Pharmacology and Toxicology of Metiamide, a Histamine H_2-Receptor Antagonist

R. W. BRIMBLECOMBE,   W. A. M. DUNCAN,   M. E. PARSONS

SUMMARY

A brief review of the pharmacology and toxicology of metiamide, a histamine H_2-receptor antagonist, is given, and evidence is presented to support the view that it inhibits gastric acid secretion by virtue of its H_2-receptor antagonist activity.

Studies are also reported which show that metiamide given either intravenously or intraduodenally inhibits histamine- or pentagastrin-stimulated acid secretion in human subjects.

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Conventional antihistaminic drugs, such as mepyramine, even in high concentrations, fail to inhibit histamine-stimulated gastric acid secretion. They also fail to antagonise the actions of histamine in increasing heart rate and in inhibiting contractions of the rat uterus. Ash and Schild[1] defined the pharmacological receptors involved in mepyramine-sensitive histamine responses as H_1-receptors. Those receptors which are refractory to mepyramine are termed H_2-receptors, and in 1972 Black et al.[2] described the drug burimamide, which satisfies all the criteria required of a competitive antagonist of histamine at these H_2-receptors. Burimamide was not particularly effective when administered to experimental animals by the oral route, but subsequently, in 1973, Black and his colleagues[3] described metiamide, another H_2-receptor antagonist, which showed good oral activity.

This article summarises the information on the toxicology of metiamide and describes some of its pharmacological actions, particularly those related to inhibition of gastric acid secretion. Reference is also made to clinical studies with the drug in patients with hypersecretion.

PHARMACOLOGY

The evidence for metiamide being a competitive antagonist of histamine at H_2-receptors is based on the results of studies using isolated guinea-pig atria or isolated rat uteri *in vitro*. The concentration of metiamide required to occupy half the receptors at equilibrium (K_B)[4] was 9,2

$\times\ 10^{-7}M$ on atrial muscle and $7,5\ \times\ 10^{-7}M$ on uterine muscle. Even at $10^{-3}M$, metiamide did not inhibit the effects of isoprenaline on either of these tissues, neither did it inhibit the effects of histamine on isolated guinea-pig ileum (mediated through H_1-receptors).

Metiamide is also an inhibitor of gastric acid secretion. Its effectiveness was estimated in two preparations: the lumen-perfused stomach of the anaesthetised rat[5] and the conscious Heidenhain pouch dog, prepared 1 - 3 years before experimentation. Metiamide was given by rapid intravenous injection during a maximal plateau of acid secretion stimulated by either histamine or pentagastrin, and the dose required to reduce this level of secretion by 50% (ED_{50}) was estimated. The results are shown in Table I and indicate that the ED_{50} values are very similar against those of both histamine and pentagastrin. Doses of up to 64 μmole/kg in the rat did not inhibit secretion stimulated by the cholinergic drug carbachol. In the Heidenhain pouch dog 8 μmole/kg metiamide given by intravenous injection inhibited carbachol-stimulated secretion, but continuous intravenous infusion of 10 μmole/kg/min, which was very effective against histamine and pentagastrin, did not inhibit the effects of carbachol. Metiamide is also effective when given orally. In Heidenhain pouch dogs the ED_{50} for inhibition of acid secretion maximally stimulated by histamine is 16 (4 - 69) μmole/kg. The oral ED_{50} of the drug for inhibition of basal secretion in gastric fistula rats is about 25 μmole/kg.
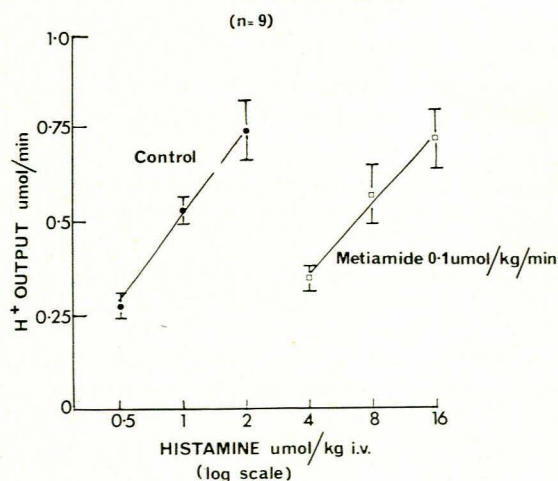

Fig. 1. Dose-response curves of acid secretion in response to histamine in the anaesthetised rat lumen-perfused stomach preparation.

