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Emesis due to Cancer Chemotherapy: Results of a Prospective, Randomised, Double-blind Trial of Varying Doses of Metoclopramide in the Management of *cis*-Platinum-induced Vomiting

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Abstract—*A randomised, double-blind prospective trial was conducted to determine the relative anti-emetic efficacy of three dose levels of metoclopramide in cancer patients receiving combination chemotherapy including* cis-*platinum. With consecutive courses of chemotherapy, 60 patients received doses of either* 3, 5 *or* 10 mg/kg *metoclopramide* (50, 54 *or* 55 *courses respectively) in a randomly assigned sequence. Major control of emesis* (≤2 *vomits) was achieved in* 38% *of* 159 *patient treatments. There were no significant differences in either anti-emetic efficacy or the incidence of side-effects between the three doses used. It is concluded that while metoclopramide is an effective anti-emetic for patients receiving* cis-*platinum therapy, no advantage accrues to the use of doses in excess of* 3 mg/kg *(total dose).*

INTRODUCTION

cis-PLATINUM has become established as one of the most active chemotherapeutic agents [1] in a variety of malignant tumours but has a powerful emetic effect which causes considerable distress to patients (and nurses) and which may lead to patient non-compliance. Established anti-emetics have proved of little use in this situation [2, 3] but novel approaches to the problem have been encouraging. For example, the use of cannabinoids [4] and dexamethasone [5] have been shown to produce considerable benefit. Metoclopramide has anti-dopaminergic receptor activity, exerting both peripheral and central effects. In conventional p.o. doses metoclopramide (40–80 mg daily) has proved disappointing against chemotherapy-induced vomiting [1, 3] but Gralla *et al.* [3] in 1981 demonstrated that high-dose metoclopramide (HDM) i.v. was extremely effective in controlling platinum-induced vomiting. With other papers [6–8] demonstrating the efficacy of HDM in this context, it has been advocated as the anti-emetic of choice for patients receiving *cis*-platinum.

Various dose regimens of HDM have been employed in these studies, ranging from 2 to 10 mg/kg (total dose) [3, 6–8], though these were not all double-blind studies. However, there has been concern expressed that the higher dose levels of metoclopramide are associated with increased adverse reactions [7, 9], particularly extra-pyramidal reactions.

In this study we have assessed in a prospective, double-blind, randomised trial the anti-emetic efficacy of three doses of metoclopramide (3, 5 and 10 mg/kg total dose) together with adverse reactions resulting from all dose levels.

MATERIALS AND METHODS

Sixty patients receiving *cis*-platinum, either as a single agent or as part of a chemotherapeutic combination (5-fluorouracil) for the first time, were admitted to the study. Fifty patients received *cis*-platinum at 100 mg/m² and ten at 30 mg/m². Each patient was assigned to a random sequence of metoclopramide of 3, 5 or 10 mg/kg total dose. Forty-eight patients completed at least one

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sequence of all three study doses, making a total of 159 assessable courses. Of the 21 courses unevaluable, 15 were due to an alteration in chemotherapy to a non-platinum regimen, four to administration of other anti-emetics and only two (in one patient) were due to lack of any apparent emetic control following the first administration of HDM. Table 1 describes the characteristics of the patients on study.

Table 1. Patient characteristics

	No.	Courses
Male	25	
(mean age, 52 yr; range, 18–70 yr)		
Female	35	
Tumour		
Ovary	26	73
Lung	18	48
Teratoma	11	27
Bladder	3	8
Melanoma	1	1
Sarcoma	1	2
cis-Platinum dose		
100 mg/m²	50	129
30 mg/m²	10	30
Total		159

HDM at 3, 5 or 10 mg/kg was prepared in 500 ml of normal saline by the pharmacy department and administered by five 100-ml aliquots, by rapid infusion, commencing half an hour before *cis*-platinum and two-hourly thereafter. *cis*-Platinum was infused over 1 hr. Evaluation of symptom control was made by one of the authors (SGA) utilising a questionnaire relating to the degree of nausea experienced, episodes of dry retching and episodes of diarrhoea. Nurses charted the number of vomits and this was cross-checked with the patient. The number of meals eaten throughout the 30 hr of admission was also recorded by nurses and cross-checked with the patient. Patients were asked about side-effects which they thought related to the anti-emetic therapy and in particular drowsiness and extrapyramidal reactions were specifically inquired about. The interview with the patient took place about 16 hr after the *cis*-platinum administration.

