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# HISTAMINE $H_2$-ANTAGONISTS MODIFY GASTRIC EMPTYING IN THE RAT

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**1** Histamine $H_2$-receptor antagonists were tested for their effect on gastric emptying in the rat.

**2** At low doses all the compounds were inactive except for burimamide which delayed and ranitidine which accelerated gastric emptying.

**3** At high doses burimamide, metiamide, cimetidine and oxmetidine delayed, whereas ranitidine accelerated gastric emptying; tiotidine remained ineffective.

**4** Changes in emptying rate were not accompanied by changes in emptying pattern which, with all the compounds examined, proceeded, as in the controls, by apparent first order kinetics.

**5** The mechanism of the ranitidine-induced acceleration of gastric emptying seemed to be connected with an interference with the cholinergic system, whereas the mechanism of cimetidine- and oxmetidine-induced slowing of gastric emptying was apparently related to cholinolytic and possibly also relaxant effects of the compounds.

**6** These different effects of the various $H_2$-blockers are consistent with the idea that changes in emptying rate are independent of $H_2$-receptor blockade.

## Introduction

In a thorough investigation concerning histamine receptors and gastrointestinal motility we observed that histamine delayed gastric emptying (GE) in the conscious rat through stimulation of $H_1$-receptors (Bertaccini, Scarpignato & Coruzzi, 1980; Scarpignato, Coruzzi & Bertaccini, 1981). In a previous study (Bertaccini, Coruzzi, Molina & Chiavarini, 1977) it was also observed that the $H_2$-blocker, burimamide, exerted a spasmogenic effect on the rat pylorus and other investigations carried out in our department (Scarpignato, Capovilla & Bertaccini, 1980; Bertaccini, De Castiglione & Scarpignato, 1981; Scarpignato & Bertaccini, 1981) have emphasized the importance of the pylorus in the regulation of gastric emptying in the rat. Several non-specific effects of the $H_2$-receptor antagonists have been reported (Bertaccini & Dobrilla, 1980; Bertaccini, 1982): some of these effects concerned gut motility. We decided to investigate more thoroughly the effect of all the available $H_2$-receptor antagonists on gastric emptying in the conscious rat.

## Methods

Male Wistar rats weighing approximately 200 g and fasted 24 h prior to experiments were used.

### *Gastric emptying*

The test meal consisted of 1.5 ml/rat of a solution of 50 mg phenol red in 100 ml of aqueous methylcellulose (1.5%), given by oral intubation. $H_2$-blockers were injected in a constant volume of saline (1 ml/kg), by the intraperitoneal route, 5 min before administration of the meal. The animals were killed at various time intervals after intubation to evaluate the duration of the pharmacological effects. The effect of the $H_2$-blockers on gastric emptying as well as the interference of other pharmacological compounds was evaluated at a fixed time (20 min). This time was selected because gastric emptying at 20 min ($54.5 \pm 3.1\%$) allowed us to evaluate drug-induced acceleration or delay in emptying. Doses employed in this study were selected on the basis of the relative activity of the various drugs on gastric secretion. In each experiment a group of 4 animals was killed immediately after the meal and considered as standard (100% of phenol red) to avoid errors connected with contraction of the stomach during terminal convulsions. In fact, the phenol red recovered from such animals always gave a lower colorimetric reading than that obtained by simple dilution of the meal. The stomach was then exposed by laparotomy, quickly ligated at the pylorus and the cardia, and removed.

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The stomach and its content was homogenized in a Waring blender with 100 ml of 0.1 N NaOH. The analytical procedure for the assay of phenol red was described in a previous paper (Scarpignato *et al.*, 1980). It involves precipitation of proteins with 20% trichloroacetic acid, realkalinization with NaOH and colorimetric assay at 560 nm. In 10 control experiments recoveries ranged from 82 to 90%. There were no significant differences in recovery of phenol red between the control (saline) experiments (85 ± 5%) and experiments involving $H_2$-antagonists (87 ± 3%).

