Br. J. clin. Pharmac. (1975), 2, 481-486

PHARMACOLOGICAL EVALUATION OF CIMETIDINE, A NEW HISTAMINE H_2-RECEPTOR ANTAGONIST, IN HEALTHY MAN

W.L. BURLAND, W.A.M. DUNCAN, T. HESSELBO, J.G. MILLS & P.C. SHARPE
The Research Institute, Smith Kline and French Laboratories Ltd, Mundells, Welwyn Garden City, Herts.

S.J. HAGGIE & J.H. WYLLIE
Department of Surgery, University College Hospital Medical School, London WC1

1 Cimetidine, a new H_2-receptor antagonist, was safely administered to eighteen healthy men by the intravenous, intraduodenal or oral route.

2 When gastric secretion was maximally stimulated by either histamine or pentagastrin, the simultaneous administration of cimetidine produced marked inhibition of both acid and pepsin secretion.

3 Cimetidine was well absorbed by mouth and had a blood half-life of 2 hours.

4 Cimetidine was rapidly excreted via the kidneys and about 70% of the excreted material was unchanged drug.

5 Clinical evaluation of cimetidine in patients with peptic ulceration is recommended.

Introduction

Metiamide has been shown to be an effective inhibitor of the actions of histamine mediated through H_2 receptors in both animals and in man (Black, Duncan, Emmett, Ganellin, Hesselbo, Parsons & Wyllie, 1973; Wyllie, Ealding, Hesselbo & Black, 1973). In chronic toxicity tests, using doses of metiamide at least twenty times the orally effective dose in the dog, some animals developed kidney damage and agranulocytosis (Brimblecombe, Duncan & Walker, 1973).

Two patients being treated with metiamide developed a readily reversible granulocytopenia (Forrest, Shearman, Spence & Celestin, 1975). Brimblecombe, Duncan, Durant, Emmett, Ganellin & Parsons (1975) have described a new histamine H_2-receptor antagonist, cimetidine (*N*-cyano-*N'*-methyl-*N''*-{2-[(5-methylimidazol-4-yl)methylthio]ethyl}-guanidine) (Figure 1), and reported that in 90-day chronic toxicity tests in the rat and dog no renal or haematological abnormalities were observed. In view of the possibility that the toxicity of metiamide might limit its clinical use to the more seriously ill patient, it was therefore decided to investigate the effects of cimetidine in healthy man prior to its clinical evaluation in patients.

Method

Materials

Cimetidine Cimetidine, labelled with ^3H in the 2 position of the imidazole ring, was administered as a sterile 5% w/v solution, pH 5-6 or in No. 2 hard gelatin capsules each containing cimetidine (100 mg); lactose (140 mg); polyvinyl-pyrrolidone (7.5 mg); stearic acid (2.5 mg).

Histamine Histamine acid phosphate (1 mg/ml) sterile solution for intravenous administration was diluted with heparinized saline (10 U/ml) and infused at a rate of 40 $\mu g\ kg^{-1}\ hour^{-1}$.

Pentagastrin Pentagastrin (0.25 mg/ml) sterile solution for intravenous administration was diluted as described above and infused at a rate of 6 $\mu g\ kg^{-1}\ hour^{-1}$.

Subjects

All the studies were made in fasting healthy male volunteers aged 21-46 years. Routine laboratory examination of blood and urine was made immediately before and at the end of each study and twice during the following week. Blood

