CHAPTER II

REVIEW OF LITERATURE

Background and Rationale

The incidence of peptic ulcer is a major cause of morbidity and absenteeism. In Thailand, it has been estimated that about 10 percent or more than four millions of Thai population were suffered from this disease (14). Generally, therapy with antacids and anticholinergics have been the primary mode of treatment, despite the lack of conclusive evidence that either regimen enhances healing or decreases the recurrence of complications of the disease. The anticholinergics inhibit the secretion of acid and antacids buffer gastric acid. The over all efficacy of these agents is not striking. While apparently rational, their limited effectiveness could be due in part to their inability to adequately reduce gastric and peptic activity.

The search for more specific inhibitors of gastric acid appeared to be a breakthrough in 1972, when Black et al. (15) identified a new histamine receptor which had properties unlike that of the conventional H_1-receptors. Studies by these investigators revealed that this newly discovered histamine receptor, which they labeled H_2, had a direct bearing on the secretion of gastrin and gastric

acid from the gastrointestinal mucosa and had potentially clinical usefulness in gastric ulcerations.

The first H_2-receptor antagonist developed by these investigators was burimamide. An intravenous injection of this drug was shown to be a more potent inhibitor of both histamine and pentagastrin stimulated gastric acid secretion than those of large intravenous doses of anticholinergics (16). However, the drug possessed some histamine agonist properties and was not well absorbed from the gastrointestinal tract following oral administration.

Modification of the structure of burimamide resulted in the synthesis of the second H_2-receptor antagonist, metiamide. This drug, in single doses of 300 mg and 400 mg orally, produced an 80 percent reduction in both basal and meal stimulated gastric acid secretion and was well absorbed from the gastrointestinal tract (17). It thus appeared that metiamide was the drug that would be developed for using in the treatment of peptic ulcers. However, in 1975, Spence et al. (18) reported a case of reversible metiamide induced neutropenia. Since thiourea containing drugs (i.e. propylthiouracil) are known to produce agranulocytosis, it was felt that the thiourea moiety of metiamide was responsible for this adverse reaction. While the exact incidence of metiamide induced agranulocytosis is not definitely known, it is felt that it may have occurred in approximately 1 percent of those

patients who took the drug (1). This problem with metiamide led to the successful search for an alternative and the eventual production of the third H_2-receptor antagonist, cimetidine.

Review of Cimetidine

Cimetidine is a specifically competitive histamine H_2-receptor antagonist. It was manufactured and marketed by the firm Smith,Kline and French under the proprietary name Tagamet ^{R}. Because of its minimal side effects, it is widely used in the therapy of peptic ulcers (1-9).

Physicochemical Properties (19-21)

Chemically, cimetidine (Figure 1) is an imidazole derivative like histamine. However, unlike histamine, it has a substituted methyl group on the 4th position of the ring with a side chain containing sulfur and a cyanoguanidine group.

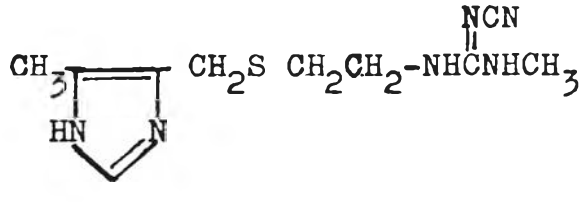

Figure 1 Cimetidine: N"-Cyano-N-methyl-N'-[2-[[(5-methyl-H- imidazol-4-yl) methyl] thio] ethyl] guanidine

Description	:	Colorless crystalline solid with bitter taste
Emperical Formula	:	$C_{10}H_{16}N_6S$
Molecular Weight	:	252.34
Melting Point	:	141-143°C
Chemical Properties	:	In water, the pKa of the ring nitrogen (-NH-) is 6.80, therefore at pH 7.4,20.7% of the substance is present as cations. The nitrogen atom on the side chain attached to the cyano moiety (-C ≡ N) has almost no basic properties, with a pKa of - 0.4, and is essentially unionized in the pH range of 2-12. Cimetidine is quite polar. The partition coefficient (octanol/water) is 2.5 at pH 9.2
Solubility	:	The solubility of cimetidine in water is 6.15 mg/ml at 25°C. Solubilities in methanol and acetonitril at 24°C are, respectively, 141 and 2.7 mg/ml.
Stability	:	Cimetidine in aqueous solution obeys first order degradation kinetics, with maximum stability occurring in the region of pH 6. Cimetidine undergoes decomposition via two pathways hydrolysis and oxidation.