In situ *rat stomach*

The technique described by Bertaccini, Impicciatore & De Caro (1973) was followed. Under urethane anaesthesia (1.2 g kg$^{-1}$ i.p.), a polythene tube was passed via the mouth and oesophagus to the stomach, the abdomen opened and the tube tied near the cardia. The proximal part of this catheter was connected with a perfusion system with a constant pressure (2 cm water). Then a small rubber tube was introduced through a cut in the duodenum up to the pylorus. This second catheter was connected at its distal end with a drop counter and the drops of the effluent were recorded on a smoked drum. The frequency of the drops coming from the duodenal catheter depended on the tone of the gastric wall.

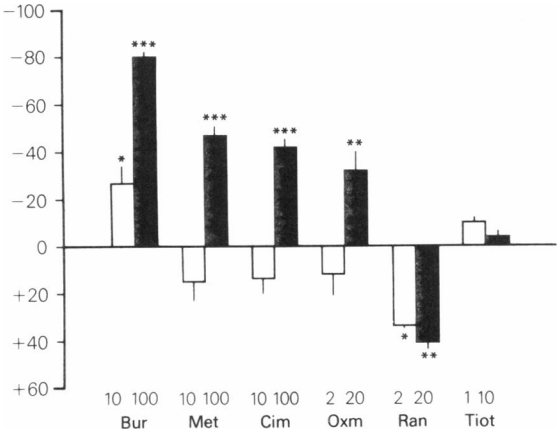


**Figure 1** Gastric emptying in conscious rats. Ordinate scale: % changes in comparison with controls ($n = 24$) taken as 0. Bur = burimamide; Met = metiamide; Cim = cimetidine; Oxm = oxmetidine; Ran = ranitidine; Tiot = tiotidine. Doses in mg kg$^{-1}$. Open columns = low doses; solid columns = high doses. Vertical bars are s.e.mean. Each column shows the mean of the values obtained from 6 to 8 rats. $*P<0.025$; $**P<0.005$; $***P<0.001$.

*Evaluation of data*

GE for each rat was calculated according to the following formula:

$$GE\,(\%) = \left[1 - \frac{\text{amount of phenol red recovered from the test stomach}}{\text{average amount of phenol red recovered from the standard stomachs}}\right] \times 100$$

Under our experimental conditions, in control rats (receiving only physiological saline) the meal leaving the stomach (that is the gastric emptying) after 20 min was 54.5 ± 3.1% (range 50–60%) in comparison with the standard. Changes in GE induced by the different compounds were calculated as % difference in comparison with controls taken as 0. The emptying half-time ($T_{\frac{1}{2}}$, min) was calculated for each drug from the regression line for the log of the gastric content *versus* time. All values refer to the mean ± standard error; Student's *t* test for unpaired data was employed for determining statistical significance.

*Drugs*

Compounds used were: burimamide, metiamide, cimetidine and oxmetidine (comp. marked SKF 92994) (kindly supplied by SKF, Welwyn Garden City, Herts), ranitidine (Glaxo), tiotidine (kindly supplied by Dr McCurdy, ICI Americas Inc.), bethanechol (urecholine chloride, MS & D), atropine sulphate (Fluka) and metoclopramide (Lepetit).

## Results

*Effect of $H_2$-antagonists on gastric emptying*

Results obtained are summarized in Figure 1. It is evident that low doses of most of the compounds used did not modify significantly GE in comparison with controls. Exceptions were burimamide, which delayed and ranitidine, which accelerated GE. At higher dose levels, burimamide, metiamide, cimetidine and oxmetidine delayed, whereas ranitidine accelerated GE and tiotidine remained ineffective.

