Br. J. clin. Pharmac. (1984), **18**, 679–684

Pharmacokinetics and efficacy of high-dose metoclopramide given by continuous infusion for the control of cytotoxic drug-induced vomiting

WENDY B. TAYLOR[1], S. J. PROCTOR[2] & D. N. BATEMAN[1]
[1]Wolfson Unit of Clinical Pharmacology, University of Newcastle upon Tyne, and
[2]Department of Haematology, Royal Victoria Infirmary, Newcastle upon Tyne

1 To avoid the accumulation of metoclopramide that occurs with repeated i.v. bolus doses, a new regimen for the administration of high-dose metoclopramide consisting of a loading dose followed by a continuous infusion was investigated to determine the pharmacokinetics and antiemetic efficacy of the drug when given in this manner.
2 Nine patients with non-Hodgkin's lymphoma entered the study, of whom six completed the study, receiving each of three dosage schedules of metoclopramide during three consecutive courses of chemotherapy. In these six patients plasma metoclopramide half-life was 5.9 ± 0.4 h (mean ± s.e. mean) and plasma clearance was 25.4 ± 4.8 l/h (mean ± s.e mean). Neither half-life nor clearance were dose-related. Steady-state was achieved during 9/18 infusions. Nausea and vomiting were completely controlled in 13/24 treatment courses (57%) and adverse effects were minimal.
3 We conclude that steady-state plasma concentrations of metoclopramide can be achieved using a weight-related infusion regimen, though the optimum plasma concentration remains to be determined.

Keywords high-dose metoclopramide cytotoxic drugs emesis

Introduction

Nausea and vomiting are common adverse effects of cytotoxic drug therapy, and in many patients may be difficult to control. In conventional doses metoclopramide is no more effective than other anti-emetic drugs, but Gralla *et al.* (1981b), have described a regimen of high doses of metoclopramide (10 mg/kg body weight in five divided doses over 9 h) which was very effective in controlling cis-platinum induced vomiting. The efficacy of high-dose metoclopramide has since been confirmed by other workers (Homesley *et al.*, 1982; Strum *et al.*, 1982).

The regimen described by Gralla is, however, cumbersome and time-consuming to administer and we have shown that metoclopramide accumulates when given at such frequent intervals (Taylor & Bateman, 1983). Since some adverse central nervous system effects are plasma drug-concentration dependent (Bateman, 1982), this accumulation could lead to increased toxicity.

If the anti-emetic effect of metoclopramide is related to the plasma concentration it should be possible to achieve similar therapeutic benefit using a simplified treatment regimen. For drugs eliminated by first-order kinetics, steady-state plasma concentrations can be achieved by giving an appropriate loading dose followed by a constant intravenous (i.v.) infusion, calculated from known pharmacokinetic parameters (Clark & Smith, 1981). Previous studies suggest, however, that metoclopramide has dose-dependent kinetics (Bateman *et al.*, 1980; Graffner *et al.*, 1979) and a suitable infusion rate is therefore more difficult to calculate.

We have investigated the use of a loading

dose and constant infusion regimen of high-dose metoclopramide to determine firstly the pharmacokinetics of metoclopramide when given in such large doses, secondly whether steady-state plasma concentrations can be achieved and thirdly whether nausea and vomiting can be adequately controlled using this type of regimen.

Methods

Patients

Nine patients (age range 18–61 years) agreed to take part in the study, which had been approved by the Newcastle Area Health Authority Ethics Committee. All patients had histologically confirmed non-Hodgkins lymphoma and had a performance status of at least 70% on the Karnofsky scale. One patient had been given her first course of chemotherapy prior to the start of the study, but none of the other patients had previously received cytotoxic drugs likely to cause vomiting. Urea and electrolytes and routine liver function test were within normal limits at the start of the study and were checked before and after each course of chemotherapy.

Study design

Patients were admitted to hospital overnight at the commencement of three consecutive courses of chemotherapy given at 3-weekly intervals. Each patient received cyclophosphamide 750 mg/m^2, adriamycin 50 mg/m^2, vincristine 1.4 mg/m^2 and bleomycin 10 mg/m^2 as single i.v. bolus injections followed by prednisolone 40 mg orally for 5 days. With each course of chemotherapy patients received, in random order, one of three dosage schedules of metoclopramide (Table 1). The patients received a loading dose of 1, 2 or 3 mg/kg i.v. over 15 min immediately before chemotherapy. The cytotoxic drugs were given over the next 10 min, followed by a continuous infusion of metoclopramide for 8 h. The infusion rates were chosen (following preliminary studies in other patients) to give approximately a three-fold range of steady-state plasma concentration of metoclopramide during the infusion, but were of necessity somewhat empirical. The total dose administered varied between 120 and 510 mg (2.3–7.6 mg/kg body weight). Intake of food and drink during treatment was not restricted. Blood samples for estimation of plasma metoclopramide were taken before treatment, at 0.25, 1, 2, 5 and 8 h after starting the infusion and at intervals for 16 to 24 h after stopping the infusion. Samples were placed in lithium heparin tubes and plasma was separated by centrifugation and stored at −20°C prior to analysis.

