Inhibition of gastric acid secretion in the dog by the H₂-receptor antagonists, ranitidine, cimetidine, and metiamide

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SUMMARY The new H₂-receptor antagonist, ranitidine, has been compared with cimetidine and metiamide as an inhibitor of gastric acid secretion in the dog. All three compounds were effective both intravenously or by mouth in inhibiting secretion induced by histamine, pentagastrin, or bethanechol. This inhibition was mainly attributable to a reduction in the volume of secretion, although there was also a significant reduction in the concentration of acid secreted. Metiamide was slightly less active than cimetidine, but ranitidine was four to nine times more potent than cimetidine, depending on the secretagogue used. The antisecretory activity of ranitidine does not result from a limitation in blood flow to the gastric mucosa.

It is now well established that the histamine H₂-receptor antagonists metiamide and cimetidine inhibit gastric acid secretion in the dog[1][2] and in man.[3][4] Furthermore, cimetidine has proved to be highly effective in the treatment of duodenal ulcer.[5] Both metiamide and cimetidine contain an imidazole ring which has been claimed to be an important feature for H₂-receptor antagonist activity.[6] However, a novel compound, ranitidine (AH 19065) has recently been described[7] which lacks an imidazole ring (see Fig. 1), but possesses both potent H₂-receptor antagonist and gastric antisecretory activity.

The purpose of the present investigation was to compare the new H₂-receptor antagonist ranitidine with metiamide and cimetidine as inhibitors of gastric acid secretion in the dog. The effects of the three H₂-receptor antagonists have been studied in conscious dogs with Heidenhain pouches during stimulation of gastric acid secretion by three different secretagogues—histamine, pentagastrin and bethanechol.

Methods

Eight male beagles (13–19 kg) with well-established Heidenhain pouches were used, following the method previously described by Daly and Stables.[8] Histamine, pentagastrin, or bethanechol was infused intravenously at a dose known to produce a 50%
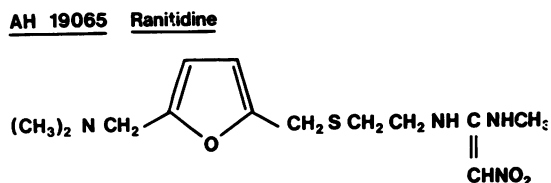
AH 19065   Ranitidine

Fig. 1 *Structure of ranitidine. Molecular weight 314·5.*

maximal secretory response in each dog. The doses used were: histamine 0·3–0·5 µg kg⁻¹min⁻¹, pentagastrin 1–4 µg kg⁻¹ h,⁻¹ and bethanechol 0·5–1·0 µg kg⁻¹ min.⁻¹ Secretion from the Heidenhain pouch drained into a collection vessel which was changed every 15 minutes; the volume of secretion was measured to the nearest 0·1 ml and acid concentration determined by titration against 0·1 mol/l NaOH to pH7 with a Radiometer TTT2 titration system. Acid output was calculated in µmol H⁺/min. The secretory stimulant was infused continuously throughout the experiment. Once a plateau of gastric acid secretion had been obtained (less than 15% variation over one hour), a single dose of ranitidine, cimetidine or metiamide was administered as an intravenous bolus or by mouth in a capsule. The three H₂-receptor antagonists were tested against each secretory stimulant over the following range of doses; ranitidine (0·03–1·0 mg/kg), cimetidine (0·1–3·0 mg/kg), and metiamide (0·3–3·0 mg/kg).

In some of these experiments the effect of ranidtidine on gastric mucosal blood flow was determine

by the tritiated aniline clearance method of Curwain and Holton,[9] using doses of ranitidine which inhibited gastric acid secretion by approximately 50%.

Results have been calculated as percentage change in the measured parameters by comparison of the test value with the mean of the four values preceding drug administration. The figures quoted refer to change in gastric acid output, unless indicated otherwise. The doses of each H_2-antagonist required to inhibit secretion by 50% (ED_{50} values) were determined by the method of least squares.

The drugs used were bethanechol chloride (Fabriques de Laire), histamine acid phosphate (BDH), pentagastrin (ICI), cimetidine (Smith, Kline and French Ltd), metiamide (kindly supplied by Dr M E Parsons, Smith Kline and French Ltd), and ranitidine HCl (synthesised at Glaxo Group Research Ltd, Ware). Drug doses have been expressed in terms of the free base throughout this paper.

