

## References

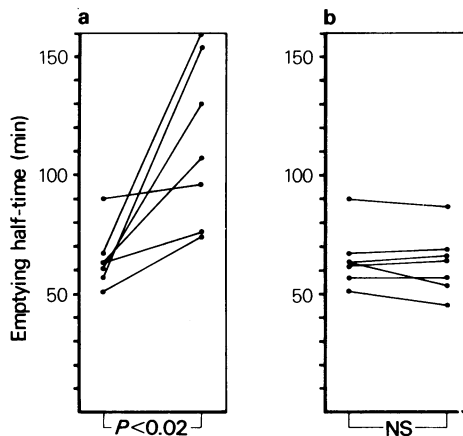
- BURGGRAF, G.W. & PARKER, J.O. (1974). Left ventricular volume changes after amyl nitrite and nitroglycerin in man as measured by ultrasound. *Circulation*, **49**, 136–143.
- DROBINSKI, G., EVANS, J.L., BOREL, P., THOMAS, D., BEJEAULEBUISSON, A. & GROSOGEGAT, F. (1980). Etude échocardiographique d'une trinitrine micro-encapsulée. *Nouv. Presse Méd.*, **9**, 2462–2465.
- FORSTER, R.E., FERRIS, B.G. & DAY, R. (1946). The relationship between total heat exchange and blood flow in the hand at various ambient temperatures. *Am. J. Physiol.*, **146**, 600–609.
- LADIPO, G.O.A., DUNN, F.G., PRINGLE, T.H., BASTIAN, B. & LAWRIE, T.D.V. (1980). Serial measurements of left ventricular dimensions by echocardiography. *Br. Heart J.*, **44**, 284–289.
- MASON, D.T. & BRAUNWALD, E. (1965). The effects of nitroglycerin and amyl nitrite on arteriolar and venous tone in the human forearm. *Circulation*, **32**, 755–759.
- MASON, D.T., ZELIS, R. & AMSTERDAN, E.A. (1971). Action of the nitrites on the peripheral circulation and myocardial oxygen consumption: significance in the relief of angina pectoris. *Chest*, **59**, 296–305.
- THAUER, R. (1966). Circulatory adjustments to climatic requirements. In *Handbook of Physiology, Circulation*, eds Hamilton, W.F. & Dow, P.H., Vol III, 1291–1966.
- THRON, H.L., SCHEPPOKAT, K.D., HEYDEN, A. & GAUER, O.H. (1958). Das Verhalten der Kapazitäten und der Widerstandsgefäße der menschlichen Hand in Abhängigkeit von thermischen Einflüssen. *Arch. Ges. Physiol.*, **266**, 150–166.
- WARRINGTON, S.J. & BURGESS, C.D. (1980). Effects of glyceryl trinitrate on the systolic time intervals. *Br. J. clin. Pharmacol.*, **9**, 292P.
- WEISSLER, A.M., LEWIS, R.P. & LEIGHTON, G. (1972). The systolic time intervals as a measure of left ventricular performance in man. In *Progress in Cardiology*, eds Yu, P.N. & Goodwin, J.F., pp 155–183. Philadelphia: Lea and Febiger.
- WEZLER, K. & THAUER, R. (1943). Der Kreislauf im Dienste der Wärmeregulation. *Z. Ges. Exptl. Med.*, **112**, 345–379.

## RANITIDINE DELAYS GASTRIC EMPTYING OF SOLIDS IN MAN

In preliminary studies we investigated the effect of a series of histamine  $H_2$ -receptor antagonists (Domschke & Domschke, 1980; Bertaccini & Dobrilla, 1980) on gastric emptying of the conscious rat. Burimamide, metiamide, cimetidine, ometidine and tiotidine, given intraperitoneally, were found to be inactive at doses capable of inhibiting gastric secretion but to cause a significant delay at much greater doses (10 times as high as the antisecretory dose). Conversely, one of the newest members of the family, ranitidine, accelerated gastric emptying when given both at antisecretory and at higher doses (2 and 20 mg  $kg^{-1}$ ). The enormous practical interest of this compound as an antiulcer drug prompted us to test it for its effect on gastric emptying also in man. Cimetidine, the most widely employed antiulcer drug, was used in the same subjects as a reference compound.

Seven healthy volunteers underwent separate studies on three different days. Ranitidine (50 mg), cimetidine (300 mg) or saline (control studies) were given intravenously 5 min prior to administration of the meal. The order of these studies was randomized. Gastric emptying was studied as described in a previous paper (Scarpignato *et al.*, 1981) using a labelled ( $^{99m}Tc$  sulphur colloid) meal and recording continuously the radioactivity remaining in the stomach through a movable scintillation detector.

Results, expressed as emptying half-time ( $T_{1/2}$ ), are shown in Figure 1. In our experimental conditions healthy subjects had an emptying half-time which ranged between 50 and 90 min. It is evident from Figure 1 that acute administration of ranitidine signi-



**Figure 1** Comparison of gastric emptying rates of solids after (a) ranitidine or (b) cimetidine injection. The lines join the rates observed with saline and the  $H_2$ -receptor blockers for each subject.

ficantly delayed gastric emptying of solids ( $T_{1/2}$  from  $64.8 \pm 4.6$  min to  $114.2 \pm 13.4$  min,  $P < 0.02$ ). Conversely, cimetidine was found to be completely ineffective ( $T_{1/2} = 63.1 \pm 4.9$  min) in full accordance with the data of the literature (for review see Bertaccini *et al.*, 1980).

