The Effect of Converting Enzyme Inhibition with SQ20,881 on Plasma and Urinary Kinins, Prostaglandin E, and Angiotensin II in Hypertensive Man

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SUMMARY The relationship between levels of angiotensin II, kinins, and prostaglandin E and the depressor response to 1 or 3 mg/kg of the converting enzyme inhibitor SQ20,881 was studied in recumbent hypertensive subjects during 109 mEq and 9 mEq/day sodium intake. In 13 sodium-replete patients, SQ20,881 decreased angiotensin II from 46.7 ± 9.2 (mean ± SEM) to 31.7 ± 5.1 pg/ml and plasma aldosterone from 6.8 ± 0.9 to 2.9 ± 0.6 ng/dl (p < 0.003) without compensatory elevations of plasma renin activity and angiotensin I. Administration of SQ20,881 had no effect on plasma bradykinin but increased mean immunoreactive prostaglandin E from 143 ± 17 to 302 ± 75 pg/ml (p < 0.02) and in some patients it increased urinary klin excretion. The distribution of the mean 2-hour depressor response was bimodal as four patients had a fall in diastolic pressure of at least 11 torr (mean 14 ± 1 torr) and nine had a minimal depressor response ≤ 4 torr, (-1 ± 1 torr); patients with a greater decrease in blood pressure showed an increase in urinary klin excretion rate, whereas the other patients showed a fall (471 ± 121 vs. 99 ± 106 ng/hr; p < 0.005); both had similar control levels and responses of plasma angiotensin II, aldosterone, immunoreactive prostaglandin E, and bradykinin. In nine sodium-depleted patients, SQ20,881 slightly decreased mean angiotensin II from 30.5 ± 4.5 to 22.4 ± 4.3 pg/ml early after drug administration, but because this was accompanied by rapid compensatory elevations of angiotensin I (which increased from < 14 pg/ml to levels as high as 513 pg/ml) and mean plasma renin activity from 4.3 ± 1.6 to 13.9 ± 4.3 ng/ml/hr, levels of angiotensin II returned toward control soon after drug administration. We found that SQ20,881 had no effect on plasma bradykinin but increased urinary klin excretion by 203 ± 63 ng/hr (p < 0.02) and in some patients increased plasma prostaglandin E. The distribution of the mean 2-hour depressor response in these nine sodium-depleted patients was also bimodal as five sodium-depleted patients had a depressor response to drug of at least 7 torr (10 ± 1 torr) while four sodium-depleted patients had a minimal response (-1 ± 1 torr). The patients with a greater decrease in blood pressure showed a greater (p < 0.05) increase in both immunoreactive prostaglandin E (248 ± 99 vs. 20 ± 12 pg/ml) and urinary klin excretion (270 ± 69 vs. 83 ± 75 ng/hr) whereas decrements in plasma angiotensin II and aldosterone were similar. Thus, the depressor response to SQ20,881 correlated better with alterations in urinary klins and plasma prostaglandin E than with changes in plasma levels of angiotensin II.

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KEY WORDS • converting enzyme inhibition • essential hypertension • SQ20,881 • bradykinin • angiotensin II • plasma renin activity • aldosterone • prostaglandin E

