Chapter V

Discussion

The present experiment was performed to study the effect of omeprazole on general circulation and the renal functions in the dog. The relationship of the mechanisms of renal hydrogen ion secretion and potassium ion reabsorption with the H-K ATPase activity was carried out.

It is known that omeprazole was gastric secretory inhibitors which have a mechanism of action quite different from others blockers of acid secretion (Olbe et al., 1982). Previous investigations have suggested a target site for omeprazole within the parietal cell beyond second-messenger activation of the acid formation process, possibly by a direct interaction with the proposed gastric proton pump, the H-K ATPase (Fellenius et al., 1981). Several studies also indicate that the duration of action for omeprazole is greater than 24 hours, even though the plasma half-life is only 1 hour (Lind et al., 1983).

Preliminary evidence using staining by monoclonal antibodies suggest that renal distal tubule and colon may contain H-K ATPase. This enzyme may act as a means of potassium ion reabsorption or acidification in these tissues. Such action of the enzyme has been detected in rabbit gastric glands suspended in Na^+-free ouabain containing solutions, in that potassium ion accumulation under these conditions

may be due to activity of the proton pump (Sachs et al., 1982). It has been demonstrated that the collecting duct possesses ouabain-insensitive, omeprazole-sensitive K-ATPase activity and a low potassium diet stimulate K-ATPase activity in the cortical and the outer medullary collecting duct (Doucet and Marsy, 1987). In the present study, the animals were induced hypokalemia. While the hypokalemic condition was occurred, H-K ATPase in the distal nephron was suspected to be more activated. The increase activity of H-K ATPase would be reflected the effects of omeprozole on renal acidification and potassium reabsorption.

The induction of hypokalemia by both acute furosemide infusion (group 1) and prolonged oral furosemide administration (group 2) have no effect on MAP, HR, and Hct. A similar observation was reported in the rat (Barret et al., 1987), cattle (Vestweber et al., 1987), and human (Schmieder et al., 1987). After furosemide infusion almost values of renal hemodynamics are not alter significantly, except for urine flow rate which markedly increased from the control volue. Moreover, furosemide caused the increase in $U_{TA}V$ and $U_{NH}V$ in the first group and $U_{Na}V$, $U_{K}V$, $U_{Cl}V$, FE_{Na}, FE_{K}, and FE_{Cl} in group 1 and 2. It was well understanding that the major effect of furosemide appears to be the inhibition of sodium and chloride transport at the ascending limb of the loop of Henle (Burg et al., 1973), resulting in an increased quantity of sodium chloride reaching the distal convoluted tubule. An increase in sodium chloride supply to this segment produced by furosemide may result in an increase in hydrogen secretion (Burg and Stoner, 1974). Many studies have indicated that diuretics which inhibit sodium chloride reabsorption at the loop of Henle also inhibit potassium reabsorption at this site (Morgan et al., 1970; Duarte et al., 1971;

Kahn et al., 1971). It was observed that $U_{TA}V$ in the second group markedly decreased by furosemide while this parameter in first group increased. This phenomenon might be explained by the fact that the prolonged oral furosemide may induce chronic acid loss, by some feedback mechanism resulting in the decreased of hydrogen ion secretion in the proximal tubule (Bosch et al., 1977). Plasma sodium, potassium, and chloride concentrations in the first group slightly decreased by furosemide while in the second group these parameters was markedly decreased. Therefore natriuretic, chloriuretic, and kaliuretic by the effect of furosemide might be suspected to occur. However, the PEG, was used as a vehicle for the administration of omeprazole, had no apparent in these animals as same as in the observation which was made by Larsson et al. (1984).

In the third group (insulin infusion induced hypokalemic dogs), insulin has no effect on MAP, BP, and Hct. It was also observed in rats (Tucker et al., 1989), dog (Bianco et al., 1986; Reikeras et al., 1986; Hall et al., 1989), and human (Airaksinen et al., 1985; Hegedus et al., 1985; Vierhappen et al., 1985). It was observed that plasma sodium and chloride concentration did not alter by insulin while plasma potassium concentration decreased. This effect of insulin on potassium metabolism is primarily the result of enhance potassium uptake by extrarenal tissues, liver and muscle. (De Fronzo and Bia, 1985; Bia and De Fronzo, 1981).

