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Comparison of the effect of cisapride and metoclopramide on morphine-induced delay in gastric emptying

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1 The effects of metoclopramide or cisapride on morphine-induced delay in gastric emptying in patients before surgery were compared.
2 Forty patients were allocated randomly to receive one of four premedications i.m.: placebo only, morphine 10 mg alone, morphine 10 mg with metoclopramide 10 mg and morphine 10 mg with cisapride 10 mg. Gastric emptying after each premedication was assessed indirectly from the rate of absorption of oral paracetamol.
3 Cisapride 10 mg reversed the delay in gastric emptying due to morphine. Its effects were significantly greater than those of metoclopramide 10 mg.

Keywords cisapride metoclopramide gastric emptying

Introduction

Inhalation of gastric contents is an important cause of anaesthetic mortality associated with surgery and obstetrics (Lunn & Mushin, 1982; D.H.S.S., 1986). Opioids delay gastric emptying (Todd & Nimmo, 1983), probably making inhalation of gastric contents more likely. A drug which reversed this effect of opioids without reducing analgesia, might be of considerable value in surgical patients.

Cisapride is a gastrointestinal prokinetic agent which has been shown to reverse the delay in gastric emptying due to morphine in patients before surgery (Rowbotham & Nimmo, 1987). Metoclopramide is also a gastric prokinetic drug, but its efficacy in reversing the delay in gastric emptying due to opioids may be less (Nimmo *et al.*, 1975a). No direct comparison has been made of the effect of cisapride and metoclopramide, when given with a morphine premedication, on the rate of gastric emptying shortly after the premedication.

In this study, we have compared the effects of cisapride and metoclopramide on morphine-induced delay in gastric emptying in patients before surgery.

Methods

Forty patients, aged 18–64 years, undergoing orthopaedic or minor general surgery were studied. Local ethics advisory committee approval and informed written patient consent were obtained. The patients had no clinical evidence of gastrointestinal disease, were not taking concurrent medication, and there was no possibility of pregnancy.

Patients were allocated randomly to receive, in a double-blind fashion, one of four premedications i.m. Group 1 received placebo only; group 2 received morphine 10 mg plus placebo; group 3 received morphine 10 mg plus metoclopramide 10 mg; and group 4 received morphine 10 mg plus cisapride 10 mg. The volume of the metoclopramide and the cisapride preparations was 2 ml and the placebo was normal saline 2 ml. The premedication was given into the thigh using a 23 gauge needle, 2 h before surgery.

Gastric emptying after premedication was measured using the rate of absorption of orally administered paracetamol (Nimmo *et al.*, 1975b). Paracetamol 1.5 g (3 Panadol tablets) was taken with water 50 ml, 20 min after the premedication.

Blood was obtained from an indwelling venous cannula before the premedication was given, and then at 15 min intervals for 90 min after the paracetamol administration. Plasma was separated immediately and stored at −20°C. Plasma paracetamol concentrations were measured subsequently by high performance liquid chromatography (Howie *et al.*, 1977). Plasma morphine concentrations in the venous blood samples taken 20 min after the premedication were also measured by high performance liquid chromatography (Aitkenhead *et al.*, 1984).

The rate of paracetamol absorption was estimated from the area under the plasma paracetamol concentration-time curve (AUC) at 60, 75 and 90 min (calculated by a trapezoid method), plasma paracetamol concentrations at each time interval, peak concentrations, and time to peak concentrations. Statistical analysis was by analysis of variance, Student's *t*-test, or Kruskal-Wallis test where appropriate.

Any adverse events occurring during the study were recorded. Groups were tested with respect to age, weight and sex using analysis of variance and Chi-square test.

Results

There were no significant differences between the groups with respect to age, sex and weight (Table 1). No serious adverse events occurred in any of the groups. Four minor complaints were recorded in the morphine-placebo group (nausea, lightheadedness, pruritus and nasal obstruction).

Paracetamol was detected in the base-line samples in three patients. Data from these patients were not included in the analysis. The mean plasma paracetamol concentrations in the four groups are shown in Figure 1 and Table 2.

There were significant differences between the groups at 45, 60, 75 and 90 min. Paracetamol concentrations were significantly greater in the placebo only group ($P < 0.05$; $P < 0.01$ at 45 min) and the morphine-cisapride group ($P < 0.001$; $P < 0.01$ at 60 min) when compared with the morphine-placebo group. Paracetamol concentrations were also greater in the morphine-cisapride group when compared with the morphine-metoclopramide group ($P < 0.05$). Paracetamol concentrations were significantly greater in the morphine-metoclopramide group compared with the morphine-placebo group at 75 and 90 min ($P < 0.05$).

