Differences in Response to the Peptidyldipeptide Hydrolase Inhibitors SQ 20,881 and SQ 14,225 in Normal-Renin Essential Hypertension

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SUMMARY We compared vascular and hormonal responses to teprotide (SQ 20,881) and captopril (SQ 14,225) in patients with normal renin essential hypertension given a 10 mEq sodium diet. In 10 patients receiving SQ 20,881, significant changes occurred in diastolic blood pressure (DBP, -13 ± 2.5 mm Hg), angiotensin II (-7.1 ± 2.1 pg/ml), and plasma renin activity (PRA, +6.6 ± 1.9 ng/ml/hr) (p < 0.01 in all cases). Twenty-one patients receiving SQ 14,225 had significant changes in mean DBP (-18 ± 1.5 mm Hg), angiotensin II (-6.6 ± 1.5 pg/ml), and PRA (+7.8 ± 2.4 ng/ml/hr) (all p values < 0.01). In spite of a significantly greater hypotensive response (p < 0.02), patients receiving SQ 14,225 showed increments in PRA and decrements in angiotensin II that did not differ significantly from those seen after SQ 20,881. Moreover, there was a significant change in plasma kinins in patients receiving SQ 20,881 (+2.0 ± 0.9 ng/ml, p < 0.01) but no change in kinins in patients receiving SQ 14,225 (0.0 ± 0.1, ns). We conclude that there are important differences in the mechanism mediating the hypotensive response to SQ 20,881 and SQ 14,225 in normal renin essential hypertension. (Hypertension 2: 604-609, 1980)

Key Words • teprotide • captopril • vascular hormonal responses • essential hypertension

THE nonapeptide teprotide (SQ 20,881, pryy-trp-pro-arg-pro-glu-ile-pro-pro), originally isolated from the venom of the Brazilian pit viper Bothrops jararaca, is a potent inhibitor of the enzyme peptidyldipeptide hydrolase (angiotensin-converting enzyme, kininase II) which converts angiotensin I to angiotensin II and also inactivates the potent vasodilator, bradykinin.1,2 SQ 20,881 has been shown to be an effective hypotensive agent in humans, but, being a polypeptide, it is not suitable for oral administration. This limitation led to the design and synthesis of a group of nonpeptide compounds that share SQ 20,881's specific effect as an inhibitor of peptidyldipeptide hydrolase and yet are active when taken orally. The most effective of these orally-active enzyme inhibitors has been captopril (SQ 14,225).3

On theoretical grounds, SQ 20,881 and SQ 14,225 should have the same mechanism of action with similar hypotensive and endocrinologic effects. To test this hypothesis, we obtained dose-response data from a group of patients with normal-renin essential hypertension receiving SQ 14,225 and compared these to the data obtained from a similar group of patients who received SQ 20,881.

Materials and Methods

Thirty-one patients with normal-renin essential hypertension, 19 to 59 years of age, were admitted to the Clinical Research Center of the Peter Bent Brigham Hospital. All patients met the following criteria: outpatient DBP greater than 90 mm Hg on at least three different occasions, documented evidence of hypertension for at least 6 months before study, normal upright plasma renin activity (PRA) in low sodium balance as previously defined in our laboratory.4 In addition, secondary causes of hypertension were eliminated on the basis of rapid sequence intravenous pyelogram, serum creatinine and electrolytes, plasma aldosterone, and 24-hour urinary vanillylmandelic acid, metanephrines, catecholamines, free cortisol, 17 hydroxy and 17 ketosteroids. Where indicated, renal arteriography and bilateral renal vein renin determinations were obtained. No antihypertensive medications had been...
taken for at least 10 days prior to study. The protocol was approved by the Human Subjects Committee of the Peter Bent Brigham Hospital, and written informed consent was obtained in all instances.

**SQ 14,225 Administration**

Twenty-one patients were studied supine, following an overnight fast, in balance on a 10 mEq Na and 100 mEq K diet. Blood pressures were monitored at 2-minute intervals with an automatic blood pressure recorder (Arteriosonde, Roche Medical). After control blood samples were drawn through a previously-positioned indwelling peripheral venous catheter, a selected dose of SQ 14,225 (10, 25, 50, or 100 mg; 0.580–5.80 μmoles/kg) was administered by mouth. Samples were obtained at 0, 30, 60, 120, and 360 minutes for PRA, angiotensin II, plasma kinins, aldosterone, and cortisol. In selecting SQ 14,225 dosage for each individual patient, the following procedure was employed; prior to the study day, under constant blood pressure monitoring, patients were given SQ 14,225 2 at 2-hour intervals beginning with a dose of 10 mg and increasing dosage incrementally until a DBP decrement of 15 mm Hg was obtained or until the patient received a 100 mg dose of SQ 14,225. In a preliminary study, 5 mg of SQ 14,225 elicited no hypotensive response in three normal renin essential hypertensives. The drug dose administered on the day following dose response curves in individual subjects, subgroups of patients received on subsequent days (study day) either 10, 25, 50, or 100 mg doses of SQ 14,225, and their hormonal responses were followed over 6 hours. Sufficient time, over 18 hours, elapsed between dose titration and study so that all vascular and hormonal parameters had returned to control. To document that prior exposure to SQ 14,225 during dose titration did not influence patients' response to SQ 14,225 on the study day, a separate group of 13 normal renin hypertensives in low-sodium balance were given SQ 14,225, 10–50 mg, without any prior exposure to the drug. Vascular and hormonal responses were measured at the same intervals as for patients who had undergone dose titration.