After insulin infusion, almost values of renal hemodynamics are not alter, except for urine flow rate which increased from the control value. Insulin enhanced an increase in $U_{Na}V$ and $U_{Cl}V$ but it

caused the decrease in $U_{TA}V$ and $U_{NH_3}V$ while it has no effect on U_KV. As observed by siegel and Civan (1976), they suggested that insulin increased $U_{Na}V$ by increasing the electromotive force (emf); the resultant slightly increased in urine flow rate. It is possible that the inhibitory effect of urinary acidification by insulin is mediated by the stimulatory effect of insulin on $U_{Na}V$, which is well known to the exchanges of sodium ion with hydrogen ion.

If distal nephron has H-K ATPase activity and omeprazole can block H-K ATPase activity, the increase of U_KV and the decrease of $U_{TA}V$ and $U_{NH_3}V$ would be occurred by omeprazole. Because the changes of these parameters reflected whether there was H-K ATPase located in the distal nephron. The present data demonstrate that in the three groups, after 5 μmole/kg.bw. of omeprazole injection which was a similar to dosoge which was used by Larsson et al. (1983), omeprazole has no significant effect on U_KV, $U_{TA}V$, and $U_{NH_3}V$. Similar results have been shown in healthy man that the daily urinary electrolyte output and urine pH were not significantly altered when oral omeprazole 60 mg/day was given (Howden and Reid, 1984). On the other hand, several studied in vitro have suggested that the renal tubular possesses K-ATPase activity that has some properties in common with gastric H-K ATPase and was also inhibited by gastric H-K ATPase inhibitor, omeprazole (Doucet and Marsy, 1987; Grag and Narang, 1987). But in the present study, omeprazole had not an effect on K reabsorption and acid secretion. It may be due partly to : 1) Urinary acidification not only occurred in the distal nephron but also in proximal tubule region. The major mechanism for proximal tubule H^+ secretion is via a Na-H exchange mechanism located in the luminal cell

membrane (Koeppen and Steinmetz, 1983). 2) In gastric model, omeprozole in intact form enters the acid compartment of the parietal cell from the serosal side. Subsequently the protonated form of omeprazole is transformed into its active inhibitor, which reacts with the gastric H-K ATPase (fig 2.1). In this way, acid induced transformation is necessary in order to produce inhibition (Wallmark, 1986). In contrastly, pH of renal tubule cell is different from acid compartment of the gastric model, therefore, it may not induced transformation of omeprazole into active inhibitor. 3) The dosage of omeprazole used in this experiment was not high enough to inhibit H-K ATPase activity. 4) The quantity of K delivery is necessary for the activity of H-K ATPase. This pump has a high activity in the hypokalemic condition, but the activity of H-K ATPase could not occur; it the quantity of K delivery reaching the distal nephron is decreased. Since this pump is electroneutral pump, which exchanges of potassium ion with hydrogen ion, greater K reabsorption yields greater hydrogen ion secretion. The distal nephron region may be contained by H-K ATPase, but the results showed that H-K ATPase has no activity in the distal nephron, it may be that K delivery reaching the distal nephron is decreased. Therefore, the experimental models of the three groups, group 1 would be used by the further study, since the quantity of K delivery reaching the distal nephron is not decreased.

In conclusion, the present study demonstrates that omeprazole has no effect on acid excretion and potassium reabsorption in the kidneys of hypokalemic dogs and not correlate to the activity of H-K ATPase. Therefore, 1) further study required to varies dosage of

omeprazole that appropiate for in vivo studies in dog kidneys or 2) omeprazole administration may be used directly to the kidneys by intrarenal injection instead of systemic administration.