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High-dose intravenous metoclopramide and intermittent intramuscular prochlorperazine and diazepam in the management of emesis induced by *cis*-dichlorodiammineplatinum

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Summary. *Intravenous metoclopramide and IM prochlorperazine and diazepam were compared in the management of vomiting occurring during treatment with cis-dichlorodiammineplatinum (cis-platinum). A total of 104 cycles in 30 patients were evaluated.*

Twenty-two patients took part in a cross-over study in which emetic profiles for each patient managed with each anti-emetic schedule were compared.

In all, 44 cycles of treatment in 22 patients were evaluated as part of a cross-over study. No significant difference in emetic control was observed between the two anti-emetic regimens.

The side-effects observed using IV metoclopramide included extrapyramidal phenomena (19%) and flushing attacks (16%).

Introduction

Cis-Platinum, an agent shown to be effective in the management of ovarian epithelial carcinoma [1–3, 6], has well documented and potentially serious side-effects [3, 7, 8]. Nausea and vomiting invariably follows its administration and is the most distressing side-effect experienced by the patient.

This study compared high-dose IV metoclopramide with IM prochlorperazine and diazepam. Intravenous metoclopramide has been shown to be effective in controlling cytotoxic-induced vomiting [4]. The anti-emetic sedative combination was included as this has been our standard practice and a new anti-emetic regimen must be shown to be superior to standard therapy.

Patients and methods

Thirty patients with epithelial ovarian carcinoma FIGO stages III and IV received a total of 116 courses of high-dose single-agent *cis*-platinum. No patient had previously been treated with chemotherapy.

Of the 116 courses, 44 have been evaluated as part of a randomized cross-over study (see below). All but 12 courses have been evaluated for anti-emetic toxicity, six because *cis*-platinum toxicity precluded the use of full dosage, three because patients had received anti-emetics within 48 h of commencing chemotherapy, two because the recording of observations was inadequate, and one because the patient received a non-protocol anti-emetic.

All the patients studied were receiving *cis*-platinum (100 mg/m^2) by IV bolus. Saline prehydration and saline and mannitol posthydration were performed routinely for all courses of chemotherapy, and all patients were catheterized during the 24 h after treatment to enable accurate hourly urine output to be assessed. Prior to each course a full history and examination was performed to assess response to treatment and toxicity. In addition, full biochemical and haematological profiles were obtained. Six patients were withdrawn from *cis*-platinum chemotherapy, four with evidence of progressive disease, one because of poor renal function, and one because of refusal to accept further treatment. Cycles studied prior to withdrawal were evaluated.

Details of the anti-emetic regimens are presented in Table 1.

This study was comprised of two parts.

A. Randomized cross-over study. Thirteen patients were randomized to receive IV metoclopramide for their first course of chemotherapy and in 10 instances were crossed over to receive prochlorperazine and diazepam for their second course. This was cross-over group A. Three patients were not eligible to continue in the study [rapidly progressing disease (1); dose reduction of *cis*-platinum (1); anti-emetic given prior to protocol treatment (1)].

Seventeen patients were randomized to receive prochlorperazine and diazepam for their first course of chemotherapy and in 12 instances were crossed over to receive IV metoclopramide for their second course. This was cross-over group B. Five patients were not eligible to continue with the protocol [rapidly progressing disease (1); dose reduction of *cis*-platinum (1); patient's request to be sedated (3)].

All patients were entered with informed consent.

Table 1. Anti-emetic regimens

1. Prochlorperazine	12.5 mg IM 1 h before chemotherapy, then 2-hourly (total doses 6)
Diazepam	10 mg IV with chemotherapy, then 2-hourly as required (maximum no. of doses 6)
2. Metoclopramide	Total dose 10 mg/kg given as 6 equal divided doses IV; first dose 1 h before chemotherapy, then 2-hourly

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B. Toxicity of anti-emetics study. Sixty cycles of chemotherapy were considered suitable for evaluation of side-effects. These patients have been excluded from the comparison of anti-emetic control as they relate to courses of chemotherapy after the initial two courses (cross-over study). As patients were allowed to choose their anti-emetic treatment after this point a bias has been introduced. These 60 cycles, along with the 44 included in the randomized study, have been combined to analyse the side-effects associated with the two anti-emetic regimens.

No medication was given during the 24 h prior to treatment. Normal eating and drinking were permitted, and any complaint of nausea or vomiting was recorded.

Chemotherapy was given as an IV bolus and recordings commenced. The time of onset of vomiting and the time and volume of subsequent vomiting were recorded. The time between the first and last vomiting episodes was the total duration of emesis. Level of consciousness was assessed objectively by nursing and medical staff and recorded as alert, mildly drowsy, moderately drowsy, or severely drowsy. In the group randomized to receive prochlorperazine and diazepam, diazepam was given 2-hourly to maintain a steady state of sedation. Any other side-effects were noted if and when they occurred.

On the day following treatment each patient was interviewed by one of us (DML) and asked to comment on her treatment, with particular reference to comparison with her previous treatment.

C. Statistical methods. Wilcoxon's paired analysis was used to compare the emetic parameters in cycle 1 and cycle 2 for each cross-over group (A and B).

Wilcoxon's unpaired test was used to compare the emetic characteristics of each regimen when given in cycle 1 and with the same regimen when given in cycle 2.

Results

The emetic profiles of all cases in both treatment groups are presented in Tables 2 and 3.

1. Cross-over study

(i) Group A. No significant differences were seen in the 10 patients crossed over from IV metoclopramide to intermittent IM prochlorperazine and diazepam when duration of emesis, number of emetic episodes, or volume of emesis was compared.

