	Ketanserin	Placebo	Ketanserin
Blood pressure (mmHg)						
supine	116/77 ± 8/6	112/72 ± 9/11	147/102 ± 18/11	136/93 ± 23/14*	155/96 ± 16/6	145/90 ± 17/9
upright	114/81 ± 9/11	110/80 ± 11/10	144/106 ± 16/13	135/99 ± 14/10*	151/101 ± 19/7	148/96 ± 17/11
Heart rate (beats/min)						
supine	69 ± 5	66 ± 11	68 ± 11	66 ± 11	74 ± 8	69 ± 10
upright	84 ± 10	83 ± 17	79 ± 13	79 ± 12	89 ± 11	84 ± 17
Body weight (kg)	66.1 ± 12	67.2 ± 12.6*	74.6 ± 14.5	74.3 ± 14.8	77.0 ± 11.6	78.1 ± 12.3*
Exchangeable sodium (mmol/l)	2644 ± 452	2741 ± 481	2927 ± 621	3086 ± 590	3057 ± 301	3099 ± 499
Blood volume (ml)	3539 ± 605	3856 ± 682	3468 ± 1083	4076 ± 819	3875 ± 667	4081 ± 939
Plasma sodium (mmol/l)	138 ± 2	138 ± 2	140 ± 3	141 ± 3	137 ± 4	141 ± 3
potassium (mmol/l)	4.0 ± 0.3	4.0 ± 0.2	4.3 ± 0.3	4.2 ± 0.3	4.0 ± 0.3	4.0 ± 0.2
calcium (mmol/l)	2.13 ± 0.08	2.08 ± 0.08	2.20 ± 0.12	2.21 ± 0.10	2.21 ± 0.18	2.25 ± 0.11
glucose (mmol/l)	5.2 ± 1.6	5.1 ± 1.9	5.1 ± 0.5	5.6 ± 0.6	13.9 ± 7.1	10.0 ± 4.5
renin activity (ng/ml per h)						
supine	2.9 ± 0.3	2.7 ± 0.3	3.3 ± 0.2	3.3 ± 0.7	3.1 ± 0.6	3.1 ± 0.5
upright	4.7 ± 0.5	4.7 ± 1.1	4.3 ± 0.5	4.9 ± 1.0	4.3 ± 1.1	4.2 ± 0.9
aldosterone (ng/dl)						
supine	12 ± 3	13 ± 4	12 ± 3	14 ± 3	13 ± 3	15 ± 5
upright	22 ± 7	17 ± 5	19 ± 4	24 ± 3	16 ± 6	22 ± 10
norepinephrine (ng/dl)						
supine	26.5 ± 8.2	28.2 ± 8.4	28.1 ± 10.3	32.7 ± 17	128.8 ± 9.4	32.3 ± 7.2
upright	58.9 ± 31.5	54.1 ± 7.4	69.5 ± 30.5	66.9 ± 32	51.0 ± 13.5	56.9 ± 10.4
epinephrine (ng/dl)						
supine	8.4 ± 3.5	7.3 ± 2.7	8.1 ± 5.1	5.8 ± 2.9	7.9 ± 3.2	2.8 ± 8
upright	12.6 ± 5.5	10.4 ± 4.9	10.1 ± 6	10.9 ± 6.3	11.1 ± 8	14.3 ± 11.1
Urinary sodium (mmol/24 h)	177 ± 87	203 ± 95	186 ± 60	141 ± 70	161 ± 62	132 ± 38
potassium (mmol/24 h)	62 ± 15	64 ± 15	78 ± 39	67 ± 37	74 ± 23	69 ± 17
Creatinine clearance (ml/min per 1.73 m)	128 ± 22	117 ± 31	122 ± 53	105 ± 36	127 ± 36	105 ± 25

*$P < 0.05$, versus placebo. Values given were means ± s.d.

Table 2. Infusion studies in normal subjects and hypertensive patients before and after ketanserin treatment.