P EPTIDYLDIPEPTIDE hydrolase, which is also known as angiotensin-converting enzyme, cleaves C-terminal dipeptides from the decapetide angiotensin I, the nonapeptide [des-Asp]-angiotensin I and the nonapeptide bradykinin.1,3 Its net physiological effect is vasoconstriction and stimulation of sodium-retaining steroid production as it converts inactive angiotensin I to the potent pressor and steroidogenic peptide angiotensin II, and inactivates the potent vasodilator peptide, bradykinin.1,2 Converting enzyme is widely distributed along the endothelium of many vascular beds4,5 and is present in renal tubular cells6 as well as other tissues such as the pituitary gland and the central nervous system6,7 and fluids such as plasma6 and renal lymph.8 In normal man, the pulmonary circulation has the highest capacity for angiotensin I conversion and bradykinin inactivation; 20-40% of angiotensin I is converted to angiotensin II8 and 84-96% of bradykinin is destroyed in one pulmonary passage.
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Table 1. Patient Characteristics and Plasma Renin Activity (Upright) Values (PRAU) and the Concomitant 24-hour Excretion Values for Sodium (UNaV) and Aldosterone (AER)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Race</th>
<th>Sex</th>
<th>UNaV (mEq/24 hrs)</th>
<th>PRAU* (ng/ml/hr)</th>
<th>AER (μg/24 hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39</td>
<td>B</td>
<td>M</td>
<td>13</td>
<td>7.7</td>
<td>14.3</td>
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<tr>
<td>2</td>
<td>45</td>
<td>B</td>
<td>F</td>
<td>7</td>
<td>0.1†‡</td>
<td>20.7</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>B</td>
<td>F</td>
<td>109</td>
<td>6.3</td>
<td>8.2</td>
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<tr>
<td>4</td>
<td>56</td>
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<td>M</td>
<td>25</td>
<td>1.7†</td>
<td>13.5</td>
</tr>
<tr>
<td>5</td>
<td>42</td>
<td>W</td>
<td>M</td>
<td>13</td>
<td>11.2</td>
<td>18.2</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>B</td>
<td>M</td>
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</tr>
<tr>
<td>7</td>
<td>56</td>
<td>W</td>
<td>F</td>
<td>19</td>
<td>14.5</td>
<td>28.0</td>
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<td>F</td>
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<td>15.1</td>
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<td>F</td>
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<tr>
<td>13</td>
<td>58</td>
<td>W</td>
<td>F</td>
<td>6</td>
<td>1.9†</td>
<td>43.1</td>
</tr>
</tbody>
</table>

*Three patients (Cases 2, 4 and 13) had values of plasma renin activity that were below normal.
†Supine.
‡Low renin.

(unpublished observation). This conversion and inactivation may not be due solely to converting enzyme, however, since there are other enzymatic pathways that convert angiotensin I\(^1\) and inactivate bradykinin.\(^1\)

The nonapeptide, SQ20,881, inhibits converting enzyme in vitro,\(^1\) potentiates the depressor effects of exogenous bradykinin, and inhibits the pressor effects that result from the in vivo conversion of exogenous angiotensin I.\(^1\) SQ20,881 also blocks the formation of [des-Asp\(^1\)]-angiotensin II,\(^1\) a putative steroidogenic peptide in man,\(^1\) and enhances the release of prostaglandin E by bradykinin in vitro.\(^1\) In hypertensive man, SQ20,881 has a vasodepressor effect that has been positively correlated with the basal levels of plasma renin activity (PRA).\(^1\)

Thus, because of its many actions, SQ20,881 is not simply a selective inhibitor of the renin-angiotensin system as is the antagonist and partial agonist, [Sar\(^1\), Ala\(^4\)]-angiotensin II. The latter had no significant depressor effect in normal-renin hypertensives,\(^1\) but SQ20,881 significantly decreased diastolic pressure in more than 90% of normal-renin hypertensives.\(^1\)

Because of the proposed multiple actions of converting enzyme inhibition we investigated the extent to which changes in levels of kinins and prostaglandins, as well as angiotensin II, might contribute to the depressor effects of SQ20,881 in patients with normal and low-renin hypertension.

Methods

Patients

Thirteen patients with uncomplicated moderate hypertension were studied. Their characteristics are shown in table 1. They ranged in age from 39–58 years (mean 48); nine of the patients were black and four were white; seven were women. Mean blood pressure on admission was 157/103 ± 5/3 torr. Patients were excluded if they had a myocardial infarction or stroke within the past year, if serum creatinine exceeded 1.5 mg/dl, or if they were women of child-bearing potential without adequate contraception. With the exception of one patient who received oral contraceptives, no one received any medication for the 3 weeks prior to or during the study.

