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Delayed Emesis Following High-dose Cisplatin: A Double-blind Randomised Comparative Trial of Ondansetron (GR 38032F) Versus Placebo

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Despite recent advances in control of acute emesis, delayed nausea and vomiting following cisplatin-based chemotherapy remain a significant cause of treatment-related morbidity. Ondansetron, a selective $5HT_3$ receptor antagonist, is effective in preventing acute emesis in the initial 24-h period following high-dose cisplatin. The efficacy and safety of ondansetron in preventing the delayed emesis syndrome during days 2–5 after cisplatin ($\geq$100 mg/m^2) were evaluated in a double-blind, placebo-controlled multicentre trial. 50 patients having two or fewer emetic episodes during the first 24 h were randomised to receive ondansetron (16 mg) or placebo orally three times daily beginning 24 h after cisplatin. Rates of complete control of emesis were higher in ondansetron-treated patients during each study day, 59–78%, compared with 39–50% in placebo-treated patients, but the differences were statistically superior only on the third study day ($P = 0.009$). 40% of patients in the ondansetron treatment arm and 33% treated with placebo had complete control of emesis during the entire 4-day study period ($P = 0.648$). Withdrawal from study due to nausea and vomiting occurred in 13% of ondansetron-treated patients compared with 33% in the placebo arm ($P = 0.102$). Control of nausea was better with ondansetron, but differences were not statistically significant. Adverse effects of oral ondansetron given in this dose schedule were minimal. These data suggest that the delayed emesis syndrome may be partially mediated through the $5HT_3$ receptor, but that a serotonin antagonist alone provides inadequate control. Further investigation of ondansetron-based therapy in this clinical setting is warranted.
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INTRODUCTION

CISPLATIN CHEMOTHERAPY results in two distinct patterns of nausea and vomiting, the first a well described and studied acute emetic response, and the second a less well recognised syndrome of delayed emesis [1–4]. Despite recent advances in the control of acute emesis following cisplatin, delayed nausea and vomiting remain a significant cause of treatment-related morbidity and patient refusal of further chemotherapy. Even using the currently accepted standard of oral metoclopramide and dexamethasone, approximately one-half of cisplatin-treated patients still experience delayed emesis [5].

Ondansetron (GR 38032F) is a selective antagonist of the serotonin subtype 3 receptor ($5HT_3$) type with demonstrated efficacy in preventing acute emesis following cisplatin therapy [6, 8]. Two randomised comparative trials of ondansetron vs. metoclopramide have recently demonstrated superior efficacy and a reduced toxicity profile for the antiserotonin agent during the acute emesis phase (initial 24 h) following cisplatin therapy [9, 10]. In contrast to the numerous studies of ondansetron for acute cisplatin-induced emesis, little information is available regarding this agent in the setting of delayed emesis. The following report reviews previous studies of this problem and presents the results of a randomised trial of ondansetron vs. placebo in the prevention of delayed cisplatin-induced emesis.

PATIENTS AND METHODS

Study design

The current study was designed as a double-blind, randomised, stratified placebo-controlled evaluation of ondansetron in the prevention of delayed emesis following high-dose cisplatin therapy ($\geq$100 mg/m^2) with a 4-day study period beginning 24 h after cisplatin administration.

Patient eligibility

Patients $\geq$18 years of age with a Karnofsky performance score $\geq$60%, receiving their initial dose of cisplatin ($\geq$100 mg/m^2) were eligible if they had two or less emetic episodes during the initial 24-h period following cisplatin while enrolled in an acute emesis protocol [10]. All patients had adequate haematological, renal and hepatic function. Exclusion criteria included significant psychiatric, cardiovascular or

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Table 1. Patients' characteristics

