Effects of the Nonpeptide V1 Vasopressin Receptor Antagonist SR49059 in Hypertensive Patients

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Abstract—We assessed the clinical and pharmacological profile of the orally active V1 vascular vasopressin (AVP) receptor nonpeptide antagonist SR49059 (SR) during the osmotic stimulation of AVP release in hypertensive patients. In a double-blind crossover-versus-placebo study, 24 untreated stage I or II essential hypertensive patients (12 whites and 12 blacks) received a single 300 mg oral dose of SR 2 hours before the stimulation of AVP secretion with a 5% hypertonic saline infusion. Hemodynamic, hormonal, and pulmonary parameters were monitored for up to 28 hours after drug administration. SR did not alter blood pressure or heart rate before the saline infusion and did not reduce the blood pressure increment induced by the hypertonic saline infusion. However, the blood pressure peak at the end of the hypertonic saline infusion was slightly lower in the presence of SR (P=0.04). Heart rate was significantly faster between 4 and 6 hours after SR administration (P=0.02). The rise in plasma sodium and osmolality triggered by the saline infusion was not modified by SR, but AVP release was slightly greater in the presence of SR (P<0.0003). AVP-induced aggregation of blood platelets in vitro was significantly reduced by SR, with a peak effect 2 hours after drug administration that coincided with the SR peak plasma concentration. Plasma renin activity and aldosterone before and after the saline infusion were not modified by SR. Urine volume and osmolality were not altered by SR administration. SR effects were similar in the 2 ethnic groups as well as in salt-sensitive versus salt-resistant patients. In a situation of AVP osmotic release and volume expansion in hypertensive patients, a single oral dose of the V1 vascular AVP receptor nonpeptide antagonist SR49059, which is able to block AVP-induced platelet aggregation, exerts a transient vasodilation effect that is not associated with a sustained blood pressure reduction. SR49059 is a pure V1 vascular receptor antagonist that is devoid of V2 renal receptor actions. (Hypertension. 1999;34:1293-1300.)

Key Words: vasopressins n nonpeptide antagonist n vasopressins n hypertension, essential n osmoregulation

The neurohypophyseal hormone arginine vasopressin (AVP) is involved in the regulation of body fluid osmolality, blood volume, blood pressure, cell contraction, cell proliferation, and adrenocorticotropic hormone secretion via the stimulation of specific receptors currently classified into V1 vascular (V1R), V2 renal (V2R), and V3 pituitary (V3R) subtypes with distinct pharmacological profiles and intracellular second messengers.1

AVP has been shown to be one of the most powerful in vitro vasoconstrictor substances,2 and its vasoconstrictor and mitogenic actions may contribute to the pathogenesis of arterial hypertension, heart failure, and atherosclerosis.3,4 AVP plays a role in the maintenance of blood pressure in several conditions, including upright posture, dehydration, hemorrhage, adrenal insufficiency, and cardiac failure, and during surgery.5,6 An abnormal vascular reactivity specific for AVP has been noted in models of genetic and experimental hypertension, and AVP is instrumental in the genesis and maintenance of several models of experimental hypertension.3,4,6 AVP implication in the development or maintenance of hypertension, or both, was based on measurements of plasma and urinary AVP levels and responses to specific AVP antiserum, peptide or nonpeptide antagonists.7–9 For instance, a recent study demonstrated that in young spontaneously hypertensive rats, the nonpeptide V1R antagonist OPC-21268 attenuated the development of hypertension in adult animals.10 Several potent and selective AVP receptor peptide antagonists have been developed since the original synthesis by Manning and Sawyer of the first potent and selective V1 receptor antagonist, d(CH2)5Tyr(Me)AVP.11 However, the lack of oral bioavailability and the short half-life of these peptide compounds have limited their use in clinical medicine. Recently, nonpeptide AVP antagonists were discovered through the random screening of chemical entities.12–14 The availability of such orally active compounds now allows the assessment of the potential therapeutic applications of AVP receptor blockade in human diseases.

