offered in early breast cancer then it becomes of paramount importance to consider the psychological impact of treatment to be offered.

The degree of psychosocial morbidity among the patients treated by local excision and radiotherapy was a disappointing finding, but one which cannot be ignored. These women clearly need just as much counselling support as patients who undergo mastectomy.

As more surgeons start to advocate breast conservation it is important that we have more basic research into the causal factors of the psychiatric morbidity experienced by women who receive this treatment.

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Optimising antiemesis in cancer chemotherapy: efficacy of continuous versus intermittent infusion of high dose metoclopramide in emesis induced by cisplatin

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Abstract

Thirty three untreated patients being given cisplatin received metoclopramide (7 mg/kg) for antiemesis by either continuous or intermittent infusion in a random order. Each patient received intravenous dexamethasone in addition. High pressure liquid chromatography was used to measure plasma concentrations of metoclopramide. The two regimens were evaluated for antiemetic efficacy and the incidence of side effects.

The intermittent metoclopramide regimen resulted in peak and trough plasma concentrations of metoclopramide with accumulation at eight hours, while the loading dose and continuous infusion resulted in mean plasma concentrations greater than 0·85 μg/ml (2·8 μmol/l) throughout the eight hour period. The continuous infusion was associated with a significant improvement in nausea and vomiting and reduction in diarrhoea.

Major control of emesis (two episodes or fewer) was achieved in 27 patients receiving continuous metoclopramide compared with 18 receiving intermittent metoclopramide.

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Introduction

Current chemotherapy strategies still of necessity use highly emetogenic drugs. Clinical experience together with psychological studies confirm that the gastrointestinal sequelae of chemotherapy are of paramount importance.[1] Cisplatin is one of the most emetogenic compounds known but is widely used in curative and palliative chemotherapy for cancer. Only recently have effective antiemetics been developed, and much effort has been focused on the control of emesis induced by cisplatin: high dose metoclopramide given by intermittent infusion has proved useful,[2-5] and we showed that dexamethasone significantly enhances its antiemetic effect.[6] In our previous study, however, only 65% of patients achieved major control (two or fewer episodes of vomiting); further improvement is required. Using an intermittent regimen, Meyer *et al* found that effective antiemesis required a minimum plasma metoclopramide concentration of 0·85 μg/ml (2·8 μmol/l).[7]

High dose intermittent infusion as reported by Gralla *et al* results not only in wide variations in plasma concentrations of the drug but also in accumulation.[3 8] As a relation between plasma concentrations and antiemetic effect has been described failure of control may be the result of subtherapeutic concentration of metoclopramide at a critical time in the onset of vomiting, which is usually within two hours after the administration of cisplatin.

We compared the antiemetic efficacy and side effects of a conventional intermittent infusion of metoclopramide with those of a loading dose and continuous infusion of metoclopramide designed to provide a constant drug concentration; in addition, we measured the plasma concentrations of metoclopramide achieved with both regimens.

Patients and methods

Thirty three previously untreated patients due to receive cisplatin were enrolled in the study. They comprised one man and 32 women (mean age 54·2 (range 30-68) years with tumours of the ovary (28 cases), cervix (two), bladder (one), prostate (one), and lung (one). Patients received cisplatin either alone (16 cases) or in combination with some of the following: fluorouracil, doxorubicin, methotrexate, mitozantrone, vindesine, prednimustine, and hexamethylmelamine. The dose of cisplatin was either 100 or 30 mg/m^2 (25 and eight patients, respectively). Antiemetic, sedative-hypnotic, and tranquillising drugs were stopped 24 hours before treatment. Patients with impaired renal function were excluded from the study, and therefore delayed elimination of metoclopramide would not be expected.[9]

Each patient received either a loading dose and a continuous infusion or an intermittent infusion of metoclopramide in a randomised sequence. The same total dose of metoclopramide, 7 mg/kg, was given in both regimens. With both treatments dexamethasone (20 mg) was given as a 15 minute infusion (in 0·9% sodium chloride 50 ml), beginning 30 minutes before cisplatin. The continuous metoclopramide regimen consisted of metoclopramide given as a loading dose of 3 mg/kg in 50 ml 0·9% sodium chloride over 15 minutes before cisplatin, followed immediately by a continuous infusion of 4 mg/kg in 500 ml 0·9% sodium chloride over eight hours. The doses of metoclopramide were calculated from standard pharmacokinetic equations to achieve plasma concentrations of approximately 0·85 μg/ml (2·8 μmol/l).[10] With the intermittent infusion of metoclopramide the total dose, 7 mg/kg, was made up to 500 ml with 0·9% sodium chloride and administered in 100 ml aliquots 15 minutes before cisplatin and thereafter on four occasions two hours apart.

