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The effect of oxytocin on basal and pethidine-induced delayed gastric emptying

O. U. PETRING
Department of Anaesthesia and Department of Clinical Physiology and Nuclear Medicine, Rigshospitalet, Copenhagen Ø. DK-2100 Denmark

1 Continuous infusion of oxytocin (0.33 u min^{-1}) accelerated gastric emptying of semisolid TC-99m labelled Chelex-100 resin/oatmeal in 10 healthy volunteers under basal conditions.
2 Administration of oxytocin did not change the pattern of gastric emptying delayed by pethidine.
3 The emptying pattern of semisolid has confirmed the existence of a lag phase.

Keywords gastric emptying semisolids radionuclides pethidine oxytocin

Introduction

A variety of pharmacological agents are known to influence gastric emptying (Ricci & McCallum, 1988). Gastric emptying and thus drug absorption determined by paracetamol absorption or by scintigraphic measurement is delayed by the administration of opioid analgesics (Minami & McCallum, 1984; Nimmo, 1984). Use of opioids is the major cause of delayed gastric emptying in the perioperative period, making aspiration of gastric contents more likely (Nimmo, 1984). Reversing the gastric effects of opioids without reducing analgesia, might, therefore, be of particular value in all surgical patients.

Several hormones affect gastrointestinal motility and are believed to constitute a future source of drugs that might be useful for acceleration of gastric emptying, although at present none has been used therapeutically. A preliminary report suggested that continuous infusion of oxytocin reversed gastric atony following vagotomy (Hashmonai *et al.*, 1979).

The aim of the present study was to evaluate, by a scintigraphic technique, whether intravenously administered oxytocin would accelerate basal and pethidine-induced delayed gastric emptying of a semisolid meal.

Methods

The study was approved by the Regional Ethics Committee and informed consent was obtained from each subject. Ten healthy subjects, five women and five men (age 21–39 years, body weight 55–85 kg) were studied on three occasions with an interval of at least 1 week between studies. The tests were performed in the morning. After an overnight fast for a minimum of 8 h the volunteers sat while eating a semisolid meal consisting of 30 g oatmeal, 5 g sugar and 100 ml of cold milk uniformly mixed with 37 MBq of Tc-99m Chelex-100 resin (Wirth *et al.*, 1983; Petring *et al.*, 1986). To control the extent of mastication, the subjects had to eat the semisolid meal within 10 min. Immediately after, with the subjects in supine position, gastric emptying was studied in the anterior projection using a gammacamera with low energy parallel-hole colimator (Maxi 500, G.E.) on line to a computer system (gamma 11, D.E.C., Maynard, M. A.). Successive 60 s images were obtained over a 90 min period.

The stomach was outlined using an irregular region of interest in sequential 5 min images of the study and the activity curve from this region was calculated over the period of the study after

Correspondence: Dr Oscar Ulf Petring, Department of Anaesthesia, Rigshospitalet, Copenhagen Ø, DK-2100 Denmark.

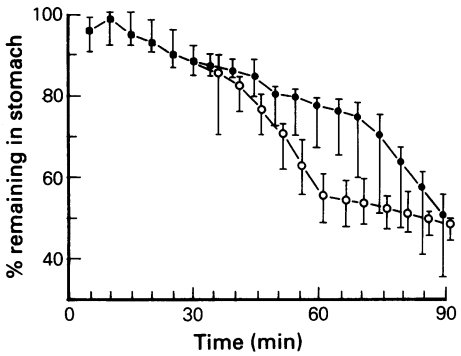

Figure 1 Median percentage of radioactivity emptied from stomach (± inter-quartile range) under basal condition (■---■) (n = 10), following sequence 1 (oxytocin + placebo) (○---○) and sequence 2 (placebo + oxytocin) ●---●).

correction for decay of the 99m-technetium marker (Petring *et al.*, 1986). Gastric emptying values were expressed as a percentage of initial counts in the stomach region.

In order to study the effect of oxytocin on normal gastric emptying, 30 min after beginning of the study the subjects received in a double-blind fashion, one of two treatment sequences. Sequence 1 group received continuous i.v. infusion of 0.33 units min^{-1} of oxytocin (Syntocinon®, Sandoz AG) (20 units in 500 ml of 0.9% w/v NaCl); and sequence 2 group received placebo (0.9% w/v NaCl). Thirty minutes later the treatment was crossed-over, so volunteers who initially had received 10 units of oxytocin received NaCl later and *vice versa* for the last 30 min of the study. In order to study the effect of oxytocin on pethidine-induced delayed gastric emptying, each subject participated in two further studies 1 week apart. On each study, thirty min after beginning of the study a single i.v. bolus of pethidine (Petidin®, SAD, Denmark) 1 mg kg^{-1} was given. Thirty minutes after injection of pethidine, under double-blind conditions, either continuous i.v. infusion of oxytocin 0.33 units min^{-1} or placebo (0.9% w/v NaCl) was started for the last 30 min.