SR49059 [(2S)-1-[(2R,3S)-5-chloro-3-(2-chloro-phenyl)-1-(3,4-
dimethoxybenzene-sulfonyl)-3-hydroxy-2,3-dihydro-1H-indole-2-carbonyl[pyrrolidine-2-carboxamide] was developed through the chemical optimization of a lead compound found on random screening. It is the most potent and selective orally active V1R antagonist described so far. It has a marked affinity, selectivity, and efficacy toward both animal and human V1 receptors and is devoid of partial agonist activity. This compound inhibits AVP-induced vascular smooth muscle cell contraction and blood pressure elevation for at least 8 hours. In healthy human volunteers, SR49059 inhibits exogenous AVP-induced platelet aggregation, skin blanching, and vasoconstriction. In the present article, we report the results of the first administration of the nonpeptide V1R antagonist SR49059 to untreated hypertensive patients before and during an hypertonic saline infusion that produces a significant osmotic release of AVP in the circulation.

Methods

This monocenter, single-oral-dose, placebo-controlled, double-blind, crossover study was approved by the Institutional Review Board of University Hospitals of Cleveland. Written informed consent was obtained from all subjects. Twenty-four nonsmoker male patients (12 whites and 12 blacks) with stage I or II essential hypertension completed the entire study. These patients were free of any acute or chronic disease except for arterial hypertension. Secondary forms of hypertension were ruled out through the usual procedures. Eligible patients already receiving antihypertensive agents were switched at screening visit, then on days 0, 1, 7, and 8 for measurement of blood pressure and heart rate (HR) were monitored at frequent intervals. Baseline MABP recorded every 10 minutes was observed after discharge at noon on day 2. A standardized lunch was served (1800 to 2000 Kcal per day: 100 to 250 mmol sodium, 50 to 100 mmol potassium, 1500 mL mineral water). Beverages containing caffeine were not allowed during the stays in the GCRC. Plasma osmolality (pOsm), sodium (pNa), AVP (Nichols Institute RIA), and blood hematocrit (Hct) were measured on days 1 and 8 at H0, at H+1, q30min from H+2 to H+4, and at H+5. At H6, H+2, and H+4, blood was drawn for measurement of plasma renin activity (PRA; RIANEN AE; Dupont), plasma aldosterone (PA; DPC Coat-a-count RIA), in vitro AVP-induced platelet aggregation (ChronoLog aggregometer), and plasma SR49059 (liquid chromatography–mass spectrometry/mass spectrometry assay, limit of detection 0.2 ng/mL). The 24-hour urine collections were completed at the screening visit, then on days 0, 1, 7, and 8 for measurement of volume, pOsm, creatinine, and sodium, potassium, and calcium levels.

Results

The characteristics of the patients at baseline are summarized in Table 1. The white and black groups were identical in terms of age, height, weight, baseline values for resting supine blood pressure, HR, clearance of creatinine, and sodium and potassium excretion. Calcium excretion was significantly lower in the black patients than in the white patients, suggesting a larger circulating blood volume in the former group.

Blood Pressure and HR Alterations

Sixty-three measurements of blood pressure and HR were obtained between H-1 and H+28. The mean arterial blood pressure (MABP) profile after placebo and SR49059 administration is shown in Figure 1. Baseline MABP recorded every 15 minutes between H-1 and H0 was similar in the 2 treatment groups (100±2 and 101±2 mm Hg before placebo and SR49059 administration, respectively). During the first 2 hours after drug administration (H0 to H+2), no significant alteration of MABP recorded every 10 minutes was observed.
regardless of whether the patients received the placebo or 300 mg of SR49059 (average MABP 100±2 mm Hg). The hypertonic saline infusion administered between H+2 and H+4 produced a significant rise in blood pressure that peaked at the end of the infusion, with the peak being lower after SR49059 administration than after placebo (MABP 114±2 versus 118±2 mm Hg, P<0.04; Figure 1A). However, there was no treatment difference in the average blood pressure during the period of H+2 to H+6. Between H+6 and H+28, no significant difference in blood pressure levels was noted between the 2 treatment groups, and SR49059 administration did not affect the circadian rhythm of blood pressure noted after placebo ingestion (Figure 1B). Regardless of treatment administration, the average MABP between H+6 and H+28 remained higher in the black patients than in the white patients (106±2 versus 98±2 mm Hg, P=0.03), because of a smaller circadian variation in the former group. Finally, no overall difference in terms of blood pressure alterations after placebo or SR49059 administration was observed when the patients were divided between salt-sensitive (blood pressure rise during the saline infusion, n=18) and salt-resistant (no blood pressure rise during the saline infusion, n=6) subgroups.

