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Papers

A Randomised Double Blind Crossover Study of Domperidone and Prochlorperazine Suppositories for Controlling Emesis in Outpatients Receiving Chemotherapy

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Patients receiving outpatient chemotherapy, without cisplatin, were randomised to receive four doses of either domperidone 60 mg or prochlorperazine 25 mg suppositories every 4 h, starting 30 min before the chemotherapy. They were crossed over for the next chemotherapy cycle. To enable analysis of 100 patients who had received identical chemotherapy in each course, 136 patients were randomised. Patients experienced a higher grade of nausea on domperidone ($P = 0.05$). Only 18% of patients vomited on domperidone and 14% on prochlorperazine, but the number of vomits was higher on domperidone ($P = 0.003$) and the duration was significantly increased ($P = 0.02$). Patients experienced significantly more diarrhoea on domperidone ($P < 0.0001$), although it was predominantly mild. Patients were significantly more sedated on prochlorperazine on the second course ($P = 0.006$), but not on the first course ($P = 0.9$). More patients preferred their second course ($P < 0.0001$), and were significantly less anxious ($P = 0.0002$). Patients reported tolerating their treatment similarly for both antiemetics, but more patients preferred prochlorperazine ($P = 0.003$), mainly due to reductions in nausea and vomiting and other side-effects, particularly diarrhoea.

Keywords: antiemetic, domperidone, prochlorperazine, outpatient chemotherapy, randomised, double-blind, crossover

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INTRODUCTION

CYTOTOXIC DRUGS causing severe emesis, such as cisplatinum or dacarbazine, are often given with intravenous antiemetics and the patients treated as inpatients. Other cytotoxics, usually associated with less emesis, can be delivered to outpatients, and the nausea and vomiting controlled with oral or per rectal antiemetics [1].

Domperidone is a dopamine agonist related to the butyrophenones, with antiemetic properties similar to those of metoclopramide. Unlike metoclopramide, however, it does not readily cross the blood–brain barrier and seldom causes extrapyramidal side-effects [2]. Intravenous domperidone was effective, particularly with cytotoxic regimens of moderate emetogenicity which did not contain cisplatinum [3, 4]. However, serious side-effects including cardiotoxicity caused the intravenous formulation to be withdrawn [5–7].

Antiemetic suppositories are useful for the control of vomiting in outpatients following cytotoxic chemotherapy when there may be difficulty absorbing oral medication. Peak plasma levels of domperidone are reached 1–4 h after per rectal administration [8]. Small studies have demonstrated the efficacy of domperidone suppositories when used with moderately emetogenic chemotherapy [9–11].

The aim of the current study was to compare our practice of using prochlorperazine suppositories for outpatients receiving moderately emetogenic chemotherapy with the use of domperidone suppositories in a prospective randomised double blind crossover study.

PATIENTS AND METHODS

Patients with histologically documented malignancy who were receiving outpatient chemotherapy containing drugs or combi-

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nations likely to cause mild to moderate nausea and vomiting, e.g. cyclophosphamide, doxorubicin, carboplatin, methotrexate and etoposide, were eligible for this study. Patients must have had a performance status of ECOG 0–2 and no serious concomitant medical illnesses. Women who were pregnant or lactating were excluded, and patients who had received phenothiazines or domperidone within 24 h of the study, or had experienced previous adverse reactions to domperidone or phenothiazines were excluded. The protocol was approved by the Ethics Committee at the Peter MacCallum Cancer Institute, and each patient gave written informed consent before entering the study.

The study was a randomised double blind crossover study conducted over two consecutive courses of chemotherapy with the patients acting as their own controls.

Domperidone suppositories were supplied by Janssen-Cilag Pty. Ltd. (NSW, Australia) and administered at a dose of 60 mg per rectum every 4 h for four doses starting 30 min prior to chemotherapy. Prochlorperazine suppositories, 25 mg, were given following the same dosing schedule.