Urine for estimation of free and conjugated metoclopramide was collected for 24 h from the start of treatment from four patients on a total of eight occasions. Aliquots were stored at −20°C prior to analysis.

Nausea was assessed by a visual analogue scale which patients scored every 2 h during the daytime and the number of vomiting episodes in the first 24 h was counted. Sedation was also assessed by the patients every 2 h on a visual analogue scale and any other adverse effects were noted.

Metoclopramide assay

Metoclopramide was measured by high-performance liquid chromatography (h.p.l.c.). Acid-washed silanised glassware was used for the extraction and samples and standards were assayed in duplicate. Plasma (2 ml) or standard were added to each tube and 50 μg disopyramide, the internal standard, and 0.6 ml 1 M borate buffer (pH 10) were then added. Metoclopramide was extracted by mixing with 5 ml dichloromethane for 15 min. After centrifugation the aqueous layer was discarded and the organic phase was transferred to a clean tube. Samples were evaporated to dryness under nitrogen then reconstituted with 50 μl of mobile phase consisting of methanol:dichloromethane:diethylamine (70:30:0.5). After vortex mixing 20 μl was injected onto the h.p.l.c. column. A silica (5 μm) packed stainless steel

Table 1 Bolus dose and infusion rates for the three metoclopramide dosage schedules

	Bolus dose	*Continuous infusion rate*	
		weight < 50 kg	*weight > 50 kg*
Low dose	1 mg/kg	10 mg/h	15 mg/h
Middle dose	2 mg/kg	20 mg/h	25 mg/h
High dose	3 mg/kg	25 mg/h	30 mg/h

column and a LDC Spectro Monitor III variable wavelength ultraviolet detector was used. The flow rate of the mobile phase was 1.4 ml/min and the detector was set at 308 nm. The assay was linear in the range 0 to 200 ng/ml with a lower limit of sensitivity in undiluted plasma of 10 ng/ml and a coefficient of variation of 9% at this level. Plasma samples with a concentration of greater than 200 ng/ml were diluted up to 1 in 20 with distilled water prior to extraction.

Metoclopramide was extracted from urine using the same method with 250 μg disopyramide as internal standard and the detector set at 300 nm. The assay was linear over the range 0–2000 ng/ml and the coefficient of variation was 4% within this range. The N^4-sulphonate and glucuronide conjugates of metoclopramide were measured in urine after differential acid hydrolysis (Arita *et al.*, 1970).

Pharmacokinetic calculations

Mean plasma concentrations during the infusion phase were calculated from the area under the plasma concentration-time curve over this period divided by the time to the end of the infusion. The terminal half-life of metoclopramide was calculated by regression analysis using the plasma concentrations measured after the end of the infusion. The area under the plasma concentration curve ($AUC_{0-\infty}$) was calculated by the trapezoidal rule and the unknown area to infinity calculated from the slope and the last measured plasma concentration.

Plasma clearance was then calculated using the formula:

$$\text{Clearance} = \frac{\text{Dose}}{AUC_{0-\infty}}$$

Statistical analysis

Plasma metoclopramide half-life and clearance at different doses were compared by the paired *t*-test and nausea and sedation were compared using Friedman two-way analysis of variance.

Results

Six patients completed the study receiving each of the three dosage schedules of metoclopramide. One patient died after two courses of chemotherapy, one patient withdrew from the study after two courses because she disliked staying in hospital overnight, and a third patient was withdrawn after two courses because of uncontrolled vomiting and recurrent acute dystonic reactions to metoclopramide. Only the results of the patients completing the study have been included in the comparison of plasma and urinary concentrations of metoclopramide, but all completed courses of chemotherapy were evaluated for anti-emetic response and adverse effects.

