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THE EFFECTS OF BURIMAMIDE AND METIAMIDE ON BASAL GASTRIC FUNCTION IN THE CAT

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1 Burimamide injected intravenously in the anaesthetized or conscious cat produced significant increases in gastric acid secretion: in the anaesthetized cat it produced increased gastric mucosal blood flow.

2 Metiamide, in doses which inhibited pentagastrin-stimulated acid secretion, produced no increase in gastric acid secretion in conscious animals, or gastric acid secretion or gastric mucosal blood flow in the anaesthetized cat.

3 Metiamide did not influence the amount of acid which diffused out of the stomach when instilled at pH values between 1.5 and 6.0.

4 The possible mode of action of burimamide in increasing basal gastric secretion is discussed.

Introduction

Burimamide (N-methyl-*N'*-(4-(4(5)-imidazolyl)-butyl)thiourea) has been reported as a competitive inhibitor of histamine H_2-sites based on data obtained on guinea-pig isolated atrium and rat isolated uterine horn and *in vivo* experiments on gastric acid secretion in rat, cat, dog and man (Black, Duncan, Durant, Ganellin & Parsons, 1972; Wyllie, Hesselbo & Black, 1972). A later compound, metiamide (N-methyl-*N'*-(2[(5-methyl imidazol-4-yl)methylthio]-ethyl)thiourea) has also been shown to antagonize competitively the action of histamine on atrial and uterine receptors and to be approximately ten times more powerful in this respect than burimamide and to be approximately five times more potent in reducing histamine- or pentagastrin-stimulated acid secretion *in vivo* (Black, Duncan, Emmett, Ganellin, Hesselbo, Parsons & Wyllie, 1973).

This paper describes an investigation into the effects of burimamide and metiamide on basal gastric acid secretion and blood flow in the anaesthetized cat, and on acid secretion in the conscious cat. We have also studied back diffusion of H^+ from the stomach in anaesthetized cats.

Methods

All animals were starved for 36 h before experiments but allowed free access to water.

Anaesthetized cats

Anaesthesia was induced with ether and maintained by a single intravenous injection of chloralose (80 mg/kg). The vagus nerves were sectioned in the neck and the splanchnic nerves cut extraperitoneally. The stomach was intubated with a wide bore catheter via an incision in the cervical portion of the oesophagus and the pylorus occluded with a tape ligature. Arterial blood samples were taken through a catheter placed in a femoral artery; this catheter also served to monitor arterial blood pressure.

Routinely 50 ml of a 5 : 1, v/v mixture of 300 mosmol/kg solutions of mannitol and glycine, adjusted to pH 3.4 by addition of HCl, was instilled into the stomach at the beginning of each 15 min collection period, drained between 14 and 15 min and replaced by a further 50 ml. Acid content was determined by electrometric titration of a 25 ml sample to pH 7.0 with 0.02N NaOH. Samples of gastric juice washout fluid were stored for measurement of mucosal blood flow by the technique of Harper, Reed & Smy (1968), described for use in the anaesthetized cat.

Amidopyrine concentrations in gastric washings and arterial plasma were determined by the method of Brodie & Axelrod (1950). Burimamide or metiamide was given by a single intravenous

injection (2 mg/kg) during basal secretion of acid.

In a series of three experiments the effect of metiamide on the back diffusion of H^+ from the stomach was investigated. Fifty ml aliquots of mixtures of isosmotic (300 mosmol/kg) solutions of mannitol, glycine and HCl over the pH ranges 6.0, 4.0, 3.0, 2.5, 2.0 and 1.5 were instilled into the stomach. Loss of H^+ was determined by subtraction of the recovered acid, estimated by titration after 15 min in the stomach, from the known amount of acid instilled.

Conscious cats

These experiments were carried out on ten cats in which chronic gastric fistulae (Emås, 1960) had been prepared at least three months earlier. Animals were given no solid food for 36 h prior to experiments but were allowed milk up to 16 h before each experiment: all animals were allowed free access to water.

During experiments animals were supported in canvas slings and the gastric secretions collected in small, calibrated plastic receptacles attached to the cannulae. The collection vessels were replaced at 15 min intervals and the contents titrated to pH 7.0 with 0.05N NaOH to determine acid output. Experiments were carried out in five groups:

(i) basal acid secretion.
(ii) effect of burimamide (2 mg/kg i.v.) on basal acid secretion.
(iii) acid response to pentagastrin (Peptavlon, ICI, 6 μg/kg s.c.).
(iv) effect of metiamide (4 mg/kg i.m.) on the acid response to pentagastrin.
(v) effect of metiamide (4 mg/kg i.m.) on basal acid secretion.