All patients underwent a diagnostic evaluation that included plasma and urinary electrolytes, creatinine clearance, urine culture, urinary vanillylmandelic acid, rapid sequence intravenous pyelography (and/or renal arteriography if indicated), plasma renin activity and aldosterone excretion rate. All patients had essential hypertension with the exception of one woman (Case 12, table 1) who had an 80% stenosis of her left main renal artery and had been taking oral contraceptives (Ovral-21) for 15 years. All patients had normal plasma renin activity (table 1) except three patients (Cases 2, 4, and 13) who had low values.*

Study Protocol

The converting enzyme inhibitor SQ20,881† was administered to patients receiving two levels of dietary salt:

**Low renin activity** is defined as a value obtained from a patient depleted of sodium that is ≥ 2 σ from 4.1 ± 1.9 ng/ml/hr (subject supine) or 9.7 ± 3.3 ng/ml/hr (subject upright). The latter values were derived from 20 normal subjects with sodium excretion of 1 ± 2 mEq/day and reported elsewhere.\(^1\)

†Kindly supplied by E. R. Squibb & Sons, Inc., through the auspices of Dr. Ewa Rucinska.
1) Thirteen patients were studied after at least 5 days of a constant diet containing 9 mEq/day of sodium, 100 mEq/day of potassium and 2500 ml/day water (including water of oxidation and water content of food) and supplemented by 100 mEq of sodium chloride.

2) Nine patients were restudied at least 7 days after discontinuation of the supplements of sodium chloride.

Control observations of blood pressure and pulse rate and measurements of the appropriate substances in urine were made on the day before each administration of SQ20,881. Procedures on the 2 days differed in that samples of blood were drawn only on the day of administration of drug.

One mg/kg of SQ20,881 was given as a single intravenous injection to the first five patients during the sodium-replete phase and to four of the same subjects during the sodium-depleted phase. The last eight subjects received a dose of either 1 mg or 3 mg/kg of SQ20,881, depending on the blood pressure response to a trial dose several days before the study; the three mg/kg doses were administered to all eight subjects in the initial phase and to three of the five in the second phase. No patient experienced any untoward reaction to the drug.

Each study began at 8 a.m. after the patient had been recumbent overnight. Blood pressure and heart rate were measured automatically every 2 minutes for 5 hours, using the Arteriosonde (Hoffman-La Roche) and Hewlett-Packard monitors, respectively; mean values were computed for 15-minute intervals for each variable. At the midpoint of baseline recordings (one-half hour) a 19-gauge butterfly needle was inserted intravenously for the administration of 5% dextrose in water at a rate of 100 cc/hour; a 20-gauge Longdwel teflon catheter needle (Becton, Dickinson) was placed in a brachial artery for the withdrawal of blood for assays for bradykinin, renin activity, angiotensin I and II, aldosterone, and immunoreactive prostaglandin E. The arterial catheter was kept patent by periodic flushing with a solution of 300 units of heparin/250 ml of 5% dextrose in water. Arterial blood samples were drawn immediately before injection of drug at 9 a.m. and thereafter at 15, 30 (last eight subjects only) 60, 120 and 240 minutes, whereupon the catheter was removed. The patient voided in the recumbent position immediately before injection of drug and thereafter collected urine during the subsequent 24 hours in consecutive periods of 2, 2, 4, 8 and 8 hours. On other days urine was collected daily in 24-hour periods for assay for sodium, potassium, creatinine, kallikrein, kinin, and aldosterone. The patients remained supine for the first 2 hours after injection of drug, were sitting (five subjects) or supine (eight subjects) for the next 2 hours, and had ad libitum activity for the subsequent 20 hours.

All subjects were hospitalized at the Clinical Center of the National Institutes of Health during the study. The protocols for this study were approved by the Peer Review Committees of the NIH and all subjects gave written informed consent. Plasma renin activity, plasma aldosterone concentration, and urinary aldosterone, were measured (under contract by Hazelton Laboratories, Inc., Vienna, VA) by radioimmunoassay by methods validated in our laboratories. Angiotensin II was measured by radioimmunoassay in extracts of blood samples collected in acetone. Blood angiotensin I, in the extracts prepared by acetone precipitation and ion-exchange chromatography, was measured by radioimmunoassay; a specific antiserum with negligible cross-reaction with the octapeptide was used.

