Chapter II

Background Information

H-K ATPase inhibitor : omeprazole

Omeprazole, a new potent substituted benzimidazole, has proved to be an effective anti-ulcer agent and inhibitor of gastric acid secretion in the several animal models, including human (Wilson, et al., 1983), as well as in vitro with the isolated guinea pig gastric mucosa (Wallmark et al., 1983)

Mechanism of action of omeprazole

The inhibition of acid secretion by omeprazole has been extensively studied in several in vitro gastric preparations. Furthermore, omeprazole has found to inhibit the isolated H-K ATPase, a mechanism has been proposed in which omeprazole inhibit gastric acid secretion by blockade of the gastric H-K ATPase (Fig 2.1). Omeprazole in intact form enters the acid compartment of the parietal cell, it will be protonated and accumulated, provided the pH of the acid compartment is below the pKa value of omeprazole. Subsequently the protonated form of omeprazole is transformed into its active inhibitors, which reacts with the gastric H-K ATPase. In this way, acid induced transformation is necessary in order to produce inhibition. The fact that omeprazole is activated close to the H-K ATPase, an enzyme that appear unique for the gastric mucosa, enhances the selectivity of the inhibitor (Wallmark, 1986)

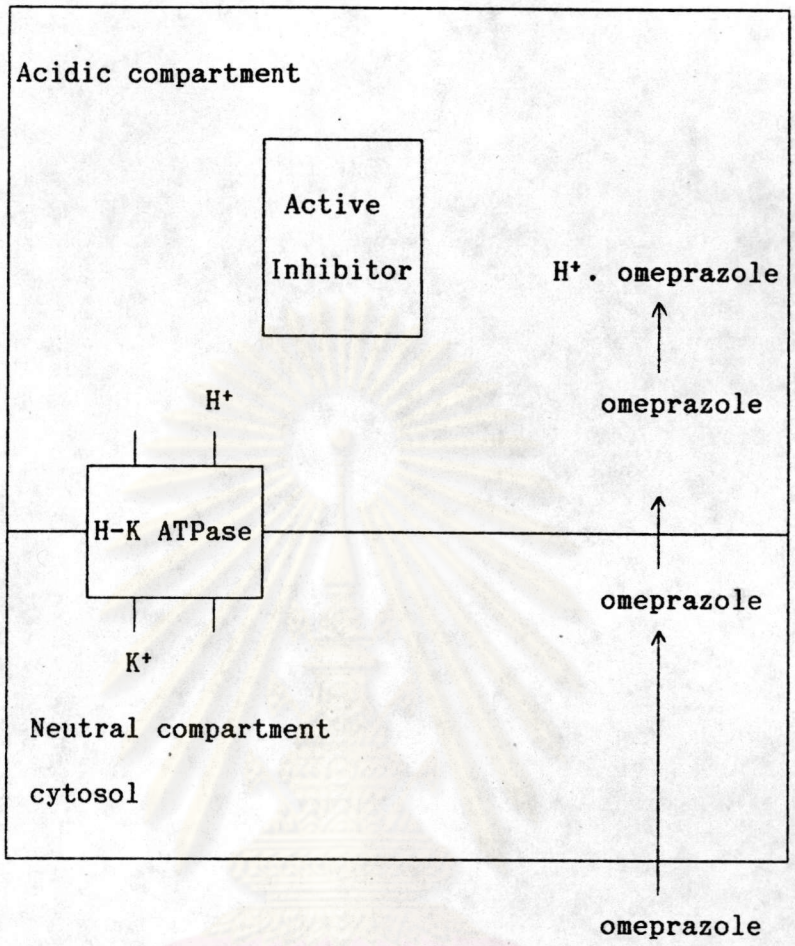

Fig 2.1 : A scheme for acid induced transformation of omeprazole into an active inhibitor of acid secretion within the parietal cell.

The Regulation of potassium

Potassium is the most abundant exchangeable cation in the body. It exists predominantly in the intracellular fluid at concentration of 140 to 150 mEq/L and in the extracellular fluid at concentration 3.5 to 5 mEq/L. (only 2 percent of the total body potassium) (Thier, 1986). Therefore a gradient exists for the diffusion of potassium from intracellular to extracellular fluid.

This gradient causes problem in the interpretation of total body stores since the serum level is affected by shifts of potassium between the intracellular and extracellular fluids in addition to the total body balance. Therefore estimation of the magnitude of a deficit or excess of total body potassium extrapolated from the serum potassium level is an imprecise determination (Brown, 1984). Hypokalemia could occur when a large potassium have loss, usually 200 mEq or more (Valtin, 1979).

