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Effect of chlorpromazine on drug absorption and gastric emptying in man

In a double-blind study the effect of a single IV dose (25 mg) of chlorpromazine on gastric emptying, as determined by the rate of paracetamol absorption, was measured in seven healthy volunteers. Each volunteer acted as his/her own control. There was no significant difference between the maximum paracetamol concentration, the time to reach the plasma maximum concentration, and the area under the plasma concentration time curve from 0–120 minutes on the two occasions, indicating unchanged gastric emptying after administration of chlorpromazine.

Nausea and vomiting are controlled through the vomiting centre, which in turn is influenced by psychic factors, the vestibular nucleus, the chemoreceptor trigger zone and sensory afferents from the pharynx, the gastrointestinal tract or the genitalia.¹ Delayed gastric emptying with increased gastric contents together with sensory input from the gastrointestinal tract can result in nausea and vomiting.² The effect of antiemetic drugs on gastric emptying is therefore important.

The antiemetic effect of phenothiazines has been clearly established.^{1,3,4} Chlorpromazine appears to be particularly efficient against drugs acting on the chemoreceptor trigger zone, while larger doses may also depress the vomiting centre.¹ Rentzhog and Wikström showed no improvement of retarded gastric motility in rats after use of small doses of chlorpromazine following laparotomy, but its effect on gastric emptying in man is not clear.⁵

In the present study we report the effect of chlorpro-

mazine on drug absorption and liquid phase gastric emptying in man using paracetamol absorption as an index of gastric emptying rate. Simultaneous measurements of paracetamol absorption and gastric emptying have confirmed measurements of the rate of paracetamol administered orally as a dependable expression of gastric emptying.^{6,7}

Methods

Informed consent was obtained from each subject, and the experimental study was approved by the local ethics committee. We studied seven healthy volunteers, three women and four men (aged 21–39 years, body weight 45–85 kg), on two occasions in random order, with an interval of at least two weeks. On each occasion, after an overnight fast, the subjects laid at rest in bed and were given, in a double-blind fashion, chlorpromazine 25 mg or 0.9 per cent NaCl (saline) IV. All patients received a slow intravenous infusion of 1.0 litre normal saline during the study. Following the administration of chlorpromazine all volunteers developed typical behavioural effects as drowsiness and diminished response to a variety of stimuli and were thus aware of the treatment they had received.

On both occasions the subjects ingested 20 mg·kg⁻¹ paracetamol with 200 ml of water 30 min after chlorpromazine or placebo injection. Venous blood samples were taken from an indwelling cannula before and 10, 20, 30, 40, 50, 60, 75, 90, 105 and 120 min after paracetamol administration.

The maximum plasma concentration for a person was designated C_{max} , and the corresponding sampling time T_{max} . The area under the plasma concentration-time curve AUC was calculated by the trapezoidal rule without extrapolation to infinity.

Serum was separated and stored at -20°C until measurement of serum paracetamol concentration by high performance liquid chromatography was performed.⁸ Samples were analyzed in duplicate and in random order. The coefficient of variation of the assay was three per cent, and the recovery of paracetamol in blank plasma 97 ± 3 per cent (s.d.).

Key words

GASTROINTESTINAL TRACT: gastric emptying, paracetamol absorption; ATARACTICS: chlorpromazine.