	Normal subjects		Esssential hypertension		Diabetes-associated hypertension	
	Placebo	Ketanserin	Placebo	Ketanserin	Placebo	Ketanserin
Phenylephrine						
Threshold dose (ng/kg per min)	655 ± 245	929 ± 290*‡	452 ± 239	880 ± 410†‡	304 ± 182	512 ± 346
Pressor dose (ng/kg per min)	1069 ± 577	2231 ± 489‡	1319 ± 580	2384 ± 1301†‡	1474 ± 703	1471 ± 613
Slope	20 ± 5	23 ± 4	20 ± 7	29 ± 16	15 ± 6	20 ± 7
Norepinephrine						
Basal plasma norepinephrine (ng/dl)	32 ± 21	25 ± 6	35 ± 23	34 ± 22	25 ± 6	26 ± 7
Threshold dose (ng/kg per min)	53 ± 43	49 ± 41	28 ± 18	41 ± 38	33 ± 17	27 ± 20
Pressor dose (ng/kg per min)	243 ± 134	186 ± 81	177 ± 186	197 ± 136	156 ± 94	111 ± 42
Slope	13 ± 5	14 ± 6	14 ± 6	13 ± 3	14 ± 3	14 ± 5
Angiotensin II						
Basal plasma angiotensin II, (pg/ml)	12 ± 5	11 ± 2	14 ± 4	15 ± 7	12 ± 4	13 ± 4
Threshold dose (ng/kg per min)	0.9 ± 0.7	1.2 ± 0.4	1.1 ± 0.5	1.4 ± 1.0	1.2 ± 1	1.2 ± 0.8
Pressor dose (ng/kg per min)	10.6 ± 7.8	9.6 ± 8.2	10.3 ± 9.9	10.9 ± 11.5	3.7 ± 2.1	7.7 ± 4.0
Slope	11 ± 5	13 ± 5	11 ± 4	12 ± 4	19 ± 15	11 ± 6

*$P < 0.05$, †$P < 0.025$ versus placebo; ‡$P < 0.05$ by Wilcoxon test. Values given are means ± s.d.

tionships between NE-induced increments in mean blood pressure and the corresponding variations in heart rate did not differ significantly between placebo and ketanserin conditions in the three groups (F = 2.35, 0.17 and 0.62, respectively).

Plasma NE concentrations measured at the end of each NE infusion step correlated closely with the corresponding infusion rates and correlations were similar during placebo and ketanserin treatment in normal subjects ($r = 0.85$; $P < 0.001$, $\ln y = 0.84 \ln x + 1.54$ and $r = 0.81$, $P < 0.001$; $\ln y = 0.75 \ln x + 1.95$, respectively), patients with essential hypertension ($r = 0.80$,