The HR profile after placebo and SR49059 administration is shown on Figure 2. Baseline HR between H-1 to H0 was similar in the 2 treatment groups (62±2 and 61±2 bpm before placebo and SR49059 administration, respectively). During the first 2 hours after drug administration, no significant alteration of HR was observed regardless of whether the patients received the placebo or SR49059 (mean HR 60±1 bpm). The hypertonic saline infusion administered between H+2 and H+4 produced a significant acceleration in HR that peaked ~1 hour after the end of the saline infusion (Figure 2A). The average HR was faster between H+4 to H+6 after SR49059 administration than after placebo administration (mean HR 70±2 versus 67±2 bpm, P=0.02; Figure 2A). After discontinuation of the hypertonic saline infusion, HR slowed down and no significant differences in HR were noted thereafter between the 2 treatment groups (Figure 2B). No difference in HR was noted between the 2 ethnic subgroups.

**pOsm, pNa, AVP, and Blood Volume Alterations**

pOsm, pNa, plasma AVP (pAVP), and Hct alterations after placebo and SR49059 administration are shown in Figure 3. During the first 2 hours after drug administration, no significant alteration in pOsm, pNa, pAVP, or Hct was observed regardless of whether the patients received the placebo or SR49059. The hypertonic saline infusion administered between H+2 and H+4 produced a significant rise in pOsm (from 286 to 305 mosm/kg on placebo and from 286 to 306 mosm/kg on SR49059), pNa (from 139 to 148 mmol/L on placebo and from 140 to 149 mmol/L on SR49059), and pAVP (from 2.9 to 6.6 pg/mL on placebo and from 2.8 to 7.6 pg/mL on SR49059). These alterations reflect the hyperosmotic challenge and its related AVP release. Alterations in pOsm and pNa were similar after placebo and SR49050 administration and comparable in the 2 groups. Mean pAVP response to the hypertonic infusion was higher after SR49059 administration than after placebo (crossover ANOVA performed on pAVP area under the curve between H+2 and H+5, P=0.0003; analysis performed on the first period only
due to a significant carry-over effect). Correlation analysis of pAVP versus pNa was statistically significant (P < 0.0001) after the administration of placebo (pAVP = 38.2 ± 0.30 pNa) and SR49059 (pAVP = 50.1 ± 0.38 pNa). The slopes of the regression lines differed significantly between the 2 treatments (P = 0.0001). In addition, the linear regression analysis of pAVP versus pOsm was statistically significant (P < 0.0001) after the administration of placebo (pAVP = 41.7 ± 0.16 pOsm) and SR49059 (pAVP = 52.3 ± 0.19 pOsm). The slopes of the regression lines differed significantly between the 2 treatments (P < 0.0001). The volume expansion produced by the saline infusion translated into a significant decrease in Hct (P < 0.0001) that seemed to be greater (although not statistically significant) after SR49059 administration (Figure 3). Average Hct was higher in the white patients than in the black patients, but this difference did not reach statistical significance (P = 0.082). Onset and intensity of thirst sensation were the same after placebo and SR49050 administration and identical in the 2 groups.

PRA and PA Alterations

PRA and PA were measured at baseline (H0) and before (H+2) and at the end of the hypertonic saline infusion (H+4). The administration of SR49059, as well as the placebo, did not alter PRA or PA measured 2 hours after drug ingestion. At the end of the hypertonic saline infusion, PRA and PA were expectedly reduced (P < 0.0001) but to the same level regardless of whether the patients received the placebo (PRA from 0.63 ± 0.02 to 0.38 ± 0.02 ng angiotensin [Ang] I · mL · h⁻¹; PA from 7.6 ± 0.1 to 3.9 ± 0.06 ng/dL) or SR49059 (PRA from 0.63 ± 0.03 to 0.39 ± 0.01 ng Ang I · mL · h⁻¹; PA from 8.1 ± 0.2 to 4.1 ± 0.10 ng/dL). Analysis of the two groups revealed that PRA and PA were significantly lower in the black patients than in the white patients at baseline (PRA 0.80 ± 0.13 versus 0.46 ± 0.09 ng Ang I · mL · h⁻¹, PA 8.98 ± 0.7 ng/dL). Within each ethnic group, PRA and PA profiles were similar after placebo and SR49059 administration (data not shown).