*Emptying pattern*

Figure 2, which shows a semilogarithmic plot of gastric retention *versus* time, indicates that gastric emptying of phenol red in controls proceeded by apparent first order kinetics. This finding confirms previous data of Reynell & Spray (1956) who showed that stomach content after a liquid meal decreases in

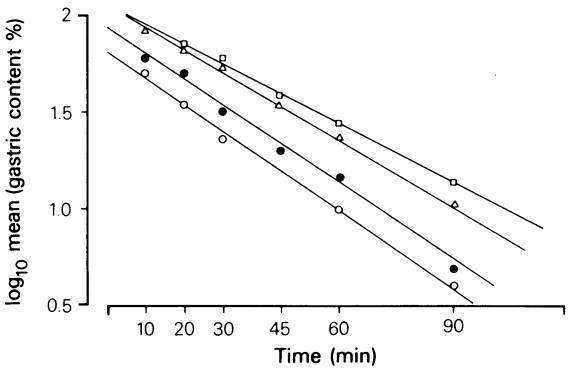


**Figure 2** Semilogarithmic plot of gastric content versus time. The lines are the calculated least squares regression lines.
(●) Controls; $r = -0.875$, $n = 57$; $T_{\frac{1}{2}} = 16.5 \pm 5.2$ min
(○) Ranitidine; $r = -0.891$, $n = 42$; $T_{\frac{1}{2}} = 7.3 \pm 3.4$ min*.
(△) Oxmetidine; $r = -0.811$, $n = 42$; $T_{\frac{1}{2}} = 29.1 \pm 8.4$ min**.
(□) Cimetidine; $r = 0.802$, $n = 42$; $T_{\frac{1}{2}} = 34.0 \pm 10$ min**.
* $P < 0.001$ *versus* control group; ** $P < 0.01$ *versus* control group.

an exponential fashion with time. In our experimental conditions the emptying half-time in control animals was 16.5 ± 5.2 (95% confidence limits) min. It is evident from Figure 2 that ranitidine, oxmetidine and cimetidine modified GE, although in a different direction, but they did not modify the kinetics.

*Mechanism of action*

Since tiotidine was always ineffective and burimamide and metiamide were not available in sufficient amounts, the mechanism of action was investigated only for ranitidine, oxmetidine and cimetidine.

Ranitidine, the only compound which significantly accelerated gastric emptying, is known to possess remarkable cholinomimetic actions and to contract the rat gastric fundus through excitation of muscarinic receptors (Bertaccini & Coruzzi, 1982). To check whether the cholinergic system could also be involved in the effect of ranitidine on GE, the effects of atropine and of bethanechol were investigated (Table 1). Table 1 shows that ranitidine at subthreshold doses (0.1 mg/kg) was able to potentiate the subthreshold dose (10 μg/kg) of bethanechol giving rise to a significant acceleration of GE. On the other hand atropine, at doses (0.5 μg/kg) that did not modify *per se* GE, was able to inhibit completely the effect of ranitidine. Other non-cholinergic drugs,

**Table 1** Effects of bethanechol and atropine on the action of ranitidine on gastric emptying of the rat

| *Treatment* | *GE* (%) | *Significance versus saline* (*P* value) |
|---|---|---|
| Saline | 57.5 ± 3.1* | — |
| Ranitidine 20 mg $kg^{-1}$ | 81.2 ± 7.0 | < 0.005 |
| Ranitidine 2 mg $kg^{-1}$ | 77.5 ± 5.6 | < 0.025 |
| Ranitidine 0.5 mg $kg^{-1}$ | 80.0 ± 2.0 | < 0.005 |
| Ranitidine 0.1 mg $kg^{-1}$ | 66.0 ± 6.0 | NS |
| Bethanechol 100 μg $kg^{-1}$ | 88.0 ± 1.8 | < 0.001 |
| Bethanechol 30 μg $kg^{-1}$ | 79.0 ± 1.5 | < 0.005 |
| Bethanechol 10 μg $kg^{-1}$ | 63.0 ± 10.4 | NS |
| Bethanechol 10 μg $kg^{-1}$ + Ranitidine 0.1 mg $kg^{-1}$ | 75.6 ± 4.6 | < 0.025 |
| Atropine 10 μg $kg^{-1}$ | 35.8 ± 4.7 | < 0.005 |
| Atropine 1 μg $kg^{-1}$ | 48.2 ± 6.0 | < 0.05 |
| Atropine 0.5 μg $kg^{-1}$ | 55.8 ± 7.0 | NS |
| Atropine 0.5 μg $kg^{-1}$ + Ranitidine 2 mg $kg^{-1}$ | 60.8 ± 9.2 | NS |

*Each value represents the mean (± s.e.) of the values obtained from 6–8 rats. NS = not significant.
Ranitidine was administered 5 min before the meal; bethanechol or atropine 10 min before the meal (5 min prior to ranitidine).