Six patients felt that their emetic control was better, three worse, and one no different as a result of their change in anti-emetic scheduling.

(ii) Group B. No significant differences were seen in the 12 patients crossed over from intermittent IM prochlorperazine and diazepam to IV metoclopramide when duration of emesis, number of emetic episodes, or volume of emesis was compared.

Table 2. Group A. Cross-over from metoclopramide to prochlorperazine and diazepam

Case no.	Course 1			Course 2			Impressions
	Duration (h)	Episodes	Volume (ml)	Duration (h)	Episodes	Volume (ml)	
1	0	0	0	2.5	8	215	Worse
2	0.25	1	100	3.4	4	250	Same
3	3	5	150	3	5	250	Better
4	3.5	8	410	1	3	380	Better
5	0	0	0	2.8	5	90	Worse
6	0.5	3	220	1.25	4	500	Worse
7	9.5	14	470	5	3	245	Better
8	3	5	350	2.25	5	250	Better
9	3.5	11	305	2.7	5	230	Better
10	12	10	897	4	12	1,390	Better

Table 3. Group B. Cross-over from prochlorperazine and diazepam to metoclopromide

Case no.	Course 1			Course 2			Impressions
	Duration (h)	Episodes	Volume (ml)	Duration (h)	Episodes	Volume (ml)	
1	3.5	5	450	17	6	1,100	Worse
2	3.25	9	250	3.5	5	155	Better
3	2.1	5	200	4	5	285	Worse
4	1.5	4	140	0.2	1	30	Better
5	3.5	6	370	5.1	8	680	Worse
6	1.75	10	135	6.5	13	351	Worse
7	2.8	5	220	0	0	0	Same
8	2.8	5	200	5	6	685	Worse
9	3.5	6	315	3	5	150	Same
10	3.5	8	310	1.5	4	220	Better
11	3	8	550	5	12	600	Worse
12	2	6	375	3.25	8	375	Worse

Table 4. Side-effects of treatment

Observation	Prochlorperazine and diazepam (%)	Metoclopramide (%)
Alert	22.3	61
Mild drowsiness	59.7	30.5
Moderate drowsiness	17.9	8.3
Severe drowsiness	0	0
Diarrhoea	41.8	30.5
Flushing attacks	5	16.6
Headache	1.4	8.3
Extrapyramidal signs	0	19.4
Restlessness	3	13.8

Three patients felt that their emetic control was better, seven worse and two no different as a result of their change in anti-emetic scheduling.

2. Correlation with patients' impressions

Changes in duration of emesis and the number of emetic episodes generally correlated well with the opinions patients gave with regard to their emetic control.

3. Comparison of anti-emetic efficacy of the same regimen in separate courses

The number of emetic episodes, volume and duration of emesis did not differ significantly when the first and second (and vice versa) treatment courses were compared in the different treatment groups. This, in effect compared metoclopramide control in course 1 with metoclopramide control in course 2 and likewise for prochloperazine and diazepam.

4. Toxicity of anti-emetic regimens

A total of 104 cycles of treatment have been evaluated, 62 of which were managed by prochlorperazine and diazepam and 42 by IV metoclopramide. The side-effects observed are presented in Table 4.

Flushing attacks, headache, extrapyramidal signs (trismus 2, oculogyric crises 1, coarse tremor 4, dysarthria 2) and restlessness occurred almost exclusively in cycles managed with metoclopramide.

The group receiving diazepam were more drowsy but no cases of inhalation of vomit occurred, and all patients had enough recall, when interviewed immediately after treatment, to make comparisons with previous treatments.

Diarrhoea occurred in both groups; this may be due to the use of mannitol.

Discussion

cis-Platinum is a potent emetic agent. Many studies reporting on its use have noted nausea and vomiting in almost every patient. In this study vomiting occurred in 100 of 104 treatment cycles. Control of this side-effect, by either anti-emetic regimen, cannot be judged to have been successful, and no superiority of one regimen over the other could be demonstrated using the predetermined parameters of duration and volume of emesis and number of emetic episodes.

Many previous attempts to assess the degree of emesis have employed grading systems ranging from poor to excellent; various parameters have been employed to construct such scales including the patients' subjective impressions and feelings of nausea. The importance of the latter is not disputed, but it is suggested that many individual factors, not necessarily related to the efficacy of anti-emesis, and impossible to control, may affect a patient's overall impression of treatment. In addition, quantification of such feelings is fraught with difficulty. In this study the dose of *cis*-platinum was standardized and all patients had the same neoplasm: it was not possible to control for many other variables. Several measurable parameters were compared and none was found to differ significantly between the two anti-emetic regimens.

High-dose IV metoclopramide has been shown to be superior to prochlorperazine alone in one study [4]. It is uncertain why the addition of sedation should shorten the period of emesis, but it has been suggested that combined medication may confer an advantage [9, 10], probably by blocking more afferent inputs to the chemoreceptor trigger zone (CTZ) than dopamine receptor blockade on its own could achieve [5, 10]. Conscious input to the vomiting centre and CTZ almost certainly occurs and would, in part, explain the phenomenon of anticipatory vomiting. Central nervous system sedation probably has a role theoretically in the management of this type of vomiting; the data from this study support such a theory.

The anterograde amnesia effect induced by benzodiazepine may also contribute to blocking 'learned' or anticipated vomiting. This effect, however, is more likely to be seen after several courses of therapy.

This study has not demonstrated improved emetic control of one regimen (metoclopramide) over a combination regimen (prochlorperazine and diazepam). The more unpleasant and less manageable side-effects of the former suggest that its routine use in anti-emetic management should be avoided.

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