A single dose pharmacokinetic study of Gastrobid Continus and Maxolon in the perioperative period

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- 1 A single dose pharmacokinetic comparison of Gastrobid Continus and Maxolon was carried out perioperatively in two groups of 12 gynaecological patients; each group comprised six patients for major surgery and six patients for minor surgery.
- 2 The areas under the plasma drug concentration-time curves were similar after both preparations.
- 3 In the minor surgery group after Gastrobid Continus the plasma drug concentration-time curve was wider at half $C_{\max}$ ($P < 0.01$), $C_{\max}$ was reduced ($P < 0.05$) and delayed (median (range) 4 (3-6) vs 2.5 (2-4) h) compared with Maxolon, and the log of the metoclopramide concentration did not have a linear relationship with time from 2-9 h.
- 4 A flattening of the plasma drug concentration-time curve was the only difference between the two preparations in the major surgery groups.
- 5 The plasma drug concentration-time curve was wider ($P < 0.05$) at half $C_{\max}$ in the minor compared with the major surgery groups receiving Gastrobid Continus.
- 6 Pharmacokinetic parameters were similar for Maxolon in both surgical groups.
- 7 Sustained release pharmacokinetic characteristics were most pronounced in the minor surgery group which did not receive opiate medication but in which there were more moderately anxious patients prior to induction and in whom anxiety may have delayed gastric emptying.

Keywords Gastrobid Continus Maxolon preoperative administration metoclopramide pharmacokinetics

Introduction

Gastrobid Continus is a new sustained release formulation of metoclopramide, which could be expected to produce a delayed and lowered peak plasma drug concentration with a later extension of the plasma drug concentration-time curve, possibly accompanied by fewer side effects and a prolonged therapeutic action compared with standard oral metoclopramide (Maxolon). The kinetics of drugs given orally can be affected by a number of factors in the perioperative period which are not present in volunteer studies, such

as anxiety and concurrent opiate medication. These variables have been shown to delay gastric emptying thereby altering the rate of intestinal drug absorption (Simpson & Stakes, 1987; Nimmo *et al.*, 1975). Two aspects of anxiety can be measured using questionnaires; the State anxiety score increases with stressful situations and is a measure of a temporary emotional state, the Trait anxiety score is a stable score related to anxiety proneness. A State anxiety score greater than the Trait anxiety score has been associated

with delayed gastric emptying preoperatively (Simpson & Stakes, 1987). Efficacy studies of antiemetic medication are often conducted on gynaecological patients since these patients have a high incidence of postoperative emetic sequelae (Palazzo & Strunin, 1984). Prior to conducting a therapeutic trial, a comparison of the pharmacokinetics of Gastrobid Continus with the original oral formulation of metoclopramide (Maxolon) in the perioperative period was carried out. The purpose of the study was to ascertain whether the new formulation has the characteristics of a sustained release preparation when used in surgical patients.

Methods

Twenty-four fit women, weighing 50 to 70 kg and awaiting gynaecological surgery, gave consent to take part in the study, which was approved by the Hospital Ethics Committee. Pregnant or lactating women, patients with Parkinson's disease or with a history of oculo-gyric crisis were excluded. Patients completed a Trait anxiety questionnaire on the day before surgery and a State anxiety questionnaire (Spielberger, 1975) just before induction of anaesthesia. Each patient received 30 mg of metoclopramide as either Gastrobid Continus or Maxolon tablets in a randomised double-blind fashion. Tablets were taken orally with 30 ml of water, 2 h preoperatively. Each group of 12 subjects comprised six patients for major surgery (MAJ) and six patients for minor surgery (MIN). The anaesthetic technique was standardised; patients having major surgery received parenteral opiates (papa-veretum) 1 h preoperatively, during and post-operatively, patients having minor surgery were unpremedicated and did not receive any opiates.

An indwelling cannula in an antecubital vein was used to collect blood samples before administration of drug, pre-induction (2 h after drug administration) and subsequently at 3, 4, 6, 9, 12, 18 and 24 h. These samples were centrifuged and the plasma was removed and stored at -20°C prior to analysis. Metoclopramide concentrations were measured by h.p.l.c. (analysed by the Bioanalytical Department, Napp Research Centre). The lower limit of detection was 2.5 ng ml^{-1} and at which concentration the coefficient of variation was 13.4%.

Statistical comparisons were made using Student's *t*-test (unpaired), analysis of variance and linear regression for parametric data. Mann Whitney U and Fisher's Exact test were used for nonparametric data.