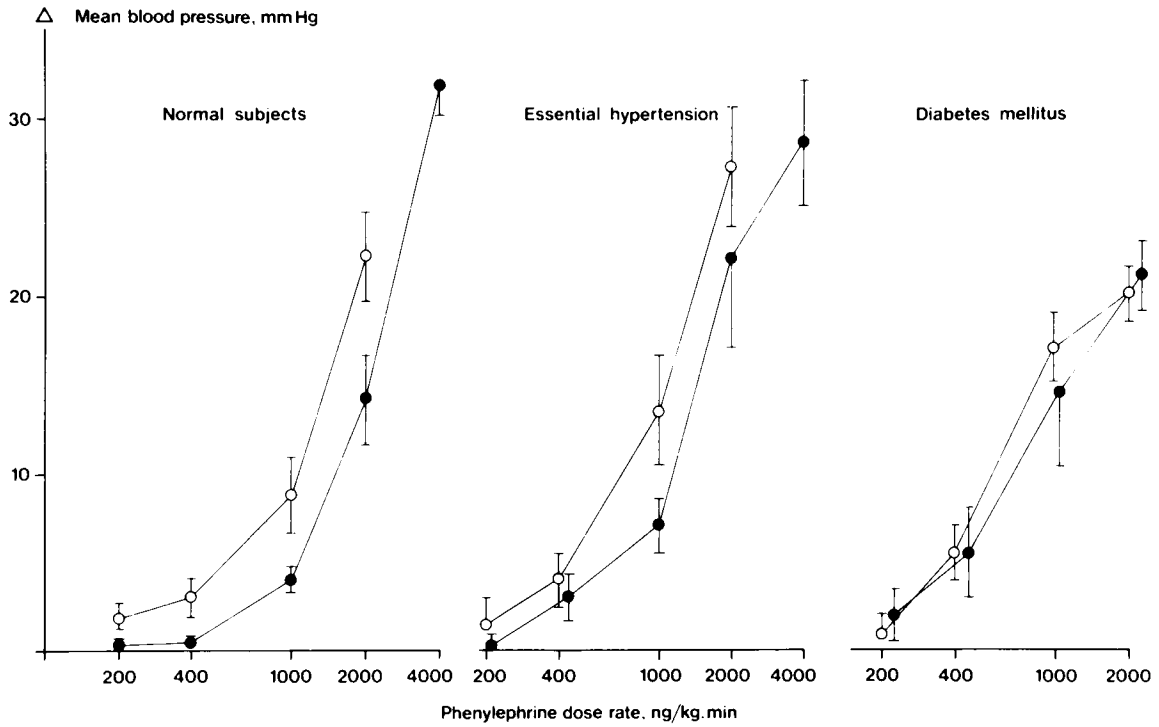

Fig. 1. Relationships between arterial pressure and phenylephrine dose rates before and after ketanserin in normal subjects and patients with essential or diabetes-associated hypertension. ○ (placebo), ● (ketanserin) show mean values, bars indicate standard error. The dose–response curve was shifted to the right after ketanserin in normal subjects ($F = 8.01$; $P < 0.05$) and was unchanged in essential hypertensives ($F = 3.04$; NS) or diabetes mellitus ($F = 0.06$; NS).

$P < 0.001$; $\ln y = 0.64 \ln x + 2.08$ and $r = 0.79$, $P < 0.001$; $\ln y = 0.71 \ln x + 1.87$) and hypertensive diabetics ($r = 0.87$, $P < 0.001$; $\ln y = 0.82 \ln x + 1.78$ and $r = 0.81$, $P < 0.001$; $\ln y = 0.77 \ln x + 2.02$). Pre-infusion plasma levels of epinephrine averaged 7.7 ± 2.8, 7.9 ± 5.1 and 8.6 ± 3.9 ng/dl after placebo and 5.6 ± 1.5, 5.4 ± 2.4 and 10.6 ± 4.7 ng/dl after ketanserin, respectively; they did not change significantly during NE infusion during either placebo or ketanserin phases. The concentration–response curve of arterial pressure and plasma NE concentration was not significantly displaced after ketanserin as compared to placebo in the three study groups (Fig. 2).

Compared with placebo conditions, pre-infusion plasma levels of Ang II, Ang II threshold and pressor doses were unchanged after ketanserin treatment in normal subjects and patients with essential or diabetes-associated hypertension (Table 2). Pre-infusion plasma renin activity was also comparable (3.2 ± 0.6, 3.6 ± 0.8 and 3.6 ± 1.0 ng/ml per h versus 3.4 ± 0.8, 3.8 ± 1.0 and 3.4 ± 0.8 ng/ml per h). Heart rate did not change significantly during Ang II infusion under either set of study conditions.

The plasma Ang II levels measured at the end of each infusion dose rate correlated closely with the corresponding infusion rates; the correlation was similar after placebo and ketanserin treatment in normal subjects ($r = 0.89$, $P < 0.001$; $\ln y = 0.81 \ln x + 2.53$ and $r = 0.82$, $P < 0.001$; $\ln y = 0.78 \ln x + 2.71$), patients with essential hypertension ($r = 0.80$, $P < 0.001$; $\ln y = 0.81 \ln x + 2.53$ and $r = 0.82$, $P < 0.001$; $\ln y = 0.78 \ln x + 2.71$) and diabetics with arterial hypertension ($r = 0.82$, $P < 0.001$; $\ln y = 0.89 \ln x + 3.03$ and $r = 0.84$; $P < 0.001$; $\ln y = 0.81 \ln x + 2.81$). The relationships between the Ang II-induced increases in diastolic arterial pressure and plasma Ang II concentration were not modified by ketanserin as compared with placebo conditions (Fig. 3).

