Converting Enzyme Inhibition in Essential Hypertension: The Hypotensive Response Does Not Reflect Only Reduced Angiotensin II Formation

STEPHEN L. SWARTZ, M.D., GORDON H. WILLIAMS, M.D., NORMAN K. HOLLENBERG, M.D., PH.D., THOMAS J. MOORE, M.D., AND ROBERT G. DLUHY, M.D.

SUMMARY To determine the relative importance of hormonal factors in mediating the hypotensive response to converting enzyme inhibition (CEI), plasma renin activity (PRA), angiotensin II, and bradykinin responses to SQ20,881 were measured in 20 supine patients with essential hypertension in balance on a 10 mEq sodium diet. Patients were divided into two groups according to their diastolic blood pressure response: responders had a decrement in diastolic pressure which exceeded 9 mm Hg, the upper value of the 95% confidence limits for normotensive patients studied under similar conditions; nonresponders did not. Compared to the nonresponders, responders not only had a higher control PRA (8.7 ± 1.7 ng/ml/hr vs 4.8 ± 2.1, p < 0.05) and larger decrement in plasma angiotensin II (18.7 ± 4.9 pg/ml vs 3.2 ± 1.7, p < 0.01), but also had a higher control bradykinin (3.2 ± 0.7 ng/ml vs 1.1 ± 0.2, p < 0.05) and larger increment in bradykinin (4.5 ± 1.3 ng/ml vs 1.0 ± 0.4, p < 0.05) following SQ20,881. Because SQ20,881 altered both angiotensin II and bradykinin concentrations, we assessed the contribution of blockade of angiotensin II formation by administering angiotensin II infusions to seven responders during converting enzyme blockade, with the angiotensin II dose adjusted to restore diastolic pressure to control levels. The plasma angiotensin II level required to return blood pressure to control was 45 ± 15 pg/ml higher than the control plasma angiotensin II level (p < 0.01), suggesting that some other factor(s), perhaps bradykinin, are also responsible for the hypotensive response to converting enzyme inhibition. (Hypertension 1: 106-111, 1979)

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

The response to pharmacological interruption of the renin-angiotensin system has been used as an index of the role of angiotensin in the control of blood pressure in normal and hypertensive states. Case et al.¹ have suggested, primarily on the basis of the prevalence of hypotensive responses to converting enzyme inhibition (CEI), that the renin-angiotensin system may contribute to the raised arterial pressure in perhaps as many as 85% of patients with essential hypertension. The premise underlying their interpretation is that this agent's effect on arterial pressure is mediated primarily by blocking the conversion of angiotensin I to angiotensin II. However, the angiotensin converting enzyme is probably identical to the enzyme (kininase II) that inactivates bradykinin, a potent vasodilator.² Thus, the hypotensive response to the synthetic nonapeptide converting enzyme inhibitor SQ20,881 could result from either decreased amounts of angiotensin II and/or increased amounts of bradykinin. The present study was designed to determine whether blockade of angiotensin II formation was the sole mediator of the depressor response to SQ20,881.

Materials and Methods

Patient Selection

Twenty patients with essential hypertension, 17 to 71 years of age, were admitted to the Clinical Research Center of the Peter Bent Brigham Hospital. The criteria for inclusion of patients in the study were as follows: out-patient diastolic blood pressure in the...
supine position greater than 90 mm Hg determined on at least three different occasions, and documented evidence of hypertension for at least 6 months before study. All antihypertensive medications were discontinued at least 2 weeks before admission. In addition, results of the following studies performed to eliminate known secondary causes of hypertension were normal: intravenous pyelography and where indicated renal arteriography, creatinine clearance, urine culture, urinalysis, serum electrolytes and aldosterone levels and 24-hour urine vanillylmandelic acid, metanephrines, catecholamines, 17-hydroxysteroid, and 17-ketosteroid excretion rates.

Protocols

All patients were studied supine after an overnight fast after balance had been achieved on a 10 mEq sodium, 100 mEq potassium isocaloric diet.

Converting Enzyme Inhibition

After control blood samples for plasma renin activity (PRA), angiotensin II, bradykinin, aldosterone, cortisol, sodium and potassium were drawn through a previously positioned indwelling peripheral venous catheter, an intravenous infusion of SQ20,881 was given over a 3-minute period beginning with 10 μg/kg (six patients) or 30 μg/kg (14 patients). Blood pressures were monitored at 2-minute intervals with an automatic blood pressure recorder (Arteriosonde, Roche) for a 30-minute control period and throughout the infusion studies. Increasing doses of SQ20,881 (10, 30, 100 and 300 μg/kg) were given every 20 minutes until either the diastolic blood pressure fell to 80 mm Hg or until the highest dose was achieved. Blood sampling was obtained at the end of each 20-minute infusion period.