Results

The effects of ranitidine on histamine-stimulated gastric acid secretion are shown in Fig. 2. Intra-
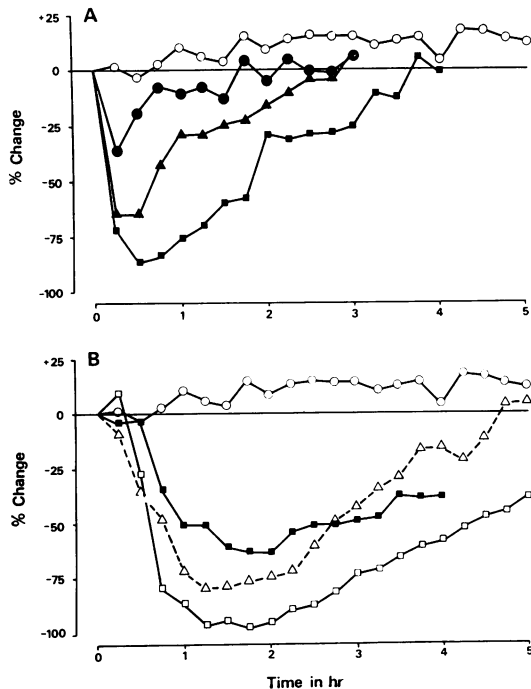
Fig. 2 *Effect of ranitidine on histamine-induced gastric acid output after intravenous (A) and oral (B) administration. Values are means from five dogs. Symbols: control ○, ranitidine dose (mg/kg) 0·03 ●, 0·10 ▲, 0·30 ■, 1·0 □. Cimetidine at 3·0 mg/kg (△ ---- △) is also shown in B.*
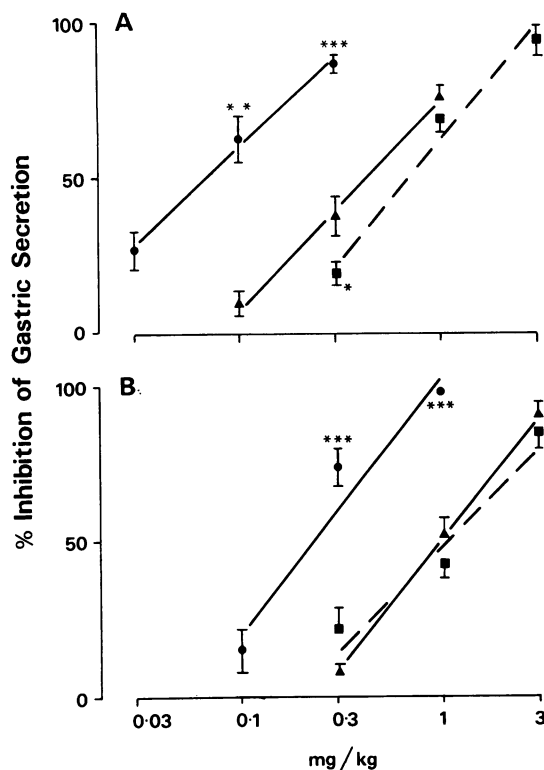
Fig. 3 *Inhibition of histamine-induced gastric acid secretion after intravenous (A) and oral (B) doses of ranitidine ● (solid line), cimetidine ▲ (solid line), and metiamide ■ (broken line). Values are means ±SE from at least five dogs. The lines shown are calculated lines of best fit; there is no significant difference in slope for the three drugs. Asterisks indicate where a value is significantly different from that achieved with the same dose of cimetidine, at *P< 0·05, **P< 0·01, ***P< 0·001 (unpaired t test).*

venous doses of 0·03–0·30 mg/kg produced dose-related decreases in acid output, peak effect was reached in 15 to 30 minutes after dosing and recovered within four hours at the top dose level. Ranitidine was also markedly effective when given orally at doses of 0·3 and 1·0 mg/kg, peak effects being attained 1¼ to two hours after dosing and there was still appreciable antisecretory activity five hours after the oral dose of 1 mg/kg. Results obtained with an oral dose of cimetidine of 3 mg/kg are shown in Fig. 2B. The peak effect of this dose of cimetidine, which was intermediate in effect between ranitidine at 0·3 and 1·0 mg/kg, was reached 1¼ to 1½ hours after dosing and complete recovery was observed by 4¾ hours. Thus, the duration of action of ranitidine given orally is as long, or longer, than that of cimetidine. Comparison of the

