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Comparison of the anti-emetic efficacy of different doses of ondansetron, given as either a continuous infusion or a single intravenous dose, in acute cisplatin-induced emesis. A multicentre, double-blind, randomised, parallel group study

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Summary A total of 535 chemotherapy naive, hospitalised patients (263 male/272 female) scheduled to receive cisplatin (50–120 mg m^{-2})-containing regimens participated in a randomised, double-blind, parallel group study to evaluate the efficacy and safety of three intravenous dose schedules of ondansetron in the prophylaxis of acute nausea and emesis. One hundred and eighty two patients received a loading dose of 8 mg of ondansetron followed by a 24 h infusion of 1 mg h^{-1} (group 1); 180 and 173 patients received single doses of 32 mg (group II) and 8 mg (group III) respectively, followed by a 24 h placebo infusion. Complete and major control ($\leqslant$2 emetic episodes) of acute emesis was achieved in 74% of patients in group I, 78% in group II and 74% in group III. Seventy seven per cent of the patients in group I, and 75% of patients in groups II and III respectively experienced no or mild nausea during the 24 h observation period. A retrospective stratification of the efficacy data on the basis of patient gender showed the response rate in females to be significant lower (43% *vs* 67%; <0.001). Ondansetron was well tolerated; mild headache was the most commonly reported adverse event (11% of patients) with a similar incidence in the three groups of patients. In conclusion, a single intravenous dose of 8 mg of ondansetron given prior to chemotherapy is as effective as a 32 mg daily dose given as either a single dose or a continuous infusion in the prophylaxis of acute cisplatin-induced emesis.

A considerable advance was made in alleviating one of the most distressing side effects of cytotoxic treatment when it was demonstrated that high-dose metoclopramide considerably improved the control of cisplatin-induced emesis (Gralla *et al.*, 1981). Since then, high-dose metoclopramide has been the cornerstone of effective anti-emetic combinations (Kris *et al.*, 1987; Roila *et al.*, 1989). However, it can induce extrapyramidal reactions especially in adolescents, and this remains a major drawback. A recent advance has been the development of specific 5-HT_3 receptor antagonists which prevent chemotherapy or radiotherapy-induced emesis without inducing extrapyramidal reactions (Clark *et al.*, 1990).

The 5-HT_3 receptor antagonist ondansetron (Zofran^R) has been shown to be superior to high-dose metoclopramide in the control of acute cisplatin-induced emesis when given intermittently as short infusions (0.15 mg kg^{-1} × 3, 4-hourly) (Pendergrass *et al.*, 1990) or by a constant infusion (8 mg, then 1 mg h^{-1} 24 h^{-1}) (de Mulder *et al.*, 1990; Marty *et al.*, 1990). The pattern of emesis observed in the latter two studies indicated that for patients who received metoclopramide and then experienced emesis, this occurred most frequently in the first 6–12 h following cisplatin. This pattern was not evident with ondansetron suggesting good control in this early period. The patterns of emesis observed with ondansetron and metoclopramide were similar for the remainder of the 24 h period. The urinary excretion of 5-hydroxyindole acetic acid (5HIAA), a metabolite of 5-HT, also has been shown to increase in the 4–6 h period after cisplatin paralleling the onset of emesis (Cubeddu *et al.*, 1990). These observations suggested that shorter treatment regimens of ondansetron may be as effective as the continuous infusion or multiple dose schedules employed in the initial comparative studies. Moreover, results from studies with high-dose metoclopramide (Roila *et al.*, 1991) and other 5-HT_3 receptor antagonists, granisetron and tropisetron (Soukop, 1990; Sorbe *et al.*, 1990), have shown that single doses of these agents, given prior to chemotherapy, are effective in controlling acute symptoms.

This study was therefore designed to determine whether the recommended daily dose of 32 mg of ondansetron (de Mulder 1990; Marty *et al.*, 1990), when given as a single intravenous dose prior to chemotherapy, is as safe and effective as the established 24 h continuous infusion in the prevention of acute cisplatin-induced emesis. It further investi-

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gated the contribution made by the continuous infusion of 1 mg h^{-1} to efficacy by the inclusion of a third dosing arm, a single 8 mg dose. If affective, single prophylactic doses would be advantageous in terms of convenience and ease of administration benefiting both patients and nursing staff; the 8 mg dose would have the additional advantage of reducing cost of treatment.

