**Effects of Converting Enzyme Inhibitor (SQ 20881)
on Changes in Blood Pressure and Plasma
Aldosterone Induced by Angiotensin I or
Acute Hemorrhage in Rabbits**

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SUMMARY

The effects of angiotensin converting enzyme inhibitor (CEI) upon blood pressure and plasma aldosterone (PA) were studied in rabbits with a simultaneous infusion of angiotensin I (ANG I) or with hemorrhagic hypotension.

Pretreatment with CEI (SQ 20881), 1.0 mg/Kg, inhibited the effects of infused ANG I, 30 ng/Kg/min, upon PA and blood pressure at 30 min of the infusion, but the inhibition on PA was not significant at 60 min of the infusion. The same dose of CEI was ineffective in blocking the effect of 100 ng/Kg/min of ANG I on PA and blood pressure even at 30 min of the infusion.

In rabbits with hemorrhagic hypotension, injection of CEI resulted in the decrement in blood pressure, whereas no decrement in blood pressure was observed in normal control rabbits.

This study suggests that CEI exerts its effect in part by inhibiting conversion of ANG I to angiotensin II (ANG II), but this can't exclude other mechanisms.

Additional Indexing Words:

Plasma renin activity

IN recent years, 2 kinds of inhibitors of the renin-angiotensin system have been found as useful in the diagnosis and management of hypertensive diseases.¹⁾ One class of agent is an inhibitor of the enzyme that is responsible for the conversion of ANG I to ANG II. The inhibition of pressor response to ANG I by CEI was well established,^{2),3)} while the effect of CEI upon the steroidogenic response induced by ANG I has not been well documented. Although it is considered that ANG I possesses its biological activity after the conversion to ANG II,⁴⁾ there is a possibility that ANG I per se does have biological activity in stimulating steroidogenesis as shown in the in vitro

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experiment with adrenal slices.⁵⁾ Thus, it would be of interest to study the effect of ANG I on steroidogenesis in animals treated with CEI.

In the present study, the effects of 2 different doses of ANG I (30 ng/Kg/min and 100 ng/Kg/min) on blood pressure and PA were examined in rabbits with or without pretreatment of CEI, and then the effect of CEI alone upon blood pressure in rabbits with hemorrhagic hypotension was also examined.

MATERIAL AND METHODS

Studies were carried out in 18 female rabbits, weighing 2.3 to 3.6 Kg. They were fed on a standard laboratory diet and a tap water ad libitum. Under general anesthesia with sodium pentobarbital, 25 mg/Kg, intravenously, femoral artery and vein were cannulated for continuous measurement of blood pressure, collection of blood and the infusion of agents, respectively.

Experiment 1. Effects of ANG I on blood pressure and PA were examined with or without CEI. Following 90 min of control period, blood was collected for the determination of basal PA. After the first collection of blood, bolus injection of SQ 20881, 1.0 mg/Kg, or saline was performed, and then ANG I, at a dose of 30 ng/Kg/min or 100 ng/Kg/min, was infused for 60 min. Blood was obtained 30 min after the start of infusion of ANG I and at the end of the infusion. ANG I was obtained from Protein Research Foundation, Osaka. SQ 20881 was obtained from the Squibb Institute for Medical Research, Princeton, New Jersey.

Experiment 2. Effect of SQ 20881 upon blood pressure was studied in 9 rabbits. After the collection of blood for the determination of plasma renin activity (PPA), effect of bolus injection of SQ 20881, 0.5 to 1.0 mg/Kg upon blood pressure was examined as the control experiment. And then, 40 to 50 ml of blood was withdrawn to stimulate the endogenous renin-angiotensin system and the same procedure as control experiment was done.

Blood pressure was monitored continuously by connecting the femoral arterial catheter to a pressure transducer and a recorder (Nihon Koden Co, Tokyo) and the response to agents is reported as a maximal changes.

PA was determined by radioimmunoassay.⁶⁾ PRA was measured by the method of Skinner.⁷⁾

Statistical analysis was carried out using Student's t-test. Values are presented as mean $\pm$ standard error.