Blood samples for estimation of plasma metoclopramide concentrations were taken at 0, 0·5, 1, 2, 5, and 8 hours in patients receiving the continuous regimen and at time 0 and immediately before and after the doses at 2, 4, 6, and 8 hours in patients receiving the intermittent regimen to monitor peak and trough concentrations. Samples were collected in lithium-heparin tubes, and the plasma was stored at −20°C until analysed.

Patient assessment—Standard questionnaires were completed in consultation with the patients 24 hours after the cisplatin was administered. Assessments were performed predominantly by one of us (PSW), with the patients recording their experience of nausea on a visual analogue scale: they were asked to indicate on a 10 cm line the severity of their nausea, 0 cm representing no nausea and 10 cm representing the most extreme nausea. The number of episodes of vomiting, retching, and diarrhoea was recorded by the patient and in interview with the nursing staff and the incidence of drowsiness, extrapyramidal effects, and akathisia documented. During their second admission for chemotherapy patients were asked the duration of nausea and vomiting after the administration of cisplatin.

Assay of metoclopramide—Metoclopramide concentration was measured by high performance liquid chromatography with a modification of the method of Taylor *et al.*[11] Disopyramide was used as an internal standard, and metoclopramide was extracted from alkalinised plasma with dichloromethane. Calibration curves were linear with a coefficient correlation of >0·998. The detection limit was roughly 1 ng metoclopramide (100 ng/ml plasma), and the extraction recovery from plasma was 92-98%.

Results

All 33 patients received both the intermittent and the continuous infusions. Metoclopramide concentrations were measured in plasma samples from 13 patients receiving the continuous infusion and 14 patients receiving the intermittent infusion.

Nausea as indicated on the visual analogue scale was significantly reduced ($p<0·0001$, Wilcoxon signed rank test) when the patients received the continuous metoclopramide infusion compared with the intermittent infusion (fig 1). There was no significant reduction in retching ($p<0·1$), although there was a trend towards better control with the continuous regimen. Vomiting was significantly better controlled ($p<0·05$) by the continuous infusion, 27 patients having two episodes of vomiting or fewer compared with 18 receiving the intermittent infusion. Fifteen patients had three or more episodes of vomiting while receiving the intermittent infusion compared with only six patients receiving the continuous infusion (table I).

Table I shows the incidence of adverse reactions. Diarrhoea may have been a side effect of the cisplatin or the metoclopramide, or both. Only one patient experienced diarrhoea (one or more abnormally loose stools) while receiving the continuous metoclopramide regimen, compared with eight patients receiving the intermittent infusion ($p<0·05$). There was no significant difference in the incidence of other side effects between the two

