SUMMARY  The short-term cardiovascular and endocrine effects of an orally active angiotensin converting enzyme inhibitor, SQ14,225, were evaluated in 17 subjects with drug-resistant hypertension (10 with essential and seven with renovascular hypertension). On normal dietary sodium, SQ 14,225 (after 3 days at average doses of 664 mg/day) reduced mean arterial pressure (MAP) significantly (from 141 ± 4 to 122 ± 4 mm Hg, (SE), p < 0.001). However, only eight of the patients achieved blood pressures within the normotensive range. Of eight patients with residual hypertension, seven exhibited further decreases in MAP (from 132 ± 4 to 108 ± 6 mm Hg (SE), p < 0.001) when dietary sodium was reduced to 10 mEq/day. No rebound hypertension was noted when treatment was temporarily discontinued for 3 days in 11 patients. The reductions in blood pressure were not associated with either orthostatic hypotension or interference with baroreceptor reflexes. The values of supine plasma renin activity (PRA) were not always predictive of blood pressure responsiveness to the drug. With treatment, plasma aldosterone concentrations (PAC) decreased modestly (values from 40 ± 9 to 22 ± 3 ng/dl (SE), p < 0.05). The plasma concentrations of cortisol, norepinephrine and serum potassium were left unchanged during the period of studies.

The present study has not defined the exact mechanism by which SQ 14,225 lowered blood pressure. Nevertheless, it indicates that this agent may be a practical therapeutic adjunct in the treatment of certain subsets of the human hypertensive population. The lack of serious interference with cardiovascular and humoral homeostasis adds to its attractiveness as a therapeutic agent. (Hypertension 1: 39-46, 1979)
Materials and Methods

Seventeen patients with resistant hypertension, 35–62 years of age, were admitted to the Research Ward of the Cleveland Clinic Hospital. The diagnosis of essential hypertension (EH) in 10 patients (four women, six men) was based on prior complete evaluation for vascular, adrenal, and renal causes, including selective renal arteriography. The diagnosis of renovascular hypertension in seven patients (four women, three men) was based on the demonstration of significant stenosis of a renal artery by selective arteriography associated with two- to threefold increases in renal vein renin activity of the involved side. All had been receiving combination antihypertensive therapy, which included a diuretic (hydrochlorothiazide or furosemide, with or without spironolactone), a sympatholytic agent (either propranolol or alpha methyl dopa) and a vasodilator (either hydralazine or minoxidil). Since their blood pressure control was less than satisfactory and because of constitutional side effects and the inconvenience of multiple therapy with potent drugs, the patients chose to participate in these studies. Most patients were weaned off their medications for at least 10–14 days before admission. Two patients (Cases 12 and 16) continued to take furosemide (160 mg per day) because of a previous history suggestive of cardiac decompensation.

On admission to the hospital, patients were placed on an isocaloric diet containing 10 mEq sodium (Na) and 80 mEq potassium (K). Supplementation sodium, 90 mEq, was given in the form of sodium chloride tablets. The following were measured: body weight, temperature, and respiration, twice daily; supine and standing brachial arterial pressure and heart rate, every 2 hours during waking hours; 24-hour urinary sodium and potassium excretion rates; serum electrolytes, creatinine and blood urea nitrogen daily. Supine morning (8 a.m.) plasma renin activity (PRA), plasma aldosterone concentration (PAC), plasma cortisol concentration (PCC), and plasma norepinephrine (NE) were measured every 3–4 days after overnight fast. Toxicity studies, which included a urinalysis, a 12-lead electrocardiogram and measurements to assess hemolytic, autoimmune, renal, hepatic and other endocrine responses, were performed at appropriate intervals before and during drug administration.

Following an equilibration period of at least 3 days on 100 mEq Na diet, control measurements were obtained and SQ14,225 was started at small incremental doses at 3-hour intervals until a fall of at least 10 mm Hg mean arterial pressure was achieved or the maximum allowable dosage was reached. During this dose-ranging period, cardiac rate and rhythm were monitored continuously with an electrocardiogram; brachial arterial pressure was measured every 3 minutes with a mercury sphygmomanometer. At the onset of the study, the maximum allowable dosage of SQ14,225 was 1000 mg per day (250 mg every 6 hours). Three months later it was reduced, on recommendation from E. R. Squibb & Sons, Inc., to 200 mg per day (50 mg every 6 hours). For this reason Cases 6 and 8 received only 200 mg per day although the minimum blood pressure reduction of ≥10 mm Hg mean arterial pressure was not achieved. Presently, the maximum allowable dosage has been increased to 600 mg per day.