**SQ 20,881 Infusion**

Ten patients were studied under the same conditions as for the SQ 14,225 administration. After control blood samples were obtained, an intravenous infusion of SQ 20,881 was given over a 3-minute period. Increasing doses of SQ 20,881 (30,100, and 300 μg/kg; 0.024–0.240 μmoles/kg) were administered over three successive 20-minute intervals or until a 15 mm Hg drop in DBP was noted. Blood samples were obtained at the end of each 20-minute infusion.

All blood samples were collected on ice and spun immediately, and the plasma or serum separated and frozen until time of assay. Plasma kinins were measured by a modification of the radioimmunoassay technique by Talamo et al. as previously described. Plasma renin activity and angiotensin II were measured by double-antibody radioimmunoassay. Group means have been presented with the standard error of the mean (SEM) as a measure of dispersion. Statistical probability was evaluated using Student's t test, analysis of variance, or Fisher's exact test.

**Results**

Patients receiving SQ 20,881 and SQ 14,225 were similar in age, weight, serum creatinine, urine and serum electrolytes, and control blood pressure. Control kinins and plasma renin activity were similar in the two groups, although angiotensin II concentrations were significantly higher in patients receiving SQ 20,881 (p < 0.01) (table 1).

**Vascular Responses to Peptidyldipeptide Hydrolase Inhibition**

Both SQ 20,881 and SQ 14,225 led to significant decrements in mean DBP (p < 0.01) although the decrement after SQ 14,225 was significantly greater than that after SQ 20,881 (−18.3 ± 1.5 vs −13.1 ± 2.5 mm Hg, p < 0.02; Fisher exact test). Further, SQ 14,225 led to a decrement in DBP of ≥10 mm Hg in 20 of 21 patients, while only 6 of 10 patients had a similar decrement with SQ 20,881 (fig. 1). Blood pressure decrement in a group of patients who had no prior exposure to SQ 14,225 (−15 ± 2.0 mm Hg) did not differ significantly from study patients who had undergone dose titration with SQ 14,225 (fig. 2).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SQ 20,881</th>
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<tbody>
<tr>
<td>number</td>
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<td>21</td>
</tr>
<tr>
<td>age (yrs)</td>
<td>42 ± 5</td>
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<tr>
<td>weight (kg)</td>
<td>78.8 ± 3.0</td>
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<td>serum sodium (mEq/liter)</td>
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<td>1.1 ± 0.1</td>
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<tr>
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<tr>
<td>urine potassium (mEq/24 hrs)</td>
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<td>77 ± 4</td>
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<tr>
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<td>19.9 ± 3.4</td>
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<tr>
<td>supine plasma renin activity (ng/ml/hr)</td>
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<td>supine plasma kinins (ng/ml)</td>
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<td>mean diastolic blood pressure (mm Hg)</td>
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<td>mean admission diastolic blood pressure (mm Hg)</td>
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</table>
Hypertension

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Hypertension

Vascular response to peptidyl-dipeptide hydrolase inhibition in sodium-restricted patients with normal renin essential hypertension receiving SQ 20,881 (n = 10) or SQ 14,225 (n = 21). Values are expressed as change in supine diastolic blood pressure from control (mean ± SEM).

**Figure 1.** Vascular response to peptidyl-dipeptide hydrolase inhibition in sodium-restricted patients with normal renin essential hypertension receiving SQ 20,881 (n = 10) or SQ 14,225 (n = 21). Values are expressed as change in supine diastolic blood pressure from control (mean ± SEM).