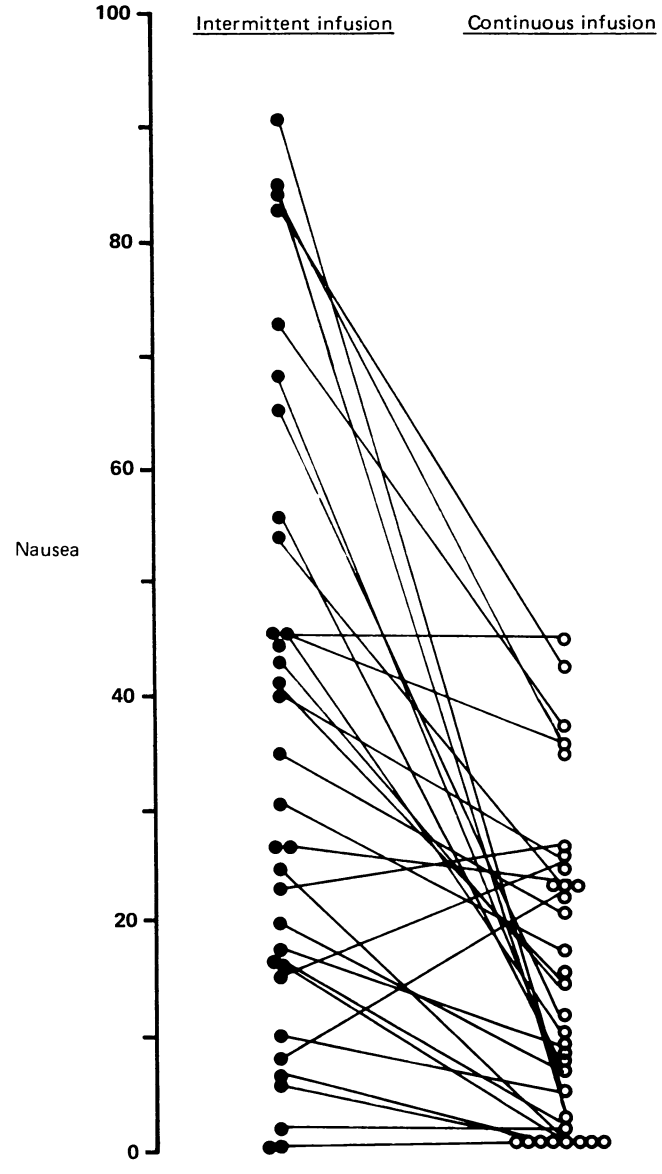

FIG 1—Changes in nausea experienced by individual patients as recorded on visual analogue scale. 0=No nausea; 100=severe nausea.

TABLE I—*Prevalence of side effects of treatment (n=33)*

	Intermittent infusion	Continuous infusion	Significance*
Retching:			
0-2 episodes	21	28	p<0·1
≥3 episodes	12	5	
Vomiting:			
0-2 episodes	18	27	p<0·05
≥3 episodes	15	6	
Diarrhoea	8	1	p=0·02
Extrapyramidal reactions	1		
Tremulousness	6	7	p<0·9
Drowsiness	23	27	p<0·5
Patient preference†	5	18	p<0·05

*All variables assessed with χ^2 test except diarrhoea, for which Fisher's exact test was used.
†Ten patients expressed no preference.

different methods of administration. Significantly more patients preferred the continuous to the intermittent infusion ($p<0.05$); 10 patients expressed no preference. With both regimens drowsiness was the most common side effect.

After the first course of chemotherapy 21 of the 33 patients (10 having received intermittent metoclopramide and 11 having received continuous metoclopramide) were assessed for delayed or prolonged nausea and vomiting. Nausea occurred in 17 patients (81%), eight of whom had received continuous metoclopramide and nine intermittent metoclopramide. The nausea lasted for from one to 14 days (median three days) with both regimens. Vomiting lasted for from one to seven days (median two days) and was reported in 10 of the 21 patients (46%) (four receiving the continuous infusion and six the intermittent infusion). There was no significant difference (table II) in the results obtained after the two methods of administration.

TABLE II—*Prevalence of delayed or prolonged nausea and vomiting (n=21)*

	Nausea	Vomiting	Significance (χ^2 test)
Continuous infusion	8	4	$p<0.75$
Intermittent infusion	9	6	$p<0.90$

Figure 2 shows that the loading dose and continuous infusion of metoclopramide resulted in a mean plasma concentration of metoclopramide above 0·85 μg/ml (2·84 μmol/l) throughout the eight hour period. The intermittent infusion of metoclopramide produced mean plasma concentrations below this value during the first four hours with accumulation of metoclopramide at eight hours.

Discussion

This study shows that the application of simple pharmacokinetic principles in the administration of high dose metoclopramide can optimise the drug's antiemetic effect in patients receiving cisplatin. Thus the incidence of nausea was reduced during the continuous metoclopramide arm compared with the intermittent infusion arm. Major control of vomiting (two episodes or fewer) was achieved in 82% of the patients during the continuous infusion arm and only 55% during the intermittent infusion arm. As emesis in patients receiving cisplatin begins two to four hours after the start of the infusion[11] the therapeutic goal should be to achieve adequate plasma concentrations of metoclopramide at an early stage. In this study none of the patients receiving the intermittent infusion had achieved plasma concentrations of metoclopramide ≥0·85 μg/ml before their dose at four hours and only one patient achieved this concentration before the dose at six hours.

