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Ondansetron – a new safe and effective antiemetic in patients receiving high-dose melphalan

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Summary. A total of 33 patients with myeloma receiving treatment with high-dose melphalan (140–200 mg/m^2 i.v.) were given the $5HT_3$ antagonist Ondansetron (Glaxo) as an antiemetic. In 42% of patients, emetic episodes were either abolished (15%) or reduced to two or less (27%). Efficacy was not related to scheduling (two regimens) or total dose. No sedative or other significant side effects were seen. Ondansetron is a highly effective non-sedative antiemetic that justifies further assessment in combination with other antiemetics in patients receiving cytotoxic drugs associated with the production of severe nausea and vomiting.

Introduction

High-dose chemotherapy with i.v. melphalan is used in the treatment of myeloma [13, 14], leukaemia [9], Hodgkin's disease [15] and paediatric tumours [1]. This treatment causes severe nausea and vomiting in all patients, which can only be controlled partially by a combination of conventional antiemetics at the cost of heavy sedation.

Ondansetron is a highly selective $5HT_3$ receptor antagonist [4] that is a very effective antiemetic in experimental animals [6]. Initial studies have shown remarkable antiemetic effects for this agent in cancer patients receiving cytotoxic chemotherapy at conventional doses [7], where it also showed a striking lack of sedative effect and a lack of extrapyrimidal effects. Phase II clinical studies with this anda similar compound have been reported [2, 5, 8, 10, 11], notably as prophylaxis against platinum-induced vomiting [3].

In this open study we evaluated the role of Ondansetron in the prevention of nausea and vomiting due to high-dose melphalan (HDM). Two different regimens were evaluated and the pharmacokinetics of Ondansetron were studied in selected patients.

Patients and methods

Patients

A total of 33 patients with multiple myeloma were studied. These patients had previously received chemotherapy with a variety of antiemetics. All had reported some nausea, some had vomited, but none reported anticipatory vomiting. In all, 6 patients received 140 mg/m^2 HDM i.v. without autologous bone marrow transplantation (ABMT) and 27 patients received 200 mg/m^2 i.v. with ABMT at 12 h post-melphalan. These patients also received 1.5 g methylprednisolone daily for 5 days, starting on the day following the melphalan injection [15]. The study was approved by the Royal Marsden Hospital Ethics committee. Patients were given a full explanation of the procedure, to which they gave witnessed informed consent. Patient characteristics are given in Table 1.

Treatment regimens for Ondansetron

Regimen 1. This low-dose regimen was begun on day 1, when a loading dose of 8 mg Ondansetron in 8 ml normal saline was infused i.v. over 15 min. Melphalan was then given, followed by a continuous infusion of Ondansetron at 1 mg/h for 48 h. The infusion was stopped for 1 h at 12 h and an injection of 1 mg was given immediately prior to the infusion of bone marrow.

On days 3–7 Ondansetron was given orally 1 h before meals and last thing at night at a dose of 8 mg q 6 h. The first oral dose was taken at the end of the 48-h i.v. infusion.

Regimen 2. This high-dose regimen began on day 1, when Ondansetron was given i.v. at a dose of 12 mg in 12 ml normal saline over 15 min. Melphalan was then given, followed by a continuous infusion of Ondansetron at 3 mg/h for 24 h. The infusion was interrupted at 12 h for ABMT. An i.v. bolus of 3 mg Ondansetron was given immediately prior to the infusion of bone marrow.

On days 2–7, Ondansetron was given orally at a dose of 8 mg 8 h for 6 days. The first oral dose was taken at the end of the 24-h infusion. In this regimen an option to restart the oral Ondansetron after 6 days was allowed. If patients experienced any nausea and vomiting after completion of the total 7-day course, the drug could be restarted and continued for a further 7 days. At that point it was stopped and only restarted, on the same basis, if nausea and vomiting recurred. The maximal duration of Ondansetron administration allowed by the protocol was 1 month.

Assessment

Both groups of patients were monitored daily for antiemetic efficacy and toxicity whilst receiving Ondan-

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Table 1. Patient characteristics

Melphalan dose	Patients (n)	Regimen 1	Regimen 2	Sex (M : F)	Median age	Diagnosis
140 mg/m^2	6	2	4	6 : 0	49	Myeloma
200 mg/m^2	27	15	12	20 : 7	49	Myeloma
All patients	33			26 : 7	49	Myeloma

Table 2. Concentrations of ondansetron base (ng/ml plasma) during infusion

Patient number	1	2	3	4
Time (h) from the start of 1 mg/h infusion:				
Pre-dose	< 1.0	< 1.0	3.2	[a]
0	48.3	44.2	29.8	50.7
1	40.8	35.5	29.1	58.4
2	43.4	37.3	NS	60.3
4	26.9	45.8	29.6	NS
6	NS	NS	NS	62.2
8	44.6	48.6	48.1	NS
10	NS	NS	NS	66.1
12	52.3	97.8	27.0	69.4
13	NS	69.0	27.6	71.9
18	47.4	[b]	30.2	102
24	47.7		24.9	106
32	NS		NS	72.1
40	53.8		30.5	68.6
48	52.7		NS	61.2

[a] No date (data from the analysis of this sample were lost due to instrumental failure; there was insufficient sample for repeat analysis)
[b] This patient was withdrawn from the study
NS, no sample

setron. Nausea was assessed daily using a visual analogue scale. The number and timing of any emetic episode was recorded by the patient on a standard form throughout the treatment period.