Urine Kallikrein

Samples were assayed in duplicate at pH 8.0 and 23°C by a modification of the radiochemical esterolytic method of Beaver et al. Values are expressed as TAME (n-transyl-L-arginine-3H-methyl ester) esterase units (TU) excreted per 24 hours or as mU TAME units (MTU) per hour. One esterase unit is defined as that amount of kallikrein which hydrolyzes one micromole of TAME per minute in a titrametric assay.

Plasma Bradykinin and Urinary Kinins

Urine and arterial blood were collected and processed as previously described. Both urinary kinins (bradykinin and lys-bradykinin) and plasma bradykinin (P BK) were determined by the same radioimmunoassay as recently reported. In the radioimmunoassay each tube contained a total volume of 0.7 ml which consisted of 0.2 ml 1H-lysosine-8-bradykinin (13,000 dpm), 0.30 ml antibody (1:10,000 dilution), 0.05 or 0.1 ml sample, and 0.10 or 0.15 ml 0.2 M tris-acetate buffer, pH 6.4, with 0.01 M EDTA and 1 mg/ml lysozyme. After incubation overnight, free and bound bradykinin were separated with 0.45 μm Millipore filters (Millipore Corp., Bedford, MA) and counted in scintillation fluid. A standard curve with values from 125 to 2000 pg was run with each assay and analyzed by computer program along with duplicate unknown samples. In 20 assays, the antibody gave 35 ± 5.4% (mean ± SD) binding 1H-lysosine-8-bradykinin at a 1:10,000 dilution of antibody. The slope was −0.99 ± 0.09 in a log-logit plot of dose of bradykinin vs the fraction of 1H-lysosine-8-bradykinin bound; 50% inhibition of binding for bradykinin occurred with 300 ± 36 pg and the computed minimal detectable dose (i.e., the smallest amount of bradykinin the assay can determine to be different from zero) was 12 ± 8 pg/sample volume (120 ± 8 pg/ml sample). In those 20 assays, as with all assays, three control urine samples were run, showing interassay variability of 7.6, 9.2, and 10%. Any duplicate samples whose values differed by more than 15% were repeated, and any assay in which there was more than a 2-SD difference in the three quality control samples was repeated. Values for plasma bradykinin were derived by computer from the mean of samples processed in duplicate. Each processed sample was assayed in duplicate, and the values were
corrected for recovery of 45 nCi bradykinin triacetate, which was added to each syringe before venipuncture. Values for urinary kinins are expressed as µg/day or ng/hr and those for plasma bradykinin as ng/ml.

Plasma Immunoreactive Prostaglandin E

Arterial blood for prostaglandin E was collected, processed, and measured as previously described. Values for plasma immunoreactive prostaglandin E (PiPGE) are expressed as pg/ml of whole blood.

Statistical Methods

Values are reported as mean ± SE unless stated otherwise. Student's t test was used to determine statistical significance and p < 0.05 was considered to be significant. Values for AI, AII, PRA, plasma aldosterone concentration, PiPGE, and PBK are compared to the value obtained at time zero, just before the start of the infusion. Values for blood pressure and all substances measured in urine were compared to values obtained at the same time on the previous day. Data processing and statistical analyses were performed via the Statistical Analysis System (SAS-76).

Results

Effects of SQ20,881 in Hypertensive Patients Fed 109 mEq/Day Sodium

The mean effects of 3 mg/kg of SQ20,881 on either diastolic blood pressure or angiotensin II were not significantly greater than the effects of 1 mg/kg when patients were fed 109 mEq/day of sodium. The administration of 3 mg/kg to eight patients decreased mean diastolic pressure by a maximum of 8 ± 2 torr and decreased mean angiotensin II by a maximum of 22.1 ± 9.7 pg/ml whereas 1 mg/kg given to five other patients decreased mean diastolic pressure by a maximum of 9 ± 2 torr and mean angiotensin II by a maximum of 17.0 ± 6.1 pg/ml.