These results support the findings of Meyer *et al* that plasma concentrations of metoclopramide >0·85 μg/ml are necessary to achieve optimum antiemetic effect.[7] Furthermore, our study clearly showed the superiority of the loading and maintenance dose in achieving early, effective, and sustained plasma concentrations. McDermed *et al*, however, could not relate antiemetic effect to metoclopramide concentrations in a study population receiving intermittent infusions of the drug.[12] A previous study of ours failed to show a significantly enhanced antiemetic effect with increasing dose of intermittently infused metoclopramide at 3 mg/kg, 5 mg/kg, or 10 mg/kg, although there was a trend in favour of the higher doses.[4] Possibly in these two studies wide variability in the plasma concentrations of metoclopramide between patients, who were receiving metoclopramide by intermittent infusion, and the failure to achieve adequate plasma concentrations in the first four hours of administration led to erratic antiemetic efficacy. In the present study the patients acted as their own control and received the same dose of cisplatin during each admission.

Plasma concentrations of metoclopramide achieved varied considerably between patients. The loading dose and continuous infusion produced plasma metoclopramide concentrations ranging from 0·62 to 2·36 μg/ml (2·1 to 7·9 μmol/l). A loading dose of 3 mg/kg produced plasma concentrations ranging from 0·77 to 2·36 μg/ml (2·6 to 7·9 μmol/l), with only one patient having a concentration below 0·85 μg/ml (2·8 μmol/l). In two patients in whom plasma metoclopramide concentrations fell below 0·85 μg/ml during the continuous maintenance infusion and the antiemetic effect was