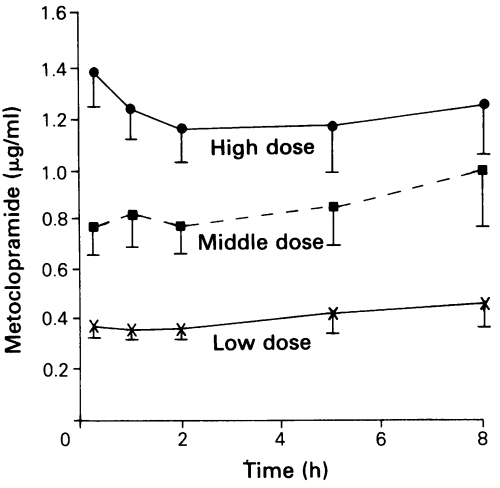

Figure 1 Mean plasma concentrations of metoclopramide achieved by loading dose and continuous infusion in six patients given three different dosage schedules (see Table 1).

Plasma

The concentrations achieved during the infusion at the three dosage levels are shown in Figure 1. Mean concentrations (± s.e. mean) were 441 ±63 ng/ml, 856 ± 145 ng/ml and 1198 ± 151 ng/ml respectively. Steady-state was obtained for the duration of the infusion in nine of the 18 courses of treatment, but was not achieved during the remaining infusions since, due to the empirical choice of infusion rates for these preliminary studies the infusion rate was inappropriate to the patient's weight.

After the infusion period plasma concentrations of metoclopramide declined mono-exponentially. The plasma half-life (mean ± s.e. mean) was 5.9 ± 0.39 h and did not differ significantly for the three doses given (Figure 2). Mean plasma clearance was 25.4 ± 4.8 l/h and was also not significantly dose-related (Figure 3). However plasma clearance was significantly correlated to be patient's body weight ($P < 0.05$). Plasma half-life and clear-

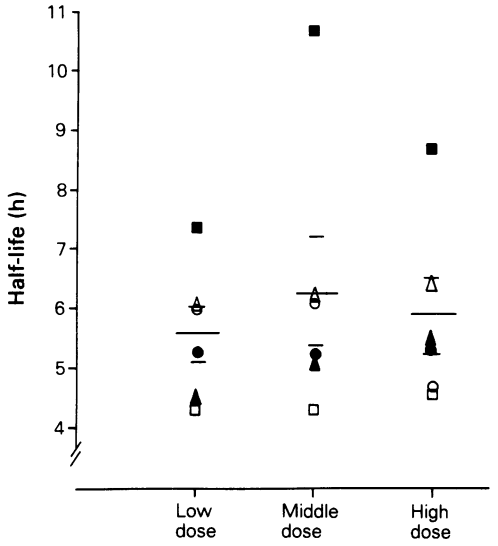

Figure 2 Plasma half-lives in six patients following each of three doses of metoclopramide. Each patient is represented by a different symbol and mean ± s.e. mean are shown as horizontal lines.

ance in patients who did not complete the study was not significantly different from those who did.

Urine

The total excretion of free metoclopramide and conjugates over 24 h varied between 32 and 48% of the dose given. Urine collection from one patient was continued for 44 h and only a further 2.2% of the dose was excreted suggesting that most urinary excretion occurs in the first 24 h. The remaining 50% of the dose was unaccounted for. 10.3–21.6% of the dose was excreted as free metoclopramide and the N^4-sulphonate conjugate accounted for 17.9–31.0% of the dose. Only 0.3–2.5% appeared as N^4 glucuronide. The percentage of free and conjugate metoclopramide did not vary with the different dosage schedules given.

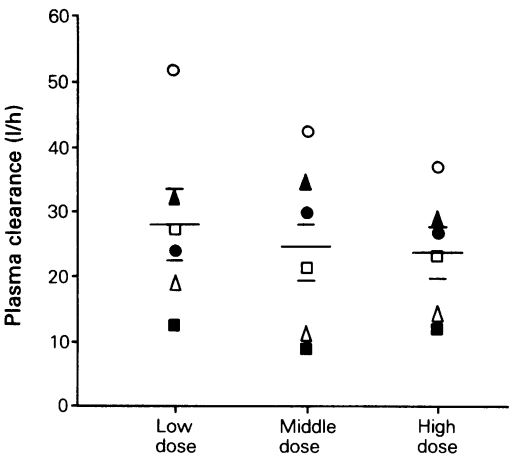

Figure 3 Plasma clearance in six patients for each of three doses of metoclopramide. Each patient is represented by a different symbol and mean ± s.e. mean are shown as horizontal lines.