Patients were asked to complete a questionnaire at 24 h and to mail it back to the data managers. Patients assessed the severity and duration of pre- and post-treatment nausea and vomiting, and recorded any toxicities, but specifically sedation, restlessness, muscle spasms, dry mouth, diarrhoea, rash and headache.

Patients who experienced any nausea in the 24 h after receiving chemotherapy were asked to grade the severity as mild, moderate, severe or very severe, and indicate how soon after chemotherapy it started: less than 1 h, 1–2 h, 3–5 h, 6–10 h or 11 or more h, and how long it lasted: less than 1 h, 1–2 h, 3–5 h, 6–10 h, 11 or more h. The same categories were used for the severity, time of onset and duration of vomiting. Patients also indicated whether they vomited (or dry retched) 1–2, 3–5, 6–10 or 11 or more times. Sedation, diarrhoea, restlessness and tolerance were graded on 5-point categorical scales by the patient.

It was planned to accrue patients until 100 eligible, fully evaluable patients (i.e. those who had received identical chemotherapy doses in both study courses) had been entered. Based on estimates of within-patient variances from a previous crossover study, this would enable a difference of 14% in the rate of complete protection from nausea and vomiting to be detected with a power of 0.8 when tested at a significance level of point 0.05 using a two-tailed test of significance, assuming an average complete protection rate of 25%. Although higher complete protection rates of up to 50% were anticipated for this study, it was not expected that the higher rates would seriously affect the power calculations. At worst, if the complete protection rates in courses 1 and 2 were independent (no correlation within patients) and the average complete protection rate was 50%, then an absolute difference of 21% from 40 to say 60% would be detected with a power of 0.8 when tested at a significance level of 0.05.

Three comparisons between domperidone and prochlorperazine were made based on all patients who received course 1 (134 patients), all patients who completed the crossover (119 patients) and patients who received equal chemotherapy in both courses (100 patients). Results for the last comparison are representative and are presented, being the most valid. Three significance tests were performed for each outcome variable: one to test for the significance of any carry-over effect, one comparing the results of courses 1 and 2 to test for a period effect, and finally, a test for the differences in treatment effect between domperidone and prochlorperazine using standard non-parametric tests for the analysis of crossover studies [12, 13].

Graded data were placed by scores of 1–5 or 1–6 depending on the number of prerecorded categories. For each graded variable, a carry-over test was performed by comparing the sum of scores for courses 1 and 2 for patients randomised to receive prochlorperazine first with those for patients randomised to receive domperidone first using the Wilcoxon rank sum test. Period effects were tested by subtracting the score obtained on the prochlorperazine course from that obtained on the domperidone course, and comparing the resulting differences between patients randomised to receive prochlorperazine first with those for patients randomised to receive domperidone first. Likewise, treatment effects were tested by subtracting the score obtained in course 2 from the score obtained in course 1, and comparing these differences for patients in the two randomisation arms. Thus, treatment comparisons were valid even if period effects were present and *vice versa*. Prescott's test was used to compare course preferences and complete protection rates. Two-tailed significance levels have been reported throughout.

RESULTS

A total of 136 patients were entered into the trial before the target of 100 patients receiving identical chemotherapy for each course was reached. Fifty-eight per cent of these patients received chemotherapy regimens containing prednisolone (Table 1). One patient in each arm withdrew before commencing treatment, 9 did not receive the planned chemotherapy and 6

Table 1. *Patients' characteristics*

	All patients	Equal chemotherapy
Patient number	136	100
Median age, years (range)	47 (28–74)	47 (28–74)
Sex		
Male	10	8
Female	126	92
Prior chemotherapy		
Yes	39	27
No	97	73
Chemotherapy regimens		
CMFP	72	50
CMF	34	27
A	10	8
CA	3	3
CTP	3	2
CBDCA	2	1
CVP	2	2
N	2	1
CAVP	2	2
AV	1	0
CBDCA/E	1	1
EPI	1	0
CNVP	1	1
M/N/MMC	1	1
CFP	1	1