Results

The mean age and weight of the patients in the groups were similar (Table 1). Half of the patients receiving Gastrobid Continus in the major and in the minor surgery groups had State anxiety scores greater than Trait anxiety scores (Table 2). A similar proportion of patients receiving Maxolon were more anxious than usual prior to induction. The Anxiety State scores (with a minimum score of 20 and a maximum score of 80) were subdivided such that scores of 20–39 were graded as mild, scores of 40–59 were graded as moderate and scores of 60–80 were graded as severe. The same proportion of patients were moderately anxious in the two surgical groups receiving Maxolon. However, more patients receiving Gastrobid Continus were moderately anxious in the minor surgery group than in the major surgery group (Table 3).

Table 1 Anthropometric details (mean $\pm$ s.d.) of patients receiving Gastrobid Continus or Maxolon and having major (MAJ) or minor (MIN) surgery

	Gastrobid		Maxolon	
	MAJ n = 6	MIN n = 6	MAJ n = 6	MIN n = 6
Age (years)	47 $\pm$ 14	36 $\pm$ 15	38 $\pm$ 12	29 $\pm$ 8
Weight (kg)	61 $\pm$ 4	57 $\pm$ 4	57 $\pm$ 6	57 $\pm$ 7

Table 2 Number of patients with Anxiety State scores greater than Anxiety Trait scores

	Gastrobid	Maxolon
Major surgery (n = 6)	3	2
Minor surgery (n = 6)	3	1

Table 3 Number of patients receiving Gastrobid Continus or Maxolon having major (MAJ) or minor (MIN) surgery with mild or moderate anxiety

	Gastrobid		Maxolon	
	MAJ	MIN	MAJ	MIN
Mild anxiety	5	1	4	4
Moderate anxiety	1	5*	2	2

* $P < 0.05$ Significantly more patients with moderate anxiety than Gastrobid subgroup having major surgery (Fisher's Exact Test).

Areas under the plasma drug concentration-time curves 0–24 h (AUC) were similar after both preparations in all surgical groups (Table

Table 4 Parameters describing the pharmacokinetics of metoclopramide (mean $\pm$ s.d.) after Gastrobid Continus or Maxolon in patients having major (MAJ) and minor (MIN) surgery

	<i>Gastrobid</i>		<i>Maxolon</i>	
	<i>MAJ</i> n = 6	<i>MIN</i> n = 6	<i>MAJ</i> n = 6	<i>MIN</i> n = 6
AUC (ng ml ⁻¹ h)	463 ± 115	547 ± 115	472 ± 176	461 ± 83
C _{max} (ng ml ⁻¹)	53 ± 13	47 ± 10	62 ± 30	64 ± 13*
W (h)	7.5 ± 3*	12 ± 3†‡	4 ± 2	5.5 ± 2

W = Width of the plasma drug concentration-time curve at half $C_{\max}$; † $P < 0.01$, * $P < 0.05$ Significantly greater than equivalent group having alternative medication. ‡ $P < 0.05$ Significantly greater than group having Gastrobid Continus and major surgery. (Student's *t*-test).

Figure 1 Mean ($\pm$ s.d.) plasma metoclopramide concentration after Gastrobid Continus ($\blacktriangle$) or Maxolon ($\bullet$) in patients having minor surgery ($n = 6$). ** $P < 0.01$, * $P < 0.05$ indicates significant difference between groups.

Figure 2 Plasma metoclopramide concentration (log scale) plotted against time for patients receiving Gastrobid Continus and having minor surgery ($\times 3$ = incidence of identical values).

4). The width of the plasma drug concentration-time curve at half $C_{\max}$ was significantly greater after Gastrobid Continus compared with Maxolon in patients having major surgery (mean $\pm$ s.d. 7.5 ± 3.0 vs 4.0 ± 2.0 h). However, this was the only difference between the two preparations in these subgroups.