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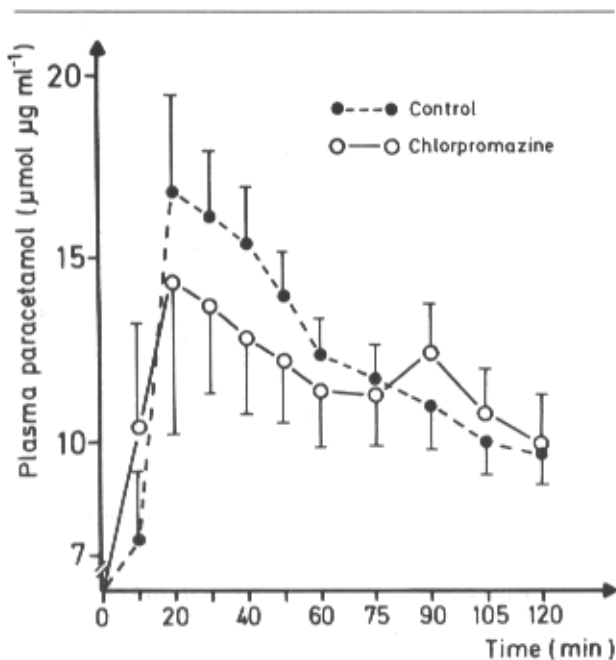


FIGURE 1 Mean plasma paracetamol concentrations (\pm SEM) at each sampling time with and without chlorpromazine administration.

Statistics

Data were compared using Student's *t* test for paired data. *P* values <0.05 were considered statistically significant.

Results

Mean plasma paracetamol concentrations at each sampling time are given in the Figure. None of the observed differences, i.e., C_{max} , T_{max} , AUC attained statistical significance ($p > 0.10$).

The individual values of C_{max} , T_{max} and AUC are given in the Table. At no sampling time did the mean paracetamol concentration after chlorpromazine administration differ significantly from the mean concentration after placebo ($p > 0.05$).

After placebo administration the mean (\pm SEM) C_{max} was $18.5 \pm 2.1 \mu\text{g}\cdot\text{ml}^{-1}$ ($n = 7$), the mean T_{max} was 35.7 ± 5.3 min, and the mean AUC was $1403 \pm 122 \mu\text{g}\cdot\text{min}\cdot\text{ml}^{-1}$. After chlorpromazine the mean C_{max} was $18.6 \pm 3.2 \mu\text{g}\cdot\text{ml}^{-1}$, the mean T_{max} was 35.0 ± 9.9 min and the mean AUC was $1363 \pm 170 \mu\text{g}\cdot\text{min}\cdot\text{ml}^{-1}$ ($p > 0.05$).

Gastric emptying was delayed slightly in one subject and accelerated slightly in two subjects, as compared with the differences from the two occasions in the other persons. The differences in C_{max} , T_{max} , and AUC were not statistically significant; data and the results of paired *t* test analysis are given in the Table. The mean differences and the 95 per cent confidence limits were: C_{max} :

$-0.06 \mu\text{g}\cdot\text{ml}^{-1}$ (95 per cent: -7.8 to 7.9), T_{max} : 0.7 min (95 per cent: -14 to 16); and AUC: $40 \mu\text{g}\cdot\text{min}\cdot\text{ml}^{-1}$ (95 per cent: -346 to 426).

Discussion

In the present study paracetamol absorption was used as an index of gastric emptying. This method has been demonstrated to correlate well with other methods used to estimate gastric emptying of liquids.⁷ The relationship between gastric emptying of solids and paracetamol absorption is unknown. Liquid and solid phase empty at different rates and pattern, and patients may demonstrate normal emptying of liquid while actually retaining the solids. However, in normal persons there is a correlation between the rates of emptying of solids and liquids.⁹

This study demonstrates that paracetamol absorption was not significantly changed by a single, modest dose of chlorpromazine 25 mg IV to seven healthy volunteers receiving paracetamol $20 \text{ mg}\cdot\text{kg}^{-1}$ dissolved in 200 ml of water.

The patterns of gastric emptying were similar in the seven subjects. However, gastric emptying was delayed slightly in one subject (# 3) and accelerated slightly in two others (# 2 and # 6) after chlorpromazine IV. This may reflect small, insignificant individual variations in the rate of gastric emptying produced by chlorpromazine, as the changes were independent of sex and body weight of the volunteers.