An emetic episode was defined as any vomit productive of liquid; a retch was defined as any movement not producing liquid; 1–5 retches within a 5-min period was arbitrarily defined as a single emetic episode. The response to Ondansetron was graded as follows: complete, no emetic episodes/day; major, 1–2 emetic episodes/day; minor, 3–5 emetic episodes/day; failure, >5 emetic episodes/day.

The following values were monitored daily: haemoglobin, leucocyte count, differential, platelets; sodium, potassium, urea, creatinine, alanine transaminases, alkaline phosphatase, gamma glutamyl peptidase, bilirubin, albumin, total protein, calcium and phosphate.

Pharmacokinetics

Analysis was carried out by high-performance liquid chromatography. The samples were assayed against calibrated standards in the range of 0–2 ng/ml, with 0 ng/ml being the lowest standard and limit of quantification when assaying a 1-ml sample. When samples contained >20 ng Ondansetron base/1 ml plasma, they were diluted with control plasma to within the calibration range of the assay. Quality control (QC) samples (control plasma spiked with GR38032 base and stored at a nominal temperature of −20° C) were assayed with the samples in each analytical run.

Results

Pharmacokinetics

Pharmacokinetic studies were carried out in four patients on regimen 1. The plasma concentrations of Ondansetron base obtained during infusion of the compound are shown

Table 3. Concentrations of Ondansetron base (ng/ml plasma) during oral dosing with 8 mg Ondansetron in tablets given q 6 h

1:			3:			4:		
Day	Time	Concentration (ng/ml)	Day	Time	Concentration (ng/ml)	Day	Time	Concentration (ng/ml)
3	06.00T	51.2	3	06.00T	26.9	3	07.00T	74.8
3	11.00T	96.4	3	17.00T	25.2	3	08.30P	87.8
3	12.30P	148	3	18.30P	46.2	3	11.00T	96.9
4	06.30T	39.9	4	06.00T	41.2	4	07.00T	50.0
4	17.00T	39.8	5	06.00T	28.0	4	08.30P	68.4
4	18.30P	99.4	6	06.00T	6.6	4	11.30T	62.1
5	06.00T	30.6	6	11.00T	17.3	5	08.30P	66.1
5	08.30P	64.4	6	12.30P	43.9	5	11.00T	55.9
5	11.00T	53.8	7	11.00T	15.7	5	17.00T	40.5
6	06.00T	44.0	7	12.30P	36.8	6	07.00T	21.8
6	11.00T	21.8				6	08.30P	55.2
6	12.30P	100				6	11.00T	44.9
7	06.00T	14.1				7	07.00T	15.0
7	14.00T	20.6				7	08.30T	22.9
7	18.30P	17.5				7	11.00T	30.8

P. peak sample; T, trough sample

Table 4. Extent of control of vomiting by Ondansetron over 7 days

	Patients	Emetic episodes:			
		0	1–2	3–5	>5
Regimen 1	17	4	5	2	6
Regimen 2	16	1	4	3	8
Totals	33	5 (15%)	9 (27%)	5 (15%)	14 (42%)
		42%			

$P = 0.38$ according to Fisher's exact test; no significant difference

Table 5. Extent of control of vomiting by Ondansetron on day 1

	Patients	Emetic episodes:			
		0	1–2	3–5	>5
Regimen 1	17	6	7	1	3
		35%	41%	59%	17%
		76%			
Regimen 2	16	7	4	1	4
		43%	25%	6%	25%
		68%			

Table 6. Visual-analogue-scale results for regimen 1

Day		1	2	3	4	5	6	7
Patients (*n*)		17	14	13	13	12	12	11
Response:	None	4	7	9	10	10	10	7
	Mild	4	2	1	1	1	–	2
	Moderate	6	4	3	1	1	1	2
	Severe	3 (W)	1 (W)	0	(W)	0 (W)	1 (W)	0

(*W*), withdrawn
Visual analogue scores: 0, complete; <2 cm, major; <8 cm, minor; >8 cm, failure

Table 7. Visual-analogue-scale results for regimen 2

Day		1	2	3	4	5	6	7
Patients (*n*)		16	13	11	10	9	8	7
Response:	None	6	3	5	5	7	5	5
	Mild	–	1	2	3	1	1	1
	Moderate	7	7	3	1	0	1	1
	Severe	3 (W)	2 (W)	1 (W)	1 (W)	1 (W)	1 (W)	0

(*W*), withdrawn
Visual analogue scores as shown in Table 6

in Table 2. After 12 h from the start of the 1 mg/h infusion, the plasma concentrations of Ondansetron base did not change greatly from one time point to the next in patients 1 and 3, with mean concentrations of 50.8 and 28.0 ng/ml, respectively. These data suggest that a steady-state plasma concentration of Ondansetron base was reached in these patients. Patient 2 was withdrawn from the study during the infusion, but the plasma concentration of Ondansetron base was similar to those found in the other patients up to 13 h. Patient 4 did not have a steady-state plasma concentration of Ondansetron base, but the infusion rate was increased from 1.0 mg Ondansetron base per hour to 1.5 mg/h at 20.75 h after the start of the continuous infusion because of nausea and was reduced back to 1.0 mg/h at 24 h as per protocol. The change in dose is reflected in the plasma concentrations of Ondansetron base that were reassessed, although the increased plasma concentrations were observed before the recorded time at which the dose was changed.

