Effects of angiotensin I converting enzyme inhibitor (SQ 14225) on control of aldosterone

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Abstract. To study effects of angiotensin I converting enzyme inhibitor (CEI), SQ 14225, on plasma aldosterone (PA), angiotensin I (A1), angiotensin II (AII), potassium and ACTH were administered with or without the simultaneous injection of SQ 14225 in rabbits. The direct effect of bradykinin on PA was also examined, since it is suspected to augment the action of kinin under the administration of CEI.

In rabbits the dose of 1 mg/kg of SQ 14225 by a bolus injection resulted in a marked elevation of plasma renin activity (PRA) and moderate but significant decreases in circulating AII and PA with only a little change of blood pressure. Decrements in circulating AII and those in PA observed after the injection of SQ 14225 were well correlated ($r = 0.585$, $P < 0.05$). Stimulatory effects of AII, potassium and ACTH on PA were not affected by SQ 14225, however, those of A1 on PA and blood pressure were completely inhibited by pre-treatment of SQ 14225. The infusion of bradykinin showed a remarkable reduction in blood pressure and a small increment in PRA, circulating AII and PA.

These results may suggest that the inhibitory effect of acutely administered SQ 14225 on PA is mainly due to the inhibition of conversion from A1 to AII, but not direct effects on adrenal glands. Furthermore, it was suggested that the augmented kinin is not related to the inhibitory effect of SQ 14225 on PA. In addition, the administration of SQ 14225 does not change the effects of potassium and ACTH on PA.

SQ 14225, an orally active CEI, is expected to be a new type of antihypertensive agent (Ondetti et al. 1977), and its depressor mechanism has been well investigated (Ferguson et al. 1977; Gavras et al. 1978; Brunner et al. 1979). Although CEI is also considered to be useful in delineating the role of the renin-angiotensin system in regulating blood pressure (Murthy et al. 1977; Rubin et al. 1978; Harris et al. 1978) and aldosterone (Watkins et al. 1978; Aguilera & Catt 1978), the effect of CEI on aldosterone has been less thoroughly studied. Some investigators reported that the administration of SQ 14225 reduces PA and speculated that those results are due to a decrement in circulating AII. However, there are some difficulties in explaining that all the effects of CEI are solely due to suppression of endogenous AII production, since CEI may also potentiate the action of kinin (Greene et al. 1972). The present experiments were designed to evaluate whether the inhibitory effect of CEI on PA is due to direct effect on adrenal glands. Furthermore, the influences of SQ 14225 on the effects of potassium and ACTH on PA are also examined. Bradykinin also was infused to estimate the participation of the kallikrein-kinin system.

Material and Methods

In this study rabbits weighing 2.5 to 3.8 kg fed with a standard laboratory diet and tap water ad libitum were employed. After sodium pentobarbital anaesthesia, the
right femoral vein was cannulated for the infusion of agents. Cannulation of the right femoral artery was also performed for direct measurement of arterial blood pressure and arterial blood sampling. To suppress the endogenous ACTH secretion, 0.2 mg/kg of dexamethasone phosphate was injected IM before the operative procedure. The following experiments were started after the control period of 2 h from the end of the operation. All agents were dissolved in 5% dextrose and the infusion rate was 5.1 ml/h. Blood was collected in tubes containing EDTA, Dimercaprol and 8-OH Quinolin, and cooled rapidly in an ice box.

**Experiment 1.** In four normal rabbits, 1 mg/kg of bolus injections of SQ 14225 were repeated three times at every 20 min. Blood samples were collected before each injection and 20 min after the last injection of SQ 14225.

**Experiment 2.** In four more rabbits, bradykinin (Protein Research Foundation, Osaka, Japan) was infused at the dose of 1.0, 2.5, and 5.0 μg/kg/min for each 20 min, and blood samples were taken as in the Experiment 1.

**Experiment 3.** Twenty female rabbits were used in this study. A I or A II (Protein Research Foundation, Osaka, Japan), 30 or 300 ng/kg/min, were infused in each four rabbits for 40 min. Blood samples were obtained before and at the end of the infusion. And then, 5% dextrose was infused for recovery for about 1 h. Thereafter, the same dose of A I or A II was infused under the simultaneous administration of SQ 14225, which were injected 1 mg/kg every 20 min by a bolus injection. Blood samples were also obtained before and at the end of the infusion. Furthermore, 1000 ng/kg/min of A I with simultaneous administration of SQ 14225 was also tried.

**Experiment 4.** Potassium chloride, 1 mEq./kg/h, was infused in four rabbits just as in Experiment 3. Furthermore, the effect of 1-24β-Cortrosyn, 0.25 mg, on PA was also studied. The effect of 1-24β-Cortrosyn alone and of the simultaneous administration of SQ 14225 was studied in four other rabbits.