Converting Enzyme Inhibition with Superimposed Administration of Angiotensin II

In seven of the 14 patients who had a hypertensive response to SQ20,881, angiotensin II (Hypertensin, Ciba) was infused during CEI. The angiotensin II infusion was started 20 minutes after the last dose of SQ20,881, and was administered in gradually increasing doses, starting with 0.1 ng/kg/min. The rate of infusion of angiotensin II which restored the diastolic blood pressure to control levels was continued for an additional 20-minute period and repeat blood samples were obtained for PRA, angiotensin II, bradykinin, aldosterone, cortisol, sodium and potassium.

Laboratory Procedures

All blood samples were collected on ice, spun immediately, and the plasma separated and frozen until time of assay. Plasma bradykinin was measured by a modification of the radioimmunoassay techniques of Talamo and his colleagues as described in a previous publication. The intra-assay coefficient of variation was ±10%, with an inter-assay value of ±18%. Plasma renin activity and angiotensin II were measured by double-antibody radioimmunoassay. Urine and serum sodium and potassium concentrations were measured by flame photometry, with lithium used as an internal standard.

Group means have been presented with the standard error of the mean as the index of dispersion. Statistical probability was evaluated with the Student t test where appropriate. Otherwise, the Wilcoxon rank-sum or Fisher exact test for nonparametric data were used. The null hypothesis was rejected when the p value was less than 0.05. The protocol was approved by the Human Experimentation Committee of the Peter Bent Brigham Hospital. Written permission for the procedure was obtained after a complete description of the protocol.

Results

Response to Converting Enzyme Inhibition

The depressor response observed with SQ20,881 administration fell along a continuum, with the largest fall in diastolic pressure being 28 mm Hg and the smallest 2 mm Hg. Because 95% of normotensive sodium-restricted patients given SQ20,881 had a fall in diastolic blood pressure < 9 mm Hg, we divided our hypertensive study patients into two groups according to the magnitude of their depressor response to CEI: Patients were considered to be responders when the decrement in diastolic blood pressure exceeded 9 mm Hg; in nonresponders the fall was less than 9 mm Hg.

The characteristics of the 14 responders and six nonresponders studied on a 10 mEq sodium, 100 mEq potassium intake are summarized in table 1. There were no significant differences between the two groups with respect to age, weight, serum creatinine, sodium or potassium, or urinary sodium and potassium at the time of the study. Mean diastolic blood pressure on admission and on the study day were also not significantly different between the two groups. However, control plasma renin activity, angiotensin II and bradykinin levels were significantly higher in the responders (p < 0.05).

Infusion of SQ20,881 induced a decrement in angiotensin II and an increment in bradykinin concentration in all patients. Responders had higher control plasma renin activity (8.7 ± 1.7 ng/ml/hr vs 4.9 ± 2.1, p < 0.05), angiotensin II (52 ± 10 pg/ml vs 27 ± 4, p < 0.05) and bradykinin levels (3.2 ± 0.7 ng/ml vs 1.1 ± 0.2, p < 0.05), and greater decrements in angiotensin II (19 ± 5 pg/ml vs 3 ± 2, p < 0.01) and increments in bradykinin (4.5 ± 1.3 ng/ml vs 1.0 ± 0.4, p < 0.05) with CEI than nonresponders (fig. 1).

Regression analysis comparing changes in diastolic blood pressure after SQ20,881 administration with control PRA, angiotensin II, bradykinin and with changes in plasma angiotensin II and bradykinin with increasing doses of SQ20,881 demonstrated no significant correlations.
Comparison of the dose-response curves in responders for changes in diastolic blood pressure, angiotensin II and bradykinin with increasing doses of SQ20,881 (fig. 2) revealed an absence of parallelism between the fall in diastolic blood pressure and changes in angiotensin II or bradykinin levels. While diastolic pressure continued to fall with increasing doses of CEI, both the decrement in angiotensin II and increment in bradykinin was greatest at the lowest dose and less at higher ones.

