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THE EFFECT OF METOCLOPRAMIDE AND PROPANTHELINE ON THE GASTROINTESTINAL ABSORPTION OF CIMETIDINE

Patients treated with cimetidine may also take metoclopramide or anticholinergic drugs in order to relieve nausea or to increase the therapeutic efficacy of the treatment. The combination drug therapy may be appropriate in the refractory cases (Finkelstein & Isselbacher, 1978). Despite the rapidly gained and widespread use in the treatment of duodenal and gastric ulcer, few studies have been published on the pharmacokinetics of cimetidine (Grahnen, von Bahr, Lindström & Rosen, 1979). In this work we have studied the simultaneous effect of relatively large dose of metoclopramide and propantheline on the gastrointestinal absorption of cimetidine.

This study was carried out in eight ambulant healthy volunteers prevented from unusual exertion aged 20 to 23 (mean 21) years and weighing between 53 to 80 (mean 61) kg. Each volunteer was shown by medical history and examination to be in good physical condition, with normal routine blood, liver and urine laboratory values. The nature of the experiment was explained to the volunteers and their consent was obtained. The subjects were given in randomized order single oral doses of cimetidine 200 mg, cimetidine 200 mg + metoclopramide 20 mg, and cimetidine 200 mg + propantheline 30 mg at intervals of 1 week (cimetidine = Ulcur®, Leiras; metoclopramide = Metopram®, Leiras; propantheline = Neo-Gastrosedan®, Star). The drugs were taken between 08.00 h and 09.00 h after a 12 h overnight fast. Water (200 ml) was given with the drugs and 4 h thereafter a standardized lunch was given. Drugs, including alcohol, were prohibited for at least 48 h prior to each study period. Blood samples were drawn from an indwelling venous cannula at 0, 15, 30, 45, 60, 75, 105 and 120 min and at 2.5, 3.0, 3.5, 4.0, 5.0 and 6.0 h after the administration of the drugs. The blood samples were collected in heparinized test tubes, plasma was separated by centrifugation for 10 min at 3000 rev/min and stored at −20°C until analysis (not more than 2 months). Cimetidine plasma samples were assayed by an HPLC method measuring concentrations of cimetidine as low as 0.05 μg/ml (Randolph, Osborne, Walkenstein & Intoccia, 1977). The within-assay-variation was 4% at the level of 0.25 μg/ml and 5% at 2.5 μg/ml.

The concentrations of cimetidine in the plasma are presented in Figure 1. On most occasions two peaks in the plasma level curve were distinguished. With metoclopramide, however, the second peak was almost abolished. The individual first peak levels tended to occur slightly earlier with metoclopramide and later with propantheline. Both co-treatments reduced the AUC-value of cimetidine, but only propantheline decreased significantly the individual peak levels (Table 1).

Generally, two marked peaks have been found in the gastrointestinal absorption of cimetidine (Griffiths, Lee & Taylor, 1977; Walkenstein, Dubb, Randolph, Westlake, Stote & Intoccia, 1978; Bodemar, Norlander, Fransson & Wahlan, 1979; Grahnen *et al.*, 1979). The mechanism of the second peak has not been adequately explained. Possible causes are irregular absorption in the gastrointestinal tract, enterohepatic circulation, or the reduction of the sulphoxide metabolite of cimetidine back to intact cimetidine caused by faecal bacteria (Spence, Greak & Celestine, 1977; Taylor, Gresswell & Bartlett, 1978; Grahnen *et al.*, 1979). In the present study metoclopramide abolished the second peak and consequently reduced the AUC. Similarly, in the study of Bodemar *et al.*, (1977) food abolished the second peak. If the second peak level was caused by absorption of cimetidine at a limited site in the intestine, an increased motility due to metoclopramide