	Ondansetron	Placebo
Number of patients	31	19
Age		
Median	57	59
Range	41–81	43–74
Sex		
Male	23 (74%)	15 (79%)
Female	8 (26%)	4 (21%)
Chemotherapy		
Cisplatin plus others	21 (68%)	13 (68%)
Cisplatin alone	10 (32%)	6 (32%)
Cancer type		
Head and neck	14 (45%)	4 (22%)
Lung	7 (23%)	6 (32%)
Ovarian	2 (6%)	2 (11%)
Other	8 (26%)	6 (34%)
Previous acute antiemetic treatment		
Ondansetron	13 (42%)	11 (61%)
Metoclopramide	18 (58%)	7 (39%)

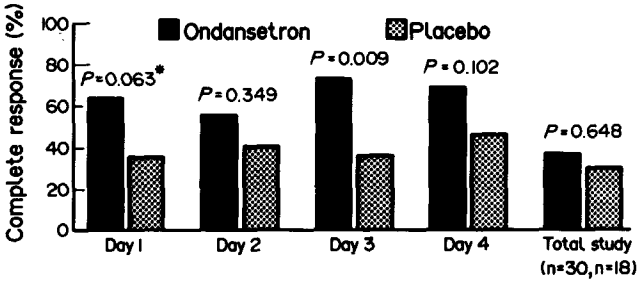

Fig. 1. Delayed emesis study (study S3A-291). Complete response data by study day and total study period. *Mantel–Haenszel test on complete response vs. other categories combined.

cerebrovascular disease, concurrent abdominal radiotherapy, and use of any other medications with potential antiemetic effects.

Acute antiemetic therapy: during the 24-h period following cisplatin and preceeding the current study, patients received either ondansetron 0.15 mg/kg intravenously every 4 h for three doses, or metoclopramide 2 mg/kg intravenously every 2 h for three doses, and then every 3 h for an additional three doses, while participating in a randomised comparative trial [10].

Table 2. Emetic complete response and failure by study day

	Study day	Ondansetron	Placebo	*P*-value*
Complete response	1	20/30 (67%)	7/18 (39%)	0.063
	2	17/29 (59%)	8/18 (44%)	0.349
	3	21/27 (78%)	7/18 (39%)	0.009
	4	20/27 (74%)	9/18 (50%)	0.102
Failure or withdrawn†	1	1/30 (3%)	2/18 (11%)	0.286
	2	5/29 (17%)	6/18 (33%)	0.210
	3	4/27 (15%)	6/18 (33%)	0.148
	4	5/27 (18%)	6/18 (33%)	0.263

*Mantel–Haenszel test.
†Includes patients withdrawn due to nausea and vomiting, adverse events or administrative error.

Treatment plan

After obtaining informed consent, patients were randomised on a 2:1 schedule to receive ondansetron 16 mg orally three times daily for 4 days, or an identical placebo. Study medications were begun 24 h following cisplatin. All patients received a packet of rescue antiemetics for use in the event of treatment failure, study medication toxicity, or patient request for removal from study.

Methods of assessments

Emetic response for each study day was defined as follows—complete response: no emetic episodes (vomits); major response: 1–2 emetic episodes; minor response: 3–5 emetic episodes; and failure: > 5 emetic episodes or withdrawal from study. One to five retches within a 5-min period was also considered an emetic episode. Total number of emetic episodes was defined as the number of vomits plus retches.

Nausea was assessed by a visual-analogue scale (0–100 mm), as previously described, where 0 = no nausea and 100 = nausea as severe as it could be [3].

Patients kept a daily diary and were also contacted daily by a research coordinator to assess the number of emetic episodes, severity of nausea, medication compliance, and occurrence of any adverse events.

Statistical analysis

Treatment groups were compared for the number of emetic episodes each day using the Wilcoxon rank sum test and for complete response and failure using the Mantel–Haenszel test. Severity of nausea was compared using the Wilcoxon rank sum test and proportion of patients having nausea by Fisher's exact test. All tests were two-sided at a significance level of 0.05.