Clinical effects

Complete response to metoclopramide (no nausea or vomiting) was obtained in 13 out of 24 courses of treatment (57%) and patients complained only of nausea during a further four courses. Therapeutic failure (more than two vomiting episodes) occurred for only four of the 24 courses (17%) and in two of these most of the vomiting episodes occurred after the metoclopramide infusion had been stopped. Nausea and vomiting did not appear to be related to the dose or plasma concentration of metoclopramide (Table 2), nor to the order of treatment.

The most common adverse effect noted was sedation which occurred during 13 of the 24 courses of treatment, but only one patient found the drowsiness unpleasant. There was wide variation in the degree of sedation experienced but sedation was not significantly related to the dose or plasma concentration of metoclopramide.

Diarrhoea was noted by three of the patients but was not severe enough to require treatment. In one patient diarrhoea was associated with mild colicky abdominal pain.

Extra-pyramidal side-effects occurred in two patients. One patient was noted to develop mild facial grimaces, lip-smacking and motor restlessness during the first bolus infusion of metoclopramide. These signs disappeared without treatment after 2–3 min and the patient was unaware that any reactions had occurred. She had no further extra-pyramidal reactions during the subsequent infusion of metoclopramide nor with subsequent courses. The other patient, an 18 year old girl, had an oculogyric crisis on both occasions when she was given high-dose metoclopramide. On the first occasion this reaction occurred within 30 min of stopping the metoclopramide infusion and responded rapidly to diazepam 10 mg i.v. On the second occasion the reaction occurred during the infusion and was not prevented by diazepam given prophylactically with the chemotherapy.

No other adverse effects were noted.

Table 2 Efficacy of three different doses of metoclopramide in controlling cytotoxic-induced nausea and vomiting

	No nausea or vomiting	*Nausea only*	*Vomiting*
Low dose	3	2	1
Middle dose	5	0	1
High dose	4	0	2

Discussion

High-dose metoclopramide is an important advance in the treatment of cytotoxic-induced vomiting. However, the regimen recommended by Gralla leads to accumulation of the drug (Taylor & Bateman, 1983). Such accumulation could be of particular importance when cytotoxic drugs are given on several consecutive days with metoclopramide as antiemetic prophylaxis. Furthermore, in patients with impaired renal function there is an increased risk of accumulation as at routine clinical doses the half-life of metoclopramide is considerably prolonged (Bateman *et al.*, 1981). As a large proportion of metoclopramide is metabolized, probably in the liver (Bateman *et al.*, 1980), elimination is also likely to be impaired in patients with abnormal liver function, for example patients with secondary deposits in the liver.

This study has shown that the kinetics of metoclopramide, when given in large doses, are linear, despite the dose-dependent kinetics previously reported at conventional doses (Bateman *et al.*, 1980; Graffner *et al.*, 1979). The reason for this difference is not clear. There does not seem to be a change in elimination pathways as the proportion of free and conjugated metoclopramide excreted in urine in our study are in agreement with those reported after conventional i.v. or oral doses.

In practice, the linear kinetics of high-dose metoclopramide suggest that steady-state plasma concentrations could be readily achieved by an infusion regimen. A regimen consisting of a loading dose of metoclopramide followed by a continuous infusion is simple to administer. Such a technique was reported by Gralla to be as effective as repeated infusions but was not extensively investigated (Gralla *et al.*, 1981a). We calculate from our results that a patient given a loading dose of 3.1 mg/kg metoclopramide followed by an infusion of 0.4 mg kg^{-1} h^{-1} should achieve a steady-state plasma concentration of 1 μg/ml. Doses need to be related to the patient's body weight because of the correlation between body weight and plasma clearance.

The efficacy of any antiemetic regimen has to be interpreted with caution. Patients who vomit during their first course of treatment will anticipate emesis during subsequent courses and may therefore be more likely to vomit. In this pilot study the group of patients was probably too small to demonstrate this order effect. However high-dose metoclopramide appeared effective in controlling vomiting induced by the moderately emetic drugs cyclophosphamide and adriamycin, and the incidence of adverse effects was low.

Although these patients agreed to stay in hospital overnight for the purposes of the trial, many patients receiving these drugs are treated as outpatients. For them an oral antiemetic regimen may be more suitable.

We are therefore carrying out further studies in a larger group of patients to determine the plasma concentration of metoclopramide required to give optimum control of nausea and vomiting. A study of the bioavailability of high dose metoclopramide is also in progress to allow an appropriate oral regimen to be evaluated in outpatients.

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(Received April 2, 1984, accepted June 23, 1984)