The Research Institute, Smith, Kline and French Laboratories Ltd, Welwyn Garden City, Hertfordshire, England
R. W. BRIMBLECOMBE
W. A. M. DUNCAN
M. E. PARSONS

TABLE I. THE POTENCY OF METIAMIDE IN INHIBITING STIMULATED ACID SECRETION IN THE RAT AND THE DOG
(Mean values with 95% confidence limits)

	Histamine		Pentagastrin	
	Rat	Dog	Rat	Dog
ED_{50} μmole/kg	1,6	3,1	2,4	6,1
	(1,2 - 2,2)	(2,0 - 4,9)	(1,9 - 3,0)	(1,4 - 26,9)
No. of experiments	35	21	14	17

The evidence so far presented does not prove that metiamide inhibits gastric acid secretion by virtue of its H_2-receptor antagonist action, but there are various pieces of evidence to support this view. In the first place it is clear that the drug is not simply a non-specific inhibitor of secretion, since it does not inhibit secretion stimulated by dibutyryl cyclic-AMP.[6] Secondly, as is shown in Figs 1 and 2, metiamide given by intravenous infusion causes

DOG GASTRIC SECRETION

Fig 2. Dose-response curves of acid secretion in response to histamine in the Heidenhain pouch dog preparation.

a parallel displacement to the right of the dose-response curves for histamine-stimulated acid secretion in both the rat and the dog. Thirdly, using radio-labelled metiamide in the rat, plots were made of log (plasma concentration of metiamide) against log (dose ratio −1) in experiments in which doses of histamine were given before and towards the end of a metiamide infusion. The slope of the regression was not significantly different from unity and, although the precision of the analysis was not high, the calculated apparent dissociation constant was not significantly different from those estimated on isolated tissues, i.e. the requirements for competitive antagonism appeared to be satisfied.

In the dog, from a number of experiments, log (dose ratio −1) was plotted against log (infusion concentration of metiamide). Again the regression was not significantly different from unity. Labelled metiamide was not used in these experiments, but from a separate study in the same dogs it was estimated that the plasma concentration required for 50% inhibition was between 1,0 and 1,6 μmole, which corresponds well with the in vitro estimates of the apparent dissociation constant for the H_2-receptor antagonism of 0,7 to 0,9 μmole.

These results reopen the controversy concerning the role of histamine in the control of gastric acid secretion. The view that histamine in the gastric mucosa might be the local common mediator for physiological stimulation of secretion was proposed by McIntosh in 1938[7] and restated by Code in 1965.[8] The hypothesis implies that endogenous gastrin, whether released as a result of vagal activity or by the presence of food in the stomach, acts through a histamine link. While not proving the hypothesis, the results obtained with metiamide certainly tend to support it.

TOXICOLOGY

Toxicity studies which have been completed with metiamide are listed in Table II. Results of some of these studies were discussed in more detail by Brimblecombe et al. in 1973,[9] but since that time the 1-year rat and dog studies and the 3-month baboon study have been completed.

The main findings can be summarised as follows:

1. Oral doses of metiamide of up to 40 mg/kg/day to rats (13 times the intraduodenal ED_{50} for inhibition of maximally stimulated gastric acid secretion) and dogs (10 times the ED_{50}) have been given for one year with no evidence of any adverse reactions. Oral doses of up to 160 mg/kg/day to baboons have similarly elicited no evidence of adverse reactions.