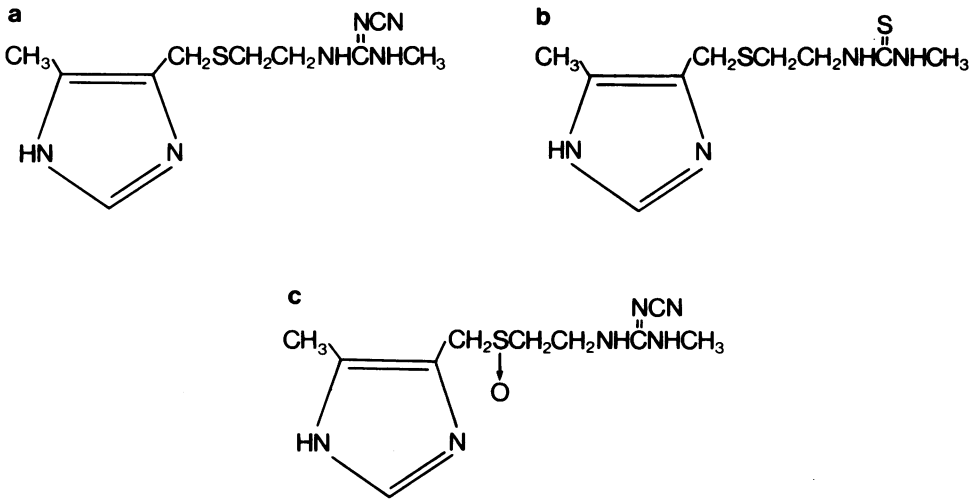

Figure 1 Structures of cimetidine (a) metiamide (b) and the sulphoxide metabolite of cimetidine (c).

pressure and electrocardiographic recordings were made throughout any study involving an intravenous infusion.

Initial intravenous infusion studies

These were conducted in two subjects; one received cimetidine (92 mg, 80 mg/h) and another cimetidine (83 mg, 100 mg/h). Only blood and urine samples were collected.

Gastric secretory studies

Intravenous infusion of cimetidine The effect of an intravenous infusion of cimetidine on the secretion of gastric acid and pepsin in fasting man was studied following maximal stimulation of gastric secretion by intravenous infusion of histamine acid phosphate in four subjects and pentagastrin in another three subjects. Gastric juice was collected by continuous suction at 4 cm Hg vacuum via a 14-F gauge naso-gastric tube. The tube was passed at the start of each study and the aspirate was collected at 15 min intervals. Basal secretion was measured for 30 min and then the agonist was infused using a constant rate infusion pump connected to a cannula inserted into a vein on the dorsum of a hand. To block the effects of histamine at H_1 receptors subjects were given mepyramine (1 mg/kg) by intramuscular injection 1 h prior to the infusion of histamine.

After 1 h cimetidine was simultaneously infused via the same cannula using a second constant rate infusion pump. The total dose of cimetidine administered in the seven subjects ranged from 75-117 mg. The duration of infusion was 45-90 min and the rate of infusion 50-100 mg/h. Infusion of the agonist was continued for at least 30 min after infusion of cimetidine was stopped to show evidence of recovery of gastric secretion.

Intraduodenal administration of cimetidine The effect of intraduodenal administration of a solution of cimetidine on maximally stimulated secretion of gastric acid and pepsin in man was studied in three fasting subjects. The technique avoided the withdrawal of the compound with the gastric secretion. At the start of the experiment the subjects swallowed a radio-telemetry capsule attached to a fine polythene tube. The movement of the capsule was followed by recording pH related transmissions from the capsule via an aerial in the form of a belt around the subject's waist. After approximately 1 h a consistently alkaline reading indicated that the tube was in place in the duodenum. The naso-gastric tube was then inserted and the subject screened by X-ray to confirm the position of both tubes. Samples of gastric juice were aspirated as described above. Basal secretion was measured for 30 min and then histamine acid phosphate was infused using a constant rate infusion pump connected to a cannula inserted into a hand vein. All the subjects were given mepyramine (1 mg/kg) by intramuscular injection 1 h before histamine was infused. After one hour's infusion of the agonist,

cimetidine (200 mg in 10 ml water) was administered via the duodenal tube, taking approximately 5 minutes. The solution was washed through with 2 ml air or water. The histamine infusion was continued throughout and the gastric secretion was collected until recovery from the effects of cimetidine was observed.

Oral administration

The blood concentrations, metabolism and excretion of cimetidine were measured after the oral administration of a solution of the compound on one occasion and a capsule on another in two studies in six subjects. The subjects fasted overnight and then swallowed aqueous solution of cimetidine (200 mg). At least one week later all the subjects were again fasted overnight then given two capsules each containing cimetidine (100 mg) and the experiment was repeated.

Analyses

Venous blood was collected at intervals during and for up to 6 h after the administration of cimetidine. All urine was collected at intervals for 24-48 hours. The concentration of cimetidine in blood was determined by scintillation counting of an octanol extract and the urinary recovery was estimated as the total recovery of the isotope excreted in the urine expressed as a percentage of the administered dose.