Table 1   *Change in histamine-stimulated gastric secretion after oral administration of ranitidine, cimetidine, and metiamide (expressed as a mean percentage reduction ± standard error from pre-dose control value)*

H_2-receptor antagonist and measurement	Dose of antagonist (mg/kg)			
	0·1	0·3	1·0	3·0
Ranitidine (n = 5)				
Volume	13·0 ± 6·6	69·9 ± 6·2	96·7 ± 0·8	Not
Acid concentration	4·3 ± 2·3	18·7 ± 4·4	53·4 ± 2·9	tested
Acid output	14·6 ± 7·2	73·4 ± 6·4	97·8 ± 0·5	
Cimetidine (n = 8)				
Volume	Not	9·8 ± 1·1	45·2 ± 5·2	91·0 ± 3·2
Acid concentration	tested	0·7 ± 0·7	9·5 ± 2·0	36·7 ± 13·1
Acid output		9·3 ± 1·3	48·8 ± 5·5	92·5 ± 3·2
Metiamide (n = 8)				
Volume	Not	21·0 ± 6·0	41·2 ± 5·6	80·7 ± 5·0
Acid concentration	tested	1·2 ± 1·0	4·6 ± 0·8	28·6 ± 8·9
Acid output		21·0 ± 7·0	43·1 ± 5·7	82·0 ± 5·1

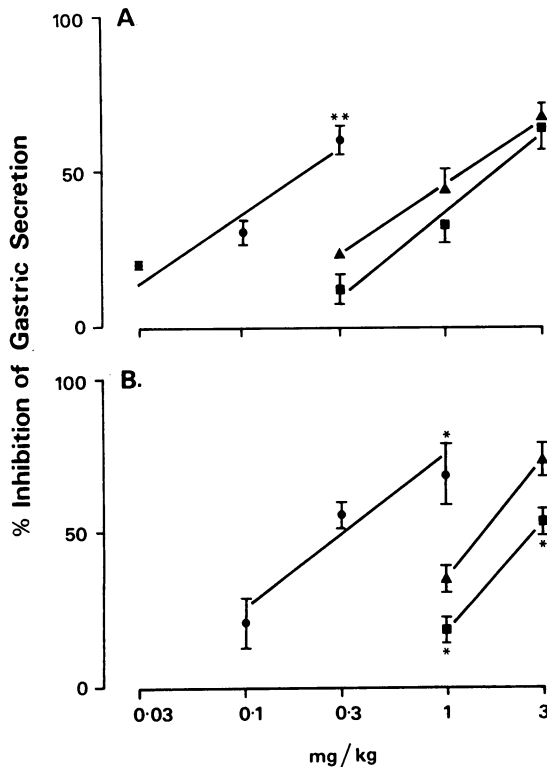n = number of experimental animals.

Fig. 4   *Inhibition of pentagastrin-induced gastric acid secretion after intravenous (A) and oral (B) doses of ranitidine ● cimetidine ▲, and metiamide ■. Values are means ±SE from at least five dogs. The lines shown are calculated lines of best fit; there is no significant difference in slope for the three drugs. Asterisks indicate where a value is significantly different from that achieved with the same dose of cimetidine, at* *P< 0·05, **P< 0·01 *(unpaired t test).*
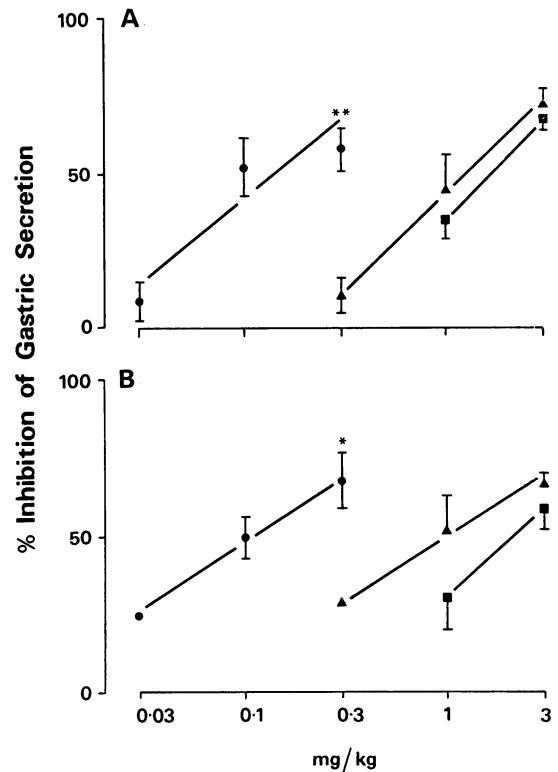
Fig. 5   *Inhibition of bethanechol-induced gastric acid secretion following intravenous (A) and oral (B) doses of ranitidine ●, cimetidine ▲, and metiamide ■. Values are means ±SE from at least five dogs. The lines shown are calculated lines of best fit; there is no significant difference in slope for the three drugs. Asterisks indicate where a value is significantly different from that achieved with the same dose of cimetidine, at* *P< 0·05, **P< 0·01 *(unpaired t test).*