Results are expressed as means ± s.e. mean; significant difference between means was determined by Student's *t* test or Cochran's modification depending on analysis of variance.

Burimamide and metiamide were supplied by Smith, Kline & French.

Results

Anaesthetized cats

In eight anaesthetized cats the injection of burimamide 2 mg/kg intravenously during basal acid secretion caused a five-fold increase of mean acid secretion and increased the mean resting mucosal blood flow (MBF) by 46% (Figure 1). In the period before injection of burimamide the mean basal acid secretion was 30.9 ± 14.8 μEq H^+/15 min and the mean resting MBF was 18.7 ± 3.7 ml/15 minutes. Peak acid secretion was seen during the third 15 min period after the injection of burimamide, 150.9 ± 24.3 μEq H^+/15 min (Figure 1a) and was accompanied by a MBF of 27.4 ± 5.4 ml/15 min (Figure 1b).

By contrast, in six other cats injection of

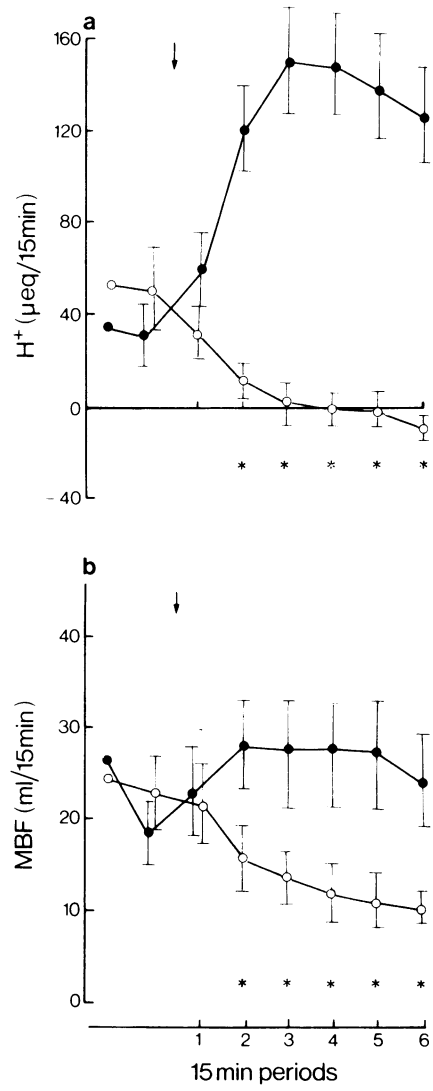

Figure 1 The effects of injection (at arrow) of burimamide (●) (2 mg/kg i.v.) and metiamide (○) (2 mg/kg i.v.) on (a) gastric acid secretion and (b) gastric mucosal blood flow (MBF) in eight anaesthetized cats. Results are expressed as mean; vertical lines show s.e. mean. Significant differences between means at the 5% level are indicated by asterisks.

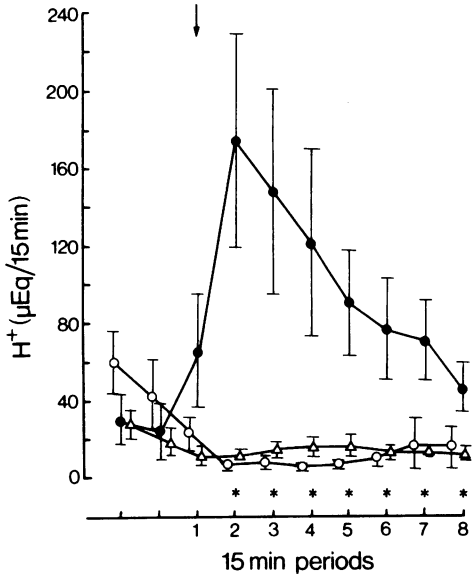

Figure 2 Results in conscious cats with gastric fistulae. The effects of injection (at arrow) of burimamide (•) (2 mg/kg i.v. in nine cats) and metiamide (○) (4 mg/kg i.m. in six cats) on gastric acid secretion compared with acid secretion in the basal state (△) in 10 cats. Results are expressed as mean; vertical lines show s.e. mean. Significant differences between burimamide-stimulated mean responses and basal secretion means are indicated by asterisks.