C, cyclophosphamide; M, methotrexate; F, 5-fluorouracil; P, prednisolone; A, doxorubicin; E, etoposide; T, teniposide; CBDCA, carboplatin; V, vincristine; N, mitozantrone; EPI, epirubicin; MMC, mitomycin.

did not receive the planned antiemetic. Patient compliance in administering the antiemetics as outpatients was satisfactory. In course 1, 82% who received domperidone first and 85% who had prochlorperazine first administered all doses as planned. With course 2, 73% who received domperidone first and 69% who received prochlorperazine first administered all doses as planned.

Of the 119 patients who completed two courses of chemotherapy, 19 had dose modifications in the chemotherapy given. Treatment comparisons are presented for the remaining 100 patients who received identical chemotherapy doses in both courses.

There were no differences in pretreatment nausea, vomiting or anxiety prior to the first course, which demonstrates that for these parameters the arms were balanced after randomisation. There was, however, more pretreatment anxiety in patients receiving their first ever chemotherapy as compared to those who had had prior chemotherapy. Differences in the efficacy of the antiemetics given in course 1 could give rise to differences in pretreatment toxicities in course 2, with patients who had experienced nausea and vomiting in course 1 more likely to have pretreatment nausea, vomiting and/or anxiety. No differences between the arms were seen in these pretreatment parameters in the second course.

Forty per cent of patients did not have any nausea on either arm, 18% had nausea on domperidone but not on prochlorperazine, 11% had nausea on prochlorperazine but not on domperidone, and 31% had nausea on both. Overall, patients experienced either more nausea or more severe nausea on domperidone ($P = 0.05$), but the duration was similar on both arms ($P = 0.4$; Table 2). When the comparisons were restricted to the 31% of patients who had nausea on both arms, there were no significant differences between the severity ($P = 0.2$) or duration ($P = 0.6$). Eighty per cent of patients vomited on neither arm, 6% vomited on domperidone but not prochlorperazine, 2% vomited on prochlorperazine but not domperidone and 12% vomited on both. Overall, there were significantly more vomiting episodes on domperidone ($P = 0.003$), and the duration was significantly increased ($P = 0.02$; Table 3). When the comparisons were restricted to the 12% of patients who vomited on both arms, there were still significantly more episodes on domperidone ($P = 0.009$) and the duration was increased ($P = 0.06$). Complete protection from nausea and vomiting was achieved on both courses for 38% of patients, on domperidone but not on prochlorperazine for 12% of patients, on prochlorperazine but not on domperidone for 19% of patients, and on neither for 30% of patients ($P = 0.2$). The overall complete protection rate was 51% for domperidone courses and 58% for prochlorperazine courses.

Table 2. Severity and duration of nausea

	Severity			Duration	
	Dom %	Pro %		Dom %	Pro %
None	52	59	None	52	58
Mild	26	25	<1 h	8	10
Moderate	11	10	1–2 h	8	5
Severe	10	5	3–5 h	11	8
Very severe	1	1	6–10 h	5	5
			11+ h	16	14

Dom, domperidone; Pro, prochlorperazine.

Table 3. Severity and duration of vomiting

	Number of vomits			Duration	
	Dom %	Pro %		Dom %	Pro %
None	82	86	None	82	86
1–2	4	5	<1 h	5	5
3–5	4	4	1–2 h	0	0
6–10	1	2	3–5 h	2	2
11+	9	3	6–10 h	2	2
			11+ h	9	5

Dom, domperidone; Pro, prochlorperazine.