The volume of each gastric aspirate was read and acidity measured by titration against 0.1 N NaOH to the phenolphthalein end-point. Acid output was calculated as the product of volume and acidity and the results expressed as mmol of acid secreted in each 15 min period. The pepsin concentration in the gastric juice was estimated by an automated method following the action of pepsin on haemoglobin (Vatier, Cheret & Bonfils, 1968). Gastric aspirates were also examined for the presence of [^{3}H]-cimetidine after intraduodenal administration of the compound.

Preliminary studies have been conducted on the urine collected from three subjects who received an intravenous infusion of cimetidine and from two who received the compound by mouth. Samples of urine (50 μl) were spotted onto thin layer chromatography (t.l.c.) plates which were developed in ethyl acetate/methanol/ammonia (5:1:1). Each plate was then divided into zones on the basis of the known position of the possible metabolites and each zone assayed by liquid scintillation counting.

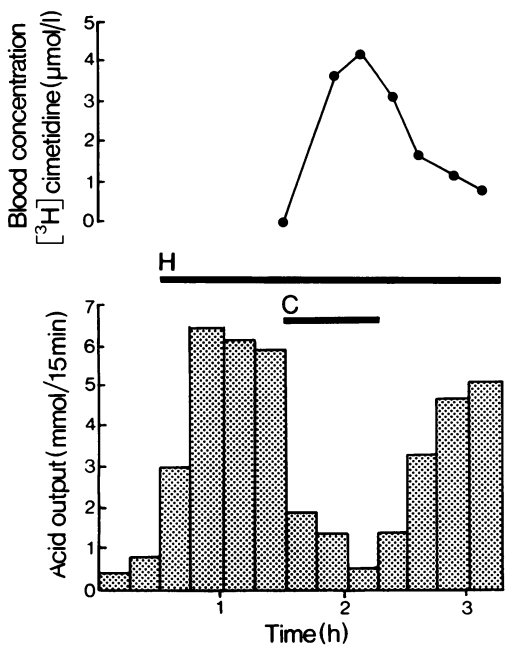

Figure 2 Intravenous administration of cimetidine (C, 100 mg/h) to one subject. Blood concentration and effect on gastric acid secretion stimulated maximally by histamine acid phosphate (H, 40 μg kg^{-1} h^{-1}).

Results

Blood concentration and excretion following intravenous infusion

Administration of cimetidine by intravenous infusion in doses of 75-117 mg to nine subjects resulted in peak blood concentrations of 2.0-4.3 μmol/litre. The concentration of cimetidine in the blood declined with half life of 123 ± 12 (± s.d.) minutes. Estimation of the total radioactivity recovered in the urine confirmed rapid excretion, with up to 60% of the administered dose being excreted in the first 2.5 h from the start of the infusion. After 24 h 81-96% of the dose had been recovered in the urine of eight of the subjects; in the ninth only 60% was recovered in the same time.

Gastric secretory studies

Intravenous infusion of cimetidine The results of the investigations in one of seven subjects are shown in Figure 2. Similar results were obtained from the remaining six subjects. Inhibition of

