Editorial

CIMETIDINE

Black et al. (1972) first demonstrated the existence of Histamine H_2 receptors which were not antagonized by classical antihistamines. Burimamide was the first drug found to be active against then receptors but was ineffective orally. Metamide was thus synthesized but unfortunately caused agranulocytosis. This lead to the discovery of cimetidine. This inhibits the histamine-stimulated gastric acid secretion by blocking histamine at gastric parietal cell H_2 receptors. The concept that gastrin and acetylcholine stimulate acid production through local increase of histamine, the final common mediator (Code 1956), helps in understanding the indirect effect of cimetidine against them. The other concept is that each of these three secretagogues has its specific receptors in parietal cells and that histamine potentiates the effects of gastrin and acetylcholine (Soll 1948). Thus cimetidine, by blocking histamine H_2 receptors, inhibits them.

Cimetidine inhibits all phases of gastric acid secretion. It causes 90-95% reduction in both basal and nocturnal acid secretion for 5-7 hours with a 300mg dose (Henn et al., 1975; Longstreth et al., 1976). It also inhibits the acid secretion stimulated by pentagastrin, histamine, insulin, bethanecol and caffeine as well as protein-rich meal. In duodenal ulcer patients, a 300mg dose inhibits the meal-stimulated secretion by about 70% over a 3 hour period as compared to a maximum dose of an anticholinergic which reduces such secretion by 25% - 30% (Henn, 1975; Feldman et al., 1977). As cimetidine and anticholinergics act differently, their effects may be synergistic (Feldman et al., 1977). Its inhibitory effect on gastric output is two-fold decrease in hydrogen-ion concentration and gastric-juice volume. There is some conflict on its effect on pepsin and intrinsic factor secretion. Fielding et al. (1977) showed that it inhibits them and Binder et al. (1978) showed its failure in stimulation of basal intrinsic factor secretion. Reduction in total pepsin output appears to be due to inhibition of gastric secretory volume because the pepsin concentrations are not decreased.

In duodenal ulcer patients, fasting serum gastrin levels appear unaffected by Cimetidine (Longstreth et al., 1976) but post-prandically, these are raised (Longstreth et al., 1977) probably due to reduced acid feed back inhibition of gastrin release. There is no "Rebound" increase in peak gastric acid output after 6 weeks therapy in a patient of duodenal ulcer as compared to pretreatment levels (Binder et al., 1978).

An oral dose produces peak blood levels in 60-90 minutes. After i/v administration serum half life is 1.5 - 2 hrs. (Ma et al., 1978). Clinically effective drug levels, after either oral or i/v dose, are maintained for 4 hours. When given with meals, although its peak levels are lowered, its absorption is delayed and action prolonged (Spence et al., 1976), a fact helpful in suppressing the acid secretion throughout the day. 50-70% of cimetidine is excreted unchanged in the urine within 24 hours after an oral or i/v dose. Dosage adjustments are required in severe renal insufficiency because serum half-life of drug is increased to 3.5 hours, and in those undergoing haemodialysis since the drug is dialyzable.

Winship (1978) demonstrated the clinical efficacy of cimetidine in duodenal ulcer in eight placebo-controlled trials, in over 650 patients. Complete ulcer healing, as evidenced by endoscopy, occurred in 70% cases after 4-6 weeks of treatment as compared to 40% in the placebo group. Acceleration of early ulcer healing occurred in as short a period as 2 weeks in 50% of patients as compared to 25% of placebo-treated patients. (Binder et al., 1978). Its effect on duodenal ulcer healing rate is comparable with those of extensive antacid regimen. Therefore, the choice of therapy becomes individualized and require consideration of such factors as its convenience and ease of administration, lack of effect on bowel motility and prompt relief of symptoms, the properties exhibited by cimetidine. But the drug is also systematically absorbed and produces its trivial and infrequent side-effects. In refractory cases of duodenal ulcer, the unusually high acid-pepsin secretory rates may respond to "combination" drug therapy i.e., use of either antacids or articholinergics or both with cimetidine. A "maintenance" dose of either 400 mg at bed time (Gray et al., 1978) or twice daily (Bodemar and Wallen, 1978) for 6-12 months resulted in significant reduction in recurrence rates.

Sixty-one patients of Zollinger-Ellison syndrome treated with cimetidine, most of

them with a dose of 1.2 g/day, showed a dramatic improvement of symptoms (McCarthy 1978). However, about 1/3 patients required a dose upto 2.4 g/day or addition of an antacid. In over half of the patients it had to be continued for more than a year with its common side effect of gynecomastia. Not only cimetidine has replaced total gastrectomy in Z-E syndrome but it is also quite effective in gastric acid hyper-secretory states e.g., short-bowel syndrome, systemic mastocytosis and basophilic leukaemia with hyperhistaminaemia.

The results of cimetidine in benign gastric ulcer are controversial. In 2 double-blind placebo-controlled trials it was found to be more effective than placebo while in 2 similar studies it was not (Freston, 1978; Frost et al., 1977). Comparing its results with those of potent antacids, cimetidine, in doses of 1.2 g/day for 6 weeks, was not found to be more effective than antacids, results in both being 60% (Englest et al., 1978).

In gastroesophageal reflux disease cimetidine has no effect on the lower esophageal sphinctor and its effectiveness is due to inhibition of gastric acid secretion. Doses of 1.2 g/day for 8 weeks, resulted in significant decrease in intensity and frequency of symptoms but the endoscopic improvement (about 50%) was similar to that in placebo group (Behar et al., 1978). Similarly, using 1.6 g/day dosage for 8 weeks, produced considerable endoscopic and histological improvement as compared to placebo group (Wesdrop et al., 1978; Dunn et al., 1978).

There was a significant reduction in the incidence of acute gastrointestinal haemorrhage in a trial of 50 patients with fulminant liver disease treated with i/v cimetidine compared to a placebo treated group (MacDougall et al., 1944). Encouraging results were also found in acute gastro-intestinal haemorrhage due to haemorrhagic gastritis and the drug stopped bleeding in 10 out of 14 patients not responding to other measures (Dunn et al., 1948). Effectiveness of the drug in peptic ulcer-related haemorrhage was seen as reduced incidence of rebleeding in cimetidine-treated patients as compared to the placebo group (Dykes et al., 1977). In acute haemorrhage it is used i/v in a dose of 300mg 6 hourly for about 48 hours after the bleeding has stopped followed by oral drug.

Cimetidine inhibits the acid-pepsin inactivation of orally ingested pancreatic enzymes and is of value when used in combination with these enzymes in treating severe pancreatic insufficiency. There is resultant increase in post-prandial trypsin and lipase activity (Regan et al., 1977).

Minor and infrequent side effects of cimetidine, in short term trials (Kruss and Littman, 1978) were headache, dizziness, skin rashes, diarrhoea, constipation and muscular pain (Kruss and Littman, 1978). Elderly patients had reversible mental confusion, agitation and coma was found but no bone marrow depression. Long term therapy resulted in transient gynaecomastia in some patients. Augmentation of delayed hypersensitivity responses to intradermal tests were found in a few patients. It also inhibits intestinal absorption of Vit. B_{12}. In about 3% of patients serum creatinine levels were transiently raised and in 3% of patients there was mild and transient rise of serum transaminases. In 2 of such patients liver biopsies showed mild centrilobular necrosis. Experiments on rats with large doses of drug for prolonged periods showed modest increase in benign Leydig cell tumour of testis (Report to US Food and Drug Administration (NDA 17 920), 1977).

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