The effect of SQ20,881 in the 13 patients given the two dose levels is shown in figure 1. During the first 2 hours of control observations (all patients supine), mean diastolic pressure ranged from 95 ± 3 to 98 ± 2 torr. After SQ20,881 administration mean diastolic pressure decreased for the 15-minute periods by a maximum of −8 ± 2 torr, compared to control pressures the day before. For the group, the decrease in pressure began 30 minutes after drug was given and was sustained for the 2 hours of observations. Heart rate (not shown) was not significantly affected. Mean arterial angiotensin II decreased from 46.7 ± 9.2 to 31.7 ± 5.1 pg/ml but the changes were not statistically significant (p = 0.06). Mean plasma aldosterone decreased significantly (p < 0.006) from 6.8 ± 0.9 to 2.9 ± 0.6 ng/dl at 15 minutes and to 3.7 ± 0.6 ng/dl at 60 minutes, but returned to control after 120 minutes. Mean arterial bradykinin was not significantly changed at any time. Mean arterial immunoreactive prostaglandin E, however, significantly increased from 143 ± 17 pg/ml to a maximum of 302 ± 75 pg/ml 15 minutes after SQ20,881. The decrease in angiotensin II was not statistically significant because three patients showed no fall in angiotensin II levels after either 1 mg/kg (Case 4, table 1) or 3 mg/kg (Cases 10 and 11, table 1) of SQ20,881; one patient (Case 4) had low PRA (1.7 ng/ml/hr when upright for 3 hours and when sodium excretion was 25 mEq/day) whereas two patients...
(Cases 10 and 11) had normal PRA (7.9 and 5.5 ng/ml/hr, respectively, when upright and when sodium excretion was 9 and 85 mEq/day, respectively). The failure of angiotensin II to fall was not caused by compensatory elevations in PRA because PRA was not increased and angiotensin I, which was measured in two of these three patients remained undetectable in one and increased slightly to a maximum of 25 pg/ml in the other.

In the remaining 10 patients (fig. 2) the decrease in levels of angiotensin II from 51.7 ± 11.3 to 29.0 ± 5.0 pg/ml after doses of 1 mg/kg (four patients) or 3 mg/kg (six patients) was obviously significant (p < 0.02). Plasma aldosterone decreased significantly (p < 0.02) after 15 and 60 minutes but returned to control after 120 minutes. Mean plasma renin activity was not significantly affected and angiotensin I increased modestly from undetectable levels (< 14 pg/ml) in only two of the six patients in whom it was measured (fig. 2). Despite the evidence of inhibition of converting enzyme provided by the reduced levels of angiotensin II in these patients, arterial bradykinin was not significantly affected. However, SQ20,881 significantly (p < 0.04) increased plasma immunoreactive prostaglandin E from 152 ± 21 pg/ml to a maximum 341 ± 92 pg/ml after 15 minutes.

The effect of SQ20,881 on urinary electrolytes, creatinine, aldosterone, kallikrein, and kinin in the 13 patients is shown in figure 3. Aldosterone excretion decreased after SQ20,881 by 156 ± 67 ng/hr and 204 ± 45 ng/hr, respectively, in the initial two 2-hour periods (p < 0.04). Mean urinary excretion of kinin increased from 468 ± 57 to 694 ± 158 ng/hr but was not significant (see below). During the last two 8-hour periods, urinary excretion of kallikrein (p < 0.02), sodium (p < 0.04) and potassium (p < 0.005) decreased significantly.