Defense against abnormalities of potassium balance occurs through two mechanisms. The long-term defense is by the kidney. Acutely, defense is achieved by extrarenal mechanisms that distribute potassium between the extracellular and the intracellular fluid (Smith et al., 1984).

Substances-induced hypokalemia :

Effect of insulin on renal potassium metabolism

Insulin has been shown to play a role in potassium homeostasis (DeFronzo and Bia, 1985). Its major mechanism of action is to enhance potassium uptake by extrarenal tissues (Zierler et al., 1966).

In humans the primary effect of hyperinsulinemia is to stimulate potassium uptake by extrarenal tissues; the resultant hypokalemia, leading to a secondary fall in potassium excretion (DeFronzo et al., 1975). Conversely, under normokalemia conditions, Insulin augments potassium uptake into the cells of the distal (initial collecting tubule)

and cortical collecting tubules (Wright and Giebisch, 1985). The resultant increase in intracellular potassium concentration would then lead to a stimulation of potassium secretion (Rossetti, 1987). Furthermore, the rise in intracellular potassium in the kidney is well known to inhibit urinary acidification in vivo studies (Arruda, et al., 1980)

Diuretic-induced hypokalemia and effect on acid and electrolyte excretion

Diuretics that either inhibit reabsorption in the thick ascending limb of Henle (drugs such as furosemide, ethacrynic acid, bumetamide) or in the early distal tubule (such as thiazides, chlorthalidone) are kaliuretic and induce hypokalemia when ingested on a chronic basis (Kassirer, 1977). The kaliuresis produced by these agents result from increased delivery of tubular fluid to the distal convoluted tubule and also possibly from increased sodium delivery to the distal nephron, especially the cortical collecting duct (Tannen, 1983).

Diuretics are chlorouretic as well as natriuretic. A primary deficit of chloride results in potassium depletion with hypokalemia, metabolic alkalosis, and mild volume contraction (Schwartz, 1968). The tubular mechanisms accounting for how chloride depletion induces renal potassium losses are still unresolved. (Seldin and Rector, 1972). Tannen and Gerrits (1983) suggested that diuretics, especially furosemide, might stimulate potassium secretion in yet another way, namely by a direct tubular effect. Their study, which utilized isolated perfused kidneys from potassium-depleted rats, indicate that furosemide can induce a kaliuresis of a magnitude that cannot be

accounted for entirely by an increase in either urine flow rate or sodium excretion. Furthurmore, studies with amiloride indicates that this direct effect of furosemide on potassium excretion results from an increase in potassium secretion rather than from a decrease in potassium reabsorption.

Acute experiments in man have demonstrated that furosemide results in an increase in bicarbonate excretion that exceeds any modest rise in ammonium or titratable acid excretion (Stein et al., 1968). Since furosemide primarily appears to inhibit chloride reabsorption in the distal nephron, it seems possible that the chronic inhibition of chloride reabsorption by this agent might also result in increased hydrogen secretion (Burg et al., 1973). Hydrogen secretion in the distal convoluted tubule increases primarily in cousequence increased avidity for sodium reabsorption in this segment of the nephron (De Sousa et al., 1974). In the animal receiving furosemide plus replacement the increased hydrogen excretion did not appear to be consequent to sodium depletion. The mechanism where by furosemide increased and maintained hydrogen secretion remain uncertain (Tannen, 1985). Burg (1973) suggested that the major effect of furosemide appears to be the inhibition of chloride transport at the ascending limb of the loop of Henle, resulting in an increased quantity of sodium chloride reaching the distal convoluted tubule. In the distal tubule sodium may be reabsorbed either in association with chloride or in exchange for hydrogen and potassium (Giebisch, 1972). Since chloride reabsorption appears to lag behind sodium in the distal convoluted tubule, an increase in sodium chloride in this segment produced by furosemide may per se result in an increase in hydrogen secretion. Alternatively, it

is possible that the increase in net acid excretion is consequent primarily to an effect of furosemide on chloride reabsorption in the distal convoluted tubule, thereby exaggerating the usual lag between sodium and chloride reabsorption in this segment (Burg, 1974).

H-K ATPase activity

H-K ATPase is enzyme which contributed to the gastric acid secretion. H-K ATPase, which is located on the secretory surface of parietal cells, catalyzes the exchange of protons and potassium ion and is postulated to be the proton pump in the secretory membrane of the parietal cell (Sachs et al., 1976). Sachs et al. (1982) have suggested that this enzyme may be condidate for potassium reabsorption and hydrogen ion secretion in the renal distal tubule.