Different effects of the H_2-antagonists on gastric emptying in the rat[1]

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Summary. H_2-receptor antagonists, in doses capable of inhibiting gastric secretion, did not generally affect gastric emptying. Exceptions were burimamide, which delayed the emptying rate, and ranitidine, which accelerated it. At higher doses burimamide, metiamide cimetidine and oxmetidine delayed gastric emptying, but ranitidine accelerated it to a greater extent. Tiotidine remained ineffective. These data suggest that changes in emptying rate are independent of the H_2-receptor blockade.

In a thorough investigation, concerning histamine receptors and gastrointestinal motility[2], we observed that histamine delayed gastric emptying (GE) in the conscious rat through excitation of H_1-receptors. In a previous study[3] 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[4-6], have emphasized the importance of the pylorus in the regulation of gastric emptying in the rat. Since preliminary results concerning different H_2-blockers were equivocal, and several non-specific effects of these compounds have been reported[7], 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 the experiments were used. The test meal consisted of a solution of 50 mg phenol red in 100 ml of aqueous methyl cellulose (1.5%) in the amount of 1.5 ml/rat, given by oral intubation. H_2-blockers were injected in a constant volume (1 ml/kg), by the i.p. route, 5 min prior to the administration of the meal. 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. The stomach was then exposed by laparotomy, quickly ligated at the pylorus and the cardia, and removed. The stomach and its contents were homogenized in a Waring blender with 100 ml of NaOH 0.1. The analytical procedure for the assay of phenol red was described in a previous paper[5]. It involves precipitation of proteins with 20% trichloroacetic acid, realkalization with NaOH and colorimetric assay at 560 nm. GE for each rat was calculated as previously described[5]. Under our experimental conditions, in control rats (receiving only physiological saline) the meal leaving the stomach after 20 min was 57.5 ± 3.1% in comparison with the standard. Drugs used were: burimamide, metiamide, cimetidine and oxmetidine (comp. marked SKF 92994) (kindly supplied by SKF, Welwyn Garden City, Herts, UK) ranitidine (Glaxo) and tiotidine (kindly supplied by Dr McCurdy, ICI Americas Inc.).

Results. Results obtained are summarized in the table. It is evident that low doses of most of the compounds used did not modify GE significantly 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 absolutely ineffective.

Discussion. Our experiments demonstrated that the behaviour of the H_2-receptor antagonists in modifying GE varied with the different members of the family. This suggests that the effects observed in this investigation are independent of H_2-receptor blockade, in accordance with our previous data, indicating that H_1-receptors are involved in the effect of histamine on rat gastric emptying[2]. The mechanism of action of these compounds is difficult to explain: burimamide may act through the already mentioned contraction of the pylorus[3] and/or through the gastric motor inhibition reported by Ridley et al.[8]; metiamide has also been found to inhibit gastric motility in the rat[9], whereas an anticholinergic effect could come into play for cimetidine and oxmetidine[10,11]. Moreover, oxmetidine was found to possess a relaxant action on the in situ rat stomach (Bertaccini, unpublished) and in the rat lower esophageal sphincter (LES) in vitro[12]. The opposite effect of ranitidine is rather puzzling, especially considering that in healthy volunteers the compound significantly delayed gastric emptying (Scarpignato et al., unpublished). At present no satisfactory explanation for such an effect can be offered. A cholinergic-like action was found to be present on the isolated rat LES: indeed, on this preparation, ranitidine showed a spasmogenic effect, which was partially inhibited by tetrodotoxin and abolished by atropine[12]. The efficacy of ranitidine was comparable, in our experimental conditions, to that of metoclopramide[13]; however, the lack of activity of ranitidine on prolactin release seems to exclude an antidopaminergic action[14]. In conclusion, our experiments indicated the possibility of an action of the H_2-antagonists which is certainly independent of the H_2-receptor blockade and may represent a nonspecific effect, related to the individual drug rather than to the entire class. Doses used to reach a clearcut effect on GE were remarkably greater than those necessary to inhibit gastric secretion; however, in other studies[15-17] similarly high amounts of H_2 blockers had to be employed to obtain evident effects on the healing of experimentally induced ulcers in the rat.