AVP-Induced Platelet Aggregation

Aggregation of platelet-rich plasma samples by AVP was measured at baseline (H0) and then before (H+2) and at the end (H+4) of the hypertonic saline infusion (ie, 2 and 4 hours after placebo or SR49059 administration). AVP induced a concentration-dependent platelet aggregation that was unaltered by the administration of the placebo (Eₘₐₓ = 41 ± 3, 42 ± 3, and 43 ± 3 mm and EC₅₀ = 16 ± 2, 15 ± 3, and 18 ± 3 nmol/L at times H0, H+2, and H+4, respectively, Figure 4A). Conversely, the administration of SR49059 provoked a dramatic reduction in AVP-induced platelet aggregation measured 2 and 4 hours after the drug ingestion (Eₘₐₓ = 40 ± 3, 13 ± 1, and 16 ± 2 mm at times H0, H+2, and H+4, respectively, F = 29.542, P < 0.0001; Figure 4B). EC₅₀ was 15 ± 3 nmol/L at H0 on the day of SR49059 administration but could not be reliably calculated at times H+2 and H+4 after SR49059 ingestion because of the dramatic blockade of the AVP effect by the antagonist. There was no difference between the ethnic groups in terms of AVP effect on platelet aggregation.

Urine Parameters

To assess the influence of SR49059 administration on renal function, urine volume, osmolality, and excretion of creatinine, the sodium, potassium, and calcium levels were mea-
As indicated in Table 2, the day on which the placebo was administered, the hypertonic saline infusion produced an osmotic diuresis characterized by a significant increase in urine volume and osmolar clearance. The osmotic release of AVP resulted in a further reduction in free water clearance. These urine parameters were similar during the day on which the patients received the hypertonic saline infusion on SR49059, thus suggesting that SR49059 did not block the AVP V2 renal receptors. Indeed, free water clearance was equally reduced by the hypertonic saline infusion regardless of whether the patients received SR49059 or placebo. Moreover, urine excretions of sodium (491 ± 625 versus 514 ± 623 mmol/d), potassium (101 ± 65 versus 103 ± 65 mmol/d), and calcium (220 ± 623 versus 229 ± 623 mg/d) were similar on the day of the saline infusion regardless of whether the patients received placebo or SR49059. A comparison of the ethnic subgroups revealed that urine volume, sodium, potassium, and osmolality, as well as osmolar and free water clearances, were similar in the 2 groups, whereas urine calcium was lower in the black patients than in the white patients (mean 156 ± 614 versus 235 ± 614 mg/d, \(P=0.003\)). Finally, sodium excretion on the day of the hypertonic saline infusion was identical in the 2 groups regardless of whether they received the placebo (510 ± 633 versus 472 ± 633 mmol/d) or SR49059 (500 ± 633 versus 529 ± 636 mmol/d).

**Plasma Levels of SR49059**

Plasma levels of SR49059 were measured with the use of liquid chromatography–mass spectrometry/mass spectrometry at 2 and 4 hours after drug administration.\(^{18}\) The levels were 14.5 ± 62.2 and 12.23 ± 62.8 ng/mL at \(H=12\) and \(H=14\), respectively, with no difference between the 2 subgroups. These levels were sufficient to dramatically reduce AVP-induced platelet aggregation, and the peak level of plasma SR49059 at \(H=12\) coincided with the maximum inhibition of aggregation. There was no relationship between blood pressure alterations induced by the saline infusion and plasma levels of SR49059.