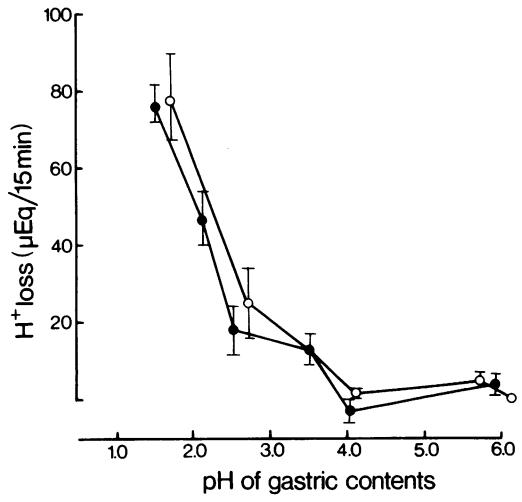

Figure 3 Comparison of H^+ loss from the stomach in anaesthetized cats at various intragastric pH values under basal conditions (○) and during intravenous infusion of metiamide (•) 2 mg $kg^{-1}h^{-1}$, following intravenous injection of 2 mg/kg. The pH values of the instilled gastric fluid are shown on the abscissae, H^+ loss (μEq/15 min) on the ordinates. Results are shown as means at each pH value studied; vertical lines show s.e. mean. There is no significant difference between corresponding means.

metiamide (2 mg/kg i.v.) during basal acid secretory conditions caused a decrease in acid output from 51.0 ± 18.4 μEq H^+/15 min to 0.8 ± 8.6 μEq H^+/15 min during the third 15 min period following the injection (Figure 1a). This reduction of acid output continued during the 1.5 h period studied. MBF also declined from 22.9 ± 4.3 ml/15 min before injection of metiamide, to 13.3 ± 2.7 ml/15 min in the third post injection period, and continued to decline over the period studied (Figure 1b).

The mean acid outputs and mean MBF values during the second and subsequent response following burimamide were significantly greater than those during the corresponding periods after metiamide ($P < 0.05$ in each case).

Conscious cats

Basal acid secretion in ten cats was small and declined slowly over the 2 h studied (Figure 2). Injection of burimamide (2 mg/kg i.v.) in nine cats produced an increase in acid secretion from 24.1 ± 15.0 μEq H^+/15 min during basal conditions to a peak 174.1 ± 56.4 μEq H^+/15 min 30 min after the injection (Figure 2). The mean acid outputs after injection of burimamide were significantly greater than those in control experiments ($P < 0.05$) with the exception of the first period after the injection (Figure 2).

Metiamide (4 mg/kg i.m.) was injected in six animals secreting acid under basal conditions. There was no significant change in acid secretion compared with the control experiments (Figure 2). Metiamide was injected intramuscularly because of its greater solubility and the dose, 4 mg/kg, was shown to be capable of reducing pentagastrin-stimulated acid secretion. In five animals, acid secretion was stimulated by a single subcutaneous injection of pentagastrin. The total acid secreted in the subsequent 2 h was measured and designated the 100% response in that animal. In the same animals the same dose of pentagastrin was accompanied by injections of metiamide (4 mg/kg i.m.) and the total acid output expressed as a per cent of the 100% response in that animal. The results of the two series were compared and showed a significant reduction of the mean of 64.4% ($P < 0.001$) when pentagastrin was injected with metiamide.

Back diffusion of acid out of the gastric lumen

was estimated in three anaesthetized cats during infusion of metiamide, 2 mg kg^{-1} h^{-1}, following an intravenous injection of 2 mg/kg. The amounts of H^+ lost from the stomach over the pH range 6.0 to 1.5 were compared with those obtained under basal control conditions by Harper, Reed & Smy (1970). There was no significant increase of H^+ loss from the stomach under the influence of metiamide (Figure 3).

Discussion

Burimamide increased the acid secretion and MBF from basal levels in the anaesthetized cat (Figure 1). An almost identical increase in acid secretion was seen following burimamide in the conscious cat (Figure 2). MBF in the conscious animal was not measured.

It is well established that burimamide causes reduction of acid secretion stimulated by histamine or gastrin in many species. (International Symposium on Histamine H_2-receptor antagonists; Smith Kline & French (1973).) This evidence, taken in conjunction with our evidence that burimamide stimulates acid secretion in the previously unstimulated stomach, might suggest a partial agonist action of burimamide. There are no reports in the literature of burimamide having a partial agonist action. However, it may be that burimamide is acting through release of some intermediary substance. In the anaesthetized cat, injection of burimamide causes a rise in arterial blood pressure; a fall in blood pressure would be expected if it were acting as a general histamine releaser. Histamine itself, if injected in a single intravenous injection, does not usually result in acid secretion but would produce a profound reduction of blood pressure. Therefore, there is little evidence that the stimulating action of burimamide reported here is due to a general release of histamine. There is some evidence that burimamide increased the rat gastric mucosal histamine output (Main & Whittle, 1974) and it is possible that this could influence gastric acid secretion.