The effect of sodium deprivation on blood pressure, plasma renin activity, and plasma aldosterone were evaluated further in eight patients who remained hypertensive on 100 mEq Na and SQ14,225. After at least 3 days on maintenance doses of SQ14,225, supplemental oral sodium was discontinued leaving the patients on a diet containing 10 mEq Na, 80 mEq K for 3–5 days.

Blood pressures and heart rates reported here represent the average values of at least 10 to 12 determinations over a 24-hour period. Pretreatment values were those taken on the third day of an equilibration period, 24 hours before drug administration. Treatment values reported were those calculated at the three follow-up periods: 1) on the third day of maintenance doses of SQ14,225, while on a 100 mEq per day dietary sodium in all patients; 2) on the seventh day of therapy, while on a 100 mEq per day dietary sodium in "good" responders (vide infra); and 3) following 3 days of sodium deprivation plus maintenance doses of SQ14,225 in "partial" and "poor" responders. These arbitrary periods were chosen to allow clearer presentation of the data obtained. Values for PRA, PAC, PCC, and plasma NE coincided with the average values of blood pressure and heart rate reported for that same day.

Patients whose mean arterial pressure fell by more than 10 mm Hg and achieved near-normal or normal blood pressures were considered "good responders." Patients were considered "partial responders" if their mean arterial pressure fell by more than 10 mm Hg but they continued to have significant hypertension. "Poor responders" were those found to have little or no response at all.

Plasma levels of renin activity, aldosterone, and cortisol were measured by radioimmunoassay methods previously described, and plasma NE by the isotope method of Engleman et al. Normal values (mean ± 1 sd) on 100 mEq Na diet are as follows: PRA, 1.2 ± 0.4 ng/ml/hr; PAC, 10 ± 4 ng/dl; PCC, 12 ± 4 ng/dl; and plasma NE, 148 ± 45 ng/liter.

Group means are presented with the standard error of the mean as the index of dispersion. Student's t test for paired observations was used for statistical analysis of the data. The protocol was approved by the Institutional Review Committee of the Cleveland Clinic Foundation. Written permission for the procedure was given by all patients after they were
given a complete description of the protocol and possible side effects of the drug and various tests.

**Results**

**Cardiovascular Response to SQ14,225**

On a dietary sodium of 100 mEq/day, SQ14,225 evoked variable blood pressure responses among the 17 patients. In 12, blood pressure was significantly reduced; only eight achieved normotensive or near-normotensive levels ("good" responders); in the other four, MAP fell by >10 mm Hg, but though improved, they remained significantly hypertensive ("partial" responders). Five exhibited minimal reductions in blood pressure ("poor" responders) (table 1 and fig. 1). Qualitatively and quantitatively the blood pressure response of patients with essential hypertension did not differ from those with renovascular hypertension. Mean arterial pressure fell by an average of 19 mm Hg in the former and by 25 mm Hg in the latter.

In the "good" responders, changes in blood pressure were not accompanied by significant alterations in salt and water balance. The initial response was maintained at similar levels during hospitalization. Resting heart rate was unchanged and the responses of blood pressure and heart rate to upright posture were quantitatively similar before and after treatment (fig. 2).

Eight patients (four "partial" and four "poor" responders), received a low salt diet because of suboptimal blood pressure reduction; all lost weight (1.6 ± 0.2 kg). Seven demonstrated further decreases in blood pressure (from 174/110 to 142/92 mm Hg, p < 0.001) (fig. 3). In Case 5 (table 2) blood pressure returned gradually to pretreatment levels over 3-5 days on SQ14,225.