**Discussion**

The potential usefulness of AVP antagonists in the treatment of human diseases remains an unanswered question because of the lack of orally active agents. Previously, the V1 R peptide antagonist d(CH\(_2\))\(_5\)Tyr(Me)AVP had been administered intravenously to human subjects. In well-hydrated and resting human volunteers, this V1 R peptide antagonist did not alter blood pressure,\(^{19}\) suggesting that AVP is not required for blood pressure maintenance in resting conditions. In patients with mild uncomplicated essential hypertension, the same peptide V1 R AVP antagonist did not produce cardiovascular alterations unless AVP release has been stimulated through various maneuvers such as cigarette smoking or a sauna.\(^{20}\) However, in patients with severe salt-induced hypertension of end-stage renal disease, where plasma AVP was found to be increased, this V1 R peptide antagonist did produce a modest but consistent fall (9 to 12 mm Hg) in supine blood pressure.\(^{21}\) In patients with “accelerated” or malignant hypertension of various causes, this V1 R peptide antagonist produced a small blood pressure fall when administered as a first agent; however, if the patients were pretreated with a sympatholytic agent (clonidine), the V1 R antagonist produced a substantial reduction in diastolic blood pressure (up to 18 mm Hg).
largest blood pressure decrease was observed in patients pretreated with doses of clonidine suppressing plasma norepinephrine levels to 80 pg/mL (normal 250 to 400 pg/mL). In addition, the administration of 1 dose of this V1R AVP peptide antagonist in diabetic hypertensive patients with autonomic neuropathy did not alter the supine blood pressure but produced an orthostatic diastolic blood pressure fall of 44 mm Hg, thus suggesting that AVP played a major role in sustaining blood pressure in the upright posture when the baroreflex system is altered.

Decreased activity of the autonomic nervous system and suppression of the renin-angiotensin system (RAS) led to a predominant role for AVP in blood pressure homeostasis. Black patients, who often have a suppressed RAS, and elderly subjects with an altered baroreflex function may have a more important AVP-mediated pressure component. This hypothesis was tested in 27 essential hypertensive patients by De Paula et al, who studied upright blood pressure levels as a function of age and race after the administration of a 0.5 mg IV bolus of the V1 R peptide antagonist d(CH2)5 Tyr(Me)AVP. Blood pressure reduction induced by the V1 R peptide antagonist was greater in the elderly and black patients (−15 mm Hg in both groups) than in the young and white patients (−8 and −7 mm Hg, respectively). Presumably, the greater reduction in blood pressure in the elderly and black patients was related to the active involvement of AVP in blood pressure maintenance in situations of autonomic dysfunction or suppressed activity of the RAS. These blood pressure differences between races prompted us to include both whites and blacks in our study. At variance with the results of De Paula et al obtained with a V1 R peptide antagonist, our data did not reveal any pharmacodynamic differences between the 2 groups after the administration of the V1 R nonpeptide antagonist SR49059. Several parameters may explain this discrepancy, including the use of different antagonists, different conditions of blood pressure recording (supine in the present study versus upright in the study of De Paula et al), distinct demographic characteristics of the population studied in terms of age and gender (male and female in the study of De Paula et al versus males only in the present study) and the lack of placebo control in the study of De Paula et al. The gender factor must be kept in mind in light of studies in the rat that suggest the vasoconstrictor and antidiuretic actions of AVP are greater in male and estrous female rats than in nonestrous female rats.

The goal of our study was to explore the pharmacodynamic profile of the orally active V1R nonpeptide antagonist SR49059 in basal conditions and after osmotic stimulation of AVP release. The rationale for the use of an hypertonic saline infusion in the present study was severalfold. The most physiological and sensitive way to stimulate AVP secretion is to raise pOsm. The administration of nicotine or other agents that stimulate AVP secretion, induction of pain, or nausea are unpredictable, poorly reproducible, and unphysiological alternatives that cannot be used reliably in a crossover protocol. The induction of AVP release by dehydration, hypovolemia, or hypotension is not desirable in a protocol aimed at testing the hemodynamic profile of a compound that may potentially reduce peripheral resistances and blood pressure. A constant-rate hypertonic saline infusion has been shown by several authors to produce a smooth rise in pOsm associated with a correlated smooth rise in pAVP; this protocol of hypertonic saline infusion has already been validated by us and several groups in human subjects.

An examination of the results of our clinical investigation revealed several important findings. The administration of a single 300 mg oral dose of SR49059 in patients on a normal sodium diet and resting in supine position did not produce a blood pressure reduction at a time corresponding to the peak plasma concentration of the medication (H+2). This 300-mg dose has been shown to effectively block AVP-induced platelet aggregation in normal volunteers and to prevent uterine contractions induced by lysine AVP in 12 healthy women. In this group of 12 normotensive women, injection of lysine AVP produced a transient increase in supine systolic blood pressure on placebo treatment (+5 mm Hg), whereas a 4 mm Hg decrease was noted after the administration of 300 mg of SR49059, with the difference between the treatments being significant at 1 and 2 hours after the dose. No significant differences in supine diastolic blood pressure or HR were observed. These different results in terms of SR49059 effects on resting supine blood pressure could be explained by differing sodium intakes and volume status.