**Hormonal Responses to Peptidyl-dipeptide Hydrolase Inhibition**

Changes in PRA, angiotensin II, and plasma kinins were examined at the time when the blood pressure fall was maximal. Both SQ 20,881 and SQ 14,225 led to significant decrements in angiotensin II and increments in PRA (p < 0.01). The decrement in angiotensin II in the patients receiving SQ 20,881 was similar to that with SQ 14,225 (-7.1 ± 2.1 vs -6.6 ± 1.5 pg/ml). The increment in PRA was also similar for the two agents (6.6 ± 1.9 vs 7.8 ± 2.4 ng/ml/hr) (fig. 3). Plasma kinins rose in each of the 14 patients receiving SQ 20,881, with a mean increment of 2.0 ± 0.9 ng/ml (p < 0.01). In contrast, plasma kinins rose in only 12 of 21 patients receiving SQ 14,225 and showed no overall mean change (0.0 ± 0.2 ng/ml) (fig. 3). There was no significant difference in hormonal response between study patients who had previously received SQ 14,225 during dose titration and a group of normal renin essential hypertensives who received similar doses of SQ 14,225 having never before received the drug (fig. 2).

**Hormonal Responses to Enzyme Inhibition as a Function of Blood Pressure**

On the basis of a similar vascular response, six patients receiving SQ 14,225 were paired with six patients receiving SQ 20,881 for the purpose of examining hormonal response to peptidyl-dipeptide hydrolase as a function of change in blood pressure. The results shown in figure 4 indicate that, with identical falls in DBP (-18 ± 2 mm Hg for both groups), increments in PRA (7.7 ± 2.5 ng/ml/hr in patients receiving SQ 20,881 vs 6.1 ± 2.4 ng/ml/hr in those receiving SQ 14,225) and angiotensin II decrements (6.3 ± 3.0 pg/ml vs 5.5 ± 1.5 pg/ml) did not differ significantly between the two groups. In contrast, the change in plasma kinins in the group of patients receiving SQ 20,881 (+0.8 ± 0.2 ng/ml) was significantly different from the change seen in the SQ 14,225 group (-0.4 ± 0.4) (p < 0.05).

**Dose and Time Response to SQ 14,225**

Dose and time response data for patients receiving SQ 14,225 are shown in figure 5. Significant decrements in DBP occurred at all doses of SQ 14,225 and all sampling times except in patients receiving the 10 mg dose of SQ 14,225 who failed to show a significant change in DBP at 30 minutes or 6 hours. Signifi-
RESPONSES TO CAPTOPRIL AND TEPROTIDE/Crantz et al.

PLASMA ANGIOTENSIN II

pg/ml - 5
-10

DIASTOLIC BLOOD PRESSURE

mm Hg -10
-20

PLASMA RENIN ACTIVITY

ng/ml/hr

PLASMA ANGIOTENSIN II

pg/ml - 5
-10

PLASMA RENIN ACTIVITY

ng/ml/hr

PLASMA KININS

ng/ml

PLASMA KININS

ng/ml

FIGURE 3. Hormonal responses to peptidylpeptide hydrolase inhibition in patients with normal renin essential hypertension in low sodium balance receiving SQ 20,881 \((n = 10)\) or SQ 14,225 \((n = 21)\). Values show mean \((\pm SE)\) change from control with patients supine.

FIGURE 4. Hormonal responses to SQ 20,881 and SQ 14,225 in six pairs of patients with similar vascular responses to the two agents. Mean \((\pm SE)\) changes from control with patients supine are shown.

cant increments in PRA occurred at all dosages of SQ 14,225. By 120 minutes, angiotensin II levels in those patients receiving 10 mg of SQ 14,225 had returned to control, and by 6 hours patients receiving 25–100 mg SQ 14,225 had angiotensin II levels not significantly different from control levels while those patients receiving 10 mg demonstrated a significant rise in angiotensin II above control \((p < 0.01)\). Plasma kinins did not change with time or dose.

While blood pressure decrements tended to be greater at larger doses of SQ 14,225, there was no statistical difference between blood pressure changes at the various doses except at 6 hours. By 6 hours, the DBP in patients receiving 10 mg of SQ 14,225 had risen to greater than control values, and mean measurements were significantly different from those in patients receiving 25 or 50 mg \((p < 0.05)\). Rise in PRA tended to be greater at higher doses of SQ 14,225 although statistical significance was achieved only in the 6-hour measurements. At this time, PRA was greater in patients receiving 100 mg of SQ 14,225 than in those receiving 10 mg \((p < 0.01)\). There was no significant difference in PRA at any time among patients receiving 25–100 mg of drug. Angiotensin II decrements were significantly greater in patients receiving 25–100 mg of SQ 14,225 than in those receiving 10 mg \((p < 0.01)\).

Discussion

The peptidylpeptide hydrolase inhibitors SQ 20,881 and SQ 14,225 have been used to explore physiology and pathophysiology and to treat various hypertensive states. The precise mechanism of action of these agents is still speculative, with some investigators arguing that the hypotensive effect results primarily from blockade of angiotensin I to angiotensin II conversion while others have suggested that additional factors such as a rise in plasma kinins are important.