effects of a range of doses of ranitidine, cimetidine, and metiamide (Fig. 3) shows that ranitidine is clearly the most potent inhibitor of histamine stimulated gastric acid secretion.

The inhibition of histamine-induced gastric secretion after the three H_2-receptor antagonists is mainly attributable to a reduction in volume of secretion but, particularly at higher dose levels, a significant reduction in the concentration of acid could also be detected. This is illustrated in Table 1 by the results obtained after oral doses of the antagonists during histamine-induced gastric secretion.

The dose levels of ranitidine, cimetidine, and metiamide shown to be effective against histamine-induced secretion have also been tested during secretory plateaux obtained with pentagastrin or bethanechol. As shown in Figs 4 and 5 all three

Table 2 *Effect of ranitidine on gastric secretion, gastric mucosal blood flow, and clearance ratio*

Stimulant	Ranitidine dose (mg/kg IV)	Percentage change (± SE) in			No. of expts
		Acid secretion	Mucosal blood flow	Clearance ratio (R)	
Histamine	0·03 or 0·1	−43·7±3·8	−16·3 ± 3·5	+50·3±5·2	3
Pentagastrin	0·20 or 0·3	−64	−45·5	+48·5	2
Bethanechol	0·1 or 0·2	−50·5	−14·0	+65·5	2

Clearance ratio (R): the ratio of mucosal blood flow (aniline clearance in ml/min) to acid secretion (μmol/min).

antagonists, whether given intravenously or by mouth, inhibit secretion stimulated by either pentagastrin or bethanechol.

To determine whether the antisecretory effect of ranitidine was the result of a reduction in blood flow through the gastric mucosa was next investigated. In preliminary experiments (Table 2) it was shown that mucosal blood flow slightly decreased after an intravenous dose of ranitidine but the ratio of blood flow to gastric secretion increased markedly, regardless of the secretagogue used. Consequently, the inhibition of gastric secretion by ranitidine does not result from a limitation in blood flow.

While cimetidine was usually slightly more active than metiamide as an antisecretory agent, ranitidine was consistently the most potent of the three H_2-receptor antagonists irrespective of the secretagogue used. Table 3 summarises the antisecretory ED_{50} values for the three antagonists, and gives relative potencies for metiamide and ranitidine in comparison with cimetidine. Metiamide was only 0·4–0·9 times as active as cimetidine, but ranitidine was 4–9·5 times more active than cimetidine depending on the secretory stimulant employed.

Discussion

Ranitidine is a potent inhibitor of gastric acid secretion in the dog and is qualitatively similar to the established H_2-receptor antagonists metiamide and cimetidine. Thus ranitidine is effective in reducing secretion from the Heidenhain pouch of the dog, whether given intravenously or by mouth; and its antisecretory effect is mainly through a reduction in the volume of gastric secretion, with a lesser effect on the concentration of acid secreted. The duration of the antisecretory effect of ranitidine after a single oral dose is as long or longer than that of cimetidine. The antisecretory activity of ranitidine is not due to any limiting action on mucosal blood flow, as the ratio of mucosal blood flow to acid secretion actually rose after administration of ranitidine. Metiamide has also been shown to increase the ratio of mucosal blood flow to acid secretion while reducing acid secretion elicited by either histamine or pentagastrin.[10]

Ranitidine, when given intravenously or orally to the dog, was always significantly more potent than cimetidine as an inhibitor of gastric acid secretion elicited by histamine, pentagastrin, or the choline ester, bethanechol. The potency of ranitidine relative to cimetidine ranged from 4·3 to 9·5, depending on which secretagogue was used. Cimetidine has been reported to be about twice as active as metiamide as an inhibitor of gastric secretion[2], but no direct comparison of their relative potencies in the dog has previously appeared in the literature. In the present study cimetidine was between 1·1 to 2·5 times as active as metiamide, but this difference in potency was not always statistically significant.