Response to Superimposed Administration of Angiotensin II

In the seven responders who received graded angiotensin II infusions during CEI, the mean decline in diastolic blood pressure with SQ20,881 before angiotensin II infusion was 17 ± 2 mm Hg, and the mean fall in plasma angiotensin II concentration was 11 ± 2 pg/ml. After the diastolic blood pressure was titrated back to control levels with gradually increasing doses of angiotensin II, the plasma angiotensin II concentration was significantly increased (+45 ± 15 pg/ml, p < 0.01) from control levels (fig. 3). Concomitant with this doubling of the plasma angiotensin II concentration, the plasma aldosterone concentration also increased twofold, from a control value of 33 ng/dl to a final concentration of 67 ng/dl (p < 0.05) (fig. 3). There were no significant changes in cortisol, sodium or potassium.

Discussion

Recent enthusiasm in the study of the renin-angiotensin system’s contribution to the pathogenesis of hypertension has revolved around the use of new pharmacologic agents that interrupt the renin-angiotensin system. Saralasin (1-sar-8-ala angiotensin II), a competitive antagonist of angiotensin II at the renal, adrenal and vascular receptor, is useful in identifying “high-renin” hypertensive patients. However, it has been suggested that this agent may underestimate the participation of the renin-angiotensin system in the maintenance of elevated blood pressure in “normal-renin” hypertension because it also functions as a partial agonist with significant angiotensin II-like properties. The introduction of a new class of agents, the converting enzyme inhibitors, was accompanied by a new wave of enthusiasm because these drugs competitively inhibit the enzyme that converts angiotensin I to angiotensin II, while lacking intrinsic agonistic activity. However, converting enzyme is probably identical to kininase II, an enzyme that participates in the kallikrein-kinin system in the degradation of the potent vasodilator, bradykinin. The fall in blood pressure seen with CEI could then be due to an increase in bradykinin as well as a decrease in angiotensin II.

Case et al. reported their experience with CEI in 65 hypertensive patients. Since 85% of their patients experienced a depressor response, they postulated that there was some degree of angiotensin II dependency in most hypertensive patients. Although their patients’ measured renin-sodium profiles were often within the normal range, they viewed these as inappropriately high, since they were associated with an elevated blood pressure, which should normally work to suppress renin secretion. Case acknowledged that an increase in plasma bradykinin could accompany SQ20,881 administration in man, but rejected the interpretation that bradykinin accumulation was a significant factor in mediating blood pressure changes with CEI because their anephric and low-renin (and thus low-angiotensin) patients failed to demonstrate depressor responses. Although they did not measure changes in bradykinin levels, they reasoned that the hypotensive responses in “medium-” and high-renin patients and lack of hypotensive responses in low-renin patients implied that the primary mechanism responsible for the depressor response to CEI was a reduction in formation of angiotensin II.

In the present study, all patients had decrements in angiotensin II and increments in bradykinin after SQ20,881 administration. However, those who had blood pressure decrements greater than normotensive control patients (responders) could be separated from those who did not (nonresponders) on the basis of their

| TABLE 1. Comparison of Physiological and Biochemical Characteristics of Responders and Nonresponders When Balance Had Been Achieved on a 10 mEq Sodium, 100 mEq Potassium Intake (Mean ± SEM).* |
|---------------|---------------|
| Responders   | Nonresponders |
| Number        | 14            | 6            |
| Female (%)    | 50            | 17           |
| Weight (kg)   | 78.0 ± 2.1    | 80.8 ± 4.3   |
| Age (yrs)     | 41 ± 4        | 42 ± 7       |
| Serum sodium (mEq/liter) | 138 ± 1    | 138 ± 1     |
| Serum potassium (mEq/liter) | 4.0 ± 0.1 | 4.2 ± 0.1   |
| Serum creatinine (mg/dl) | 1.1 ± 0.1   | 1.1 ± 0.1   |
| Urine sodium (mEq/24 hrs) | 8 ± 2      | 12 ± 3      |
| Urine potassium (mEq/24 hrs) | 90 ± 9     | 77 ± 15     |
| Supine plasma angiotensin II (pg/ml) | 52 ± 11†   | 28 ± 4      |
| Supine plasma renin activity (ng/ml/hr) | 8.9 ± 1.8† | 4.0 ± 2.1   |
| Supine bradykinin (ng/ml) | 3.3 ± 0.7† | 1.1 ± 0.2   |
| Mean diastolic blood pressure (mm Hg) | 89 ± 5    | 88 ± 8      |
| Mean admission diastolic blood pressure (mm Hg) | 109 ± 4   | 104 ± 5     |

*Responders had ≥ 9 mm Hg fall in diastolic blood pressure with administration of SQ20,881. Nonresponders had < 9 mm Hg fall in diastolic blood pressure with SQ20,881. †p < 0.05.
Figure 1. Comparison of control plasma renin activity and control bradykinin (absolute values) and changes in plasma angiotensin II and bradykinin after SQ20,881 administration in 20 patients with essential hypertension. Responders had a decrement in diastolic blood pressure of greater than 9 mm Hg; non-responders did not. All studies were performed supine in balance on a 10 mEq Na, 100 mEq K intake (mean ± SEM).

