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Original Paper

An Open Randomised Cross-over Study on Granisetron Versus Ondansetron in the Prevention of Acute Emesis Induced by Moderate Dose Cisplatin-containing Regimens*

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The aim of the study was to compare granisetron (GRA) with ondansetron (OND) in the prevention of acute emesis in consecutive chemotherapy-naive patients admitted to our department to receive a cytotoxic treatment containing cisplatinum (CP) at a dose ≥50 mg/m². Eligible patients were randomised at their first cycle to receive either OND or GRA with cross-over of the anti-emetic treatment on the second cycle. The cytotoxic treatments included five different multidrug regimens containing CP (median dose 60 mg/m², range 50–70 mg/m²) administered on day 1 and repeated every 21–28 days. OND was administered at the dose of 8 mg × 3 i.v. on day 1 and 8 mg × 2 orally on day 2. GRA was always administered at the dose of 3 mg i.v. on day 1. 124 patients entered the study. 58 patients received OND at their first cycle and 66 received GRA. Complete protection of acute emesis with OND and GRA was observed, with the first and second cycles combined as follows: nausea 53 and 60%, vomiting 68 and 71%, respectively (no statistically significant difference). The cross-over analysis comprising 101 patients confirmed no difference between the two anti-emetic treatments. 21 patients (19%) on OND and 14 patients (12%) on GRA suffered headaches ($P = 0.15$). 25 (25%) patients preferred OND, 45 (45%) preferred GRA, while 31 (30%) expressed no preference ($P = 0.003$). However, these differences also depended on the sequence of anti-emetics in the cross-over. In conclusion, in this study, a single dose of GRA is demonstrated to be as effective as multiple doses of OND in the prevention of acute emesis.

Key words: anti-emetic therapy, ondansetron, granisetron
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INTRODUCTION

ONDANSETRON (OND) IS a selective 5-HT3 receptor antagonist effective in the control of acute nausea and vomiting induced by emetogenic cytotoxic treatments, particularly by cisplatinum (CP)-containing regimens [1, 2].

Granisetron (GRA) is another 5-HT3 receptor antagonist also effective in preventing vomiting [3]. In an animal model, GRA was 5–10 times more potent in controlling vomiting than OND [4]. GRA has a plasma half-life of 9–11 h in cancer patients and a single i.v. dose of 3 mg administration is considered the standard treatment for CP-based chemotherapy administered in 1 day [5]. OND has a shorter plasma half-life, calculated to be 3.5 h in volunteers [6]. One of first considered standard regimen of OND was 8 mg 3 times i.v. on the day of the cytotoxic treatment [7].

Since 1991, OND has been introduced in the anti-emetic treatment for patients receiving CP-containing chemotherapy at our department. The subsequent availability of GRA induced us to compare the efficacy and safety of these two anti-emetic agents. At our department, OND dose and schedule for moderate dose CP-based regimen is 8 mg three times daily on day 1 and 8 mg twice daily on day 2. This was the regimen chosen as the reference treatment with which to compare GRA.

MATERIALS AND METHODS

Patients

All consecutive chemotherapy-naive patients admitted to the Medical Oncology Division of S. Orsola-Malpighi Hospital in Bologna in order to receive a cytotoxic treatment including CP at the dose ≥50 mg/m² were considered for entry to the study. Patients with gastro-intestinal cancer or symptomatic brain

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metastases, or vomiting in the previous week were excluded. No other anti-emetic drugs including corticosteroids were allowed.

Study design

Patients eligible for the study were randomised at their first cycle to receive either OND or GRA. The anti-emetic treatment was crossed-over on the second cycle.

The cytotoxic treatment included five different regimens containing CP (median dose 60 mg/m^2, range 50–70 mg/m^2) and one or two other drugs including epirubicin (50–120 mg/m^2) or cyclophosphamide (500 mg/m^2) or methotrexate (40 mg/m^2) or vinorelbine (25 mg/m^2). All the regimens were administered i.v. on day 1 and repeated every 21–28 days.

OND was administered i.v. at a dose of 8 mg × 3 on day 1 and 8 mg × 2 orally on day 2. GRA was always administered at a dose of 3 mg i.v. push on day 1 before chemotherapy.

Evaluation

The evaluation of the anti-emetic effect was performed by a physician on the basis of the presence or absence of nausea and vomiting during the first 24 h after the first two cycles of chemotherapy, and on patient preference. An episode of vomiting was defined as a single expulsion of stomach content through the mouth or an attempt to vomit. Nausea was defined as sense of vomit and loathing for food with a reduction of intake. The request for a preference was made immediately before the third cycle. Comparisons have been made on the number of patients having a complete protection from nausea and vomiting. Complete protection was defined as the absence of nausea and vomiting.