2. No evidence of toxic effects which had not been seen in shorter term studies emerged from the 1-year rat and dog studies. In the rat, daily doses of 366 mg/kg, and to a lesser degree of 122 mg/kg, caused an increase in the incidence of spontaneously occurring small necrotic foci in the liver; in the kidneys single enlarged cells with prominent nuclei occurred in one or two tubules in the cortices of a proportion of rats receiving the top dose. In the dog, the top dose used was 162 mg/kg/day. In this group 2 of 4 males and 3 of 4 females either died or were sacrificed because of their poor condition during the test. All these and the survivors from this dose group showed inflamma-
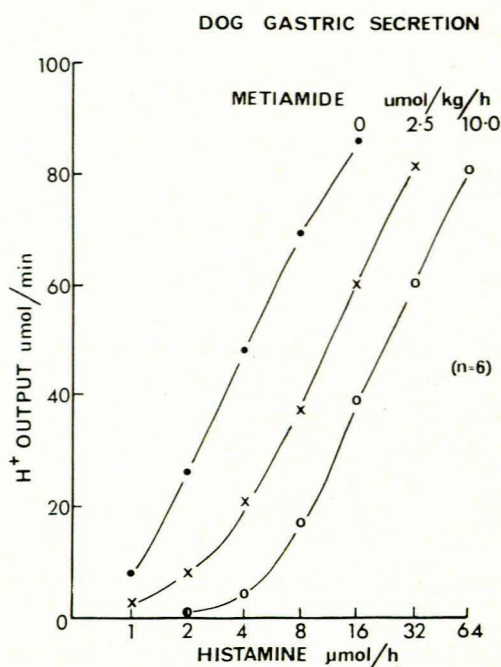
TABLE II. TOXICITY STUDIES WITH METIAMIDE

Single dose studies

Rat Mouse	} Oral and intravenous LD_{50} determinations

Guinea-pig Hamster Baboon Rabbit Cat Marmoset Dog	} Oral dosing

Repeated dose studies

Rat	10-day 1-month 3-month 1-year	
Dog	1-month 3-month 1-year	} Daily oral dosing
Baboon	3-month	

Rat	14-day	} Daily intravenous dosing
Dog	6-day	

Rat Rabbit	Segment II teratology

tory cell infiltration of the centrilobular areas of the liver in association with degeneration of a proportion of liver cells in this area. There were also widespread histological changes in the kidney involving both the glomeruli and the tubules. All animals showed changes in blood biochemistry and urinalysis consistent with kidney and liver damage. Two dogs in this group showed granulocytopenia; in one animal this progressed to agranulocytosis (polymorph count <500 cells/mm^3), which was shown to be readily and repeatedly reversible on withdrawal of metiamide treatment. Examination of the bone marrow suggested that the granulocytopenia was due to maturation arrest in the myeloid series.

In the second dose group (81 mg/kg/day), one dog died during the test. Histological changes in the liver similar to those in the top group were reported in 3 of 4 males and 2 of 4 females in this group. Kidney changes were seen in a male survivor and in the female that died. One dog in this group developed granulocytopenia, and this con-

dition also occurred in two litter-mate animals which had received this dose of drug in the earlier 3-month study. In one of these animals there was progression to agranulocytosis which again was readily reversible on withdrawal of the drug.

3. A proportion of dogs ($<10\%$) have died acutely with pulmonary oedema and pleural effusions after single oral doses of metiamide in excess of 50 mg/kg. This type of acute death has not occurred in any of the other 8 species studied where doses of up to 900 mg/kg have been given.

4. In both rats and dogs at the end of the 3-month study there appeared to be possible, but extremely subtle, effects on thyroid histology. No thyroid abnormalities were reported at the end of the 1-year studies in either species.

HUMAN STUDIES

Studies in human volunteers[3] confirmed that metiamide was effective when given either intravenously or into the intestine by nasogastric tube in inhibiting maximal gastric acid secretion. Infusion of histamine 40 μg/kg/h produced a reasonable plateau of gastric acid secretion in man; simultaneous infusion of metiamide at 2,14 mg/kg/h produced a marked inhibition of acid concentration, total acid output and pepsin output. The effect on pepsin concentration was marginal.

Under similar experimental conditions metiamide infusion also inhibited pentagastrin-stimulated acid and pepsin output and acid concentration. As was shown in the rat and the dog there was no significant difference between the time course of action of metiamide on histamine- or pentagastrin-stimulated secretion in man.

Metiamide, 1 930 mg in solution, instilled into the duodenum via a nasogastric tube, gave an average 60% inhibition of histamine-stimulated acid secretion. Subsequently, clinical trials have been carried out in patients with hypersecretion.

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