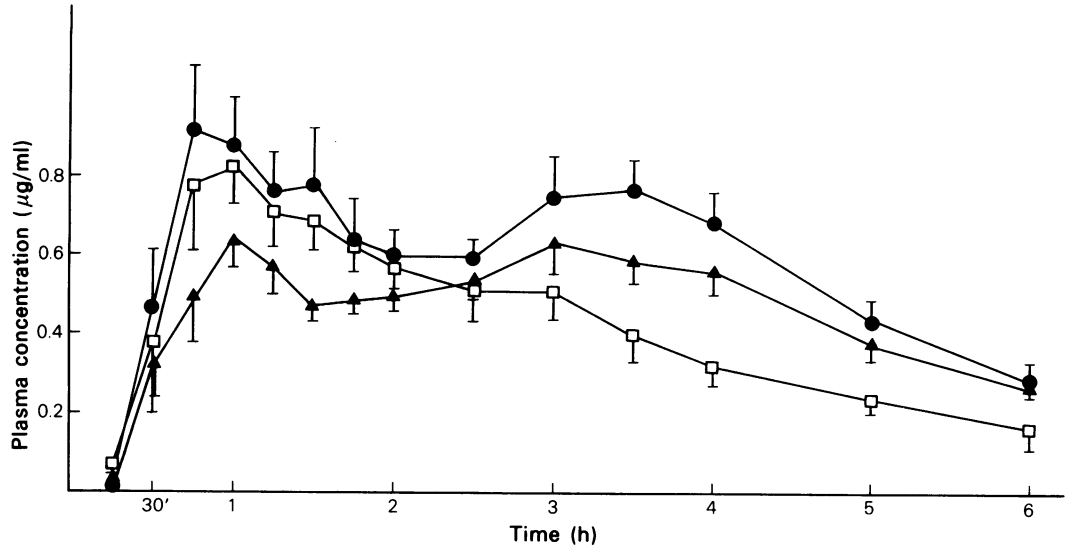

Figure 1 The concentrations of cimetidine in the plasma after a single 200 mg oral dose (●) and the effect of metoclopramide 20 mg p.o. (□) or propantheline 30 mg p.o. (▲) on those levels in eight healthy volunteers (mean ± s.e. mean).

would reduce this second phase absorption. Another explanation may be a shortened time for intestinal bacteria to reduce the sulphoxide metabolite back to cimetidine. However, this explanation may not be adequate, as microbial activity mainly occurs in the large intestine, and metoclopramide mostly affects small intestine (Kreel, 1970). In a recent work (Pedersen & Miller, 1980) it has been suggested that after oral administration in fasted subjects cimetidine accumulates in a well-perfused tissue or organ (hepato-biliary system?) during the first-pass. According to this theory, metoclopramide or food has some effect on the drug release mechanism from this storage site.

Bioavailability studies using AUC-values seem to be misleading for drugs which behave like cimetidine, because AUCs after oral doses exceed those after intravenous injection (Grahnen *et al.*, 1979).

The reduced bioavailability of cimetidine when given together with propantheline may be a consequence of delayed gastric emptying, decreased intestinal motility, and hence, reduced mixing of intestinal contents. Because the degree of inhibition of gastric acid secretion is related to the blood concentrations of cimetidine (Pounder, Williams, Hunt, Vincent, Milton-Thompson & Misiewicz, 1977), the reduced plasma concentrations of concomitant metoclopramide or propantheline may decrease the therapeutic

Table 1 Mean (± s.e. mean) individual peak levels (C_{max}), times to peak level (t_{max}), area under the plasma level-curve (AUC), and relative bioavailability. C_{max} after cimetidine + propantheline and AUC after both co-treatments were significantly decreased in comparison with cimetidine alone. AUC was determined by the trapezoidal rule. Statistical analyses were carried out using Student's *t*-test (paired data).

	Cimetidine	*Cimetidine + metoclopramide*	*Cimetidine + propantheline*
C_{max} (μg/ml)	1.12 ± 0.15	0.96 ± 0.13	0.75 ± 0.08 $P<0.05$
t_{max} (h)	0.97 ± 0.12	0.88 ± 0.08	1.22 ± 0.34
AUC (μg ml^{-1}h)	3.52 ± 0.25	2.48 ± 0.33 p<0.025	2.74 ± 0.34 p<0.020
Apparent bio-availability (%)		70.5	77.8

efficacy of cimetidine. However, other anticholinergic drugs, like poldine 8 mg p.o. and atropine 0.6 mg i.v. (Blackwood & Northfield, 1977; Pounder *et al.*, 1977), had no significant effect on the blood cimetidine levels. Our propantheline dose (30 mg) was quite high, and, hence, anticholinergics may reduce cimetidine concentrations in the plasma especially in high doses.

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MAXIMUM OR MEAN FEV_1 FOR BRONCHODILATOR AEROSOL EVALUATION IN ACUTE ASTHMATICS

The forced ventilatory capacity (FVC) and the forced expiratory volume in one second (FEV_1) are two spirometric indices which have been widely used in clinical practice and in the assessment of bronchodilator efficacy, and several regression equations and tables of normal values in various populations have been devised (e.g. Cotes, 1979). Light, Conrad & George (1977) evaluated the role of FEV_1 in the assessment of bronchodilator therapy and found it to be a sensitive and specific index as compared with several more elaborate tests of airflow obstruction.

Standards have been established for performing the forced vital capacity manouevre (Ferris, 1978; ATS statement, 1979), with exclusion of attempts influenced by practice, fatigue or other misadventure, and further requiring that repeat readings must lie within a given range. Nevertheless, there has been continuing debate as to whether the maximum or mean of repeat readings should be used. The American Thoracic Society recommends the maximum of three acceptable readings (ATS statement, 1979). Since they state that the best two readings must not differ by more than 5%, which approaches the reliability of spirometers, it is questionable whether such a distinction between maximum and mean has practical significance. In a large series of FEV_1 readings from 792 men with bronchitic symptoms, Fletcher, Peto, Tinker & Speizer (1976) also recommended use of the maximum because in their study it was more reliable. However, the standard deviation