Since the oral peptidylpeptide hydrolase inhibitor SQ 14,225 was first designed and synthesized, it has been assumed that SQ 14,225 and the intravenous preparation SQ 20,881 share the same basic mechanism of action with similar antihypertensive and endocrinologic effects. In contrast to this assump-
tion, our studies suggest that, while both SQ 14,225 and SQ 20,881 have been shown to be potent in vivo and in vitro inhibitors of peptidyldipeptide hydrolase, their antihypertensive mechanisms are in some ways basically different. First, SQ 14,225 had a more profound hypotensive effect than SQ 20,881 and was effective in a greater proportion of normal renin essential hypertensive patients. Further, SQ 14,225's greater hypotensive effect was achieved with no measurable change in plasma kinins. This argues that the effectiveness and mechanism of action of SQ 14,225 and SQ 20,881 are different and that the acute hypotensive effect of SQ 14,225 does not depend on changes in plasma kinins. Even when pairs of patients with equipotent vascular responses are selected (fig. 4), a significant difference in the response of plasma kinins between the two agents remains. The mechanism(s) responsible for the different kinin responses to captopril and teprotide are not explained in the present study. Possible explanations include differential inhibition of kininases or inhibition of different sites of the converting enzyme by these two agents.

An examination of time-response data in patients receiving SQ 14,225 (fig. 5) also suggests that the hypotensive response to SQ 14,225 may not be dependent on changes in angiotensin II. Six hours after receiving SQ 14,225, with no change in plasma kinins and at a time when angiotensin II had returned to values either greater than or not significantly different from control levels, mean DBP remained significantly below control measurements in patients receiving 25–100 mg of SQ 14,225.

The greater antihypertensive effect of SQ 14,225 might have resulted because the molar dosage of SQ 14,225 was greater than that of SQ 20,881; but considering potential differences between these two agents in intrinsic activity, protein binding, metabolism, and absorption, it is not unexpected that the dose range for each drug would be different. To assure comparability between the two drugs in the face of these difficulties, patients in both groups underwent a dose response titration beginning at the lowest dose of drug at which significant hypotensive changes were consistently seen (30 μg/kg for SQ 20,881, 10 mg for SQ 14,225) and increasing incrementally to ten times this dose (or until a 15 mm Hg diastolic blood pressure decrement occurred). Furthermore, as mentioned earlier, the differences in hormonal responses persisted even when the data were limited to those patients with equivalent vascular responses the two drugs.

Another theoretical problem in comparing our two groups involves the significantly higher control values of angiotensin II seen in the SQ 20,881 group. This difference is unexplained since both groups met the same admission criteria and were otherwise similar (table 1). In any case, our previous study has indicated that there is a positive correlation between vascular responsiveness to SQ 20,881 and control angiotensin II and plasma renin activity. Thus, the higher control angiotensin II values in the group of patients receiving SQ 20,881 would be expected to prejudice our study in

**Figure 5.** Dose and time response to SQ 14,225 in patients with normal renin essential hypertension on a 10 mEq Na diet. Values represent mean (± SEM) change from control. The dose of captopril administered to individual subjects on this study day corresponds to the highest dose received at the time of a dose titration performed several days previously (i.e., the dose that reduced diastolic blood pressure 15 mm Hg or until 100 mg was given). Thus, patients receiving identical doses of SQ 14,225 have been grouped, and their vascular and hormonal responses over 6 hours are presented.
favors a more marked hypotensive response to SQ 20,881 while, in fact, just the opposite occurred.

Diastolic blood pressure changes after varying doses of SQ 14,225 were not significantly different from one another except at 6 hours, at which time those patients receiving the 10 mg dose of SQ 14,225 had returned their DBP to control levels and differed significantly (p < 0.05) from patients receiving higher doses of medication. This observation corroborates the findings of others that blood pressure reduction in the 10 mg dose of SQ 14,225 was not significantly different from those receiving the 10 mg dose of SQ 14,225 while, in fact, just the opposite occurred.

Our study has shown quantitative differences in the antihypertensive and hormonal effects of SQ 20,881 and SQ 14,225, implying that the mechanism of action of these two drugs differs. One area of difference is their effect on plasma kinin levels. Another may be on prostaglandin secretion. Recent work by Johns et al. has shown no changes in prostaglandin levels (PGE, PGF) following SQ 20,881, while work in our laboratory has shown a significant increase in PGE, metabolites after administration of SQ 14,225 and diminution in the vascular response to this agent following administration of the prostaglandin synthetase inhibitor indomethacin. This leads one to speculate that differences in prostaglandin response may play a role in the differing vascular effect of these two agents.

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