Effects of SQ20,881 on Nine Hypertensive Patients Fed 9 mEq/Na/Day

Overall a dose of 3 mg/kg of SQ20,881 did not cause a significantly greater effect on either diastolic pressure or angiotensin II than a dose of 1 mg/kg.
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The hypertensive patients studied were separable into two groups, based on each individual's mean blood pressure response to SQ20,881 during the first 2 hours of observations following the administration of SQ20,881. In four of the 13 sodium-replete patients (fig. 7), SQ20,881 decreased mean 2-hour diastolic pressure for each subject by at least 11 torr (group mean is $-14 \pm 1$ torr) whereas the nine other patients each showed mean decreases in diastolic pressure that did not exceed 4 torr (group mean is $-1 \pm 1$ torr). Patients with depressor responses which were greater in both magnitude and duration showed a marked ($p < 0.05$) increase in excretion of urinary kinin (471 ± 121 ng/hr) during the first 2 hours after drug; in contrast, patients with minimal depressor responses or depressor responses of short duration showed reduced excretion of urinary kinin ($-99 \pm 106$ ng/hr; $p < 0.005$ for the comparison of the two groups). The mean 2-hour reductions of plasma angiotensin II and
Different effects of SQ20,881 on the renin-angiotensin system in four patients fed 9 mEq/day sodium. A and B) Angiotensin II blockade was overcome by elevations in plasma renin activity (PRA) and AII, despite evidence of converting enzyme inhibition and decreased plasma aldosterone concentration (PAC). C) Insignificant effect of SQ20,881 on AII, AI, PRA, but a transitory effect on PAC. D) Sustained blockade of AII formation without a significant increase in AI in a patient with a small renin response.

Discussion

We found SQ20,881 decreased plasma angiotensin II levels in most recumbent, sodium-replete hypertensives without compensatory elevations of PRA or angiotensin I. Inhibition of converting enzyme sufficient to reduce angiotensin II levels, did not increase plasma bradykinin but significantly increased plasma immunoreactive prostaglandin E. Patients with depressor responses to SQ20,881 that were aldosterone and increases in immunoreactive prostaglandin E were not statistically different for the two groups.

The nine sodium-depleted subjects (fig. 7), could also be divided on the basis of the magnitude and duration of depressor responses; each of five patients showed a decrease in mean diastolic pressure of at least 7 torr (group mean is $-10 \pm 1$ torr) for the first 2 hours after SQ20,881 whereas four had decreases that did not exceed 4 torr (group mean is $-1 \pm 1$ torr). The sodium-depleted patients with pronounced depressor responses had a significantly greater ($p < 0.05$) increase in mean urinary kinin ($270 \pm 69$ vs $83 \pm 75$ ng/hr) and immunoreactive prostaglandin E ($248 \pm 99$ vs $-20 \pm 12$ pg/ml) during the first 2 hours after the drug when compared to patients with minimal depressor responses, although both groups experienced similar decrements in plasma angiotensin II and aldosterone.
greater in both magnitude and duration were distinguished by a marked increase in excretion of urinary kinin but not by any significant difference in the response of angiotensin II, aldosterone, or prostaglandin E. In patients who were depleted of sodium, SQ20,881 produced only transitory decreases of plasma angiotensin II probably because of a mass action effect of elevated angiotensin I generated by large increases in plasma renin activity (figs. 5A and B). Sodium-depleted patients with a greater depressor response to SQ20,881 were characterized by a greater increase in plasma prostaglandin E and urinary kinin excretion but not by a greater decrease in angiotensin II or aldosterone than patients without a depressor response.

Previous studies have suggested that the magnitude of the depressor response to SQ20,881 in supine sodium-replete or depleted patients was dose-dependent up to 1 mg/kg and that at maximum dosage, in upright patients, the depressor response was positively correlated with basal levels of PRA. The latter and the fact that plasma aldosterone decreased as PRA increased after SQ20,881 suggested to these investigators that the depressor response to the drug was mediated solely by angiotensin II blockade, although the latter was not measured. The widespread depressor responsiveness of patients with normal renin activity suggested a wide participation of the renin-angiotensin system in essential hypertension.