Patients and methods

Patients

Male or female patients, aged at least 18 years, who were scheduled to receive their first course of chemotherapy with cisplatin at a dose of 50–120 mg m^{-2} given over a period of up to 4 h, either alone or in combination with other cytotoxic drugs, were eligible for the study. Patients were excluded if they experienced nausea or vomiting and/or received anti-emetic therapy in the 24 h period prior to the start of the treatment, had a serious concurrent illness other than cancer or another aetiology for emesis, and concurrently used corticosteroids (except for physiological supplementation) or benzodiazepines (unless given for night sedation).

A complete history and physical examination were carried out prior to treatment. Blood samples were taken for full blood cell count, electrolytes, liver and renal function prior to starting the study, and repeated after 24 h and 1–4 weeks later. Informed consent was obtained from all the patients. The study protocol was approved by local Hospital Ethics Committees and the study was conducted according to the principles of the Declaration of Helsinki.

Study design and treatment

The required number of patients was calculated under the assumption that complete and major anti-emetic control (0–2 emetic episodes) would be achieved in 75% of the patients with the continuous infusion schedule. Using two-sided tests at an overall 5% significance level and a power of 0.8, 170 patients (of whom 150 could be expected to be evaluable) would be required in each group to detect a difference of at least 15% between the continuous infusion regimen and either of the two single dose regimens. The trial design allowed for an interim analysis when approximately 50 patients in each treatment group were recruited. If the analysis provided clear evidence of a treatment difference, then the study could be terminated or recruitment could be halted into the inferior study arm.

Eligible patients were entered sequentially and randomly allocated to one of the three ondansetron schedules. The randomisation sequence was computer-generated and balanced the treatment in blocks of nine patients. The ondansetron and placebo infusions were prepared by a dedicated nurse, physician or pharmacist not involved with the care or the evaluation of the patient to ensure blindness. The loading dose of either 8 mg (group I and III) or 32 mg (group II) of ondansetron was diluted to a 100 ml of saline, and administered over 15 min starting 30 min prior to the initiation of the cisplatin infusion. This was followed by a 24 h continuous infusion, either with 1 mg h^{-1} of ondansetron (group I) or the same volume of saline solution (group II and III). The cisplatin infusion was set up 15 min after the start of the continuous infusion and run over 1–4 h.

Assessment of efficacy and side effects

All patients were monitored in hospital for the 24 h after the start in the cisplatin infusion. Nausea was assessed by the patient before treatment, and at 8 and 24 h after treatment, using a four-point graded scale (none, mild – did not interfere with normal daily life, moderate – interfered with daily life, severe – bedridden due to nausea). The timing and number of emetic episodes were recorded and cross-checked with the patient. A single emetic episode was defined as a single vomit or retch (vomit not productive of liquid), or any number of continuous vomits or retches. Each episodes was separated by the absence of symptoms for at least 1 min. The overall response criteria for emesis were: complete response (CR): 0 emetic episodes, major response (MR): 1–2, minor response (MR): 3–5, and failure (F): >5 emetic episodes. Patients who experienced three or more emetic episodes and were rescued with additional anti-emetic medication were considered to be treatment failures. Any adverse medical events that occurred during the study (or the follow-up period of 1–4 weeks) were recorded and the severity and relationship to ondansetron assessed.

Statistical analysis

All analyses were performed on the total population (intention to treat analysis) providing efficacy data were available, as well as the evaluable population (with satisfactory protocol compliance). The proportions of patients showing a complete or a complete plus major response were compared between treatments using a two-sided Mantel-Haenszel chi-square test stratified by centre. The time to first emetic episode was compared for all pairs of treatment using Wilcoxon rank sum analysis. A separate analysis was also carried out after stratification by country, using the Van Elteren method for combining Wilcoxon statistics over strata (Van Elteren, 1960). The grades of nausea for the 8 and 24 h after chemotherapy were analysed using the stratified, extended Mantel-Haenszel method. Subset analysis for the difference in gender, cisplatin dose and concurrent chemotherapy was carried out using the chi-square test of 2 × 2-, 2 × 3- and 2 × 4-tables.

Results

The interim analysis of data on the first 149 patients on an intention to treat basis indicated that complete or major control of emesis was achieved in 36/46 (78%) patients with the continuous infusion schedule (group I), 42/50 (84%) patients with the 32 mg single dose regimen (group II) and in 40/53 (76%) patients with the 8 mg single dose regimen (group III). As there appeared to be no differences between the groups, a statistical analysis was not carried out and the study was progressed to completion.