RESULTS

Experiment 1. Effects of the infusion of ANG I at a dose of 30 ng/Kg/min with or without pretreatment of SQ 20881, 1.0 mg/Kg, were shown in Figs. 1 and 2. Inhibition of a rise in blood pressure and PA by the pretreatment of SQ 20881 was observed at 30 min, but it disappeared at 60 min of

Fig. 1. Effect of SQ 20881, 1.0 mg/Kg, upon blood pressure changes induced by angiotensin I, 30 ng/Kg/min.

Fig. 2. Effect of SQ 20881, 1.0 mg/Kg, upon change in plasma aldosterone induced by angiotensin I, 30 ng/Kg/min.

infusion of ANG I. Pretreatment with SQ 20881, 1.0 mg/Kg, was ineffective in inhibiting the rise in blood pressure and PA induced by the infusion of ANG I at a dose of 100 ng/Kg/min (Figs. 3 and 4).

Experiment 2. Bolus injection of SQ 20881 at a dose of 1.0 mg/Kg didn't show any significant change in blood pressure in the normal rabbits, on the other hand, a rapid decline in blood pressure was observed in the rabbits with hemorrhagic hypotension (Fig. 5). A relationship between changes in blood pressure induced by the infusion of SQ 20881 and PRA prior to the injection of the inhibitor was significant ($p < 0.01$) (Fig. 6).

Fig. 3. Effect of SQ 20881, 1.0 mg/Kg, upon blood pressure change induced by angiotensin I, 100 ng/Kg/min.

Fig. 4. Effect of SQ 20881, 1.0 mg/Kg, upon plasma aldosterone induced by angiotensin I, 30 ng/Kg/min or 100 ng/Kg/min, at 30 min of infusion.

Fig. 5. Effect of SQ 20881, 1.0 mg/Kg, upon blood pressure in rabbits with or without hemorrhagic hypotension.

Fig. 6. Relation between control plasma renin activity and changes in blood pressure induced by the injection of SQ 20881, 1.0 mg/Kg.

DISCUSSION

In the present study, SQ 20881 was utilized as a CEI. Although 1 mg/Kg of SQ 20881 is reported to be effective in inhibiting the vasopressor effect of ANG I for 60 min at least,⁸⁾ the inhibition of ANG I-induced steroidogenesis by SQ 20881 disappeared at 60 min in this study. There are several possible explanations for this discrepancy. One is a direct stimulation by accumulated ANG I to the adrenal glands. Saruta et al⁵⁾ reported that the concentration of ANG I, approximately 1 μ g/Gm tissue, stimulated aldosterone production in the beef adrenal slices. Although this dose can be attainable in the in vitro study, it seems unlikely that plasma level of ANG I increased to such a remarkably high concentration during the infusion of ANG I. Another possibility is that accumulated ANG I and/or bradykinin stimulated steroidogenesis via the stimulation of prostaglandins. Blumberg et al⁹⁾ found that circulating peptide hormones such as ANG I, ANG II, and bradykinin stimulated the release of prostaglandin E that was one of known stimuli for aldosterone production.^{10),11)} The third possibility is the accumulation of ANG I that might break through the inhibition by CEI and result in the conversion of ANG I to ANG II.

The results that infusion of high dose of ANG I (100 ng/Kg/min) increased in blood pressure and PA with or without pretreatment of SQ 20881 could be also explained by these possibilities.

After the infusion of SQ 20881, no significant change in blood pressure was observed in normal rabbits, but a significant depressor response was

observed in rabbits with hemorrhagic hypotension. We can speculate about the mechanisms underlying the depressor response as follows. The animals might become angiotensin dependent in the maintenance of blood pressure after hemorrhagic hypotension,¹²⁾ so that inhibition of stimulated renin-angiotensin system by CEI might result in depressor response.¹³⁾ Another possibility is that CEI per se depressed the activity of the sympathetic nervous system¹⁴⁾ that might be enhanced in the animals with hemorrhagic hypotension. The third possibility is vasodilating effect and natriuretic effect of bradykinin, since CEI might also potentiate the action of bradykinin.¹⁵⁾ Although bradykinin is not only a direct vasodilator but also a stimulus for release of depressor prostaglandin, it is noteworthy that hemodynamic response to CEI¹⁶⁾ is contrasted with that to bradykinin¹⁷⁾ or prostaglandin¹⁸⁾ that is accompanied with increased heart rate. CEI might evoke the complexed humoral interaction, and unifactorial explanation can account for its effect.

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