**Table 1. Changes in Mean Arterial Pressure (MAP), Plasma Renin Activity (PRA), Plasma Aldosterone Concentration (PAC), Body Weight (BW), and Cumulative Sodium (Na) and Potassium (K) Balance in Patients on 100 mEq Na Diet Before and After 8 Days on SQ14,225**

<table>
<thead>
<tr>
<th>Case no.</th>
<th>SQ14,225 (mg/day)</th>
<th>Control MAP (mm Hg)</th>
<th>PRA (ng/ml)</th>
<th>PAC (ng/dl)</th>
<th>BW (kg)</th>
<th>SQ14,225 MAP (mm Hg)</th>
<th>PRA (ng/ml)</th>
<th>PAC (ng/dl)</th>
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Renovascular hypertension

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<tr>
<th>Case no.</th>
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<th>PRA (ng/ml)</th>
<th>PAC (ng/dl)</th>
<th>BW (kg)</th>
<th>SQ14,225 MAP (mm Hg)</th>
<th>PRA (ng/ml)</th>
<th>PAC (ng/dl)</th>
<th>BW (kg)</th>
<th>Na (mEq)</th>
<th>K (mEq)</th>
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Mean ± SE

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SE MAP (mm Hg)</th>
<th>Mean ± SE PRA (ng/ml)</th>
<th>Mean ± SE PAC (ng/dl)</th>
<th>Mean ± SE BW (kg)</th>
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<tbody>
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<td></td>
<td>141 ± 2.2</td>
<td>6.8 ± 0.9</td>
<td>40 ± 4</td>
<td>72.1 ± 3.6</td>
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<td>122* ± 3.4</td>
<td>21.2* ± 3.3</td>
<td>22‡ ± 3.5</td>
<td>72.1 ± 3.5</td>
</tr>
</tbody>
</table>

*p < 0.05.

**p < 0.001.
days. Associated with this was a slow but progressive return of PRA to pretreatment values.

Endocrine Effects of SQ 14,225

On a dietary sodium of 100 mEq/day, PRA and PAC were significantly elevated (6.75 ± 2.2 ng/ml/hr and 40.3 ± 8.9 ng/dl, respectively) and directly related to each other ($r = 0.81, p < 0.001$). With treatment, this relationship was lost ($r = -0.075$) as PRA increased markedly to $21.2 \pm 3.4$ ng/ml/hr ($p < 0.001$) and PAC fell to $22.0 \pm 2.6$ ng/dl. The fall in PAC barely attained statistical significance mainly due to unchanged or increased values in six of the

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**Figure 1.** The effect of 3 days of treatment with SQ14,225 on arterial blood pressure in 17 hypertensive patients equilibrated on a sodium intake of 100 mEq/day.

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**Figure 2.** Arterial blood pressure and heart rate responses to SQ14,225 of "good" responders on daily sodium of 100 mEq.

---

**Figure 3.** Arterial blood pressure and heart rate responses in seven "partial" and "poor" responders with residual hypertension on SQ14,225 following the addition of a low sodium diet. Case 5 in table 2 was excluded from this analysis because blood pressure did not change.
patients (Cases 2, 7–10, and 17). The degree of inhibition of PAC was directly related to the initial values of PRA; the higher the initial values, the greater and more consistent was the fall in PAC that occurred with treatment (fig. 4).

No significant changes occurred either in plasma cortisol (from 12.2 ± 1.6 to 13.3 ± 1.4 ng/dl), plasma NE (from 268 ± 19 to 266 ± 34 ng/liter) or serum potassium concentration (from 4.2 ± 0.4 to 4.6 ± 0.4 mEq/liter).

Following 3–5 days of sodium deprivation, changes in both PRA and PAC did not attain statistical significance. Results of these studies are summarized in table 2.

Relationship Between Blood Pressure Responses and PRA Values

There was no relationship between the basal values of PRA and the change in mean arterial pressure during treatment. It is obvious from an inspection of figure 5 that blood response to SQ 14,225 cannot be predicted from the basal values of PRA. Thus, several patients (Cases 4, 7, 10 and 11) with essentially normal PRA values had marked decreases in blood pressure while in others (Cases 13, 14) with distinctly elevated PRA values, arterial pressure was hardly affected by therapy (table 1). Treatment with SQ14,225 alone increased PRA significantly in all but three patients. Of these, two had no blood pressure response; but in the third, MAP fell by 12 mm Hg. The increments in PRA had no significant relation to the fall in mean arterial pressure (r = 0.42, p < 0.10).