Between September 1989, and June 1990, 535 patients with pathologically confirmed cancer were enrolled in the study. Demographic characteristics of the 535 patients entered into the trial are shown in Table I. Details of the doses of cisplatin (median 72 mg m^{-2}) and type of concurrent chemotherapy administered to patients in each treatment group are given in Table II. There were no significant differences in age, gender, average alcohol intake, primary tumour site, doses of cisplatin administered or administration times and concomitant chemotherapy among the three treatment groups. There were 42 patients who did not fully comply with the protocol. Of these, 12 received concurrent anti-emetics, seven were not chemotherapy naive, 18 received an incorrect cisplatin dose schedule, four had severe concurrent illness and one was withdrawn due to an adverse event which was unrelated to ondansetron treatment. The analyses of the efficacy results of the total and the evaluable populations did not reveal any differences in the overall conclusions. Therefore, the efficacy results presented here are for the 'intention to treat population' since this more closely reflects clinical practice.

Acute nausea and emesis

Pre-treatment nausea was absent in 94% of the patients, 5% of the patients had mild nausea. After 8 h of study treatment 88% (I), 87% (II), and 85% (III) of the patients had none or mild nausea. The percentage of patients experiencing none or mild nausea after 24 h were 77% in group I and 75% in groups II and III ($P > 0.5$). The results are shown in Figure 1.

Table I Patient demography

	Number of patients (%)			
	8 mg + 1 mg h^{-1}	32 mg	8 mg	Total
Patients randomised	182	180	173	535
Sex				
Male	82 (45)	95 (53)	86 (50)	263 (49)
Female	100 (55)	85 (47)	87 (50)	272 (51)
Age (years)				
19–29	10 (5)	12 (7)	5 (3)	27 (5)
30–65	136 (75)	117 (65)	120 (69)	373 (70)
>65	36 (20)	51 (28)	48 (28)	135 (25)
Median	57.5	60	60	59
Range	19.84	19.77	25.82	19.84
Primary tumour site				
Head and neck	31 (17)	30 (17)	27 (16)	88 (16)
Lung	30 (16)	41 (23)	39 (23)	110 (21)
Gastrointestinal	15 (8)	10 (6)	9 (5)	34 (6)
Genitourinary	28 (15)	22 (12)	25 (15)	75 (14)
Gynaecological	67 (38)	66 (37)	65 (38)	200 (37)
Bone/soft tissue	3 (2)	3 (2)	4 (2)	10 (2)
Miscellaneous	11 (4)	13 (3)	11 (1)	35 (4)
Alcohol intake				
None of <7/week	143 (79)	40 (78)	132 (76)	415 (78)
1–4 u/day	25 (14)	25 (14)	27 (16)	77 (14)
>4 u/day	14 (8)	14 (8))	13 (8)	41 (8)

1 unit of alcohol = one measure of spirit, one glass of wine or 250 ml of beer.

Results for the control of acute emesis are shown in Figure 2. Complete and major responses were achieved in 74% (Group I), 78% (Group II) and 74% (Group III) of patients. In the pairwise treatment comparisons, there were no statistically significant differences between the three dose regimens. The pattern of emesis, expressed as the total number of episodes occurring at hourly intervals over 24 h was similar in the three groups of patients (Figure 3).

Fifty two per cent of patients in group I, 53% in group II and 51% in group III had no emesis and reported none or mild nausea over the 24 h period.

Influence of cisplatin dose and concomitant chemotherapy

A retrospective stratification of efficacy data (emesis data) on the basis of the doses of cisplatin administered and concurrent treatment with other cytotoxic agents revealed that there were no statistically significant differences between the treatment groups for these prognostic factors. Stratification of the pooled data is shown in Table III. Overall, complete control of emesis was achieved in a significantly greater proportion of patients (157/242, 65%) who received cisplatin at doses <70 mg m^{-2} compared with 137 of 293 (48%) patients who received higher doses of cisplatin ($\geqslant 70$ mg m^{-2}; $P<0.001$). Of the 107 patients who received cisplatin at doses $\geqslant 100$ mg m^{-2}, complete control was achieved at 16 or 34 (47%), 21 of 46 (46%). and 11 of 27 (41%) of patients in Groups I, II, and III respectively. The concurrent use of other moderately emetogenic agents also significantly affected the degree of control of emesis; complete control was achieved in 114 of 167 (68%) patients who received cisplatin alone, compared with 84 of 190 (44%) patients who received other emetogenic cytotoxic agents concurrently ($P<0.001$).