The delay in gastric emptying induced by ranitidine is difficult to explain. It cannot be related to an anticholinergic activity since it was demonstrated that this  $H_2$ -receptor blocker is devoid of such an effect

(Bradshaw *et al.*, 1979); a dopamine agonistic action, which could account for the delay in emptying (Lanfranchi *et al.*, 1978; Proctor *et al.*, 1981), was never observed in several *in vivo* and *in vitro* experiments performed in our laboratory (Bertaccini, unpublished observations).

The action of ranitidine seems to be independent of H<sub>2</sub>-receptor blockade (with consequent inhibition of gastric secretion) as shown by the inactivity of cimetidine. The same data allowed us to exclude effects related to changes in intraduodenal pH (Cooke, 1975). However an influence of changes in plasma gastrin levels cannot be excluded on the basis of our experiments. Thus a non-specific effect of the molecule rather than an effect connected with the H<sub>2</sub>-receptor blockade must be hypothesized. Species differences may be responsible for the opposite effect observed in man (delay of gastric emptying) and in rat (acceleration of gastric emptying). The different route of administration with possible changes in bio-availability must be considered. Moreover, Parsons (personal communication) observed poor, irregular absorption of H<sub>2</sub>-antagonists after intraperitoneal administration in the rat. However, the differences in the activity of the various H<sub>2</sub>-receptor blockers

observed both in rat and in man are consistent with the idea that H<sub>2</sub>-receptors are not involved in the control of gastric emptying, at least in these two species.

The effect of ranitidine was observed after intravenous injection with consequent high blood levels of the compound; if the effect on gastric emptying is confirmed also after repeated oral administrations, ranitidine could represent a useful agent for the treatment of ulcer patients with deranged (increased) gastric motility. However, according to the only preliminary report on this topic (Mignon *et al.*, 1980), single oral administration of ranitidine does not change gastric emptying rate in man.

This work was supported by a grant of CNR, Rome

CARMELO SCARPIGNATO, GIULIO BERTACCINI, GIOVANNI ZIMBARO & FELICE VITULO

*Institute of Pharmacology, University of Parma, Parma and Department of Radiology & Nuclear Medicine, University of Messina, Messina, Italy*

Received September 15, 1981

## References

- BERTACCINI, G. & DOBRILLA, G. (1980). Histamine H<sub>2</sub>-receptor antagonists: old and new generation. *Pharmacology and clinical use. Ital. J. Gastroenterol.*, **12**, 309–314.
- BERTACCINI, G., SCARPIGNATO, C. & CORUZZI, G. (1980). Histamine receptors and gastrointestinal motility: an overview. In *H<sub>2</sub>-antagonists*, eds Torsoli, A., Lucchelli, P.E. & Brimblecombe, R.W., pp 251–261. Amsterdam: Excerpta Medica.
- BRADSHAW, I., BRITAIN, R.T., CLITHEROW, J.W., DALY, M.J., JACK, D., PRICE, B.J. & STABLES, R. (1979). Ranitidine (AH 19065): a new potent, selective histamine H<sub>2</sub>-receptor antagonist. *Br. J. Pharmacol.*, **66**, 464P.
- COOKE, R.A. (1975). Control of gastric emptying and motility. *Gastroenterology*, **68**, 804–816.
- DOMSCHKE, S. & DOMSCHKE, W. (1980). New histamine H<sub>2</sub>-receptor antagonists. *Hepato-Gastroenterol.*, **27**, 163–168.
- LANFRANCHI, G.A., MARZIO, L., CORTINI, C., TRENTO, L. & LABO, G. (1978). Effect of dopamine on gastric motility in man: evidence for specific receptors. In *Gastrointestinal motility in health and disease*, ed. Duthie, H.L., pp 161–171. Lancaster: MTP Press Ltd.
- MIGNON, M., SAUVAGE, M., LEROUX, S. & BONFILS, S. (1980). Effet des doses variées de ranitidine sur la secretion acide, la vidange gastrique et la gastrine serique lors d'un repas test chez l'homme. *Gastroenterol. clin. Biol.*, **4** (suppl. 1), 158A.
- PROCTOR, J.D., FRATKIN, M.J., EVANS, E.F. & WASSERMAN, A.J. (1981). Effect of domperidone on apomorphine-retarded gastric emptying. In *Progress with domperidone, a gastrokinetic and antiemetic agent*, ed. Towse, G., pp 37–40, The Royal Society of Medicine, London: Academic Press.
- SCARPIGNATO, C., ZIMBARO, G., VITULO, F. & BERTACCINI, G. (1981). Caerulein delays gastric emptying of solids in man. *Arch. int. Pharmacodyn.*, **249**, 89–105.

## SIX MONTHS EXPERIENCE OF NEW PROCEDURES AFFECTING THE CONDUCT OF CLINICAL TRIALS IN THE UNITED KINGDOM

Details of the new procedures affecting clinical trials in the United Kingdom have been given previously (Griffin & Long, 1981; Griffin & Diggle, 1981). In a recent editorial in this journal by Binns (1981) interest was expressed in the effect such changes would have on the testing of new chemical entities

(NCE) in the United Kingdom in the light of earlier statements that an overwhelming majority of early clinical trials of drug molecules originating within the British Pharmaceutical Industry were being conducted overseas (Cromie, 1980).

In Table 1 are shown details of the one hundred and