RESULTS

Tables 2–5 show the degree of symptom control achieved at different dose levels. Table 2 demonstrates the severity of nausea at the three dose levels. Although there was a tendency for the most severe nausea to be reduced with the highest dose of metoclopramide, none of the differences reaches statistical significance. Table 3 refers to the control of vomiting, and again no significant difference was seen at the three dose levels. Overall, major control of vomiting, including dry retching (0, 1–2), was achieved in 38% of courses. The number of meals eaten throughout treatment was similar at the three dose levels. Around 60% of patients on HDM ate all meals or missed only one. The frequency of diarrhoea is recorded in Table 4, with 18% having one loose stool, 19% 2–6 loose stools and 4% >6 loose stools. No difference was seen between varying doses of HDM. Adverse reactions to HDM are recorded in Table 5, and there was no obvious increase in adverse reactions with increasing doses of HDM. Drowsiness was the commonest side-effect, occurring with 16% of courses. Extrapyramidal reactions, consisting of jaw spasm and opisthotonos in one case, occurred in 10% of patients.

Table 2. Control of nausea by No. of courses

HDM dose	No nausea	Some nausea	Total
3 mg/kg	6	44	50
5 mg/kg	11	43	54
10 mg/kg	12	43	55
			159

No significant difference between dose levels (χ^2).

Table 3. Control of vomiting by No. of courses

HDM dose	No vomiting	1–2 vomits	>2 vomits	Total
3 mg/kg	7	12	31	50
5 mg/kg	6	14	34	54
10 mg/kg	10	11	34	55

No significant difference between dose levels (χ^2).

Table 4. Frequency of diarrhoea by No. of courses

Stool No.	HDM dose 3 mg/kg	5 mg/kg	10 mg/kg	Percentage of courses
0	28	31	34	58
1	12	8	9	18
2–6	7	13	10	19
6	3	2	2	4

Table 5. Adverse reactions to HDM

HDM dose	Drowsiness	Extrapyramidal reactions	Akithisia
3 mg/kg	8	2	1
5 mg/kg	7	3	1
10 mg/kg	10	4	1
Total	25	9	3
% of courses	16	6	2

DISCUSSION

We have found HDM to be very effective in the prevention or amelioration of the emesis associated with *cis*-platinum, with major control of emesis (2 or less) in 38% of courses. Although a higher percentage of control of emesis has been reported in other studies [3, 6], no mention was made of the frequency of dry retching in these studies. Since patients are as distressed with retching as with vomit production, we chose to include episodes of dry retching in the assessment of severity of vomiting. Metoclopramide promotes gastric emptying and may make dry retching more likely to occur when vomiting is initiated. The assessment of volume vomited is notoriously difficult and is not necessarily related to symptom control, and thus was not measured. No significant advantage was demonstrated for HDM in excess of 3 mg/kg (total dose), though there was no major increase in adverse reactions at the 5 and 10 mg/kg doses. Meyer *et al.* [10] have demonstrated a correlation between the trough serum level of metoclopramide and anti-emetic control, and this may partly explain the results here reported. It has been suggested that the severity of emesis related to platinum is dependent on the platinum dose, and the majority of our patients (50) received 100 mg/m^2 *cis*-platinum. Since these and the ten on lower dose *cis*-platinum acted as their own controls, all patient courses were analysed together. Major control of emesis (2 or less) was seen in 50% of courses at *cis*-platinum 30 mg/m^2. The number of meals eaten during admission allowed another important factor of gastro-intestinal 'well being' to be assessed and 60% of patients were found to eat all meals or miss only one.

Adverse reactions to HDM were not a major problem and no patient in this study refused HDM because of this. Drowsiness was recorded in only 16% of patients and represents a low incidence, perhaps because the HDM was administered through the night. Ten per cent of patients experienced extrapyramidal reactions which were always mild and controllable, consisting mainly of trismus but with one episode of opisthotonos. The recurrence of extrapyramidal reactions on subsequent courses of HDM, though not inevitable, did occur and early intervention with anti-cholinergics was required. Gralla *et al.* [3] found a 44% overall incidence of diarrhoea (3 or more loose stools), equal to both HDM and control groups, and we have demonstrated an overall 41% incidence of 1 or more loose stools following *cis*-platinum administration in this study. Three patients expressed concern at the explosive nature of their diarrhoea and it is possible that HDM contributed to this. Prophylactic diphenoxylate hydrochloride (Lomotil) has since proved useful in preventing such diarrhoea. In conclusion, no additional benefit was conferred by using doses of metoclopramide in excess of 3 mg/kg total dose, though adverse reactions were not significantly increased at these higher doses. The use of HDM alone provides good anti-emetic control for many patients receiving *cis*-platinum but there remains considerable room for improvement. The identification of anti-emetic receptor blocking activity [11] may allow the rational use of combinations of anti-emetics to increase anti-emetic control [12]. Studies of this kind are already under way [13].

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