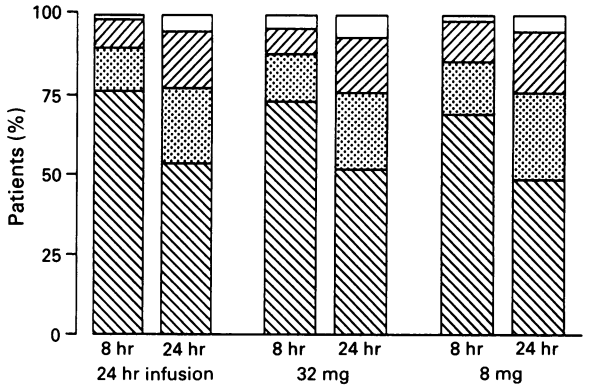

Figure 1 Control of acute nausea with the continuous infusion ($n = 182$), 32 mg single dose ($n = 17$) schedules: nausea graded as none ▧; mild ⬚; moderate ▨; severe □ at 8 and 24 h after cisplatin administration.

Influence of patient gender

A retrospective stratification of the efficacy data on the basis of patient gender revealed that there were no statistically significant differences between the treatment groups for this factor. However, stratification of the pooled efficacy data as shown in Tables III and IV indicated that overall, complete control of emesis was achieved in a significantly higher proportion of male patients (67% *vs* 43%, $P<0.001$). The observed difference was not influenced by the doses of cis-

Table II Concurrent chemotherapy and cisplatin dose

	Number of patients (%)			
	8 mg + 1 mg h^{-1}	32 mg	8 mg	Total
Patients randomised	182	180	173	535
Concurrent chemotherapy				
None	58	57	63	178
Cyclo/ifosfamide	32	37	36	105
Epi/doxorubicin	17	14	11	42
Cyclphosph/epi/ doxorubicin	13	8	11	32
Eto/teniposide	18	21	19	58
5-Fluorouracil	16	17	14	47
Miscellaneous[a]	28	26	19	73
Cisplatin dose				
<50 mg m^{-2}	11 (6)	6 (3)	10 (6)	27 (5)
50–69.9 mg m^{-2}	79 (43)	66 (37)	70 (40)	215 (40)
70–99.9 mg m^{-2}	58 (32)	62 (34)	66 (38)	186 (35)
$\geqslant 100$ mg m^{-2}	34 (19)	46 (26)	27 (16)	107 (20)
Median dose (mg m^{-2})	70	76	71	72
Range	30–125	31–124	37–153	30–153
Mean administration time (h)	2.63	2.33	2.43	2.46

[a]Miscellaneous: bleomycin, vincristine, vinblastine, vindesine, methotrexate, mitoxanthrone, mitomycin, dacarbazine.

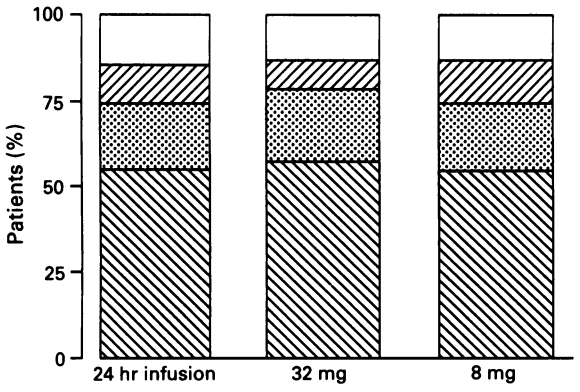

Figure 2 Control of acute emesis with the continuous infusion ($n = 182$), 32 mg single dose ($n = 180$) and 8 mg single dose ($n = 173$) schedules: complete control ▨; major control ▩; minor control ▨; failure □.

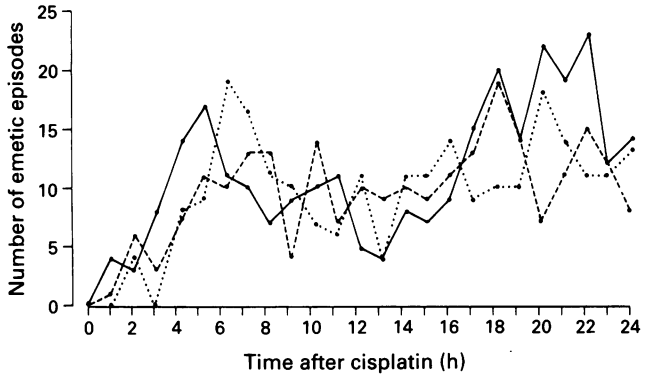

Figure 3 Episodes of emesis during the 24 h after cisplatin administration with the continuous infusion (●—●), 32 mg single dose (---) and 8 mg single dose (....) schedules.