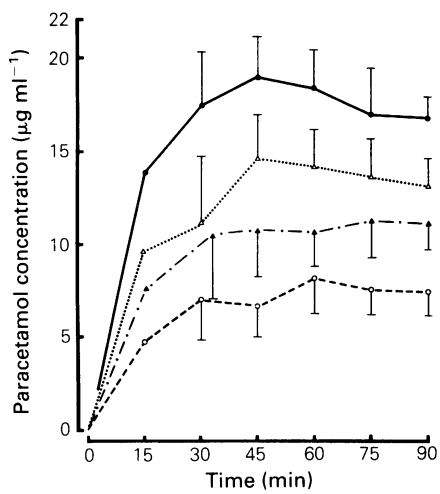

Figure 1 Mean (± s.e. mean) plasma paracetamol concentrations (μg ml^{-1}).
△···△ placebo; ○---○ morphine/placebo;
▲-·-·▲morphine/metoclopramide; ●——●morphine/cisapride.

Table 1 Demographic data (mean ± s.d.). No significant differences

Group	*Age (years)*	*Weight (kg)*	*Sex*
Placebo ($n = 9$)	39.9 ± 12.5	72.5 ± 7.6	7 male 2 female
Morphine/ Placebo ($n = 9$)	49.6 ± 11.6	67.9 ± 13.6	4 male 5 female
Morphine/ Metoclopramide ($n = 10$)	40.5 ± 12.0	74.3 ± 14.0	6 male 4 female
Morphine/ cisapride ($n = 9$)	42.6 ± 14.9	69.6 ± 15.3	5 male 4 female

Table 2 Plasma paracetamol concentrations ($\mu g\ ml^{-1}$) (mean ± s.e. mean)

Group	*15 min*	*30 min*	*45 min*	*60 min*	*75 min*	*90 min*
Placebo ($n = 9$)	9.6 ± 5.5	11.1 ± 3.0	14.7 ± 2.1*	14.2 ± 2.0*	13.7 ± 1.8*	13.2 ± 1.6*
Morphine/ placebo ($n = 9$)	4.7 ± 2.6	7.0 ± 2.2	6.7 ± 1.6	8.2 ± 1.9	7.5 ± 1.4	7.4 ± 1.4
Morphine/ metoclopramide ($n = 10$)	7.5 ± 4.0	10.5 ± 3.2	10.8 ± 2.6	10.7 ± 2.1	11.3 ± 2.0**	11.2 ± 1.6**
Morphine/ cisapride ($n = 9$)	13.9 ± 4.3	17.5 ± 2.8	19.0 ± 2.0†	18.4 ± 2.0†	17.0 ± 1.4†	16.8 ± 1.0†

* significantly greater than morphine/placebo ($P < 0.05$; $P < 0.01$ at 45 min).
** significantly greater than morphine/placebo ($P < 0.05$). † significantly greater than morphine/placebo ($P < 0.001$; $P < 0.01$ at 60 min) and significantly greater than morphine/metoclopramide ($P < 0.05$).

Table 3 Areas under the plasma paracetamol-concentration time curve (AUC) ($\mu g\ min\ ml^{-1}$) at 60, 75 and 90 min (mean ± s.e. mean)

	AUC ($\mu g\ ml^{-1}\ min$)		
	60 min	*75 min*	*90 min*
Placebo ($n = 9$)	638 ± 152	847 ± 172	1049 ± 190*
Morphine/ placebo ($n = 9$)	338 ± 90	455 ± 108	567 ± 125
Morphine/ metoclopramide ($n = 10$)	513 ± 154	678 ± 316**	848 ± 203**
Morphine/ cisapride ($n = 9$)	894 ± 119†	1159 ± 129†	1412 ± 131†

* significantly greater than morphine/placebo ($P < 0.05$).
† significantly greater than morphine/placebo ($P < 0.001$; $P < 0.01$ at 60 min).
** significantly less than morphine/cisapride ($P < 0.05$).

The AUCs at 60, 75 and 90 min are shown in Table 3. The AUC at 90 min was significantly greater in the placebo group when compared with the morphine-placebo group ($P < 0.05$). The AUCs in the morphine-cisapride group at 60, 75 and 90 min were significantly greater than the morphine-placebo group ($P < 0.001$; $P < 0.01$ at 60 min), and significantly greater than the morphine-metoclopramide group at 75 and 90 min ($P < 0.05$). There were no significant differences between the morphine-metoclopramide and the morphine-placebo group.

Mean peak paracetamol concentrations and times at which these were achieved in each group are shown in Table 4. Peak concentrations were significantly greater in the placebo group compared with the morphine-placebo group ($P < 0.05$). Concentrations were also significantly greater in the morphine-cisapride group compared with the morphine-placebo (P

< 0.01) and the morphine-metoclopramide group ($P < 0.05$). There was no significant difference between the morphine-metoclopramide and the morphine-placebo groups.