**Table 2** Effect of ranitidine and metoclopramide on the delay in emptying induced by dopamine in the rat

| *Treatment* | *GE (%)* | *Significance versus saline (P value)* |
|---|---|---|
| Saline | 57.5 ± 3.1* | — |
| Dopamine 5 mg $kg^{-1}$ | 8.3 ± 2.9 | < 0.001 |
| Ranitidine 2 mg $kg^{-1}$ | 80.0 ± 3.2 | < 0.005 |
| Metoclopramide 10 mg $kg^{-1}$ | 84.0 ± 5.6 | < 0.025 |
| Dopamine + Ranitidine | 13.5 ± 7.3[a] | < 0.001 |
| Dopamine + Metoclopramide | 75.0 ± 5.0[b] | < 0.01 |

*Each value represents the mean (± s.e.) of the values obtained from 6–8 rats.
[a]Not significantly different from the dopamine-treated group.
[b]Significantly different ($P < 0.001$) from dopamine-treated group.
Dopamine administered 5 min before the meal; metoclopramide and ranitidine administered 10 min before the meal (5 min prior to dopamine).

which increase emptying rate, are so far represented by antidopamine compounds like metoclopramide and domperidone (Greenberger, Arvanitakis & Hurwitz, 1978). In order to check whether or not an antidopamine action could be at least partly responsible for the effect of ranitidine, a series of experiments were carried out as shown in Table 2. It is evident from this table that metoclopramide, but not ranitidine at equiactive doses, was able to counteract the delay of GE induced by dopamine. Thus an antidopamine action of ranitidine seems unlikely.

Oxmetidine has an inhibitory effect on $H_1$-receptors (Blakemore, Brown, Durant, Emmett, Ganellin, Parsons & Rasmussen, 1980): however, this cannot account for the delay in GE since we demonstrated that stimulation and not inhibition of $H_1$-receptors delays GE in the rat (Scarpignato *et al.*, 1981). Oxmetidine also possesses some anti-acetylcholine properties *in vivo* (Bertaccini & Coruzzi, unpublished). For this reason oxmetidine was tested against bethanechol-induced acceleration of GE and a good antagonism by oxmetidine was found even at doses which were inactive when given alone (see Figure 3). Cimetidine behaved similarly when administered at equiactive doses. In previous papers (Bertaccini & Coruzzi, 1981; Coruzzi & Bertaccini, 1982) we demonstrated that oxmetidine at high doses also has a relaxant action, which may be related to antagonism of transport of calcium ions (Di Lisa, Ferrari, Raddino, Coruzzi & Bertaccini, 1981) and this could account for the delay in emptying rate. This relaxant effect, observed so far only *in vitro*, was also confirmed *in vivo* by measuring the transpyloric flow in the rat stomach *in situ*. Figure 4 shows the dose-dependent inhibition of transpyloric flow as a consequence of gastric wall relaxation. It seems likely that both anti-acetylcholine and relaxant properties play a role in the oxmetidine-induced delay of gastric emptying; cimetidine, in the same experimental conditions, had an erratic effect causing sometimes a slowing and sometimes an acceleration of the transpyloric flow.

