Humoral effects of the oral converting-enzyme inhibitor SQ 14 225 in hypertensive patients in supine and tilted position

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Summary
1. To evaluate the effects of converting-enzyme inhibition on the sympathetic nervous system, on renin and on the other known regulators of aldosterone secretion, we measured blood pressure, heart rate, plasma noradrenaline, adrenaline, renin activity, aldosterone, cortisol and serum potassium in 15 sodium-repleted hypertensive patients in supine position and during 30 min of 65° head-up tilt before and during treatment with SQ 14 225.

2. SQ 14 225 produced significant decreases in supine blood pressure and plasma aldosterone and significant increments in plasma renin activity and potassium; in contrast, heart rate, noradrenaline, adrenaline and cortisol were unchanged.

3. While in control tilt studies blood pressure was always maintained, during treatment three of 15 patients had vaso-vagal syncopes. In the remaining 12 blood pressure was maintained during tilt on SQ 14 225; however, while the tilt-induced responses in heart rate and adrenaline were as in control studies, the 30 min increments in noradrenaline were significantly higher.

4. Both before and during treatment the responses of plasma renin activity and aldosterone to tilt were parallel, and correlated with each other, and cortisol and potassium changed only slightly.

5. It is concluded that the SQ 14 225-induced fall in blood pressure occurs without a concomitant rise in sympathetic nervous activity; thus the increase in supine plasma renin activity, being a reflection of the interruption of the angiotensin feedback mechanism on renin release, indicates an effective suppression of angiotensin II formation.

6. During SQ 14 225 the persistence of aldosterone response to tilt and its relationship with renin activity suggest that the enzymatic blockade is over-ridden; however, in the presence of a reduced formation of angiotensin II a more pronounced response of the sympathetic nervous system is required to defend blood pressure against postural changes.

Key words: aldosterone regulation, baroreceptor reflexes, converting-enzyme inhibition, head-up tilt, noradrenaline, renin–angiotensin system.

Introduction
Administration of the orally active converting-enzyme inhibitor SQ 14 225 is known to have a potent antihypertensive effect (Gavras, Brunner, Turini, Kershaw, Tiff, Cuttelod, Gavras, Vukovich & McKinstry, 1978; Case, Atlas, Laragh, Sealey, Sullivan & McKinstry, 1978), which is haemodynamically characterized by a reduction in peripheral resistance (Cody, Tarazi, Bravo & Fouad, 1978); this action can be related either to the prevention of angiotensin II formation or to bradykinin accumulation. However, in contrast with vasodilators whose effect is restricted to the arteriolar level, the fall in blood pressure is not associated with a reflex increase in heart rate, cardiac output and noradrenaline (Cody et al., 1978; Bravo & Tarazi, 1979). These observations suggest the possibility that this compound might interfere with the neural regulation of the circulation.

Also, administration of SQ 14 225 causes hyposecretion of aldosterone which results from the elimination of the angiotensin stimulus to the adrenal glomerulosa; it remains unclear, however,
whether this action of angiotensin is actually abolished, since plasma renin activity and plasma aldosterone have been shown to increase in parallel during prolonged upright posture in hypertensive patients on treatment with SQ 14 225 (Case et al., 1978).

The evaluation of the possible interference of SQ 14 225 with the neural control of cardiovascular homeostasis has been undertaken by determining, before and during treatment, the effects of head-up tilt on blood pressure, heart rate, plasma noradrenaline and adrenaline, these last being considered humoral markers of sympathetic activity. Under the same experimental conditions we measured plasma renin activity, aldosterone, potassium and cortisol (as index of ACTH activity) to clarify how the suppression of angiotensin II formation affects the responses of aldosterone and of its known regulators to upright posture.

Methods

Fifteen patients, nine with essential and six with renovascular hypertension, were enrolled in this study. All were free of associated diseases and of complications related to hypertension. All antihypertensive medications were discontinued for at least 3 weeks before treatment. Throughout the course of the studies they were maintained on a constant diet containing 100 mmol of sodium/day and 60 mmol of potassium/day and, after achievement of the metabolic balance, they underwent control tilt studies.

Studies were always performed between 08.00 hours and noon to minimize diurnal variations. Patients were accommodated in recumbent position in a quiet room while a flow infusion of 0.9% NaCl was set up for blood sampling. After 60 min in supine position baseline blood pressure, by sphygmomanometer, and heart rate, manually, were recorded (at least five readings) and blood samples collected. Patients were then head-up tilted to 65° and remained in that position for 30 min. During tilt blood pressure and heart rate were recorded every 2 min and blood samples were collected after 15 and 30 min of tilt.

During the following days SQ 14 225 was administered in stepwise increasing doses up to an allowed maximum of 200 mg every 6 h.

Tilt studies during treatment were repeated according to the same protocol, always within 4 h after the last dose of medication, either after 2–3 days of equilibration on the dose that normalized blood pressure or on the maximum dose.

