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Response of Mineralocorticoid Hypertensive Animals to an Angiotensin I Converting Enzyme Inhibitor (40496)

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The recent development of angiotensin I converting enzyme inhibitors has made possible their use in delineating the role of the renin-angiotensin system in different types of hypertension (1). These inhibitors also block agents responsible for kinin destruction (2). Therefore, blood pressure changes due to converting enzyme inhibitors could be due to either inhibition of angiotension II formation or increased plasma kinin levels.

Bengis et al. administered the angiotensin I converting enzyme inhibitor SQ-14,225 to one- and two-kidney hypertensive rats (3). They concluded that the hypotensive effect of SQ-14,225 in rats with experimental renovascular hypertension has at least two mechanisms: A rapid decrease in arterial pressure that is proportional to the plasma renin activity and a slow progressive decrease that is accompanied by natriuresis and diuresis. They postulated that the natriuretic effect of SQ-14,225 was due in part to increased circulating and renal levels of kinins. This supposition received reinforcement when it was shown that SQ-14,225 increased plasma kinins in dogs (1).

Gavras et al. showed that saralasin, a competitive inhibitor of angiotensin, caused a blood pressure rise in animals with mineralocorticoid hypertension (4). The situation is not exactly comparable to the administration of a converting enzyme inhibitor. In the absence of angiotensin, the inherent agonist action of saralasin was unmasked.

The effect of SQ-14,225 on desoxycorticosterone acetate-sodium chloride (DCA-NaCl) hypertension has not been tested. Urinary kallikrein excretion is elevated in rats with DCA-NaCl hypertension (5). Renin and angiotensin levels should be very low in DCA-NaCl hypertension. Therefore, if blood pressure falls after SQ-14,225 is given to animals with DCA–NaCl hypertension, the effect could be attributed to increasing kinin vasodilator activity rather than decreased vasoconstriction produced by angiotensin II. The present study was designed to test this hypothesis.

Methods. Effect of SQ-14,225 on the development of DCA-NaCl hypertension. Twelve Sprague-Dawley rats weighing 241 ± 16 g initially were used. Control levels were established for weights and blood pressures. Blood pressures were determined using the method described by Friedman and Freed (6). The left kidney was removed. Following a 2-week recovery period all of the animals received 4 mg/kg/da DCA in Upjohn #98 Vehicle and 0.9% NaCl was substituted for their drinking water (7). Five animals received only the DCA-NaCl for 3 weeks and seven received the DCA-NaCl plus 15–25 mg/da of the SQ-14,225 via the drinking water for a period of 3 weeks. Bengis *et al.* demonstrated that this amount of converting enzyme inhibitor blocks the renin-angiotensin system (3). Weights and blood pressures were determined twice each week.

Effect of SQ-14,225 on established DCA-NaCl hypertension. Fourteen Sprague-Dawley rats weighing 172 ± 4 g initially were used. Control levels were established for weights and blood pressures. Blood pressures were determined as described above. The left kidney of each animal was removed. Following a 2-week recovery period they were given daily injections of 4 mg/kg/da DCA in Upjohn #98 Vehicle and 0.9% NaCl was substituted for their drinking water. After the animals developed hypertension (18 days of treatment) seven of them were given the SQ-14,225 in the drinking water in an amount such that each animal received 15–25 mg/da. They received the SQ-14,225 for a period of 5 days while they were continued on the DCA-NaCl regimen. Blood pressures and weights were determined twice each week and 3 times during the last 5 days of the study.

Results. Figure 1 (A) shows the blood pres-

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sure changes of animals which received DCA-NaCl (solid line) and of animals which received DCA-NaCl plus the SQ-14,225 (dashed line) simultaneously. After control levels were established for blood pressure the control hypertensive group (solid line) received the DCA-NaCl for a period of 16 days. During this time their blood pressure increased by approximately 65 mm Hg. The figure also shows that the blood pressure of the animals which received the SQ-14,225 and DCA-NaCl regimen simultaneously increased by approximately 65 mm Hg. The blood pressure of both groups increased significantly ($p < 0.01$) above control levels but differences between the groups were not significant. The weight of the animals in both groups increased by approximately 13% during the study. There were no group differences and weight changes indicative of edema were not present.

Figure 1 (B) shows the effect of SQ-14,225 on established DCA-NaCl hypertension. The control blood pressure was 129 ± 1 mm Hg. Administration of the DCA-NaCl to the animals for an 18-day period caused the blood pressure to increase to 179 ± 8 mm Hg ($p <$ 0.01). Figure 1 (B) also shows that the blood pressure of these animals was 186 ± 6 mm Hg after they had received the SQ-14,225 for 5 days (while continuing to receive the DCA-NaCl). The blood pressure was not significantly changed by the SQ-14,225. The blood pressure of animals which were hypertensive for the same length of time but which never received the SQ-14,225 was 181 ± 8 mm Hg. This was not significantly different from the group which received the SQ-14,225.

Discussion. The present study has demonstrated that the angiotension I converting enzyme inhibitor, SQ-14,225 is not effective in reducing the blood pressure of animals with established DCA-NaCl hypertension. If given simultaneously with DCA-NaCl it also does not prevent the development of DCA-NaCl hypertension. The failure of the SQ-14,225 to decrease the blood pressure of the DCA-NaCl hypertensive rat suggests that (1) an increase of endogenous kinins has no hypotensive effect in the rat or (2) that plasma kinin levels are so low in DCA-salt hypertension that converting enzyme inhibition of

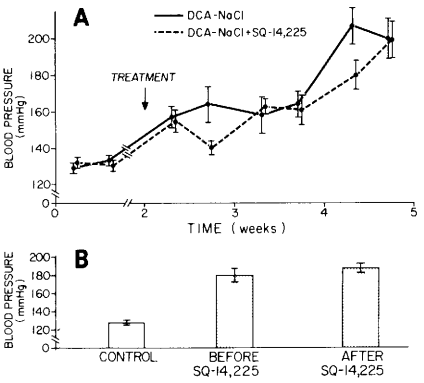

FIG. 1. The effect of an angiotensin I converting enzyme inhibitor (SQ-14,225) on the development of DCA-NaCl hypertension (A) and on established DCA-NaCl hypertension (B) is shown. Standard errors of means are indicated.

their metabolism has a negligible effect (8), or that (3) angiotensin I converting enzyme inhibition does not increase kinin levels in the rat as it does in the dog. The latter is an unlikely possibility.

Summary. The effect of the angiotensin I converting enzyme inhibitor, SQ-14,225 on DCA-NaCl hypertension was determined. The inhibitor did not affect the development of DCA-NaCl hypertension. It also did not affect the blood pressure of animals with established DCA-NaCl hypertension. This suggests that the SQ-14,225 exerts it's antihypertensive effect purely by decreasing angiotensin II and not by increasing vasodilator kinins.

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