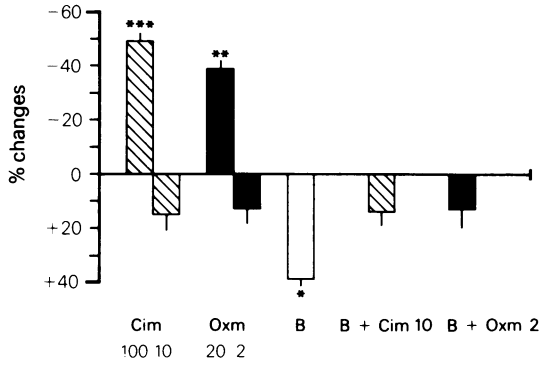


**Figure 3** Gastric emptying in conscious rat. Ordinate scale: % changes in comparison with controls taken as 0. Cim = cimetidine (mg $kg^{-1}$) given 10 min before the meal; Oxm = oxmetidine (mg $kg^{-1}$) given 10 min before the meal; B = bethanechol (30 μg $kg^{-1}$) given 5 min before the meal. Each column shows the mean of the values obtained from 8 rats. Vertical bars are s.e. ***$P < 0.001$; **$P < 0.005$; *$P < 0.001$.

## Discussion

Our experiments demonstrate that the behaviour of the $H_2$-receptor antagonists in modifying GE varies with the different types of antagonist which are remarkably different chemically. Burimamide, metiamide and cimetidine have an imidazole ring, ranitidine has an alkyl furan ring whereas tiotidine has a thiazole ring (Bertaccini & Dobrilla, 1980). This suggests that the effects observed in this investigation are independent of $H_2$-receptor blockade, in

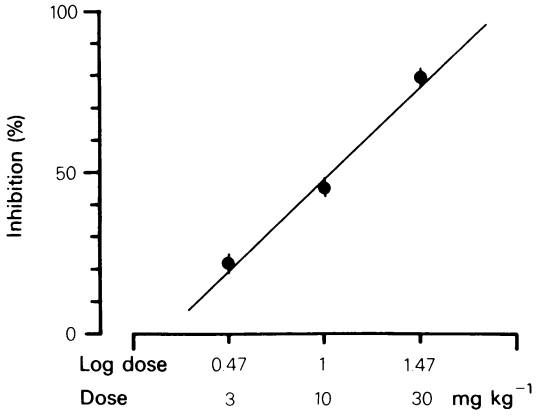


**Figure 4** Dose-dependent inhibition of transpyloric flow in the *in situ* rat stomach by intravenous oxmetidine. Basal values were arbitrarily taken as 100. Each point represent the mean of the values obtained from 7 animals. Vertical bars are s.e. The line is the least squares calculated regression line ($r = 0.9904$, $n = 21$, $P < 0.01$).

accordance with our previous data indicating that $H_1$- and not $H_2$-receptors are involved in the effect of histamine on rat gastric emptying (Scarpignato *et al.*, 1981).

The mechanism of action of these compounds is difficult to explain: burimamide may act through the already metioned contraction of the pylorus (Bertaccini, Coruzzi, Molina & Chiavarini, 1977) and/or through the gastric motor inhibition reported by Ridley, Groves, Schlosser & Massenberg (1973); metiamide was also found to inhibit gastric motility of the rat (Black & Spencer, 1973). However, the scarcity of these two compounds did not allow us to investigate their action on GE more thoroughly.

An anticholinoceptor effect could come into play for cimetidine and oxmetidine (Brimblecombe, Duncan, Durant, Emmett, Ganellin & Parsons, 1975; Bertaccini & Coruzzi unpublished). Indeed in our experiments oxmetidine in doses which *per se* did not significantly modify GE was able to counteract the acceleration induced by a cholinomimetic drug, like bethanechol. Cimetidine behaved similarly. Moreover oxmetidine, which has a relaxant action in the rat lower oesophageal sphincter (LES) *in vitro* (threshold doses = 3–10 $\mu g\,ml^{-1}$) (Bertaccini & Coruzzi, 1981; Coruzzi & Bertaccini, 1982), was also shown to possess a dose-dependent relaxant effect on the gastric wall *in vivo* and this could again account for the delay in GE.