Considering the six patients per group who had minor surgery separately, there were more differences between the preparations. $C_{\max}$ was greater after Maxolon (mean $\pm$ s.d. 64 ± 13 vs 47 ± 10 ng ml $^{-1}$ $P < 0.01$) and occurred significantly earlier (median 2.5 range 2–4 h). $C_{\max}$ occurred at a median of 4 h with a range of 3–6 h for Gastrobid ($P < 0.05$ Mann Whitney U). Figure 1 demonstrates that the mean plasma drug concentrations were greater at 2 and 3 h after Maxolon compared with Gastrobid (mean $\pm$ s.d. 63 ± 14.5 vs 36 ± 7.5 ng ml $^{-1}$ $P < 0.01$ and 63 ± 13.5 vs 43.5 ± 10.0 ng ml $^{-1}$ $P < 0.05$) in the minor surgery subgroup. The log of the plasma concentration of metoclopramide was not related

to time from 2–9 h ($r = -0.24$, $P > 0.1$) after Gastrobid in opiate-free patients (Figure 2). The log of the plasma metoclopramide concentration decreased significantly with time from 2–9 h after Gastrobid in the patients receiving opiates ($r = -0.63$, $P < 0.01$) and after Maxolon in the minor (Figure 3, $r = -0.81$, $P < 0.01$) and in the major ($r = -0.48$, $P < 0.01$) surgery subgroups. All groups and subgroups demonstrated a significant correlation of drug concentration with time from 2 to 12 or 24 h ($r = -0.53$ – -0.93 , $P < 0.01$).

Discussion

Metoclopramide has been used parenterally in the perioperative period when some authors have reported that it reduces the incidence of emetic sequelae (Handley, 1967; Dundee & Clarke, 1973; Madej & Simpson, 1986a), while others have found it to be ineffective (Ellis &

Figure 3 Plasma metoclopramide concentration (log scale) vs time in patients receiving Maxolon and having minor surgery—regression line and 95% confidence interval ($\times 2$ = incidence of identical values).

Spence, 1970; Shah & Wilson, 1972; Kortilla *et al.*, 1979; Madej & Simpson, 1986b). Some of the discrepancy may be accounted for by the short duration of action of metoclopramide (Assaf *et al.*, 1974). Metoclopramide is one of the least toxic antiemetics and its commonest side effect is drowsiness (Robinson, 1973). Extrapyramidal effects have also been reported. Dystonia and dyskinesia are more common in young women (Bateman *et al.*, 1985) and appear to be related to patient factors rather than plasma drug concentration (Bateman *et al.*, 1983). Parkinsonian-like symptoms are commoner in the elderly and can be related to plasma drug concentration (Bateman *et al.*, 1979).

A sustained release preparation might offer advantages of prolonged therapeutic action and a reduction in dose related side effects. Gastrobid Continus demonstrated lower mean plasma drug concentrations at 2 and 3 h after administration, reduced and delayed C_{max} and a wider plasma drug concentration-time curve at half C_{max} compared with Maxolon in the minor surgery groups. The log of the plasma drug concentration was stable from 2–9 h after administration suggesting that this preparation would be suitable for 8 or

12 hourly administration. However the delay in C_{max} may result in delayed or complete absence of clinical effect since a rapid rise in CNS concentration may be important for therapeutic effect (Bateman *et al.*, 1978, 1979).

The group receiving Gastrobid Continus and having major surgery differed from the equivalent group receiving Maxolon only in having a wider plasma drug concentration-time curve at half C_{max} . This difference occurred despite the plasma drug concentration-time curve being significantly narrower in the major surgery compared with the minor surgery groups receiving Gastrobid Continus. A wider plasma drug concentration-time curve is only clinically significant if the therapeutic effect can be related to the plasma drug concentration. Most of the studies relating the plasma concentration of metoclopramide to therapeutic effect have been conducted in patients receiving chemotherapy. These drugs have a profound emetic effect and only very high plasma concentrations of metoclopramide (100–850 ng ml⁻¹) have been reported to be effective (Bateman *et al.*, 1979; McGovern *et al.*, 1983; Taylor & Bateman, 1983; Meyer *et al.*, 1984). Much lower plasma drug concentrations 20 ng ml⁻¹ increase gastric emptying after intravenous administration (Bateman *et al.*, 1978).

It was not clear why the pharmacokinetic parameters of the two surgical groups receiving Gastrobid Continus differed. The major surgery group received opiates while the minor surgery group did not. Opiates could alter absorption by delaying gastric emptying. However opiates did not affect the pharmacokinetics of Maxolon. The minor surgery group had more moderately anxious patients than the major surgery group receiving Gastrobid Continus. However, fifty percent of both surgical groups had patients who were more anxious than usual and this is the characteristic which has been associated with delayed gastric emptying (Simpson & Stakes, 1987).

A therapeutic trial is required to demonstrate whether the slow release preparation of metoclopramide has any clinical advantages.

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