Plasma noradrenaline and adrenaline were determined by radio-enzymatic method (Passon & Peuler, 1973); plasma renin activity and plasma aldosterone were determined by radio-immunoassay (Sealey & Laragh, 1977; Bühler, Sealey & Laragh, 1974). Plasma cortisol concentrations were evaluated by radioimmunoassay (Farmer & Pierce, 1974) with a commercial kit (Diagnostic Product Corporation). Serum potassium determinations were performed by flame photometry.

Student's t-test for paired and unpaired data was used for statistical analysis. The significance of correlation coefficients was tested with the Spearman test.

Results

Table 1 summarizes the supine and tilt-induced changes in clinical and humoral measurements before and during treatment with SQ 14 225. After an average of 7 days of treatment and on a mean daily dose of 480 ± 60 mg, mean supine blood pressure was decreased by 14%. In nine of fifteen patients (six with essential and three with renovascular hypertension) blood pressure was normalized; of the remaining six, five had a partial antihypertensive effect and only one patient with low renin essential hypertension failed to respond.

Although supine heart rate, plasma noradrenaline, adrenaline and cortisol were unchanged, plasma renin activity rose in all patients and plasma aldosterone decreased in 13 of them. Increments in serum potassium occurred in 11 patients and varied from 0-1 to 1-1 mmol/l. During tilt before treatment none of the patients showed signs of increased parasympathetic activity; in contrast, during SQ 14 225 three of them had vaso-vagal syncopes between 15 and 30 min of tilt. These 'fainters' were those who reacted to the maintenance dose of 400 mg/day with the highest absolute and percentage increments in supine plasma renin activity. In remaining patients blood pressure was maintained during tilt; however, although the posturally induced increments in heart rate and adrenaline were similar to those observed in control studies, those in noradrenaline were, after 30 min, significantly more pronounced (476 ± 61 vs 306 ± 34 pg/ml: P < 0.05). Plasma renin activity and plasma aldosterone responded in parallel to tilt before and during converting enzyme inhibition, the percentage increases being significantly correlated on both occasions (r = 0.70 and 0.74, P < 0.01). Plasma cortisol and serum
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TABLE 1. Effects of tilt before and during treatment with SQ 14 225 on blood pressure, heart rate, plasma noradrenaline, adrenaline, renin activity, aldosterone, cortisol and serum potassium in sodium-repleted hypertensive patients

Mean ± SE values are shown. The data of tilt 'during' treatment refer to 12 patients, since the data from patients who fainted have been excluded. * Statistically significant differences between supine values 'before' and 'during' treatment; † significance of the increases observed during tilt in respect of supine values: *, † P < 0.05; **, †† P < 0.01; †††, ††† P < 0.001.

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<th>Supine</th>
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<td>±11</td>
<td>±12</td>
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<td>Serum potassium (mmol/l)</td>
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Discussion

Our results show that SQ 14 225 decreases blood pressure without inducing significant changes of the humoral markers of sympathetic activity.

Since angiotensin II is known to stimulate catecholamines secretion from the adrenals (Peach, Cline & Watts, 1966), to potentiate noradrenaline release from the neural endings (Zimmerman, Gomer & Liao, 1972) and to increase the central adrenergic outflow (Ferrario, Gildenberg & McCubbin, 1972), it is possible that the absence of these actions might have counterbalanced the sympathetic stimulant effect of the fall in blood pressure.

Thus, excluding the baroreceptor-mediated neural activation as a causative factor of the observed increase in supine plasma renin activity, it is likely that this last represents the consequence of the interruption of the angiotensin feedback mechanism on renin release. Therefore, the SQ 14 225-induced hyper-reninemia reflects the effective suppression of angiotensin II formation. Further support for this conclusion comes from the observed decrease in plasma aldosterone which occurred in absence of changes in cortisol and despite the increase in serum potassium.

SQ 14 225 does not appear to interfere with the baroreceptor reflexes in most of these sodium-repleted patients since heart rate response to tilt was similar before and during treatment; however, the more pronounced increase in noradrenaline during tilt on treatment might reflect the more intense activation of the sympathetic nervous system which is required to maintain cardiovascular homeostasis when the effects of angiotensin on the heart and on the vasculature are lacking.

The vaso-vagal syncopes might suggest that, in some patients, SQ 14 225 hampers the parasympathetic withdrawal which normally occurs during upright posture; alternatively, it is possible that, when the generation of angiotensin II is more completely suppressed, the response of the sympathetic nervous system becomes inappropriate to support blood pressure during prolonged orthostatic stress.

The persistence of aldosterone response to tilt and its correlation with that of plasma renin acti-
vity, whereas cortisol and potassium had only minor modifications, suggest that, under these experimental conditions, angiotensin II is still generated in sufficient amount to cause an acute increase in aldosterone secretion.

Acknowledgments

A.M. was the recipient of the Public Health Service International Research Fellowship FO5JW2455-02. We are very grateful to Patricia Sullivan for her enthusiastic and skillful assistance.

References