The 95 per cent confidence limits, i.e., -25 min to 38 min, are not broad enough to reflect clinically significant changes. The magnitude of changes that are clinically important are hours, as exemplified by an earlier study of buprenorphine, which prolongs gastric emptying.¹⁰ Whether chlorpromazine can change gastric emptying in such a situation is unknown.

The results suggest furthermore that the mechanism by which chlorpromazine exerts its antiemetic effect is not mediated via gastric emptying, but only through the effect on the chemoreceptor trigger zone. Chlorpromazine should, therefore, be less suitable in treatment of emesis caused by gastric retention. However, to confirm this hypothesis a study population with emetic patients must be investigated.

Chlorpromazine's lack of effect on gastric emptying of fluids is the more important finding and has clinical implications. The result suggests, for example, that chlorpromazine given before anaesthesia should not impair absorption of concomitantly administered oral medication.

As several antipsychotic agents chlorpromazine seems to act as analgesic, either alone or in combination with traditional analgesics. Shimm *et al.* have shown that patients given antipsychotic treatment could reduce or

TABLE The individual values of the peak serum paracetamol concentration C_{max} ($\text{mg}\cdot\text{ml}^{-1}$), the time from administration of paracetamol to its peak concentration T_{max} (min), the area under plasma concentration-time curve from 0–120 min AUC ($\mu\text{g}\cdot\text{min}\cdot\text{ml}^{-1}$) with and without chlorpromazine (chlorp.) administration, the differences in C_{max} , T_{max} , AUC and P values

Subject	C_{max} Saline	C_{max} Chlorp.	Diff. C_{max}	T_{max} Saline	T_{max} Chlorp.	Diff. T_{max}	AUC Saline	AUC Chlorp.	Diff. AUC
1	20.54	9.59	10.95	20	20	0	1450	804	646
2	22.49	35.25	-12.76	30	20	10	1513	2103	-590
3	15.39	16.80	-1.41	60	90	-30	1360	1072	288
4	28.33	17.31	11.02	20	20	0	1956	1590	366
5	11.99	12.86	-0.87	40	40	0	899	938	-39
6	16.04	22.38	-6.34	40	15	25	1182	1516	-334
7	14.89	15.87	-0.98	40	40	0	1458	1514	-56
Mean	18.5	18.6	-0.06	36	35	0.7	1403	1362	40
SEM	2.1	3.2	3.37	5.3	9.9	6.2	122	171	161
P value			0.99			0.91			0.81

even eliminate their narcotic treatment.¹¹ Chlorpromazine, however, is not widely used by anaesthetists as a premedicant, and therefore further studies are needed to show its usefulness to reduce the use of opioids, the major cause of delayed gastric emptying in the perioperative period.^{2,12}

Many of the undesirable side effects of chlorpromazine may be related to high plasma concentration levels seen after multiple, high-dose administration. These levels may not be necessary to provide adequate preoperative sedation as all subjects in this study showed behavioural effects as drowsiness and diminished response to a variety of stimuli after only a single dose of 25 mg IV.

Consequently, as judged from paracetamol absorption, chlorpromazine in relatively modest antiemetic and sedative doses does not alter drug absorption and gastric emptying in healthy volunteers. Nevertheless, higher and more prolonged doses of the drug have marked anticholinergic effects that possibly could have produced a different effect on gastric emptying.^{3,5}

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Résumé

Dans une étude à double insu, on a mesuré l'effet d'une dose unique i.v. (25 mg) de chlorpromazine sur la vidange gastrique tel que déterminé par le taux d'absorption de paracétamol, chez sept volontaires en santé. Chaque volontaire était son propre témoin. Les deux fois, il n'y avait pas de différence significative dans la concentration maximale de paracétamol, le temps requis pour atteindre la concentration plasmatique maximale, et la surface sous la courbe du temps de la concentration plasmatique de 0–120 minutes, ce qui démontrait une vidange gastrique inaltérée après l'administration de chlorpromazine.