RESULTS

Patients' characteristics

50 patients categorised as acute emesis responders (< 3 emetic episodes during the initial 24 h following cisplatin) were enrolled in the current study. 31 patients were randomised to ondansetron and 19 patients to placebo (Table 1). Treatment groups were similar in respect to age, sex, alcohol intake, cisplatin regimen and tumour type. A somewhat higher percentage of patients in the placebo group had received ondansetron rather than metoclopramide during the acute emesis phase preceeding the current study.

Response analysis

2 patients, 1 in each treatment group, were found to be ineligible for study entry and are excluded from response analysis. Comparison of complete response rates (no emetic episodes) for each study day and for the entire 4-day study period are shown in Fig. 1. Complete control was higher in ondansetron-treated patients during each study day, 59–78%, vs. 39–50% in placebo-treated patients (Table 2). These differences were statistically significant on study day 3 (P= 0.009) and approached significance on study day 1 (P= 0.063). Overall complete control during the entire 4-day study period was 40% in the ondansetron arm and 33% with placebo (P= 0.648). Failure or withdrawal from study occurred in 3–18% of ondansetron-treated patients vs. 11–33% of patients in the placebo group. There were no significant differences in complete control or failure between the treatment groups based on patient age, sex or previous alcohol intake (data not

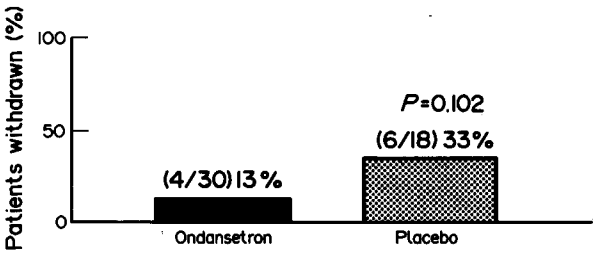

Fig. 2. Patients withdrawn for nausea or vomiting.

shown), although the small patient numbers in some categories precluded adequate statistical comparison.

13% of ondansetron patients (4/30) withdrew from the study because of nausea and vomiting (Fig. 2) compared with 33% (6/18) of placebo-treated patients ($P=0.102$). Patient assessment of nausea (yes/no and mean/median) values by visual–analogue scale is reported in Table 3. Although a smaller percentage of ondansetron-treated patients experienced nausea during each study day, none of the differences reached statistical significance.

Safety analysis

All 50 patients registered on the study were evaluable for safety analysis (Table 4). Ondansetron was safe and well-tolerated. Minor adverse events were reported by 48% of ondansetron patients and 26% of placebo-treated patients ($P=0.779$), most commonly consisting of mild headache and diarrhoea. No extrapyramidal reactions were observed.

Table 3. Nausea results

	Ondansetron	Placebo	*P*-value
Number of patients	30	18	
No Nausea*			
Day 1	16 (53%)	6 (33%)	0.237
Day 2	18 (60%)	8 (44%)	0.748
Day 3	17 (57%)	5 (28%)	0.148
Day 4	18 (60%)	6 (23%)	0.112
Nausea scores† mean (median)			
Day 1	26 (3)	38 (43)	0.218
Day 2	23 (2)	17 (3)	1.000
Day 3	10 (0)	23 (10)	0.211
Day 4	8 (1)	14 (3)	0.269

*P-values based on Fisher's Exact Test.
†P-values based on Wilcoxon Rank Sum Test.

Table 4. Adverse events

	Ondansetron	Placebo	*P*-value
Number of patients	31	19	
Number of patients with at least one adverse event	15 (48%)	5 (26%)	0.779
Number of adverse events	32	10	
Adverse events reported by more than one patient			
Central nervous system			
Headache	6 (19%)	2 (11%)	
Nervousness	1 (3%)	1 (5%)	
Gastrointestinal			
Diarrhoea	5 (16%)	1 (5%)	
Constipation	2 (6%)	1 (5%)	
Stomach cramp(s)	1 (3%)	1 (5%)	

P-value for combined data (Fisher's exact test).