In addition, in a situation of maximum osmotic release of AVP induced by the hypertonic saline infusion, 1 dose of SR49059 did not reduce the significant blood pressure rise observed during that stimulation test. One may conclude from these observations that SR49059 is not acutely an hypertensive or antihypertensive agent in a situation of normal hydration and even volume expansion. However, it appears that SR49059 did produce a vasodilation effect, as suggested by the sustained increment of HR for up to 12 hours after the drug administration and by the lower blood pressure peak after the hypertonic saline infusion (compared with the placebo treatment). The vasodilation effect of SR49059 may not have led to a blood pressure reduction in the presence of a blood volume increase.

The administration of 1 dose of SR49059 seems to slightly increase AVP release in response to an osmotic challenge, as suggested by the altered slopes of the relation between pAVP and pNa or pOsm. This suggests that the V1R antagonist may alter AVP release either (1) directly or (2) via its vasodilation effect potentiating AVP osmotic release, but SR49059 does not cross the blood-brain barrier; the more probable mechanism is (3) via antagonism at the AVP receptor level.

As expected, the volume expansion produced by the saline infusion led to a suppression of the renin-angiotensin-aldosterone axis, and that inhibition was not modified by the administration of SR49059, thus confirming the specificity of this agent for AVP receptors. As anticipated, average values for PRA and PA were lower in the black patients than in the white patients at baseline.

The assessment of AVP-induced platelet aggregation during our study resulted in some interesting findings. This test is highly reproducible in a given patient as shown by the similarity of the 3 concentration-response curves established the day on which the patients received the placebo. In the present study performed in hypertensive patients, the EC50
values were lower (range 13 to 16 nmol/L) than those in the study we reported with the same protocol in healthy volunteers (EC50 = 28 nmol/L). This difference may suggest that blood platelets of hypertensive patients are more sensitive to AVP than are platelets from normotensive patients, an observation that will require confirmation in larger series of patients. The AVP-induced aggregation profile measured at the end of the hypertonic saline infusion was not modified, thus suggesting that the platelet receptor is not downregulated by a 2- to 3-fold acute increase of AVP circulating levels. The administration of a 300-mg dose of SR49059 produced a dramatic reduction in AVP ability to trigger platelet aggregation via blockade of the platelet V1R. These dramatic changes indicate that the medication is absorbed and finds its way to the “effective compartment” (i.e., the V1R of human platelets where it efficiently blocks AVP actions). SR49059 antagonism of AVP-aggregating effect has been shown to be competitive.

The analysis of the renal parameters assessed in our study indicates that SR49059 does not block the AVP V2 renal receptors. This observation of importance confirms that SR49059 is in vivo a specific V1R antagonist that should not produce a state of nephrogenic diabetes insipidus, and its related deleterious alterations of pNa and pOsm, and that SR49059 does not have an agonist effect (V1 or V3) as observed with some peptide antagonists. This pure V1R vascular antagonist profile is of importance when one considers the “ideal” profile of a AVP antagonist to be developed as an antihypertensive agent. Based on the elegant studies performed by Sladek et al23–25 with peptide antagonists in the spontaneously hypertensive rat, a pure V1R antagonist is not expected to produce a sustained decrease in blood pressure, whereas a mixed V1/V2R antagonist will achieve a reduction in blood pressure via alterations of both peripheral resistances and circulating blood volume. However, the effective and safe ratio of V1/V2R antagonist remains to be established because of the study by Hofbauer et al26 who observed in DOCA-salt hypertensive rats that the administration of a mixed V1/V2R peptide antagonist led to a greater blood pressure reduction than a pure V1R antagonist although at the expense of water loss and hypernatremia.

In our study, the 2 groups turned out to be well matched, thus allowing intergroup comparisons. In these 2 groups, we did not observe any difference in the AVP system in terms of circulating pAVP levels, osmoregulation of AVP release, and pharmacodynamic response to the V1R antagonist SR49059.

In conclusion, in a situation of osmotic release of AVP and volume expansion in a group of male hypertensive patients, a mixed V1/V2R peptide antagonist led to a greater blood pressure reduction than a pure V1R antagonist although at the expense of water loss and hypernatremia.


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