Blood pressure was monitored continuously by connecting a catheter in the femoral artery to a pressure transducer and recorder (Nihon Koden Kogyo Co., Tokyo). PRA was determined by the method of Skinner (1967), A II was measured by radioimmunoassay after the extraction and chromatographic separation (Semple et al. 1979). PA was determined by direct radioimmunoassay (Ogihara et al. 1977).
Experiment 1. Intravenous administration of SQ 14225, 1 mg/kg, brought about rapid changes in PRA, circulating AII and PA. At 20 min after a bolus injection of SQ 14225, PRA increased from 3.0 ± 0.3 to 7.6 ± 0.9 ng/ml/h (P < 0.05), circulating AII lowered from 59.5 ± 6.1 to 42.5 ± 4.8 pg/ml, and PA decreased from 33.5 ± 2.7 to 23.4 ± 2.0 ng/100 ml (P < 0.05). Although PRA still increased slightly by repeated injection of SQ 14225, circulating AII and PA did not continue to decrease (Fig. 1). At 20 min after the injection of SQ 14225, decrements in circulating AII and in PA were well correlated (r = 0.585, P < 0.05) (Fig. 2).

Experiment 2. Infusion of bradykinin resulted in a remarkable reduction in blood pressure in a dose dependent manner. PRA, AII and PA increased slightly (Fig. 3).

Experiment 3. Effects of several doses of A1 and AII on blood pressure are shown in Fig. 4. SQ 14225 completely inhibited the effect of A1 on blood pressure. One thousand ng/kg/min, a high dose of A1, could not elevate blood pressure under the administration of SQ 14225. The effect of A1 and AII on PA is shown in Fig. 5. In the same way as with blood pressure, the effect of A1 on PA was almost completely inhibited on simultaneous injection of SQ 14225. The effects of AII on blood pressure and PA were not affected by SQ 14225.

Experiment 4. The effects of potassium infusion, 1 mEq/kg/h, on PRA, circulating AII and PA are shown in Fig. 6. Potassium infusion made an increment in plasma potassium concentration by 0.80 ± 0.36 mEq/l in the group without SQ 14225 and 0.58 ± 0.33 mEq/l in the group with SQ 14225 (N.S.). PRA and circulating AII showed no significant change at 40 min after the potassium infusion alone, however, PRA increased rapidly and circulating AII decreased slightly at 40 min after the potassium infusion with the simultaneous administration of SQ 14225. PA increased prominently in the both groups, and there was no significant change in the increment in PA despite a less responsiveness in the group with SQ 14225.
The effects of ACTH on PRA, circulating AII and PA are shown in Fig. 7. PA showed remarkable increments but no significant change between the group without SQ 14225 and the group with SQ 14225.

**Discussion**

It is reported that the administration of SQ 14225 reduces PA in hypertensive patients (Gavras et al. 1978; Brunner et al. 1979), in one-kidney hypertensive dogs (Watkins et al. 1978) and in sodium depleted rats (Aguilera & Catt 1978). In this study using normal female rabbits, PA reduced slightly, and the reduction in PA was well correlated with the decrease in circulating AII. Therefore, this suggested that the main factor for the reduction in PA after the administration of SQ 14225 is probably inhibition of conversion from AII to AII. However, it is still controversial whether decreased circulating AII might be enough to explain all the effects of CEI or not. There is a possibility that the kallikrein-kinin system has an effect on aldosterone, because CEI may potenti ate the action of kinin by inhibiting kininase II (Greene et al. 1972; Murthy et al. 1977; Rubin et al. 1978). Then, for estimating this possibility, a large amount of bradykinin was infused in rabbits. Blood pressure decreased markedly in a dose dependent manner, and PRA, circulating AII and PA rather increased. It was supposed that changes in the renin-angiotensin system were mainly induced by reduction in blood pressure or natriuresis although UNaV was not determined in this study. So we can suppose that the role of the augmented kinin is not so
Fig. 4.
Effects of A I or A II infusion with or without SQ 14225 on blood pressure.

Fig. 5.
Effects of A I or A II infusion with or without SQ 14225 on PA.
important in the control of aldosterone, even though kinin is increased by the acute administration of SQ 14225. In the chronic effects of SQ 14225, however, there may remain a possibility that persistent natriuresis induced by augmented renal kinin affects the regulation of aldosterone, but further study is necessary.

It is still questionable whether the effects of potassium and ACTH on aldosterone are influenced by the plasma or tissue level of AII (Fredlund et al. 1977) or angiotensin III. In this study, effects of potassium and ACTH on PA were not influenced by the administration of SQ 14225 in spite of a slight reduction of circulating level of AII.

From these studies, it is concluded that SQ 14225 reduces PA by diminishing circulating AII, and there is little concern of augmented kinin under the acute administration of SQ 14225. The effects of potassium and ACTH on PA are not influenced by SQ 14225, even though SQ 14225 reduced the circulating level of AII slightly.

References


Fig. 6.
Effects of potassium infusion with or without SQ 14225 on PRA, circulating AII and PA.
Fig. 7.
Effects of ACTH with or without SQ 14225 on PRA, circulating AII and PA.


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