Table 8. Extent of control of vomiting actieved with a conventional antiemetic regimen at the cost of heavy sedation

Melphalan dose	Complete	Major	Minor	Failure
200 mg/m^2	6	3	6	0
140 mg/m^2	10	5	0	2
All patients	16 (50%)	8 (25%)	6 (18%)	2 (6%)

The regimen consisted of 10–20 mg metoclopramide given i.v. q 4 h, 1–2 mg lorazepam given i.v. q 4 h, 8 mg dexamethasone given i.v. q 4 h and 12.5–50 mg chlorapromazine given i.v. as required

In patients who received a constant continuous infusion of Ondansetron, a steady-state plasma concentration of Ondansetron base was achieved and maintained after approximately 12 h of dosing. The plasma concentrations of Ondansetron base obtained from the same five patients given oral dosing in Regimen 1 are shown in Table 3. The data show that for all of these patients the plasma concentrations of Ondansetron base tended to decrease during the period of oral dosing. Predicted plasma concentrations of Ondansetron base after a regimen of 8 mg q 6 h p.o. were calculated. The predicted median concentrations were 20 ng/ml (trough) and 40 ng/ml (peak). The decrease in plasma concentrations of Ondansetron base observed at the start of the oral dosing period can be explained by the difference between the steady-state plasma concentrations achieved during the continuous infusion of Ondansetron and those achieved during oral dosing, which were lower, as predicted. During the time of oral dosing, the plasma concentration of Ondansetron base showed an underlying tendency to

decrease. The decrease observed was consistent with the reduction expected from the infusion steady-state plasma concentration to the oral regimen steady-state plasma concentration of Ondansetron base.

Efficacy

In Table 4, the extent of control of vomiting over the first 7 days as a whole is shown. Two or less emetic episodes were seen in 42% of patients, and the difference between the two regimens (regimen 1, 52%; regimen 2, 31%) was not significantly different ($P = 0.38$). All of the 14 patients who experienced more than five emetic episodes on Ondansetron recorded the occurrence of nausea on the visual analogue scale (median score, 5 cm; range, 3–10 cm). In Tables 6 and 7, the visual-analogue-scale score for each response group is shown along with the number of emetic episodes on day 1 (Table 5). With regimen 2, one patient continued with oral therapy consisting of 8 mg Ondansetron q 8 h for 2 weeks and 2 days and then became nauseated. One patient had no vomiting on day 7 whilst taking oral Ondansetron, became nauseated on day 9 and recommenced oral therapy with complete cessation of nausea and vomiting. The only reason for withdrawal of patients from the study was failure to respond to treatment.

Toxicity

One patient reported transient double vision and one, light-headness during administration of Ondansetron, but the relationship of the effect to the drug was unclear. No sedation or extrapyramidal effects were apparent. There were no drug-related haematological or biochemical abnormalities recorded.

Discussion

This open study suggests that Ondansetron is efficacious against nausea and vomiting induced by high-dose melphalan and that it is both non-sedative and free of side effects. We do not have a randomised group for comparison, but in our experience, before the use of other powerful antiemetics, all patients reported nausea and vomiting when undergoing treatment with high-dose melphalan [12]. With our previous, standard antiemetic regimen, only a relatively small percentage of patients reported nausea and vomiting, but this was at the cost of severe sedation, which in turn required specialised nursing and, usually, an indwelling urinary catheter to ensure that accurate fluid balance measurements could be made (see Table 8). With Ondansetron, 42% of our patients experienced two or less emetic episodes without sedation; unfortunately, in approximately one-half of our patients it was ineffective and alternative antiemetics were required.

We could not show any improved effect when the dose given during the first 24 h was increased (32 vs 84 mg). In addition, the limited pharmacokinetic studies in the one patient in whom the drug failed to control nausea and vomiting showed plasma levels of Ondansetron comparable with those seen in patients with good control [2]. These observations indicate that there is no dose-related response at the concentrations of Ondansetron used; furthermore, it seems unlikely that the compound's efficacy will be improved by dose increases.

$5HT_3$ receptor antagonists represent a significant advance in the management of nausea and vomiting induced by cytotoxic drugs, although there remains a substantial group of patients for whom they are not the complete answer. Further clarification of the role of these agents will come from larger and comparative studies. Their place in combination with other antiemetics in high-dose chemotherapy should now be evaluated.

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