Other investigators using submaximal depressor doses of SQ20,881 (1-3% of our dose and that used by Laragh et al. 17) have studied the effect of SQ20,881 on plasma bradykinin to determine its participation in the depressor response to converting enzyme inhibition; Mersey et al. 28 administered 30 μg/kg SQ20,881 to sodium-depleted recumbent normals and reported only a transitory and physiologically insignificant 2 mm Hg depressor effect that was associated with an
equally transitory decrease in angiotensin II and increase in plasma bradykinin. Associated with the return of angiotensin II and plasma bradykinin to control (10 minutes after drug) there was an increase in PRA which suggested that converting enzyme inhibition was effectively overcome. These same investigators studied the effects of 10 and 30 μg/kg SQ20,881 in sodium-depleted recumbent subjects, both normal and hypertensive, who had undergone renal arteriography 30 or more minutes previously. In this setting, after 20 minutes, SQ20,881 increased plasma bradykinin in hypertensive but not in normal subjects; the degree to which the findings were modified by the known vascular effects of angiographic contrast medium is uncertain, however.

In our study, 3 mg/kg SQ20,881 did not cause a greater reduction of blood pressure or plasma angiotensin II than a dose of 1 mg/kg. This is consistent with the observation of Gavras et al. who found that maximum depressor effects of SQ20,881 were obtained with a 1 mg/kg dose.

The effect of maximal doses of SQ20,881 in the majority of sodium-replete hypertensive patients was to decrease angiotensin II in a significant and sustained fashion. Unlike the results of other studies in upright patients, our study of recumbent, sodium-replete patients did not show a significant rise in PRA. This is consistent with the observation of Williams et al. who have reported that the response of renin to angiotensin II infusions and SQ20,881 was decreased in hypertensive patients and who have suggested a blunted short feedback loop in such patients. When our patients were depleted of sodium, however, SQ20,881 caused a marked increase in PRA and angiotensin I, and probably by mass action quickly restored angiotensin II levels to control levels. This latter observation is important because it suggests that SQ20,881 does not have a sustained effect on angiotensin II in sodium-depleted man.

Unlike the variable response of angiotensin II to SQ20,881, the response of plasma aldosterone was uniform in all patients. In sodium-depleted recumbent subjects SQ20,881 caused a greater fall in aldosterone concentration despite a significantly smaller decrease in angiotensin II. The proportionally greater fall in aldosterone levels in sodium-depleted recumbent patients could reflect the greater sensitivity of the adrenal gland to small changes in the angiotensins in such patients and the consequent possibility that the instantaneous blood level of angiotensin II may not reflect the cumulative biological activity of all upon the adrenal gland during the sodium depletion. The latter is supported by the reported observation in sodium-depleted normal subjects that 20 minutes after SQ20,881, angiotensin II levels were similar to control despite decrements in aldosterone that were similar to those in our patients. Plasma angiotensin II had decreased, however, early (5 and 10 minutes) after SQ20,881 in the normal subjects but had returned to control by 20 minutes.

In addition, it is possible that SQ20,881, via mechanisms unrelated to changes in angiotensin II, affects steroidogenesis and steroid metabolism. The metabolic clearance of aldosterone must be increased by SQ20,881 since aldosterone was markedly decreased 15 minutes after drug in our study and in others, despite the fact that the usual half-life of aldosterone is 34 minutes. Thus, changes in aldosterone do not simply reflect the instantaneous level of angiotensin II during converting enzyme inhibition in recumbent patients.

Systemic arterial levels of plasma bradykinin were not significantly increased by SQ20,881 in either sodium-replete patients with unequivocal blockade of angiotensin II formation or in sodium-depleted patients in whom blockade was apparently overcome. Our result is consistent with other reports and is not unexpected because the arterial level of plasma bradykinin is determined not only by converting enzyme (kininase II) but by other potent plasma and tissue proteases such as a kininase I which in plasma accounts for 90% of the destruction of bradykinin. Other studies in hypertensive patients however, report increased plasma bradykinin after SQ20,881. Some recent work indicates that plasma kinin levels may be lower than those previously reported by most workers. If this is true, it is possible that artifically high levels may have obscured anticipated responses of plasma bradykinin to SQ20,881.