Statistical analysis

Sample size for this bioequivalence study has been calculated on the basis of anti-emetic response, following the approach of Machin and Campell [8] as programmed in the statistical package 'SOLO Power Analysis' by BMDP Statistical Software, Inc. A cross-over design was assumed. Lower and upper limits of the null hypothesis were set to ±15% of the OND proportion. With $a = 0.05$ and $(1-b) = 0.8$, the required sample size for the study was 105 patients evaluable for both treatments. An 'intention to treat' analysis was performed, including all the patients who were randomised and who received at least the first cycle of chemotherapy, including 100% of the scheduled dose of CP. All the patients were included in the safety analysis.

The primary efficacy variables were response (i.e. no vomiting, no nausea) and patient preference.

The Pearson's chi-square test [9] was used to compare response proportion in the two treatment groups. A treatment by-period interaction was assessed using log-linear models [8]. In the absence of period interaction, a cross-over analysis on patients completing both treatment cycles was also performed for the efficacy variables using McNemar's test [9].

RESULTS

124 patients entered the study from March 1993 to June 1994. Their characteristics are reported in Table 1. 58 were randomised to receive OND and 66 to receive GRA at their first cycle of chemotherapy. 23 patients (9 who were to receive GRA and 14 who were to receive OND following cross-over) were not evaluable at the second cycle for the following reasons: 13 (6 on GRA and 7 on OND) had a reduced dose of cytotoxic drugs, 9 (2 on GRA and 7 on OND) did not receive the second cycle at all and 1 on GRA had protocol violation.

Complete protection of acute nausea and vomiting is reported in Table 2. A comparison between the two anti-emetic treatments, considering the first and second evaluable cycles together, demonstrated that in 53% (95% C.I. 43–63%) on OND and 60% (95% C.I. 52–70%) on GRA there was no nausea and in 68% (95% C.I. 59–77%) on OND and 71% (95% C.I. 63–80%) on GRA vomiting was not observed. The differences were not statistically significant. In the first cycle, 60% of patients on OND and 64% on GRA, did not suffer from nausea, and 74% on OND and 76% on GRA did not present vomiting. A slight reduction in the emesis protection rate occurred in the second cycle: 44% of patients on OND and 55% on GRA did not suffer nausea while 61.5 and 65%, respectively, did not present vomiting. The differences were not statistically significant. Similar results were observed when the presence or absence of nausea and vomiting were considered simultaneously.

Cross-over analysis was carried out on 101 patients who received both the first and second cycles. No period or carry-over effect was observed on the complete response and thus the results of both cycles were pooled (Table 3). 20 patients (20%) not protected from nausea by OND were protected by GRA, while 12 (12%) not protected by GRA were protected by OND; 13 patients (13%) not protected from vomiting by OND were protected by GRA, while 10 (10%) not protected by GRA were protected by OND. The differences were not statistically significant.

A significant difference was observed with overall patient preferences, being lower for OND (25%; 25/101 patients) than GRA (45%; 45/101 patients) with an odds ratio OND/GRA of 1:0.409 ($P = 0.003$; 95% C.I. for odds ratio 0.22–0.75). 31 patients (30%) expressed no preference. The statistical analysis, however, shows that the patient preference was conditioned by the type of sequence in the anti-emetic administration. Of those that were evaluable, 18 (37%) patients preferred OND against 20 (41%) who preferred GRA and 11 (22%) who did not express any preference when OND was administered at the first cycle (no statistical difference). Only 7 (13%) patients preferred OND against 25 (48%) who preferred GRA and 20 (38%) who did not express a preference when GRA was administered at the first cycle ($P = 0.019$).

No serious side-effects were attributed to anti-emetic treatment. Mild headaches during the first 24–36 h was the most frequently observed symptom. Overall, 21 patients complained of headaches (18%) on OND and 14 (13%) on GRA ($P = 0.25$). After the first cycle, 9 patients (15%) on OND and 9 patients (14%) on GRA suffered from headaches ($P = 0.76$). After the second cycle, 12 patients (23%) on OND and 5 patients (10%) on GRA had headaches ($P = 0.09$). The analysis of the 101 patients who crossed over the treatments shows that there was no period effect. 14 patients (14%) suffering from headaches on OND did not complain of the symptom on GRA, while 6 patients (6%) who suffered from headaches on GRA did not complain of the symptom on OND ($P = 0.074$ McNemar test). 5 (5%) and 3 (3%) patients on OND and GRA, respectively, suffered from mild constipation, while diarrhoea was recorded in 1 and 3 patients, respectively.