The opposite effect of ranitidine is rather puzzling, especially considering that in healthy volunteers the compound significantly delayed gastric emptying (Scarpignato, Bertaccini, Zimbaro & Vitulo, 1982). At present, only hypotheses to explain such an effect can be suggested. Ranitidine had a cholinomimetic action in the rat isolated LES: indeed on this preparation ranitidine had a spasmogenic effect which was partially inhibited by tetrodotoxin and abolished by atropine (Bertaccini & Coruzzi, 1981). Moreover subsequent studies (Bertaccini & Coruzzi, 1982) revealed that the rat fundus is also contracted by ranitidine as a consequence of a cholinomimetic activity (threshold doses ranged from 0.1 to 3 $\mu g\,ml^{-1}$): the present findings concerning the interference of atropine (which behaved as an antagonist) and of bethanechol (which acted synergistically) with ranitidine support the hypothesis of a cholinomimetic action of this $H_2$-blocker. The efficacy of ranitidine was comparable, in our experimental conditions, to that of metoclopramide (Coruzzi, Scarpignato, Zappia & Bertaccini, 1980). The lack of activity of ranitidine on prolactin release seems to exclude an action at dopamine receptors (Yeo, Delitala, Besser & Edwards, 1980). In addition, the possibility of an antidopamine action was excluded by our findings concerning the inability of ranitidine (unlike metoclopramide) to modify the dopamine-induced delay in GE.

Tiotidine was found to have a little cholinolytic activity ($pA_2 = 3.6$) comparable with that of cimetidine ($pA_2 = 3.8$) (Barker, 1981). Owing to the different ratio of activity on $H_2$-receptors ($pA_2$ for tiotidine = 7.8 and for cimetidine = 6.1) the cholinolytic effect of tiotidine was not evident in the doses employed.

In conclusion, our experiments indicated the possibility of an action of $H_2$-antagonists which is clearly independent of $H_2$-receptor blockade and may represent a non-specific effect related to the individual drugs rather than to the entire class. Doses used to obtain clear-cut effect on GE were very much greater than those necessary to inhibit gastric secretion: however, in other studies (Okabe, Takeuchi, Murata & Takagi, 1977; Pare, Glavin & Vincent, 1978; Bunce, Daly, Humphray & Stables, 1980) similarly high amounts of $H_2$ blockers had to be employed to obtain clear-cut effects on healing of experimentally induced ulcers in the rat.

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**References**

BARKER, L.A. (1981). Histamine $H_1$- and muscarinic receptor antagonist activity of cimetidine and tiotidine in the guinea-pig isolated ileum. *Agents & Actions*, **11**, 699–705.

BERTACCINI, G. (1982). Amines: Histamine. In *Mediators and Drugs in Gastrointestinal Motility*, II. ed. Bertaccini, G. pp. 201–218. Heidelberg: Springer-Verlag (in press).

BERTACCINI, G. & CORUZZI, G. (1981). Azione dei bloccanti dei recettori istaminici $H_2$ sullo sfintere esofageo inferiore (LES) isolato di ratto. *Il Farmaco* (Ed. Sc.), **36,** 129–134.

BERTACCINI, G. & CORUZZI, G. (1982). Cholinergic-like effects of the new histamine $H_2$-receptor antagonist ranitidine. *Agents & Actions*, **12,** 168–171.

BERTACCINI, G., CORUZZI, G., MOLINA, E. & CHIAVARINI, M. (1977). Action of histamine and related compounds on the pyloric sphincter of the rat. *Rend. Gastroenterol.*, **9,** 163–168.

BERTACCINI, G., DE CASTIGLIONE, R. & SCARPIGNATO, C. (1981). Effect of substance P and its natural analogues on gastric emptying of the conscious rat. *Br. J. Pharmac.*, **72,** 221–223.

BERTACCINI, G. & DOBRILLA, G. (1980). Histamine $H_2$-receptor antagonists: old and new generation. Pharmacology and clinical use. *Ital. J. Gastroenterol.*, **12,** 297–302.

BERTACCINI, G., IMPICCIATORE, I. & DE CARO, G. (1973). Action of caerulein and related substances on the pyloric sphincter of the anesthetized rat. *Eur. J. Pharmac.*, **22,** 320–324.

BERTACCINI, G., SCARPIGNATO, C. & CORUZZI, G. (1980). Histamine receptors and gastrointestinal motility: an overview. In *$H_2$-Antagonists*. ed. Torsoli, A., Lucchelli, P.E. & Brimblecombe, R.W. pp. 251–261. Amsterdam: Excerpta Medica.