The cyano group on the side chain of cimetidine molecule is susceptible to hydrolysis in acidic solution. The second route of cimetidine degradation involves the oxidation of the side chain sulfur to form the sulfoxide compound. This also happens to be the principal metabolic pathway by which a small fraction of cimetidine eliminated In Vivo (19).

Polymorphism : There are four crystalline forms of cimetidine, three anhydrous (forms A,B,and D) and a monohydrate (form C). Among the three anhydrous forms of cimetidine, form A was thermodynamically more stable than the others. Form C undergoes a slow transformation into form A.

Mode of Action

Cimetidine exerts its beneficial effect in acid peptic disorders by inhibiting gastric acid secretion. There are many theories on how H_2 antagonists inhibit gastric acid secretion. One of the more attractive theories is based on the observation that isolated parietal cells have specific receptors for each of the classical three secretogogues: histamine, gastrin, and acetylcholine. Each secretogogue may stimulate acid

secretion independently. This theory suggests that only histamine interacts with the parietal cell receptor and that gastrin and acetylcholine stimulate acid secretion solely by increasing the local availability of histamine. Cimetidine would then inhibit acid secretion by blocking the effects of histamine on its receptors and eliminating the potentiating effect of histamine on gastrin and acetylcholine (9,22). This theory is consistent with the observation that at least some cholinergic induced acid secretion is not blocked by H_2 antagonists. A clinical correlation is the observation that increased inhibition of gastric acid has been achieved in patients with duodenal ulcers and Zollinger-Ellison Syndromes by a combination of cimetidine and anticholinergic drug (22).

Toxicity

Considering the number of patients who have received cimetidine since its release, serious drug reactions appear relatively uncommon (23-25). Minor, infrequent side effects do not require discontinuation of drug therapy included headache, dizziness, fatigue, skin rash, diarrhea, constipation and muscular pain. However, potentially serious effects with possible cause-effect relationship to cimetidine have occurred in susceptible individuals. The elderly, uremic patients, and patients with impaired liver function appear susceptible to mental confusion, while rarely serious hematologic depression, cardiac depression, hypersensitivity-type hepatitis, and gynecomastia appear to show no selectivity among patients (24).

The frequency of adverse reaction is low, probably under 5 percent, and most side effects are minor (23-25). There are different causes for the side effects. Some of the unwanted effects appear to be structure-specific to cimetidine (i.e., weak anti-androgenic activity and inhibition of microsomal enzyme activity) rather than related to H_2 blockade perse. Some adverse reactions appear to be due to blockade of H_2 receptors at various sites. At least some of the central nervous systems and rare hematologic and cardiovascular reactions may be due to H_2 antagonism. There also are rare idiosyncratic reaction to cimetidine. These reactions are not predictable on a pharmacological basis and presumably depend more on the characteristics of the patients than on the properties of the drug. Examples include interstitial nephritis and cholestatic and hepatitic reactions. Finally, there is the possibility of H_2 blockade of parietal cells causing adverse effects. The most topical of such effects are the possibility of intragastric nitrosation by bacteria in a setting of gastric acid suppression. The evidence is weak, at best, that this effect might predispose to gastric cancer, but the issue is forcing a reappraisal of the wisdom of striving to induce more inhibition of acid secretion for longer period (25).

The risk/benefit ratio of cimetidine is clearly favorable in active duodenal ulcers and in prophylaxis against recurrence of ulcers. There is as yet no evidence

that low dose (i.e., 400 mg at bed time) maintenance therapy beyond one year is harmful. In most patients with Zollinger-Ellison Syndromes, the benefits of cimetidine therapy far outweigh its risks. Current evidence indicates that this is also true in uncomplicated gastric ulcer.