There were no significant differences between the groups with respect to time of peak paracetamol concentrations.

Plasma morphine concentrations 20 min after the premedication are shown in Table 5. There were no significant differences.

Discussion

Morphine delayed paracetamol absorption, presumably by reducing the rate of gastric emptying. We have confirmed that cisapride 10 mg i.m. reversed this effect (Rowbotham & Nimmo, 1987). Metoclopramide had a much lesser effect and paracetamol absorption was significantly greater in the cisapride group when compared with the metoclopramide group. Plasma morphine concentrations 20 min after the premedication show that these differences were not likely to be due to variations in absorption of morphine.

Morphine premedication is often given 1–2 h before induction of anaesthesia. The effect of prokinetic drugs, given with the premedication, on the rate of gastric emptying shortly after premedication is of clinical importance. It may be that metoclopramide and cisapride were absorbed at different rates in this study, but our

Table 4 Peak plasma paracetamol concentrations ($\mu g\ ml^{-1}$) and time to peak concentrations (min) (mean ± s.e. mean)

	Peak concentration ($\mu g\ ml^{-1}$)	*Time to peak (min)*
Placebo ($n = 9$)	21.6 ± 4.5*	52 ± 10
Morphine/ placebo ($n = 9$)	11.4 ± 2.5	58 ± 10
Morphine/ metoclopramide ($n = 10$)	15.2 ± 3.2	63 ± 10
Morphine/ cisapride ($n = 9$)	25.2 ± 2.6†	48 ± 10

* $P \pm 0.05$ compared with morphine/placebo,
† $P < 0.01$ compared with morphine/placebo, $P < 0.05$ compared with morphine/metoclopramide.

Table 5 Plasma morphine concentrations ($ng\ ml^{-1}$) 20 min after administration (mean ± s.e. mean). No significant difference

	Morphine concentration ($ng\ ml^{-1}$)
Morphine/ placebo ($n = 9$)	46.9 ± 6.1
Morphine/ metoclopramide ($n = 10$)	40.9 ± 5.1
Morphine/ cisapride ($n = 9$)	40.7 ± 7.5

aim was to investigate the pharmacodynamic action of these drugs when given with the premedication.

The paracetamol absorption method used in this study assumes that morphine, cisapride and metoclopramide do not differentially alter the disposition of paracetamol. We are not aware of any data that indicates this.

No serious adverse events occurred during this study. Four patients in the morphine-placebo group had minor complaints (nausea, lightheadedness, pruritus and nasal obstruction). There were insufficient numbers in this study to demonstrate that cisapride reduces significantly the incidence of morphine side-effects, but this will be of interest in future studies.

Metoclopramide has been shown to enhance gastric emptying preoperatively (Adelhoj *et al.*, 1985; Olsson *et al.*, 1982). However, in these studies, either no opioid premedications were used or metoclopramide was given considerably before, and gastric contents were measured shortly after, the administration of the opioid. Therefore, the effect of the opioid on gastric emptying would be minor. An increase in the rate of gastric emptying due to metoclopramide has been shown in patients in labour, but the effects on opioid induced delay was not investigated (Howard & Sharp, 1973). Metoclopramide 10 mg did not reverse the delay in gastric emptying due to pethidine 150 mg when given i.m. at the same time as pethidine to women during labour (Nimmo *et al.*, 1975a). Murphy and others (1984) in a study of the effects of metoclopramide on gastric emptying during labour after pethidine, suggested that metoclopramide improved the delay in gastric emptying. However, in their study, rates of gastric emptying were assumed following only one plasma paracetamol measurement in each patient, and the dose of pethidine was small (50 mg). Furthermore, the mean time from administration of the pethidine to assessment of gastric emptying was greater in the metoclopramide group than the placebo group (100 and 60 min respectively).

The pharmacological effects of cisapride are of considerable interest to the anaesthetist. Increasing the rate of gastric emptying preoperatively is likely to reduce the risk of regurgitation and inhalation of gastric contents. Reversing the effect of opioids on gastric emptying may be particularly useful in anaesthesia as many patients receive opioids preoperatively.

We have demonstrated that cisapride reversed the effects of morphine on gastric emptying. It probably acts by stimulating the release of acetylcholine at the myenteric plexus and, in contrast to metoclopramide, has little effect on dopaminergic receptors (Reyntjens *et al.*, 1984). Extrapyramidal side-effects, a common problem with metoclopramide (Harrington *et al.*, 1983), have not been reported with cisapride and this is likely to be another advantage.

In conclusion, cisapride 10 mg i.m., given with the morphine premedication, reversed the delay in gastric emptying due to morphine in patients before surgery. Administered in this way, its effects were significantly greater than metoclopramide 10 mg. Cisapride may reduce the incidence of inhalation of gastric contents during anaesthesia.

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