After placebo, Ang II infused at the lowest dose rate caused a significant increase of plasma aldosterone in normal subjects (from 15 ± 7 to 17 ± 7 ng/dl; $P < 0.05$), patients with essential hypertension (from 12 ± 5 to 14 ± 5 ng/dl; $P < 0.05$) and hypertensive diabetics (from 12 ± 2 to 17 ± 2 ng/dl; $P < 0.025$); further increases were caused by the following Ang II dose rates (Fig. 3). After ketanserin, the plasma levels of aldosterone increased to a comparable extent after the lowest Ang II dose rate (from 12 ± 4 to 17 ± 5 ng/dl; $P < 0.05$ in normal subjects, from 11 ± 3 to 16 ± 4 ng/dl; $P < 0.025$ in patients with essential hypertension and from 13 ± 5 to 16 ± 7 ng/dl; $P < 0.05$ in diabetics) as well as after the higher dose rates (Fig. 3). Moreover, the relationship between plasma aldosterone and plasma Ang II concentration obtained during Ang II infusion was not modified by ketanserin as compared with placebo conditions in the three groups (Fig. 4).

In the two hypertensive groups analysed separately or combined, the ketanserin-induced fall of mean arterial pressure was unrelated with the associated changes in phenylephrine threshold or pressor doses ($r = 0.05$ to 0.23; NS).

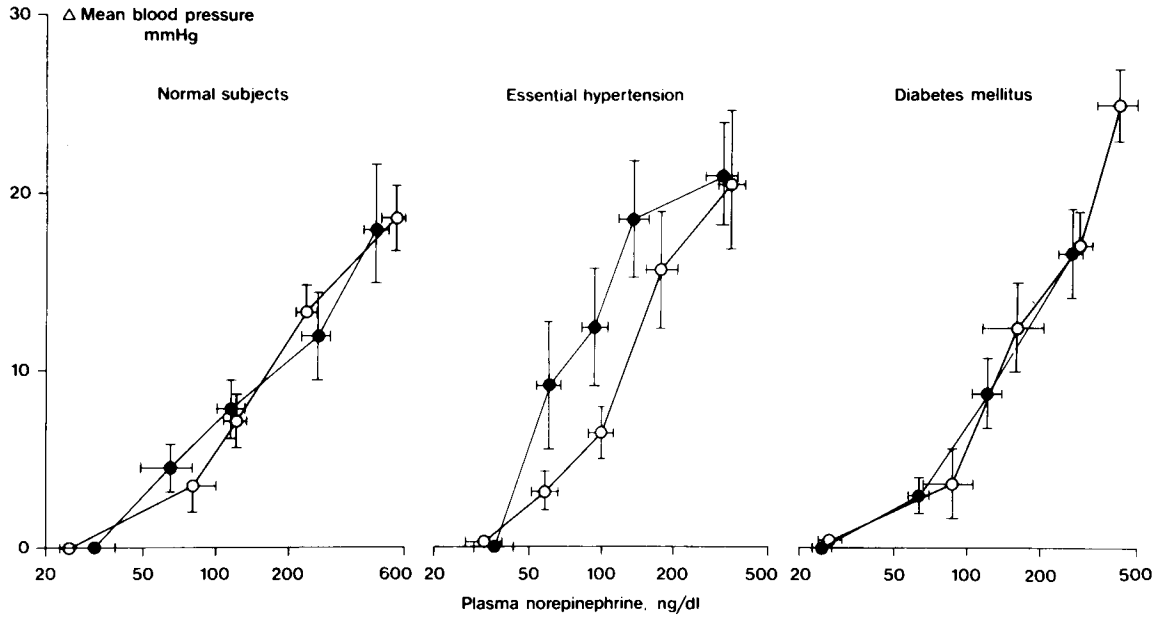

Fig. 2. Relationships between norepinephrine-induced increases in mean arterial pressure and plasma norepinephrine levels before and after ketanserin in normal subjects and patients with essential or diabetes-associated hypertension. ○ (placebo), ● (ketanserin) show mean values, bars indicate standard error. Concentration–response curves were not significantly shifted after ketanserin.