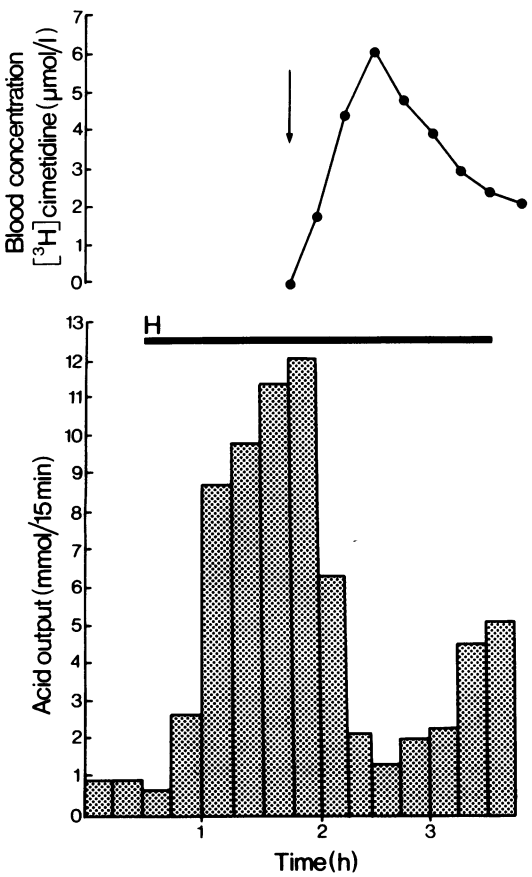

Figure 3 Intraduodenal administration of cimetidine (200 mg) at arrow to one subject. Blood concentrations and effect on gastric acid secretion stimulated maximally by histamine acid phosphate (H, 40 $\mu g\ kg^{-1}\ h^{-1}$).

gastric acid secretion was defined as a percentage decrease in acid output for each 15 min collection period after the beginning of cimetidine infusion from the acid output reached after the period of stimulation with histamine or pentagastrin alone. Maximum inhibition ranged from 53-91%, average 75%, and this was seen to be correlated with the circulating blood concentration of cimetidine at that time. The blood concentration to achieve 50% inhibition of acid output (IC_{50}) for cimetidine calculated from pooling all the results is 2 μmol/litre. The IC_{50} appeared to be the same whether histamine or pentagastrin was used as the stimulant.

Cimetidine affected both volume and acidity of the gastric juice; volume was reduced by 52-86%, average 68%, and acidity from 8-74%, average 72% and again this was a result of an effect on both concentration and volume; pepsin concentration was reduced by 11-43%, average 27 per cent.

Intraduodenal administration of cimetidine Peak blood concentrations after intraduodenal administration of cimetidine (200 mg) in solution ranged from 4.8-6.2 μmol/l at 30-90 min after dosing. Inhibition of maximally stimulated gastric secretion was apparent within 30 min of dosing in all cases. One result is shown in Figure 3. Maximum inhibition expressed as the percentage decrease in acid output varied between 75-95%. In one subject inhibition of over 80% was maintained for 2 h despite the continuing infusion of histamine. Both volume and acidity of the gastric juice were reduced in all cases. Pepsin output was reduced in parallel to the decrease in acid output, 74-92%, average 82%, but this was mainly due to the reduction in volume, there being only a small change in pepsin concentration. Less than 0.5% of the administered dose of cimetidine was recovered in the gastric aspirates. Total recovery of radioactivity in the urine 20 h after dosing was 61-87%, average 70 per cent.

Blood concentrations and excretion after oral administration

For each subject there was no difference in blood concentration obtained after the administration of cimetidine in solution or capsules. A typical result is shown in Figure 4. Peak blood concentrations following ingestion of cimetidine (200 mg) ranged from 1.2-4.3 μmol/l, average 2.8 μmol/l and occurred at times ranging from 45-75 min after dosing.

Following an oral dose of cimetidine (200 mg), 13-34% of the radioactivity was recovered in the urine 2 h after administration, and after 24 h 60-83%, average 70%, of the dose was accounted for.

Metabolism

Most of the radioactivity recovered from the t.l.c. plates was associated with unchanged cimetidine (56-85%). Up to 19% represented the sulphoxide (Figure 1); 7-17% of the radioactivity remained unidentified. There appeared to be no difference in either the actual metabolites or the quantity of them appearing in the urine after oral or intravenous administration and the results show that the metabolism of cimetidine in man is essentially similar to that shown in the rat and dog.