Statistics

The differences in the percent of meal emptied from the stomach were evaluated using the Wilcoxon's matched-pairs signed-ranks test. The Wilcoxon's rank-sum test was used for testing differences between sexes. Correlation coefficients and linear regression slopes of the median emptying values were compared by Student's t-test. In all comparisons differences were taken as significant if $P < 0.05$.

Table 1 Median percentage and range (in brackets) of radioactivity emptied from the stomach following administration of oxytocin (E_{ox}) and placebo (E_{pl}) with treatment cross-over points relocated to $t = 0$ with radioactivity remaining in the stomach = 100%. P_{values} for comparison between the groups were assessed by Wilcoxon's test.

Time (min)	E_{ox} n = 10	E_{pl} n = 10	P *value*
5	1 (0–8)	2 (0–5)	1.0
10	2 (0–18)	2 (0–14)	0.7
15	13 (2–59)	5 (1–24)	0.1
20	21 (10–65)	10 (4–40)	0.04
25	27 (17–69)	10 (6–48)	0.002
30	34 (24–74)	12 (8–55)	0.002

Results

For determination of the effect of oxytocin on normal gastric emptying four subjects were allocated to receive oxytocin from 30 to 60 min (sequence 1), and six to receive oxytocin from 60 to 90 min of the study (sequence 2).

No volunteers developed complaints following administration of oxytocin and thus all were unaware of the treatment sequence they had received. Following administration of pethidine all volunteers developed 'typical opioid' behavioural effects such as drowsiness and diminished response to external stimuli. Median gastric emptying curves for both sequences are shown in Figure 1.

For the majority of subjects the emptying of radioactivity from stomach during both sequences was found to be a linear process. The slope for the median gastric emptying curve during oxytocin treatment was –1.23 ($r = -0.99$) in sequence 1 and –1.06 ($r = -0.98$) in sequence 2. The corresponding slopes for placebo were –0.41 ($r = -0.98$) and –0.23 ($r = -0.99$), respectively. The differences in the corresponding curve slopes during oxytocin and placebo treatment were not significant (Wilcoxon's, $P = 0.30$ and 0.44, respectively).

The median difference in the radioactivity remaining in the stomach between the two sequences after 90 min was 2.5% (95% confidence limits from –37 to 11%).

Consequently, the treatment order and thus the time of administration of oxytocin did not influence the results of this study. The percent of radioactivity emptied from the stomach following administration of oxytocin and placebo, when each treatment phase is relocated to begin at $t = 0$ with radioactivity remaining in the stomach = 100%, is presented in Table 1.

In both treatment sequences the effect of oxytocin on gastric emptying appeared to be

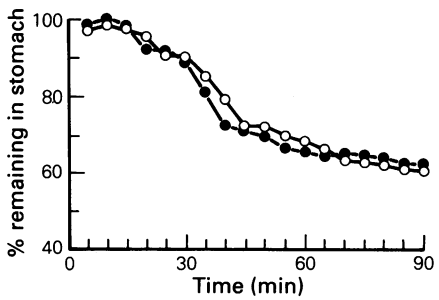

Figure 2 Median percentage of radioactivity emptied from stomach under basal condition (0–30 min), following injection of pethidine (30–60 min) and oxytocin (○---○) *vs* placebo (●---●) (60–90 min).

delayed in relation to the onset of the infusion. The difference in the percentage of radioactivity emptied from the stomach between oxytocin and placebo treatments reached significance at 20 min (Table 1). Switching off the infusion of oxytocin (sequence 1) resulted in an immediate decrease in gastric emptying in all subjects.

Two subjects showed no evidence of a lag period during control period, defined as the time between end of ingestion and appearance of first activity in duodenum. The remaining 8 subjects showed lag periods ranging from 5 to 30 min (median, 17.5 min). In subjects receiving pethidine in order to delay gastric emptying, infusion of oxytocin did not change the emptying pattern (Figure 2). Pethidine accelerated median gastric emptying in all subjects during the first 10 min after administration (Wilcoxon's, $P < 0.05$). In the remaining period gastric emptying appeared delayed with almost no emptying of the radionuclide. The median percent of the radioactivity remaining in the stomach after 90 min in the oxytocin group was 60.5% as compared to a median of 62.5% in the placebo group (Wilcoxon's, $P = 0.5$). The Wilcoxon's rank-sum test showed no difference in gastric emptying rate between sexes.