Table 4. Diarrhoea

Severity	Domperidone %	Prochlorperazine %
None	34	71
Mild	55	24
Moderate	9	5
Severe	1	0
Very severe	1	0

Patients experienced more diarrhoea on domperidone than prochlorperazine ($P < 0.0001$) although it was predominantly mild (Table 4). There were no significant differences between the two antiemetics in the incidence of anxiety, restlessness, muscle spasms, dry mouth, skin rash or headaches. Patients appeared to experience more severe sedation on prochlorperazine than on domperidone ($P = 0.04$) based on the crossover analysis, but there was evidence of a significant carry-over effect for this parameter ($P = 0.04$). There was no significant difference between the antiemetics in the first course, but patients receiving prochlorperazine in the second course experienced more sedation than those receiving domperidone in the second course ($P = 0.006$). Patients randomised to domperidone first experienced more sedation on prochlorperazine in their second course than they experienced with domperidone in their first course ($P = 0.01$, Wilcoxon's signed ranks test), but patients randomised to prochlorperazine first had no difference in their sedation for the two courses ($P = 0.6$; Table 5).

There was no difference between the arms in the patients'

Table 5. Sedation

	Course 1		Course 2		Total	
Severity	Dom %	Pro %	Dom %	Pro %	Dom %	Pro %
None	22	36	33	15	26	27
Mild	52	24	38	35	48	29
Moderate	20	24	16	23	16	22
Severe	7	16	10	22	9	18
Very severe	0	0	2	10	1	3

Dom, domperidone; Pro, prochlorperazine.

overall tolerance of their therapy, an assessment which reflects the balance between efficacy and toxicity. Significantly more patients, however, preferred prochlorperazine over domperidone (44 versus 22%, $P = 0.003$, with 34% having no preference). Significantly more patients preferred the second course to the first course ($P < 0.0001$), and were less anxious ($P = 0.0002$) and experienced fewer headaches ($P = 0.05$) in the second course.

DISCUSSION

This antiemetic study is the first to directly compare prochlorperazine to domperidone suppositories for the outpatient control of emesis after non-cisplatinum-containing chemotherapy. The patient preference was ascribed predominantly to the reduction in nausea and vomiting on the prochlorperazine arm but the lower incidence of side-effects, particularly diarrhoea was also cited. Both antiemetics used as single agents in this patient population achieved good complete control of emesis. If the comparison between the antiemetics was restricted to the patients who vomited or had nausea on both arms, there were still significantly more vomiting episodes on domperidone as compared to prochlorperazine, but there was no difference in the severity nor duration of the nausea. It must be stressed that the outpatient chemotherapy regimens were only of moderate emetic potential. In addition, 58% of them contained prednisolone, which may add to the efficacy of both antiemetic drugs, although this does not affect the comparison between them.

Patient compliance was similar in administering each antiemetic, however, with the significantly greater problem of diarrhoea with domperidone suppositories, there is a question as to whether all doses of domperidone were adequately absorbed.

The patients were specifically asked about the known side-effects of the antiemetics, that is, sedation, diarrhoea, restlessness, dry mouth, rash, headache, and were asked to grade the first three. They were then asked to describe other side-effects.

The incidence of the side-effects subject to specific questions may, therefore, be reported as higher than other side-effects which is most important. As an example, there is a high incidence of sedation reported but very few cases were severe or very severe.

This study illustrates the care which must be taken in the analysis of crossover studies. There were period effects, as demonstrated by the heightened anxiety of patients having their initial course of therapy, particularly if they were chemotherapy naive, and carry-over effects were found in the analysis of sedation. In antiemetic studies, the carry-over effects are usually not physical because of the time interval between treatments, but may be psychological based on the patients' experience in the first period. This is best illustrated by the phenomenon of anticipatory nausea and vomiting [14]. The appropriate methods of analysis of crossover data must be used to ensure that any differences between courses do not invalidate the treatment comparisons [13].

In conclusion, prochlorperazine suppositories are well tolerated for use as outpatient antiemetics for moderately emetogenic chemotherapy, and are more effective and less toxic than domperidone suppositories.

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