Effect of different H_2-receptor blockers on gastric emptying in the rat

Compound	Dose (mg/kg)	No. of animals	% Gastric emptying	Significance vs saline
Saline	-	20	57.5 ± 3.1	-
Burimamide	10	6	37.7 ± 5.7	$p < 0.025$
	100	6	0.24 ± 0.10	$p < 0.0001$
Metiamide	10	6	69.4 ± 7.0	NS
	100	6	20.3 ± 4.2	$p < 0.0001$
Cimetidine	10	8	67.3 ± 4.2	NS
	100	6	21.2 ± 1.8	$p < 0.0001$
Oxmetidine	2	6	67.9 ± 3.4	NS
(SKF 92994)	20	6	29.8 ± 7.9	$p < 0.005$
Ranitidine	2	8	77.5 ± 5.6	$p < 0.025$
(AH 19065)	20	6	81.2 ± 7.0	$p < 0.005$
Tiotidine	1	8	51.7 ± 4.8	NS
(ICI 125, 211)	10	6	55.1 ± 9.1	NS

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2 G. Bertaccini, C. Scarpignato and G. Coruzzi, in: H_2-antagonists, p.251. Ed. A. Torsoli, P.E. Lucchelli and R.W. Brimblecombe. Excerpta Medica, Amsterdam 1980.

3 G. Bertaccini, G. Coruzzi, M. Molina and M. Chiavarini, Rend. Gastroenterol. *9*, 163 (1977).
4 G. Bertaccini, R. De Castiglione and C. Scarpignato, Br. J. Pharmac. *72*, 221 (1981).
5 C. Scarpignato, T. Capovilla and G. Bertaccini, Archs int. Pharmacodyn. Thér. *246*, 286 (1980).
6 C. Scarpignato and G. Bertaccini, Digestion *21*, 104 (1981).
7 G. Bertaccini and G. Dobrilla, Ital. J. Gastroenterol. *12*, 309 (1980).
8 P.T. Ridley, W.G. Groves, J.H. Schlosser and J.S. Massenberg, in: Proceedings of International Symposium on Histamine H_2-receptor antagonists, p.259. Ed. C.J. Wood and M.A. Simkins. Deltakos Ltd, London 1973.
9 J.W. Black and K.E.V. Spencer, in: Proceedings of International Symposium on Histamine H_2-receptor antagonists, p.23. Ed. C.J. Wood and M.A. Simkins. Deltakos Ltd, London 1973.
10 R.W. Brimblecombe, W.A.M. Duncan, G.J. Durant and J.C. Emmett, J. intern. Med. Res. *3*, 86 (1975).
11 R.C. Blakemore, T.H. Brown, G.J. Durant, J.C. Emmett, C.R. Ganellin, M.E. Parsons and A.C. Rasmussen, Br. J. Pharmac. *70*, 105P (1980).
12 G. Bertaccini and G. Coruzzi, Farmaco Ed. Sc. *36*, 129 (1981).
13 G. Coruzzi, C. Scarpignato, L. Zappia and G. Bertaccini, Farmaco Ed. Sci. *35*, 466 (1980).
14 T. Yeo, G. Delitala, G.M. Besser and C.R.W. Edwards, Br. J. clin. Pharmac. *10*, 171 (1980).
15 S. Okabe, K. Takeuchi, T. Murata and K. Takagi, Eur. J. Pharmac. *41*, 205 (1977).
16 W.P. Pare, G.B. Glavin and G.P. Vincent, Pharmac. Biochem. Behav. *8*, 711 (1978).
17 K.T. Bunce, N.M. Clayton, M.J. Daly, J.M. Humphray and R. Stables, Br. J. Pharmac. *70*, 178P (1980).