Discussion

The present study has established that continuous i.v. infusion of oxytocin increases the basal gastric emptying rate of a semisolid meal administered to healthy, fasting subjects. Furthermore, it is suggested that the effect of oxytocin is independent of the volume of semisolid present in the stomach. However, administration of oxytocin does not influence the delayed gastric emptying induced by pethidine.

To compare gastric emptying under different conditions we used the percentages of the total initial counts remaining in the stomach against time. An advantage of this parameter compared with other measures is that its value can be computed directly from the observed data without extrapolation of the tail end points (Dugas *et al.*, 1982).

Liquids and solids empty from stomach at different rates and patterns. The present study has confirmed that the linear emptying pattern of semisolids is similar to that of solids (Jacobs *et al.*, 1982; Petring *et al.*, 1986). Patients with symptoms of gastric retention may demonstrate normal emptying of liquids while actually retaining the solids abnormally (Mannell & Esser, 1984). Moreover, symptoms of dumping seem to occur mostly when semisolids are consumed (Jacobs *et al.*, 1982).

Due to the initial lag period observed in our earlier study (Petring *et al.*, 1986), the subjects did not receive any treatment for the first 30 min of the study. In the present study the emptying pattern of semisolid has confirmed the existence of a variable lag phase. Using anterior detection alone, the maximum over-estimation error of the lag period and emptying time should be only 9% (Petring *et al.*, 1986), when corrected by the geometric mean method (Moore *et al.*, 1985). Such an error is not large enough to invalidate results obtained with the same method in the same subjects. Using our technique it is not possible to measure gastric emptying during the first few minutes of ingestion, to differentiate between emptying of the liquid and solid component of the meal, or to study separately emptying of the antrum and the body of the stomach. However, we were able to observe that during the lag phase the semisolid meal was distributed from the fundus to the whole stomach. As the lag period is dependent on intragastric redistribution, and antral motility (Collins *et al.*, 1988) the intersubject variation in lag period could be explained by different mastication habits. However, the mechanism of solid/liquid partition in stomach is still not clear (Houghton *et al.*, 1988).

Our study supports the findings of Hashmonai and others (1979), who treated persistent and complete post-vagotomy gastric atony with an intravenous infusion of 5–20 units of oxytocin every 4 h and noticed some contractions of the stomach twenty to thirty minutes after onset of the treatment during a fluoroscopic barium examination. On the other hand, Nimmo and others (1975), found no relation between absorption of paracetamol given orally and the administration of oxytocin in women during labour. Absorption was, as expected, markedly delayed following pethidine, diamorphine, or

pentazocine. However, in that study no time of administration or dose of oxytocin was specified (Nimmo *et al.*, 1975).

Oxytocin stimulates both the frequency and the force of contractile activity in uterine smooth muscle and mammary gland. The sensitivity of the uterus to oxytocin increases with continuous treatment, which is explained by an increase in the number of receptors for oxytocin (Fuchs *et al.*, 1982). However, the oxytocin receptors in the stomach are still unidentified. Even the relatively large dose of oxytocin used in the present study, as compared with the doses causing contractions of the uterus or the dose used in the study of Hashmonai *et al.* (1979), did not change opioid-induced delayed gastric emptying. Our study does not allow us to conclude that this lack of effect is caused by an insufficient oxytocin dosage or, by the presence of low numbers of oxytocin receptors in the stomach.

Contrary to other findings, administration of pethidine i.v. in our study accelerated basal gastric emptying during the first 10 min after administration. The discrepancies might be attributed to the methods employed, higher (150 mg) pethidine dose (Nimmo *et al.*, 1975; Slattery *et al.*, 1985) or use of the intramuscular route of administration (Slattery *et al.*, 1985).

Radiographic measurement indicates that morphine causes an initial increase in the amplitude of gastric contractions, followed by a prolonged decrease in gastric propulsive activity (Silbiger & Donner, 1968). Studies in dogs revealed that both exogenous and endogenous opiates were able to increase the amplitude, but decrease the frequency of gastric contraction (Konturek, 1980). These observations might explain our observation of an initial spurt after injection of pethidine.

Evaluation of the precise effect of pethidine on gastric emptying will require the construction of a dose-response curve.

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