Table 5. Complete control of delayed emesis following cisplatin

	Treatment arms				
Reference	DEX	MCP	MCP+DEX	OND	Placebo
5	35%	–	52%	–	11%
15	–	35%	–	33%	–
16	65%	69%	–	–	56%
Present study	–	–	–	40%	33%

DEX = Dexamethasone; MCP = metoclopramide; OND = ondansetron.

DISCUSSION

The primary objectives of the present study were to test the effectiveness and determine the safety profile of oral ondansetron in the prevention of delayed emesis during the period 24–120 h following the administration of high-dose cisplatin. The use of a placebo control in this study also provided information regarding the incidence and severity of delayed nausea and vomiting in patients who had not received a corticosteroid during the initial 24 h acute emetic phase. The results demonstrate higher complete emetic response rates and lower failure rates with ondansetron during each study day, although most of the differences do not achieve statistical significance. In addition, 33% of placebo-treated patients withdrew from study because of nausea and vomiting vs. 13% of ondansetron-treated patients. These data suggest that the $5HT_3$ receptor plays at least a partial role in mediating the delayed emesis syndrome, but that a serotonin antagonist alone provides inadequate control.

In recent years, preclinical studies using animal models such as the ferret have greatly expanded our basic understanding of the pathophysiology of acute chemotherapy-induced emesis [11–14]. These studies have demonstrated that serotonin and the $5HT_3$ receptor are important factors in promoting acute emesis following chemotherapy. In contrast, the neurotransmitter responsible for the delayed emesis syndrome following cisplatin administration remains unclear, and there are no established animal models for studying this problem.

Recent clinical studies have helped to define the incidence and natural history of the delayed emesis syndrome. In 1985, Kris *et al.* reported that 74% of patients receiving high-dose cisplatin experienced delayed emesis when treated with oral prochlorperazine alone [3]. Table 5 describes the results of subsequent clinical trials in the delayed emesis syndrome. In 1989, Kris *et al.* performed a double-blind randomised trial comparing placebo with dexamethasone and to the combination of oral metoclopramide and dexamethasone for delayed emesis following high-dose cisplatin (120 mg/m^2). Complete control of emesis during the 4 day study period was obtained in 52% of patients in the combination arm, 35% receiving dexamethasone alone, and only 11% assigned to the placebo arm [5]. Since that time, this combination has been considered standard therapy for the delayed emesis syndrome.

In a study by Marty *et al.* comparing intravenous ondansetron and metoclopramide for acute cisplatin-induced emesis (80–100 mg/m^2), a subset of patients were rerandomised to receive either oral ondansetron, 8 mg every 8 h, or metoclopramide, 20 mg orally every 8 h. There were no significant

differences in overall control of delayed emesis ($P=0.485$), but metoclopramide was apparently superior in reducing nausea ($P=0.026$) [15]. Most recently, a randomised comparative trial by Roila *et al.* in cisplatin-treated patients (50 mg/m^2, median 90 mg/m^2) demonstrated no differences in the overall incidence of delayed emesis between patients receiving either oral metoclopramide alone, dexamethasone alone, or placebo [16]. Rates of overall complete control of emesis were over 50% in all three treatment arms, including placebo. The differences in results of these clinical trials, particularly the rates of complete control in the placebo arms, are of interest, and may reflect variability in both cisplatin dose and patient selection factors, as previously described [3, 16].

By comparison, the results of the current study suggest that serotonin may not be the sole mediator of the delayed emesis syndrome. Daily rates of complete emetic control, failure and control of nausea consistently favoured ondansetron, yet differences were not statistically significant in most comparisons. These results may also reflect the relatively small number of patients in this study. Further studies of serotonin antagonists in the setting of the delayed emesis syndrome appear warranted. In particular, preclinical studies designed to elucidate the pathogenesis of delayed emesis would be helpful in clarifying the best approach to future clinical trials.

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