Adverse Effects

These were of three types. The first was a toxic reaction that developed in one patient (Case 14) on the eighth day of a daily dose of 1000 mg; it was characterized by fever (102°F) and a generalized morbilliform rash, both of which disappeared within 48 hours of discontinuing SQ14,225. Subsequent experience with another patient who was given SQ14,225 twice, suggests that this manifestation was related to the dose of SQ14,225. The patient developed fever and

### Table 2. Effect of Sodium Deprivation on Plasma Renin Activity (PRA) and on Plasma Aldosterone Concentration (PAC) During SQ14,225 Administration

<table>
<thead>
<tr>
<th>Case no.</th>
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<th>SQ14,225 + Low sodium diet</th>
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<td>MAP (mm Hg)</td>
<td>Wt (kg)</td>
<td>PRA (ng/ml)</td>
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<td>142</td>
<td>78.7</td>
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</tr>
<tr>
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<tr>
<td>± SE</td>
<td>±4</td>
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</tr>
</tbody>
</table>

*Significantly different from control, p < 0.001.
†Significantly different from values prior to sodium deprivation, p < 0.001.

Comparisons of other PRA and PAC values among the three phases of study showed no significant differences.

Abbreviations: MAP = mean arterial pressure; Wt = weight.
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following 3 days of treatment with SQ14,225 on a dietary sodium depletion controlled blood pressure without administration of the drug with less pronounced both. Both recovered with no sequelae when blood increases in serum creatinine (from 2.4 to 6.5 mg/dl) in comitantly with salt and water depletion led to in-

The third type was a hemodynamic rather than a drug side effect. Rapid reduction of blood pressure in two patients in whom SQ14,225 was given concomitantly with salt and water depletion led to increases in serum creatinine (from 2.4 to 6.5 mg/dl) in both. Both recovered with no sequela when blood pressure was allowed to recover; in both, continued administration of the drug with less pronounced sodium depletion controlled blood pressure without renal complications.

Discussion

The present studies further document the anti-hypertensive effectiveness of converting enzyme in-
hibition by SQ14,225 and describe its multifaceted effects on renin-aldosterone axis. As regards the first, our results confirm those of other centers and expand our initial observations with hemodynamic effects of the drug. With increasing experience, it has become clear that although sometimes effective when given alone, SQ14,225 frequently had to be combined with sodium deprivation by diet or diuretics for optimal blood pressure control. Of our 17 patients, eight exhibited excellent arterial pressure responses while the other nine were either “partial” or “poor” responders. In the latter group, restricting sodium intake to 10 mEq/day resulted in a significant improvement or normalization of blood pressure in all but one patient (fig. 3).

These results were particularly impressive because the trial of this drug was restricted to patients with severe hypertension who either could not be ade-
quately controlled by other drugs or developed unacceptable side effects from previous therapy. A frequent spontaneous comment from patients main-
tained on SQ14,225 was the contrast between the freedom from systemic or orthostatic symptoms with this drug and their previous experience with other antihypertensive agents.

Although it was well tolerated, side effects were noted in some patients. However, the benefits ob-
tained far outweighed the side effects produced. The skin rash was of minimal consequence; however, in one patient it was deemed prudent to discontinue treatment because of associated toxic effects. The potentiation of its blood pressure lowering effect by concomitant salt and water depletion can lead to transitory but significant renal effects; its use in volume depleted patients requires, therefore, careful monitoring of dosage to assure a smooth and gradual lowering of blood pressure.

In contrast with the unequivocal evidence of anti-hypertensive effectiveness, the mechanism by which blood pressure is lowered still remains unclear. Inhibition of angiotensin converting enzyme could decrease blood pressure by one or all of the following mechanisms: 1) decreasing the levels of circulating angiotensin II; 2) slowing degradation of bradykinin and/or increased production of vasodepressor prostaglandins; or 3) interference with sympathetic neural activity. A direct vasodilator activity might also be a possibility.

First to be considered is the relation among initial renin status, converting enzyme inhibition, and lowering of blood pressure. Although we have not measured circulating levels of angiotensin II nor tested the pressor responsiveness to intravenously administered angiotensin I, evidence of unequivocal inhibition of ACE was provided by the significant increase in PRA in all but three patients. Of the three, only one responded to SQ14,225, although in all three, PRA was left unchanged. Pretreatment levels of PRA were not always predictive of blood pressure responsiveness to ACE inhibition and were of limited clinical value. Some patients who were expected to respond

![Figure 5. Relation between pretreatment basal plasma renin activity (ranked in their order of elevation) and decreases in mean arterial pressure in individual patients following 3 days of treatment with SQ14,225 on a dietary sodium of 100 mEq/day.](image-url)
dramatically to ACE inhibition, because of initially high PRA levels, did not, whereas others with only modest elevations of PRA had remarkable decreases in blood pressure. On the other hand, there is no doubt that sodium depletion enhanced the hypotensive effectiveness of SQ14,225. However, salt and water depletion also enhance the effectiveness of practically all other antihypertensive agents; this observation, therefore, does not necessarily constitute an unequivocal argument for "angiotensin II dependency."