DISCUSSION

This study compares a multidose regimen of the first commercially available 5-HT3 antagonist, OND, with one dose of the subsequently available antagonist GRA in the prevention of CP-induced acute emesis. It is a 'spontaneous', unsponsored trial comparing the two anti-emetics exclusively in CP-treated pati-

Table 1. Patient characteristics

Patients	Entered (no.)	124
	Outpatients	20%
	Inpatients	80%
Sex	Male	75%
	Female	25%
Age	Median (range)	62 (32–77)
PS (Karnofsky)	Median (range)	80 (50–100)
Primary tumour	NSCLC	76
	Bladder	34
	Ovary	7
	Others	7
Previous emesis*		5%
Alcohol use†		20%
Chemotherapy‡	CP (60) + VNR (25)	54
	CP (60) + EPI (120)	22
	CP (60) + EPI (60)	7
	CP (50) + EPI (50) + CTX (500)	7
	CP (70) + EPI (60) + MTX (40)	34

*Kinetosis, during pregnancy.
†>0.75 l daily of wine. ‡CP, cisplatinum; VNR, vinorelbine; EPI, epirubicin; CTX, cyclophosphamide; MTX, methotrexate. The i.v. in mg/m² on day 1 is reported in parentheses.

Table 2. Complete protection from acute emesis

		OND	GRA	P^*
First cycle	*n*	58	66	
	No nausea	35 (60%)	42 (64%)	0.70
	No vomiting	43 (74%)	50 (76%)	0.83
	No nausea and vomiting	34 (59%)	41 (62%)	0.69
Second cycle	*n*	52	49	
	No nausea	23 (44%)	27 (55%)	0.25
	No vomiting	32 (61.5%)	32 (65%)	0.73
	No nausea and vomiting	21 (40%)	26 (53%)	0.20
First and second cycle	*n*	110	115	
	No nausea	58 (53%)	69 (60%)	0.27
	No vomiting	75 (68%)	82 (71%)	0.61
	No nausea and vomiting	55 (50%)	67 (58%)	0.21

*Pearson's chi-square.
Analysis by log-linear model for period effect (OND → GRA and GRA → OND) is not statistically significant.

ents. Our study has homogeneous characteristics because it was monocentric, enrolling only chemotherapy-naive patients and using only a limited number of emetogenic regimens, all including CP at the median dose of 60 mg/m². It was designed as an open cross-over trial.

A high proportion of patients were lost after the first cycle, and problems due to a sequence effect are considered major disadvantages of cross-over studies [10]. The cycle by cycle analysis of the results, including all patients who had received the first cycle, and the use of adequate statistical bioequivalence analysis and a preventive analysis on the existence of period or carry-over effect, in our opinion, limits the magnitude of these disadvantages.

The initial hypothesis of this study was that the two anti-emetics were similar in the prevention of emesis. The results observed confirm this hypothesis. However, 45% of patients preferred GRA as against 25% who preferred OND and 30% who expressed no preference. There is no explanation for this difference. In some patients, a headache, even if of mild intensity, and moderate to severe emesis could have played a role in the preference assessment, but the severity of emesis was not investigated in this study. In addition, a period effect was evident in the patient preference assessment. When OND was the first anti-emetic drug, no difference in the preference was expressed. However, the preference was clearly in favour of GRA if it was the first administered drug. Furthermore, being an open study, the multiple administrations of OND versus only one of GRA may have influenced patient preference. In our

Table 3. Cross-over analysis of anti-emetic effect (101 evaluable patients)

		OND		
		Protected	Not protected	
Nausea				
GRA	Protected	38 (38%)	20 (20%)	$P^* = 0.157$
	Not protected	12 (12%)	31 (31%)	
Vomiting				
GRA	Protected	56 (55%)	13 (13%)	$P^* = 0.531$
	Not protected	10 (10%)	22 (22%)	

*McNemar test.

Table 4. Toxicity

	OND ($n = 115$)	GRA ($n = 110$)	P
Headache	21 (18%)	14 (13%)	0.25*
Constipation	5 (4%)	3 (3%)	0.77†
Diarrhoea	1 (1%)	3 (3%)	0.58†

*Pearson's chi-square. †Yates corrected chi-square.

opinion, the difference in the patient preference should not be overemphasised because of the observed period effect and the intrinsic limitation of the patient's subjective judgement.