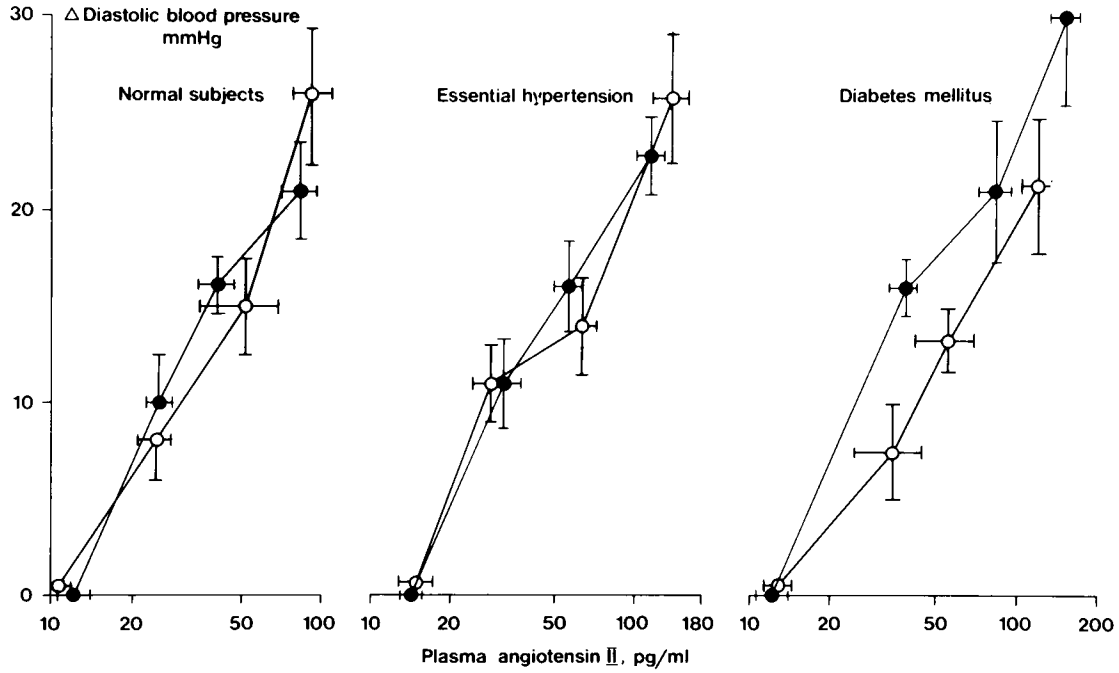

Fig. 3. Relationships between angiotensin II-induced increments of diastolic blood pressure and plasma angiotensin II levels before and after ketanserin in normal subjects and patients with essential or diabetes-associated hypertension. ○ (placebo), ● (ketanserin) show mean values, bars indicate standard error. Concentration–response curves were not significantly shifted after ketanserin.

Discussion

The findings of this study suggest that the antihypertensive efficacy of ketanserin is not mediated by adrenergic inhibition. Thus, although in normal subjects, the administration of this compound over 8 weeks caused a significant decrease of the pressor reactivity to the α_1-agonist phenylephrine, no significant shift of the dose–response