Figure 2. Responses of plasma angiotensin II, bradykinin and diastolic blood pressure in 14 responders. All patients were studied supine in balance on a 10 mEq Na, 100 mEq K intake (mean ± SEM).
FIGURE 3. Responses of diastolic blood pressure, plasma angiotensin II, and aldosterone to SQ20,881 and superimposed angiotensin II infusions in seven responders. All studies were performed supine in balance on a 10 mEq Na, 100 mEq K intake (Mean ± SEM). The plasma angiotensin II level required to restore the diastolic blood pressure back to control was significantly greater than the starting angiotensin level (p < 0.01). The aldosterone level at the end of the angiotensin II infusion was also significantly greater than the control aldosterone level (p < 0.05).

control and post-CEI PRA, angiotensin II and bradykinin levels. Similar to Case's observations, our patients who responded to SQ20,881 also had significantly higher control PRA levels than did nonresponders. In addition, our responders also had a higher control bradykinin and a larger increment in bradykinin following CEI blockade. Conversely, patients who did not have a significant fall in blood pressure with SQ20,881 not only had lower PRA levels, but also had lower and unresponsive bradykinin levels.

The relationship between the dose of CEI given and the vascular and angiotensin II responses supports the concept that factors other than angiotensin II must be involved in mediating the hypotensive effect. The greatest decrement in angiotensin II occurred at the lowest dose of CEI. At higher doses the decrement was actually less, presumably because the reactive increase in PRA overcame the converting enzyme blockade. Yet the vascular response was consistently dose related (fig. 2). However, the changes in blood pressure could not be related to changes in bradykinin concentration either: as with angiotensin II, the greatest change was produced by the smallest dose of SQ20,881. These findings are confirmed by the lack of significant correlation between either change in bradykinin or angiotensin II and change in blood pressure following converting enzyme blockade. Therefore, although angiotensin II and bradykinin concentrations change from control levels after administration of the CEI, other as yet unrecognized factor(s) probably also participate in the hypotensive response to SQ20,881.

Because SQ20,881 altered both angiotensin II and bradykinin and because the response of neither paralleled the progressive depressor response to increasing SQ20,881 dosage, it is difficult to attribute the vascular response to the drug to either hormone alone. To assess the contribution of blockade of angiotensin II formation, graded doses of angiotensin II were given during CEI blockade until blood pressure was restored to control levels. The increment in plasma angiotensin II concentration above control necessary to restore blood pressure to control was highly significant, again suggesting that other factors are also responsible for SQ20,881's hypotensive effect. These results cannot be explained on the basis that the amide of angiotensin II was infused since it cross reacts 100% in our assay. A reduction in angiotensin II's metabolism also seems unlikely, since the absolute levels measured at each infusion rate were similar to those previously reported by our laboratory in both normotensive and hypertensive subjects given only angiotensin II. Furthermore, the infused angiotensin II was biologically as well as immunologically active since the plasma aldosterone concentration increased twofold as the plasma angiotensin II concentration doubled. A decrease in vascular sensitivity with SQ20,881 also appears unlikely since converting enzyme blockade, if anything, enhances the pressor response to angiotensin II in the salt-depleted animal. Finally, all patients were studied on a 10 mEq Na diet, which enhances the activities of both the renin-angiotensin and kallikrein-kinin systems, thereby potentiating the effects of converting enzyme inhibitors. Similar responses of decreased magnitude would be anticipated in sodium-replete patients, but the current study was only performed under conditions of sodium restriction.

In conclusion, converting enzyme inhibitors have many features that make them useful antihypertensive agents. However, their ability to identify angiotensin mediated hypertension is probably limited since other factors are also important in mediating their hypotensive effects.
References

Converting enzyme inhibition in essential hypertension: the hypotensive response does not reflect only reduced angiotensin II formation.
S L Swartz, G H Williams, N K Hollenberg, T J Moore and R G Dluhy

Hypertension. 1979;1:106-111
doi: 10.1161/01.HYP.1.2.106

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/1/2/106

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/