The safety analysis shows no statistical difference. The possibility that the slightly higher incidence of headache reported on OND (18% versus 13%) could be due to the high total dose of OND given over 2 days (24 mg on day 1 + 16 mg on day 2) should be treated with caution because the correlation between headache incidence and cumulative dose of OND has never been demonstrated.

Three other studies, comparing OND and GRA, have recently been reported in full-length papers [11–13]. Two of these trials were sponsored by pharmaceutical companies [12, 13]. These trials were very differently designed, including: (a) both pretreated and untreated patients [11, 13] or only chemotherapy-naive patients [12] and (b) ≥ 50 mg/m^2 CP-based regimens only [13], or CP or ifosfamide 5-day fractionated chemotherapy [12] or various non-CP-based chemotherapy regimens [11]. Two were cross-over studies [11, 12] and one was a parallel study [13]. Discordant results also emerged from these trials. GRA at a single dose of 3 mg was reported to be superior to OND 8 mg in one study [11], while in the others, GRA was equal to a loading dose of OND at 8 and 32 mg, respectively [13], or at a fractionated dose of 24 mg [12]. Both the cross-over studies reported a higher proportion of patients preferring GRA to OND [11, 12]. None of the studies reported any significant difference in side-effects and, in particular, the incidence of headaches.

Our results confirm many of these observations and, in particular, the equivalence of the two anti-emetic treatments in terms of efficacy. In our study, the regimen with GRA has some advantages over the regimen of OND in terms of treatment simplification and drug cost. However, since the indications are that three doses of OND are not statistically superior in efficacy to one dose of 8 mg [7], we cannot exclude that a single dose regimen of OND could be as effective as the regimen of GRA used in the present trial. In conclusion, this study indicates that GRA and OND under the conditions studied have no major differences in the prevention of emesis.

1. Cabeddu LX, Hoffmann IS, Fuenmayor NT, *et al.* Efficacy of Ondansetron (GR38032F) and the role of serotonin in cisplatin-induced nausea and vomiting. *N Engl J Med* 1990, **322**, 810–816.
2. Marty M, Pouillart P, Scholl S, *et al.* Comparison of the 5-hydroxytryptamine 3 (serotonin) antagonist ondansetron (GR38032F) with high-dose metoclopramide in the control of cisplatin-induced emesis. *N Engl J Med* 1990, **322**, 816–821.
3. Chevallier B on behalf of the Granisetron Study Group. Efficacy and safety of Granisetron compared with high-dose metoclopramide plus dexamethasone in patients receiving high-dose cisplatin in a single-blind study. *Eur J Cancer* 1990, **26**, Suppl. 1, s33–s36.
4. Andrews PLR. The pharmacologic profile of Granisetron (Kytril). *Sem Oncol* 1994, **21**, Suppl. 5, 5–7.
5. Kamanabrou D on behalf of the Granisetron Study Group. Intravenous Granisetron—establishing the optimal dose. *Eur J Cancer* 1990, **26**, Suppl. 1, s6–s11.
6. Blackwell CP, Harding SM. The clinical pharmacology of ondansetron. *Eur J Cancer Clin Oncol* 1989, **25**, Suppl. 1, s21–s24.
7. Beck TM, Hesketh PJ, Madajewicz S, *et al.* Stratified, randomized, double-blind comparison of intravenous ondansetron administered as a multiple-dose regimen versus two single-dose regimens in the prevention of cisplatin-induced nausea and vomiting. *J Clin Oncol* 1992, **10**, 1969–1975.
8. Machin D, Campbell MJ. *Statistical Tables for the Design of Clinical Trials.* Oxford, Blackwell Scientific, 1987.
9. Dixon WJ. *BMDP Statistical Software—Rel 7.* Los Angeles, California, University of California Press, 1992.
10. Tonato M, Roila F, Del Favero A. Methodology of antiemetic trials: a review. *Ann Oncol* 1991, **2**, 107–114.
11. Jantunen IT, Muhonen TT, Kataja VV, *et al.* 5-HT3 receptor antagonists in the prophylaxis of acute vomiting induced by moderately emetogenic chemotherapy. A randomised study. *Eur J Cancer* 1993, **29A**, 1669–1672.
12. Noble A, Bremer K, Goedhals L, *et al.* A double-blind, randomised, crossover comparison of Granisetron and Ondansetron in 5-day fractionated chemotherapy: assessment of efficacy, safety and patient preference. *Eur J Cancer* 1994, **30A**, 1083–1088.
13. Ruff P, Paska W, Goedhals L, *et al.* Ondansetron compared with granisetron in the prophylaxis of cisplatin-induced acute emesis: a multicentre double-blind, randomised, parallel-group study. *Oncology* 1994, **51**, 113–118.