Since ACE is also responsible for inactivating bradykinin, its inhibition would lead to concomitant increases in vasodilator (bradykinin) and decreases in vasoconstrictor (angiotensin II) factors. Also, bradykinin can release prostaglandins from various organs in the body that could enhance its hypotensive effects. However, increased circulating vasodilator agents cannot by themselves account entirely for the hypotensive response to SQ14,225. Ferguson et al. found that normal volunteers with unequivocal ACE inhibition from SQ14,225 not only maintained a normal blood pressure, but in addition had either unchanged or enhanced pressor responsiveness to intravenously administered angiotensin II. Furthermore, there is no evidence of blunted response to the vasoconstrictive action of angiotensin II during ACE inhibition. Additional evidence in support of this conclusion accrues from two recent studies. We have found in preliminary studies that SQ14,225 normalized blood pressure in renovascular hypertensive patients without affecting urinary PGE2. Cody et al. reported unchanged cardiac output and heart rate in hypertensive patients responding to SQ14,225, which is contrasted with increased output and heart rate resulting from bradykinin infusions.

Samuels and co-workers reported that decreased plasma catecholamines accompanied the acute hypotensive response of normal sodium-depleted dogs to ACE inhibition with SQ20,881. In contrast, oral therapy in these patients was not associated with significant changes in circulating norepinephrine (fig. 6). In addition, there was no indication of interference with baroreceptor reflexes as heart rate and total peripheral resistance rose normally in response to upright posture.

The mechanism of the arterial pressure response to SQ14,225 remains, therefore, somewhat of a mystery. Interference with angiotensin generation does not account entirely for blood pressure control since the drug is effective in experimental models with low renin hypertension. The drug has reportedly no central vasodilator effect is questionable in view of the report that it left unchanged the response to various vasodepressor and vasoconstrictor agents.

A final point to consider is the response of plasma aldosterone to chronic ACE inhibition. Although a statistically significant reduction in PAC was found, the responses of individual patients were less clear-cut. Certain patients with distinct evidence of ACE inhibition (as judged from significant blood pressure reduction) had either no change or increases rather than decreases in plasma aldosterone (figs. 4 and 5, table 1). Of the patients exhibiting minimal or inconsistent changes, most had relatively lower basal levels of PRA and PAC. However, the higher the initial levels of PRA and PAC, the more consistent and dramatic was the fall that occurred with treatment. In those who exhibited marked reductions in PAC, the levels were maintained at normal or near-normal values.

Failure to inhibit aldosterone production sufficiently despite evidence of angiotensin blockade could result from: 1) increased ACTH release; 2) potassium retention; or 3) presence of circulating angiotensin II at levels sufficient to maintain significant aldosterone production. The first two possibilities can be readily dismissed since plasma cortisol was unchanged with treatment and the changes in external potassium balances were not of sufficient magnitude to influence either serum potassium concentration or total body potassium. In regard to the third alternative, it has previously been shown that sodium depletion, normotensive subjects treated with SQ20,881, a nonapeptide converting enzyme inhibitor, maintain sufficiently high plasma angiotensin II levels to sustain significant aldosterone production, although at reduced amounts. In addition, it is quite plausible that the renin-angiotensin system had little participation in the regulation of aldosterone in those patients with relatively normal levels of plasma aldosterone.
In summary, our study has confirmed and extended the observation of others that SQ14,225 is a potent, orally-active, competitive inhibitor of ACE in hypertensive man. It has proven to be a useful alternative to combination antihypertensive therapy in these selected patients with resistant hypertension. It should be noted, however, that half of the patients required salt and water depletion for better blood pressure control. The demonstration that the compound reduces arterial pressure without seriously compromising cardiovascular and humoral homeostasis adds to its further attractiveness as a therapeutic agent.

Acknowledgments

We are grateful to E. R. Squibb and Sons, Inc. for generously supplying SQ14,225 and to Dr. D. N. McKinstry for her help and courtesy. The secretarial help of Miss Susan Bir is also gratefully acknowledged.

References

Converting enzyme inhibition with an orally active compound in hypertensive man.

E L Bravo and R C Tarazi

*Hypertension*. 1979;1:39-46
doi: 10.1161/01.HYP.1.1.39

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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