Pharmacokinetic Studies

Cimetidine is a weak imidazole base that is well absorbed from the small intestine. Peak blood levels are achieved by 60 to 90 minutes after an oral dose of up to 400 mg . The concentration of cimetidine required to produce a 50 percent inhibition of gastric acid secretion has been identified as 0.5 μg/ml (1,3,9). Therapeutic concentration in plasma usually falls in the range of 0.5-1.5 μg/ml (23). Following intravenous administration, the plasma concentration profile follows multicompartmental characteristics (26). The volume of distribution of cimetidine has been calculated to be about 1 to 2 litres/kg, suggesting the drug is distributed throughout most of the body (1,23,26). The elimination half life is 1.5-2.0 hours in subject with normal renal function (9,27). Plasma protein binding is 20 percent and there is no relevant effect of changes in binding on the pharmacokinetics of cimetidine. The total clearance is high (500 to 600 ml/min) and is mainly determined by renal clearance (26).

Cimetidine when taken orally without food after an overnight fast produces a blood concentration curve

with a pronounced second peak that does not appear after parenteral administration or when the drug is taken with food (3,28-31). Bioavailability after oral administration is about 70 percent (1,3,23). Walkenstein et al.(28) also indicated that the intramuscular and intravenous routes are virtually interchangeable for parenteral cimetidine. When given by mouth before meals, cimetidine produces higher peak drug levels than those when given with meals. However, giving the drug with meals, absorption is delayed, and the inhibitory effect is prolonged. Hence, food itself buffers gastric acidity for at least an hour after a meal, this delayed effect of cimetidine might be complemented by food. Consequently, a schedule of cimetidine administration with meals appears to be effective as well as convenient. Studies to measure In Vivo acid secretion in patients with duodenal ulcer in response to meals have confirmed the efficacy of this regimen in suppressing acid secretion throughout the day (9).

Cimetidine is rapidly excreted via the kidney, within 24 hours after oral or intravenous administration. About 50 to 70 percent of the drug is excreted unchanged into the urine, together with about 10 percent as the sulphoxide metabolite and about 5 percent as the 5-hydroxy-methyl derivative. Up to about 10 percent of the dose is eliminated in the faeces (9,23). In patients with several renal insufficiency, the elimination half-life is increased to approximately 3.5 hours, and drug dosages

must be reduced accordingly. Since cimetidine is dialyzable, further adjustments in drug dosage are necessary for patients with severe renal insufficiency undergoing hemodialysis (9,22). Larsson et al. (32) provide dosage recommendation for cimetidine in patients with declining renal function based on creatinine clearance. No dosage reduction is necessary for patients with hepatic failure in the setting of normal renal function (9).

Cimetidine crosses the placenta and is detectable in the fetus in considerable concentrations. It is also secreted into breast milk of nursing mothers and may reach the infant in amounts of several milligrams daily (26).

Dose (33)

1. By Mouth

Adult : 400 mg twice daily (with breakfast and at bed time) or 200 mg 3 times daily and 400 mg at bed time. Doses should be taken for at least 4 weeks (6 weeks in gastric ulceration) ; when necessary the dose may be increased to 400 mg 4 times daily or rarely to a maximum of 2 g daily in divided doses to maintain intragastric pH above 4.

Child : 20-40 mg/kg daily in divided doses. Reflux oesophagitis, Zollinger-Ellison Syndrome, 400 mg 4 times daily (continued in reflux oesophagitis for 8 weeks). Maintenance, 400 mg at night or 400 mg morning

and night. Gastric acid reduction (prophylaxis of acid aspiration), obstetrics 400 mg at start of labour, then 200 mg every 2 hours to a maximum of 1.6 g ; surgical procedures 400 mg 90-120 minutes before induction, supplemented when necessary. Short-bowel Syndrome, 1 g daily in divided doses to reduce malabsorption and fluid loss.

2. By Intramuscular or Slow Intravenous Injection

200 mg every 4-6 hours ; maximum 2 g daily.

3. By Intravenous Infusion

Adult : 100-150 mg/hour (or 2 mg/kg/hour) for 2 hours, repeated after an interval of 4-6 hours or by continuous infusion up to 75 mg/hour over 24 hours, maximum 2 g daily.

Child : by slow intravenous injection or infusion, 20-40 mg/kg daily in divided doses.