Whether local tissue levels of bradykinin were increased in our patients is unknown but the likelihood that they were is supported by the fact that urinary kinins increased markedly in all patients who had a substantial and sustained depressor response to drug. That is, Nasjletti et al. have demonstrated that SQ20,881 markedly increased both the excretion of urinary kinins and the plasma concentration of bradykinin in the renal venous blood of dogs. Because urinary kinins are normally generated in the distal tubule where kininase activity is low, it is likely that the increased excretion of kinins results in part from inhibition of kinin destruction in the proximal tubule; at this site, with its high concentration of converting enzyme, filtered kinins are normally inactivated. Available data, therefore, suggest that the increased excretion of urinary kinins after SQ20,881 is caused both by an increase in renovascular kinins and decreased destruction of kinins in the nephron. Thus, despite the fact that systemic arterial levels of bradykinin were not increased, it is likely that local levels such as those in the kidney may have been increased by SQ20,881. Because bradykinin is a potent stimulus for prostaglandin synthesis such an increase may account in part for the significant increase in plasma prostaglandin E that we observed. Indeed Blumberg et al. have recently shown that SQ20,881 enhanced the release of PGE by bradykinin in rabbit mesenteric vessels in vitro but did not affect the release of PGE by angiotensin II. However, it is unlikely that urinary kinin was the only factor that may have increased prostaglandin E since PGE increased in sodium-replete patients when urinary kinin excretion did not increase.

Kallikrein excretion was decreased by SQ20,881 in
both sodium-replete and sodium-depleted patients several hours after the drug was administered at a time when aldosterone excretion was similar to control. This is an exception to our previously reported correlation of aldosterone with kallikrein excretion and suggests that kallikrein excretion may be influenced by factors other than aldosterone. Of interest is the association of sodium and potassium retention with depressed levels of kallikrein excretion.

This study demonstrated that although converting enzyme inhibition in sodium-replete and recumbent patients decreased levels of angiotensin II and aldosterone and increased plasma prostaglandin E in most patients, only those patients with marked elevations in urinary kinin, in addition to increased prostaglandin E and decreased angiotensin II, had pronounced and sustained depressor responses. Sodium depletion altered this hormonal response to converting enzyme inhibition as it promoted compensatory elevations of plasma renin so that angiotensin II decreased only transiently relative to the depressor response. Sodium-depleted patients with pronounced and sustained depressor responses not only had greater elevations in urinary kinin excretion but also a greater increase in plasma immunoreactive prostaglandin E than patients with minimal responses. Thus, our data suggest that bradykinin and prostaglandin may contribute to the depressor effect of SQ20,881 and that converting enzyme inhibition has significant vasodepressor action in addition to inhibition of angiotensin II production. The latter has been clearly demonstrated by Thurston and Swales in a comparative study of SQ20,881 and Saralasin in rats. That prostaglandins may participate in the depressor response to converting enzyme inhibition is supported by the finding that indomethacin, a prostaglandin synthetase inhibitor, decreased the duration of the depressor response to bradykinin after converting enzyme inhibition in rabbits.

Because converting enzyme inhibition has influence over several vasoactive systems that are of potential importance in the regulation of blood pressure, its use as a pharmacologic aid in the diagnosis of angiotensin-dependent hypertension is questionable. Inhibitors of converting enzyme, however, offer a new therapeutic approach to the treatment of hypertension because of their combined mechanism of action, in association with their ability to increase renal blood flow and the availability of a new oral preparation.

Addendum

While this manuscript was undergoing editorial review the following paper appeared in Hypertension which also suggests that bradykinin may be responsible for the hypotensive response to converting enzyme inhibition with SQ20,881. (Swartz SL, Williams GH, Hollenberg NK, Moore TJ, Dluhy RG: Converting enzyme inhibition in essential hypertension: The hypotensive response does not reflect only reduced angiotensin II formation. Hypertension 1: 106, 1979).

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