In addition to its greater potency, ranitidine also

Table 3 *Antisecretory ED_{50} values and relative potencies (with 95% confidence limits) for ranitidine, cimetidine, and metiamide in the dog*

Secretory stimulant	Antagonist		Antisecretory ED_{50} (mg/kg)	Potency relative to cimetidine
	Route	Compound		
Histamine	IV	Ranitidine	0·07 (0·05–0·09)	5·9* (4·4–8·2)
		Cimetidine	0·43 (0·34–0·54)	1
		Metiamide	0·69 (0·58–0·82)	0·6* (0·5–0·8)
	Oral	Ranitidine	0·23 (0·17–0·29)	4·3* (3·2–5·8)
		Cimetidine	0·96 (0·80–1·15)	1
		Metiamide	1·05 (0·83–1·29)	0·9 (0·7–1·2)
Pentagastrin	IV	Ranitidine	0·21 (0·14–0·42)	6·4* (3·6–10·7)
		Cimetidine	1·28 (0·83–2·09)	1
		Metiamide	1·80 (1·32–2·79)	0·7 (0·4–1·1)
	Oral	Ranitidine	0·30 (0·22–0·45)	5·0* (3·3–7·2)
		Cimetidine	1·51 (1·17–1·87)	1
		Metiamide	2·66 (2·08–4·10)	0·5* (0·3–0·8)
Bethanechol	IV	Ranitidine	0·14 (0·10–0·27)	9·5* (5·4–16·5)
		Cimetidine	1·24 (0·85–2·14)	1
		Metiamide	1·65 (1·05–2·45)	0·8 (0·5–1·5)
	Oral	Ranitidine	0·11 (0·04–0·26)	9·2* (3·4–23·8)
		Cimetidine	0·97 (0·17–2·85)	1
		Metiamide	2·15 (1·31–13·67)	0·4 (0·1–1·0)

*Significantly different from cimetidine at $p < 0.05$.

differs from cimetidine in its chemical structure. Ranitidine is a substituted aminomethyl furan, whereas metiamide and cimetidine are both based on the imidazole ring structure of histamine itself. Metiamide was withdrawn from clinical use after there had been a few cases of reversible agranulocytosis.[11] This toxic effect is probably associated with the presence of a thiourea group in the metiamide molecule, and does not appear to be a problem with cimetidine, a close structural analogue in which thiourea is replaced by cyanoguanidine.[12] A low incidence of minor side-effects has been reported for cimetidine[12] and, if these are unrelated to H_2-receptor blockade, they may not occur with a non-imidazole compound like ranitidine.

Initial reports claimed that the H_2-receptor antagonists burimamide and metiamide did not antagonise secretion induced by choline esters in the dog.[10 13] However, more recently metiamide and cimetidine have both been described as effective against secretion stimulated by choline esters.[2 14] The effectiveness of metiamide as an inhibitor of secretion induced by choline esters in the dog appears to be dependent on the experimental design used.[15]

In other systems cimetidine, metiamide, and ranitidine have been shown to be selective antagonists of the effects of histamine at H_2-receptors but, in the stomach, these antagonists are effective inhibitors of several gastric secretagogues other than histamine. The reason for this paradox is probably that histamine can increase gastric secretion in two ways—firstly, by a direct stimulant action of its own on the parietal cells and, secondly, by potentiating the stimulant actions of gastrin (or pentagastrin) and acetylcholine (or other similar choline esters).[16 17] An H_2-receptor antagonist can antagonise both the direct effect of histamine and its potentiating action and thus reduces gastric secretion elicited by histamine, choline esters, or gastrin. Consequently, the effectiveness of ranitidine as an inhibitor of gastric secretion elicited by bethanechol, pentagastrin, or histamine is entirely consistent with its known properties as an H_2-receptor antagonist.

Ranitidine, as well as inhibiting gastric acid secretion induced by histamine, pentagastrin, and bethanechol in the dog, will also markedly reduce secretion elicited by 2-deoxy-D-glucose or a test meal.[18]

Ranitidine has recently been shown to be a potent inhibitor of pentagastrin stimulated gastric secretion in patients with duodenal ulceration[19] and thus this drug appears to be highly suitable for clinical trial for the treatment of peptic ulceration.

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