Albinus & Sewing (1973) have shown that burimamide increased arterial blood pressure and heart rate, and decreases histamine-stimulated acid secretion in the anaesthetized cat. The increase in heart rate was abolished by propranolol, and the inhibition of histamine-stimulated acid secretion partly reversed by phenoxybenzamine. This evidence is consistent with the action of burimamide being explained, at least in part, by release of catecholamines. However, this would not explain the acid secretory stimulation, since catecholamines reduce gastric acid secretion (Jacobson, Linford & Grossman, 1966; Albinus & Sewing, 1973). There is no available evidence as to whether burimamide releases any other acid secreting agonist such as gastrin or acetylcholine.

Metiamide, in doses which produce significant reduction of pentagastrin-stimulated gastric acid secretion, does not produce an increase in acid secretion when injected under basal conditions (Figures 1 and 2). It, therefore, does not share the stimulant action of burimamide in the cat. Metiamide has been reported to be five to ten times more effective than burimamide as an H_2-receptor antagonist (Black *et al.*, 1973). This difference might, in part, be explained by a partial agonist action of burimamide. However, the doses of metiamide and burimamide used in this study were not of equal inhibitory potency (Black *et al.*, 1973) and experiments, as yet, have not been carried out using ranges of doses. Without this information it is difficult to discuss partial agonism.

We have previously reported (Reed, Smy, Venables & Harris, 1973) that burimamide injected in the unstimulated anaesthetized cat does not produce gastric acid secretion. However, these results were obtained in the later parts of experiments in which secretion had previously been stimulated by histamine, gastrin or pentagastrin infusion. Therefore, it seems likely in view of our current evidence that previous secretion, and possibly the associated phenomenon of tachyphylaxis to pentagastrin, had disguised this effect.

It is not surprising that there is a rise in MBF associated with the rise in acid secretion following burimamide injection (Figure 1). Ample evidence shows that the rise in acid secretion produced by a wide variety of stimulants is accompanied by an increase in MBF (Jacobson *et al.*, 1966; Harper *et al.*, 1968; Reed & Sanders, 1971). However, the mean Δ MBF/ΔH^+ i.e.

$$\frac{\text{the increased MBF above basal rate (ml/15 min)}}{\text{the increased } H^+ \text{ secretion above basal rate } (\mu\text{Eq/15 min})}$$

during the peak burimamide-stimulated acid secretion was 0.065 ± 0.02. This represents the lowest mean ratio we have observed to any stimulant, the previous lowest recorded ratio being 0.087 seen during pentagastrin stimulation. Furthermore, we have reported that in the cat the Δ MBF/Δ H^+ seen during histamine stimulation with concomitant H_1-site blockade with mepyramine is considerably greater than that observed during pentagastrin stimulation. Jacobson & Chang (1969) have suggested that the excessive blood flow relative to acid secretion,

which they have also reported to occur during histamine stimulation, is due to a direct effect of histamine on the gastric vasculature in addition to an acid secretory-linked hyperaemia. It might, therefore, be argued, since burimamide produces less vasodilatation per unit acid secretion than does histamine, that this suggested histamine-sensitive receptors on both the parietal cell and the gastric vasculature, the former being stimulated preferentially by burimamide.

However, we have reported (Reed & Smy, 1971) that the Δ MBF/Δ H^+ ratio is proportional to the dose of histamine infused i.e. the Δ MBF/Δ H^+ during infusion of histamine acid phosphate 4.5 $\mu g\ kg^{-1}min^{-1}$ is lower than that during infusion of 45 $\mu g\ kg^{-1}min^{-1}$. Since acid secretion is also related to the dose of histamine and since the acid secretory response to burimamide is lower than that seen to the lower dose of histamine, any suggestion of separate parietal and gastric vascular H_2-receptors must be tentative.

The acid stimulating action of burimamide in the resting stomach reported here in the cat, was not seen in the Heidenhain pouch dog (Black *et al.*, 1972) at doses of up to 10 mg/kg intravenously. This suggests either a species difference between cat and dog or possibly a difference between the responsiveness of the denervated pouch and the intact stomach. Comparison of Figures 1 and 2 shows little difference between the acid responses in the anaesthetized and conscious animals. Moreover, the responses in anaesthetized cats were obtained in acutely splanchnectomized and vagotomized animals, whereas the conscious animals had intact gastric innervation. It, therefore, seems that it is more likely to be a species difference although to which species and which H_2-receptor sites it is limited, remains to be seen.

Finally, it has not previously been established whether part of the inhibitory effect of burimamide and metiamide is due to an action on the gastric mucosal barrier, i.e. whether these drugs allow a greater back diffusion of H^+ and therefore only apparently cause inhibition of acid secretion. It is clear from the results reported here (Figure 3) that metiamide causes no such effects over the pH range which is seen during gastric acid secretion. The effect of burimamide on back diffusion could not be established because this drug stimulates acid secretion.

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