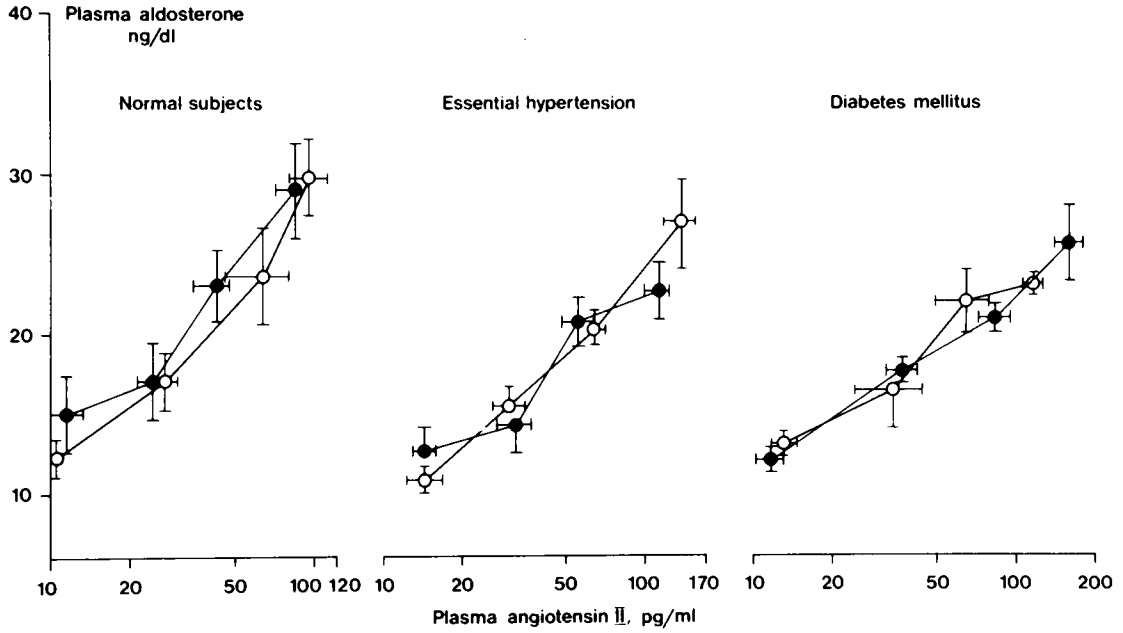

Fig. 4. Relationships between plasma aldosterone and plasma angiotensin II concentrations before and after ketanserin in normal subjects and patients with essential or diabetes-associated hypertension. ○ (placebo), ● (ketanserin) show mean values, bars indicate standard error. Dose–response curves were not modified after ketanserin.

curve could be demonstrated in patients with essential or diabetes-associated hypertension. Moreover, the relationship between the endogenous sympathetic activity and the pressor reactivity to the physiological neurotransmitter NE was not modified. This contrasts with the effects of α_1-antagonists, the antihypertensive effect of which is associated with a marked inhibition of the pressor reactivity to NE [25]. Moreover, ketanserin did not modify the Ang II-dependent pathways for blood pressure and aldosterone regulation.

This investigation has confirmed the blood pressure lowering potential of ketanserin in patients with essential hypertension. Blood pressure was significantly decreased in the supine and upright position in 10 hypertensive patients who received a daily dose ranging from 80 to 120 mg. In contrast to essential hypertension, the blood pressure response of diabetics with arterial hypertension did not achieve statistical significance. Considering the small number of patients included, it is difficult to draw conclusions about the possibility of a weaker antihypertensive efficacy of ketanserin in diabetes-associated hypertension. This form of hypertension is associated with the combination of elevated body sodium, normal blood volume and exaggerated pressor reactivity to NE [15,22]. The eight hypertensive diabetics examined in this study had an elevated mean body sodium level (111%) and a normal blood volume (97%); the pressor dose of infused NE tended to be lower, on average, than in normal subjects, but similar to those patients with essential hypertension, as has been reported in larger patient groups [15]. It is unknown whether and to what extent sodium retention may counteract, at least partly, the hypotensive influence of S2-inhibition. While considering the hypotensive effect in essential hypertension, the disturbed noradrenergic-dependent blood pressure regulation should not be expected to modify the consequences of S2-blockade. On the other hand, the association of diabetes mellitus with low plasma renin activity or with disturbances of renin and aldosterone responsiveness to postural stimulation [26,27], does not appear to influence the blood pressure response to ketanserin, since in essential hypertension the latter is independent from the pre-treatment plasma renin activity [28].

Several mechanisms could theoretically participate in the regulation of pressor reactivity, including the metabolism of sodium and potassium, baroreceptor sensitivity and the metabolism of the infused agents. Sodium tends to potentiate [29] and potassium to blunt [30] pressor responsiveness. Sodium and potassium metabolism, as judged by the plasma levels and urinary excretion rates, were not modified by ketanserin in the three study groups. Sodium retention could develop during chronic α_1-blockade [31], and an increase in body weight can occur in hypertensives receiving ketanserin [32]. A similar tendency appeared in our normal and diabetic subjects. However, the increases in body sodium and circulatory volume were only mild and not significant during the 8-week treatment period. Moreover, the lack of a significant suppression of sodium-dependent hormones such as NE, Ang II and aldosterone [32] argues against a metabolic relevance of these variations in body sodium/fluid volume state. Baroreflex sensitivity modulates pressor responses [33]. Diabetes mellitus may be accompanied by a disturbance of baroreflex sensitivity, which could contribute to the enhanced pressor reactivity to NE [34]. Baroreflex sensitivity, as judged from the responses of heart rate to the phenylephrine, NE or Ang II-induced increases in blood pressure, appeared to be unaltered after ketanserin in our three study groups. The metabolism of infused NE or Ang II, as judged from the

correlations relating plasma levels to the corresponding infusion rates, was also unchanged after ketanserin in normal subjects and patients with essential or diabetes-associated hypertension. These factors, therefore, could have played at most only a minor role in the regulation of cardiovascular pressor reactivity during treatment with ketanserin.