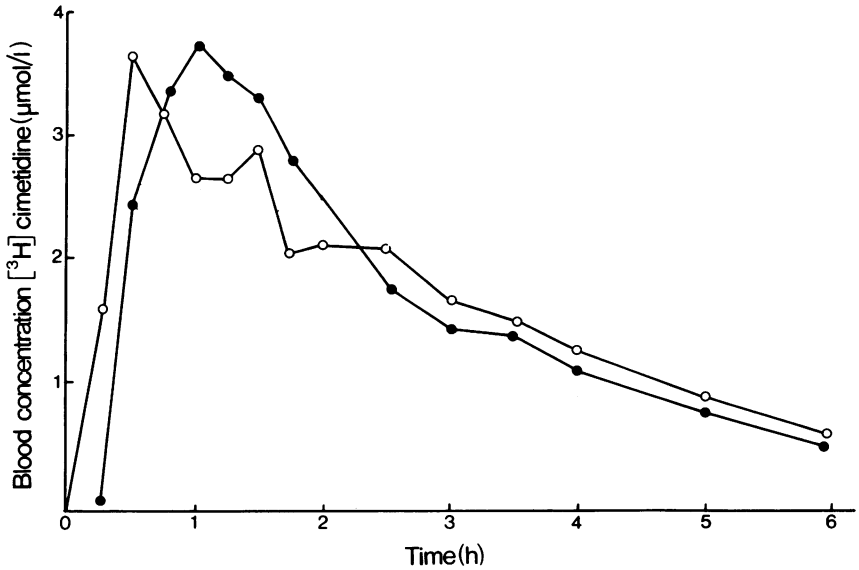

Figure 4 Blood concentrations in one subject after oral administration of cimetidine (200 mg) solution (○) and capsules (●).

Clinical observations and safety studies

Clinical observations carried out during the studies showed no adverse effects attributable to the administration of cimetidine. Blood pressure and electrocardiographic recordings remained unaffected by intravenous administration of cimetidine. Symptoms occurring during the evening and day following cimetidine administration were reported by three out of eighteen subjects. Two experienced mild dyspeptic symptoms and one nausea of short duration.

All laboratory analyses of blood and urine prior to the administration of cimetidine were normal. Laboratory analyses of blood and urine taken immediately after the administration of the compound and at intervals over the following week, remained normal with the exception of a few isolated values which returned to normal on analysis of the same or a subsequent sample.

All the subjects who received histamine acid phosphate were pre-treated with mepyramine but in all cases flushing was observed during histamine infusion, particularly on the face and neck and along the vein used for infusion. This flush disappeared during cimetidine infusion.

Discussion

The role of acid and pepsin in the aetiology of peptic ulcer and the inhibition of their secretion as factors in the healing of an ulcer, remain controversial. However, it has been well documented that surgical procedures which reduce gastric secretion are of value in treating patients with duodenal ulcer. The inhibition of gastric acid and pepsin secretion by histamine H_2-receptor antagonists may, therefore, be valuable in the treatment of peptic ulcer. Thjodleifsson & Wormsley (1974) have shown that metiamide effectively inhibits gastric secretion in patients with peptic ulcer and Carter, Forrest, Werner, Heading, Park & Shearman (1974) have also reported the inhibition of vagally stimulated gastric secretion. Nocturnal acid secretion has also been shown to be inhibited by metiamide (Milton-Thompson, Williams, Jenkins & Misiewicz, 1974) as also has basal and meal-stimulated secretion (Mainardi, Maxwell, Sturdevant & Isenberg, 1974; Richardson & Fordtran, 1974). Clinically, metiamide gives marked symptomatic relief to patients with peptic ulcer (Pounder, Williams, Milton-Thompson & Misiewicz, 1975) and healing of recalcitrant multiple ulcers has been reported following treatment with metiamide (Haggie, Clark, Black & Wyllie, 1975; Thompson, Venables, Miller, Reed, Sanders, Grund & Blair, 1975). The only significant side effects which have been reported following treatment with metiamide have been two cases of a readily reversible granulocytopenia (Forrest *et al.*, 1975). As a result of these cases, clinical trials with metiamide have

been limited to the more seriously ill patient with proven peptic ulcer resistant to other therapeutic treatment.

In animals the pharmacokinetic and pharmacodynamic properties of metiamide and cimetidine are similar, although cimetidine may be more potent *in vivo* as an inhibitor of gastric secretion (Brimblecombe *et al.*, 1975). Following both intravenous and intraduodenal administration cimetidine effectively inhibited both histamine and pentagastrin stimulated gastric secretion in man. Our results confirmed that both qualitatively and quantitatively the pharmacological properties of cimetidine and metiamide are similar although cimetidine may be more potent than metiamide. The concentration of cimetidine in the blood required to give a 50% inhibition of stimulated acid output is approximately 2 μmol/litre. Following oral administration cimetidine is rapidly absorbed and doses of 200 mg gave peak blood concentrations of 1.2-4.3 μmol/l (average 2.9 μmol/litre). The major route of excretion is via the kidney and approximately 70% of the excreted material is cimetidine. The major metabolite is formed by oxidation of the sulphur to give the sulphoxide. The metabolic pathway in man is similar to that reported for animals (Brimblecombe *et al.*, 1973). Cimetidine has a blood half life in man of 124 ± 12 min which is greater than that reported for metiamide (Black *et al.*, 1973). Clinical observation carried out during the studies showed no adverse effects attributable to the administration of cimetidine. The evidence presented here indicates that cimetidine may be safely administered to patients for the purposes of clinical study.