BLACK, J.W. & SPENCER, K.E.V. (1973). Metiamide in systematic screening tests. In *Proceedings of International Symposium on Histamine $H_2$-receptor Antagonists*. ed. Wood, C.J. & Simkins, M.A. pp. 23–26. London: Deltakos Ltd.

BLAKEMORE, R.C., BROWN, T.H., DURANT, G.J., EMMETT, J.C., GANELLIN, C.R., PARSONS, M.E. & RASMUSSEN, A.C. (1980): SK & F 92994: a new histamine $H_2$-receptor antagonist. *Br. J. Pharmac.*, **70,** 105P.

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

BUNCE, K.T., CLAYTON, ??, DALY, M.J., HUMPHRAY, J.M. & STABLES, R. (1981). $H_2$-receptor antagonists protect against aspirin-induced gastric lesions in the rat. *Agents & Actions*, **11,** 167–168.

CORUZZI, G. & BERTACCINI, G. (1982). Histamine Receptors in the lower esophageal sphincter (LES). *Agents & Actions*, **12,** 1–5.

CORUZZI, G., SCARPIGNATO, C., ZAPPIA, & BERTACCINI, G. (1980). Effetto della benzquinamide sulla motilità gastrointestinale. *Il Farmaco* (Ed. Pr.) **35,** 466–472.

DI LISA, F., FERRARI, R., RADDINO, R., CORUZZI, G. & BERTACCINI, G. (1981). Effect of oxmetidine, a new $H_2$-receptor antagonist, on the isolated rabbit heart. *J. mol. cell. Cardiology*, **13** (Suppl. 1) 22.

GREENBERGER, N.J., ARVANITAKIS, C. & HURWITZ, A. (1978). *Drug Treatment of Gastrointestinal Disorders.* New York: Churchill Livingstone.

OKABE, S., TAKEUCHI, K., MURATA, T. & TAKAGI, K. (1977). Effects of cimetidine and atropine sulfate on gastric secretion and healing of gastric and duodenal ulcers in rat. *Eur. J. Pharmac.*, **41,** 205–208.

PARE, W.P., GLAVIN, G.B. & VINCENT, G.P. (1978). Effects of cimetidine on stress ulcer and gastric acid secretion in the rat. *Pharmacol. Biochem. Behav.*, **8,** 711–715.

REYNELL, P.C. & SPRAY, G.H. (1956). The simultaneous measurement of absorption and transit in the gastrointestinal tract of the rat. *J. Physiol.*, **131,** 452–462.

RIDLEY, P.T., GROVES, W.G., SCHLOSSER, J.H. & MASSENBERG, J.S. (1973). $H_2$-antagonist action on interdigestive gastric acid secretion and motility in the rat. In *Proceedings of International Symposium on Histamine $H_2$-receptor Antagonists.* ed. Wood, C.J. & Simkins, M.A. pp. 259–264, London: Deltakos Ltd.

SCARPIGNATO, C. & BERTACCINI, G. (1981). Bombesin delays gastric emptying in the rat. *Digestion*, **21,** 104–106.

SCARPIGNATO, C., BERTACCINI, G., ZIMBARO, G. & VITULO, F. (1982). Ranitidine delays gastric emptying of solids in man. *Br. J. clin. Pharmac.*, **13,** 252–253.

SCARPIGNATO, C., CAPOVILLA, T. & BERTACCINI, G. (1980). Action of caerulein on gastric emptying of the conscious rat. *Archs int. Pharmacodynam.*, **246,** 286–294.

SCARPIGNATO, C., CORUZZI, G. & BERTACCINI, G. (1981). Effect of histamine and related compounds on gastric emptying of the conscious rat. *Pharmacology*, **23,** 185–191.

YEO, T., DELITALA, G., BESSER, G.M. & EDWARDS, C.R.W. (1980). The effects of ranitidine on pituitary hormone secretion *in vitro*. *Br. J. Clin. Pharmac.*, **10,** 171–173.

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