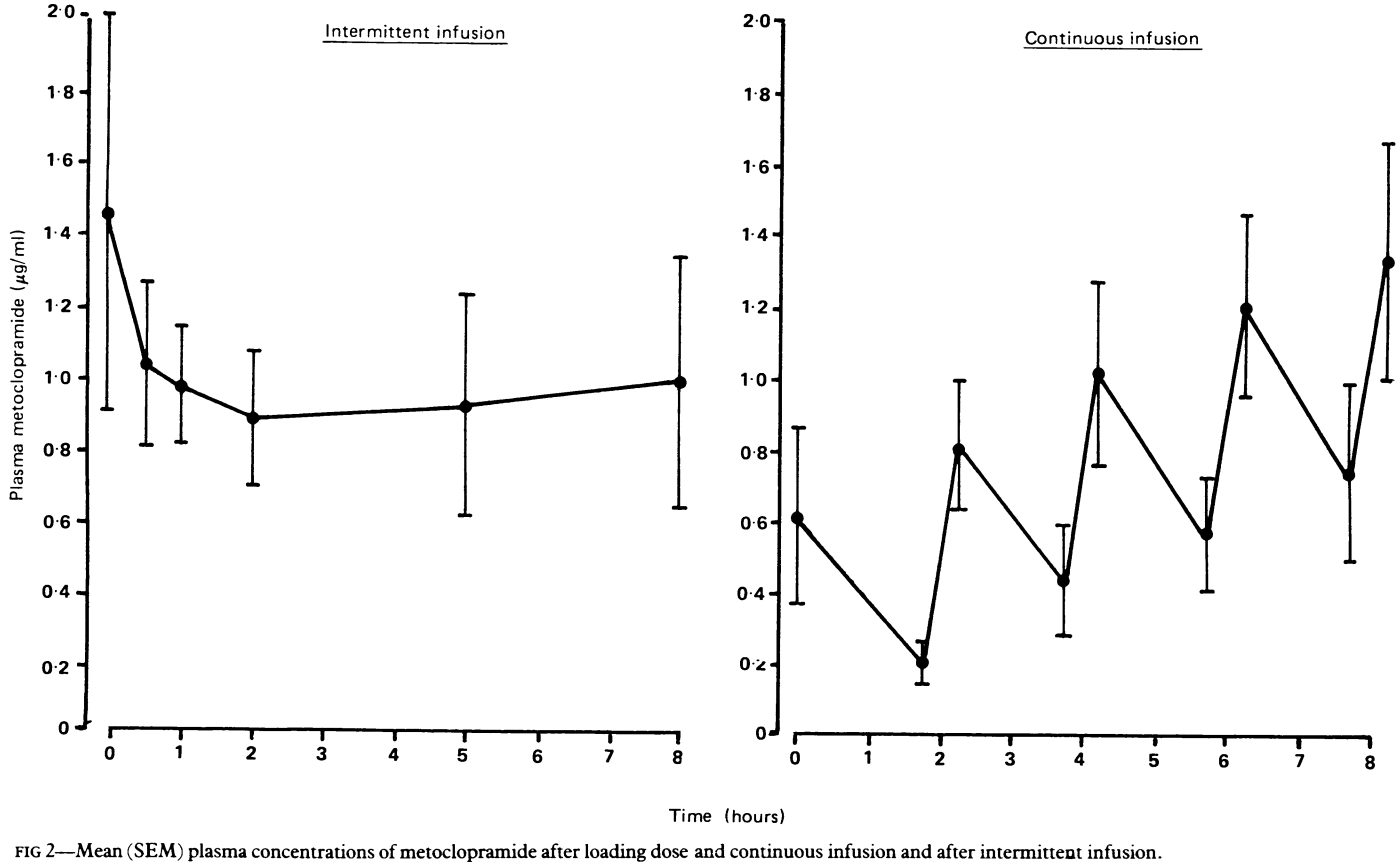

FIG 2—Mean (SEM) plasma concentrations of metoclopramide after loading dose and continuous infusion and after intermittent infusion.

poor, nausea and vomiting were reduced by increasing the dose of the maintenance infusion during subsequent treatment to 5 and 6 mg/kg, respectively. This shows that the antiemetic effect of the drug can be optimised individually.

Neither regimen produced excessive side effects. Interestingly, diarrhoea was considerably reduced in the group receiving the continuous infusion, and it may be that wide fluctuations in plasma metoclopramide concentrations result in excessive intestinal hurry with resultant diarrhoea. Extrapyramidal reactions to metoclopramide are rare in this age group.

In view of an increasing tendency towards combination antiemetic treatment for emesis induced by cytotoxic drugs and the attendant concern over potential drug interactions the optimal use of individual antiemetics is considerably important. Thus we are encouraged by the considerable improvement in antiemetic effect achieved by high dose metoclopramide given as a loading dose and maintenance infusion after the application of simple pharmacokinetic principles. Future studies need to address the problems of the route and technique of administration of antiemetics and the dosage as well as identifying new compounds and combinations. Kris *et al* documented the time course of nausea and vomiting after administration of cisplatin.[2] They showed that nausea persisted for five days in 40% of patients and vomiting in 20%, with a peak incidence at three days after administration. In our study there was no difference in the duration of nausea and vomiting between the two arms, but the peak incidence of delayed nausea at three days agrees with the study of Kris *et al*.[2] This suggests that control of acute emesis after cisplatin does not necessarily reduce subsequent delayed emesis, and thus further improvements are required.

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Dose dependent response of symptoms, pituitary, and bone to transdermal oestrogen in postmenopausal women

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Abstract

The effect of the plasma oestradiol concentration on climacteric symptoms, gonadotrophin release, and bone resorption was studied in three groups of postmenopausal women given 0·025 mg, 0·05 mg, or 0·1 mg transdermal oestradiol daily. There was a dose related reduction in symptoms, plasma follicle stimulating hormone concentration, and urinary calcium and hydroxyproline excretion. The relation of the response to plasma oestradiol values was similar for each variable with an initial large reduction and little change in response to increases in the plasma oestradiol concentration above 150 pmol/l (41 pg/ml).

Hormone replacement therapy producing an effect equivalent to higher oestradiol concentrations is likely to increase the risk of side effects without conferring any additional benefit.

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Introduction

Oestrogen replacement in postmenopausal women reduces both symptoms of the climacteric and excess bone resorption in a dose dependent manner.[1,2] During the menstrual cycle, however, though the changes that occur in the plasma oestrogen concentration are of the same order of magnitude as those in women receiving postmenopausal hormone replacement therapy, they are not accompanied by any change in either oestrogen dependent symptoms or bone turnover.[3] A possible explanation for this difference is that the response to oestrogen is near maximal at the plasma concentration present during menstruation and that only small changes in response occur with oestrogen concentrations within and above the premenopausal range.

If the response in bone to oestrogen has this relation it has implications for postmenopausal hormone replacement treatment, since the adverse effects of oestrogen treatment are dose related.[1,4] Moreover, high doses of oestrogen have unwanted effects on bone as a result of inhibition of bone formation, which would be avoided by using the minimal dose of oestrogen to suppress resorption.

The establishment of such a dose has thus far been difficult because oestrogens are usually given by mouth. This causes hepatic "first pass" metabolism of the oestrogen, which appears in plasma as various metabolites with variable biological activity[5] and increased concentrations of sex hormone binding globulin, which reduces the free hormone.[6] Taken together these two phenomena make it impossible to assign any meaningful biological value