References

BLACK, J.W., DUNCAN, W.A.M., EMMETT, J.C., GANELLIN, C.R., HESSELBO, T., PARSONS, M.E. & WYLLIE, J.H. (1973). Metiamide – An orally active histamine H_2-receptor antagonist. *Agents and Actions*, 3, 133-137.

BRIMBLECOMBE, R.W., DUNCAN, W.A.M., DURANT, G.J., EMMETT, J.C., GANELLIN, C.R. & PARSONS, M.E. (1975). Cimetidine – A non thiourea H_2-receptor antagonist. *J. int. med. Res.*, 3, 86-92.

BRIMBLECOMBE, R.W., DUNCAN, W.A.M. & WALKER, T.F. (1973). Toxicology of metiamide. In *International Symposium on Histamine H_2-receptor antagonists.* ed. Wood, C.J. & Simpkins, M.A., pp. 53-72. Smith Kline & French Laboratories Ltd.

CARTER, D.C., FORREST, J.A.H., WERNER, M., HEADING, R.C., PARK, J. & SHEARMAN, D.J.C. (1974). Effect of histamine H_2-receptor blockade on vagally induced gastric secretion in man. *Br. med. J.*, 3, 554-556.

FORREST, J.A.H., SHEARMAN, D.J.C., SPENCE, R. & CELESTIN, L.R. (1975). Neutropenia associated with metiamide. *Lancet*, i, 392-393.

HAGGIE, S.J., CLARK, C.G., BLACK, J.W. & WYLLIE, J.H. (1975). Clinical experience with metiamide. *Fed. Proc.* (in press).

MAINARDI, M., MAXWELL, V., STURDEVANT, F.A.L. & ISENBERG, J.I. (1974). Metiamide, an H_2-receptor blocker, as inhibitor of basal and meal-stimulated gastric acid secretion in patients with duodenal ulcer. *New Engl. J. Med.*, 291, 373-376.

MILTON-THOMPSON, G.J., WILLIAMS, J.G., JENKINS, D.J.A. & MISIEWICZ, J.J. (1974). Inhibition of nocturnal acid secretion in duodenal ulcer by one oral dose of metiamide. *Lancet*, i, 693-694.

POUNDER, R.E., WILLIAMS, S.G., MILTON-THOMPSON, G.J. & MISIEWICZ, J.J. (1975). Relief of symptoms of duodenal ulcer by oral metiamide. *Br. med. J.*, 2, 307-309.

RICHARDSON, C.T. & FORDTRAN, J.S. (1974). Effect of metiamide, a histamine H_2-receptor antagonist, on food-stimulated acid secretion in patients with duodenal ulcer. *Gastroenterology*, 66, A-207/861.

THJODLEIFSSON, B. & WORMSLEY, K.G. (1974). Gastric response to metiamide. *Br. med. J.*, 2, 304-306.

THOMPSON, M.H., VENABLES, C.W., MILLER, I.T., REED, J.D., SANDERS, D.J., GRUND, E.R. & BLAIR, E.L. (1975). Metiamide in Zollinger-Ellison syndrome. *Lancet*, i, 35-36.

VATIER, M.M., CHERET, A.M. & BONFILS, S. (1968). Automatic titration of the proteolytic activity of gastric juice (Fr). *Biologie et Gastroenterologie*, 9, 15-29.

WYLLIE, J.H., EALDING, W.D.P., HESSELBO, T. & BLACK, J.W. (1973). Inhibition of gastric secretion in man by metiamide: A new, orally active histamine H_2-receptor antagonist. *Gut*, 14, 424.

(Received March 17, 1975)