Ketanserin, in the stable phase of treatment, decreased the cardiovascular reactivity to α_1-selective agonists in previous studies [9,10]. This effect was of different magnitude in the three groups studied in this investigation; it could be clearly demonstrated in normal subjects, did not entirely achieve statistical significance in essential hypertension and was absent in diabetics. The sympatho-adrenal activity, as judged by the plasma concentrations of NE and epinephrine measured in the basal state and after postural stimulation, was not modified in normal subjects and hypertensive patients. An acute stimulation of plasma catecholamines has been noted in response to acute ketanserin-induced hypotension [1,7]. A slight increase in basal or stimulated NE and epinephrine was also reported in 14 patients with essential hypertension treated for 6 weeks with ketanserin [9], but no changes in plasma NE were observed in a larger study comprising 24 hypertensive patients treated for 8 weeks with a daily 80-mg dose of ketanserin [32]. In this study, the unchanged noradrenergic activity was associated with an unchanged pressor reactivity to NE after S2-serotonergic inhibition. Both variables are physiologically inversely interrelated [11] and their physiological relationship after ketanserin suggests that this compound does not interfere with noradrenergic-dependent blood pressure regulation. This pattern contrasts markedly with the influence of α_1-adrenoceptor antagonists, which is associated with a stimulation of circulating NE and a marked decrease of the pressor responsiveness to NE [25], or of other antihypertensive agents such as thiazide-like diuretics or calcium antagonists, which decrease the pressor reactivity without variations in endogenous noradrenergic activity [14,35,36]. Although modifications of the relationship between sympathetic activity and the noradrenergic responsiveness of the cardiovascular system are not involved in the antihypertensive mechanism of serotonin S2 antagonist with ketanserin at the dosage used in this study, it is possible that an adrenolytic component may be involved at doses higher than those usually applied in the pharmacotherapy of essential hypertension [37]. *In vitro*, an α_1-adrenoceptor antagonism can be revealed at higher doses of ketanserin than those causing serotonin S2 antagonism [37]. Finally, although the data of this investigation does not support this possibility, it is possible that under particular circumstances, adrenergic mechanisms different from α_1-inhibition may contribute to the antihypertensive effect of ketanserin, such as inhibition of the amplifying effect of serotonin on the pressor effects of NE [1].

Serotonin increases plasma renin levels in rats [38] and influences renin release through a central mechanism in man [39]. Cyproheptadine, an unselective serotonin antagonist, decreases the stimulation of renin in response to sodium depletion [39]. On the other hand, experiments *in vitro* suggest that ketanserin is able to reduce the stimulatory capacity of glomerulosa cells to serotonin, Ang II and potassium [40]. Studies in normal subjects or patients with essential hypertension indicate that, after acute administration, [6,7,9,41], ketanserin may cause a transient increase in plasma renin activity without changes in plasma aldosterone or cortisol levels [1,6,7,41]. However, the short- or long-term treatment with ketanserin is not associated with significant modifications of the activity of the renin-angiotensin-aldosterone system [28,32,42]. This is confirmed in this study; plasma levels of renin, Ang II and aldosterone were not modified in either normal subjects or patients with essential or diabetes-associated hypertension; plasma cortisol was not monitored. Moreover, two Ang II-dependent functions, namely pressor and aldosterone sensitivity to Ang II, were not modified by ketanserin. Therefore, the unchanged pressor responsiveness to Ang II does not support the concept that serotonin S2 receptors may be directly involved in the modulation of Ang II pressor activity under clinical conditions, while the unchanged aldosterone-Ang II interrelationship after ketanserin indicate that serotonin S2 receptors on adrenal glomerulosa cells could play at least a minor role in the regulation of aldosterone secretion.

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