Levodopa effect on norepinephrine and dopamine brain levels after portocaval shunt in rats

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Summary. In various brain areas in the rat, after 7 days of portocaval shunt with levodopa administration, we found an increase in norepinephrine and dopamine levels.

The etiology of portal systemic encephalopathy (PSE)[3] is not clear, but many factors have been described[4-6]. The 'false neurotransmitters theory'[7] explains the syndrome by catecholamine (CA) depletion and increase of octopamine found in acute hepatocellular insufficiency[8].

It has been suggested that false neurotransmitters can replace norepinephrine (NE) and dopamine (DA) in hepatic coma, which may explain the arousal effect of levodopa (L-3,4,dihydroxyphenylalanine) in acute hepatic encephalopathy treatment[9,10]. Based on the same mechanism of action, levodopa has been also employed in the treatment of chronic PSE but not always with beneficial results[11,12]. This failure was attributed to the ineffective action of levodopa when employed in later periods of PSE, because in this period the morphologic changes in the CNS are irreversible[11]. For this reason levodopa must be employed in an early state of PSE in which it is possible to reverse the metabolic cerebral changes, especially by increase of CA synthesis.

To investigate this hypothesis we have measured NE and DA levels in CNS of portocaval shunt (PCS) rats in an early state after the operation, and studied the changes produced after levodopa administration.

Material and methods. Male Sprague-Dawley rats weighing 200–250 g were used. PCS was made following the method of Lee and Fisher[13] with modifications[14]. The body weight diminished 10% after 7 days of PCS compared to the control rats. Hepatic weight diminished parallel to the body weight.

CA levels were measured by the fluorimetric method[15] in noradrenergic areas (hypothalamus and amigdala) and dopaminergic areas (olfactory tubercle and striatum nucleus) after 7 days of PCS.

4 groups of animals were used: 1. Control group, 2. PCS group after the 7th post-operatory day, 3. control group after administration of levodopa (100 mg/kg p.o.) coadministered with a levodopa peripheral decarboxylase inhibitor (LPDI), benserazide (N'-[DL-seryl]-N^2-[2,3,4]-trihydroxybencyl hidracine clorhydrate) (25 mg/kg p.o.) and 4. PCS group after the 7th post-operatory day and the administration of levodopa and LPDI, both at the same dose as the former group. The drugs were administered orally and all the rats were decapitated 1 h after the administration. Cerebral areas were dissected as described by Glowinsky and Iversen[16].

Results and discussion. NE levels decreased after 7 days of PCS in noradrenergic areas (45% in hypothalamus, 28% in amygdala). Levodopa plus LPDI produced the elevation of NE levels in the noradrenergic areas studied in PCS rats. These levels approximate to those of the control group (table 1).

Table 1. NE levels in control and PCS rats (7 days of postoperatory) and after levodopa + LPDI administration

NE levels (ng/mg)	Dopaminergic system		Noradrenergic system	
	Olfactory	Striatum	Amygdala	Hypothalamus
Control rats	0.60 ± 0.07 (18)	0.40 ± 0.11 (16)	0.47 ± 0.07 (18)	2.20 ± 0.29 (17)
Control rats + levodopa + LPDI	1.08 ± 0.09 (13)**	0.96 ± 0.11 (13)**	0.81 ± 0.13 (12)**	2.47 ± 0.14 (13)
PCS	0.45 ± 0.11 (16)	0.38 ± 0.03 (17)	0.36 ± 0.08 (17)*	1.20 ± 0.18 (18)**
PCS + levodopa + LPDI	1.19 ± 0.13 (12)**	0.94 ± 0.07 (15)**	0.80 ± 0.087 (15)**	2.39 ± 0.14 (14)

Number of experiments in parenthesis. Statistically significant values compared to control group: * $p < 0.05$; ** $p < 0.001$.