Table III Proportions of patients with complete responses stratified on the basis of patient gender, cisplatin dose and concomitant chemotherapy

Prognostic factor	*Total number of patients (%)*[a]
Patient	
Male	177/263 (67%)
Female	117/272 (43%)
Cisplatin dose	
< 70 mg m^{-2}	157/242 (65%)
70–99 ng m^{-2}	90/186 (48%)
$\geqslant 100$ mg m^{-2}	47/107 (44%)
Concomitant chemotherapy	
None	114/167 (68%)
Mildly emetogenic	96/178 (54%)
Moderately emetogenic	84/190 (44%)

[a]Pooled data; the differences were consistent within each treatment group. Concomitant chemotherapy: moderately emetogenic: cyclophosphamide, ifosfamide, epi/doxorubicin, dacarbazine; mildly emetogenic: 5-fluorouracil, mitoxanthrone, mitomycin, bleomycin, etoposide, vinblastin, vincristine.

platin or concurrent cytotoxic agents administered to the patients.

Adverse events

All three dosage schedules were well tolerated; in particular, the 32 mg single dose was not associated with an increase in the incidence of adverse events. The most commonly reported events considered by the investigator to be possibly, probably or almost certainly related to ondansetron are listed in Table V. Headache was the most commonly reported adverse event (11% of patients). None of these patients were withdrawn from the study and the symptoms resolved spontaneously or were treated with mild analgesics. Two major adverse events were considered to be possibly related to ondansetron treatment: one case of severe constipation and one case of pseudomembranous colitis, which resolved spontaneously. Transient changes in ALT/AST which were considered to be related to ondansetron, occurred in four patients of group I, in seven patients of group II and in two patients of group III. All changes resolved at follow-up, and none were associated with any clinical signs or symptoms.

Table IV Proportions of male and female patients with complete responses, stratified on the basis of cisplatin dose and concomitant chemotherapy

	Number of patients (%) *Male*	*Female*
Cisplatin dose		
< 70 mg m^{-2}	89/114 (78)	68/128 (53)
70–99 mg m^{-2}	53/84 (63)	37/102 (36)
$\geqslant 100$ mg m^{-2}	35/63 (56)	13/44 (27)
Concomitant chemotherapy		
None	84/109 (77)	30/58 (52)
Mildly emetogenic	71/123 (58)	25/55 (45)
Moderately emetogenic	22/31 (71)	62/159 (39)

Concomitant chemotherapy: moderately emetogenic: cyclophosphamide, ifosfamide, epi/doxorubicin, dacarbazine; mildly emetogenic: 5-fluorouracil, mitoxantrone, mitomycin, bleomycin, etoposide, vinblastin, vincristine.

Discussion

Several studies have shown ondansetron to be a safe and efficacious anti-emetic in the prevention of cisplatin-induced emesis. Pharmacokinetic modelling suggested that ondansetron given as an 8 mg intravenous loading dose followed by 1 mg h^{-1} for 24 h would give consistent plasma levels of 30 ng ml^{-1}. These levels were considered to be optimal for blocking $5HT_3$ receptors and maximising anti-emetic efficacy. Two comparative trials which investigated the efficacy of this selected dosing schedule (de Mulder *et al.*, 1990; Marty *et al.*, 1990) showed ondansetron to be superior to high-dose metoclopramide in the prophylaxis of acute cisplatin-induced emesis. This trial has investigated whether single prophylactic doses of ondansetron are as effective as the constant infusion schedule and the contribution of the 24 h continuous infusion to overall efficacy. Single dose prophylaxis would have obvious benefits to patients and hospital staff alike, and in addition, lower effective doses would reduce the cost of treatment.

The most striking observation in this study is the similarity in anti-emetic control achieved with the three treatment schedules, either for complete and/or major response (approximately 75% of patients) as well as for the control of emesis and nausea considered together (approximately 52% of patients). These results are consistent with two other comparative trials that investigated the efficacy of the con-

Table V Adverse events

Adverse event	*Number of patients (%)* *8 mg + 1 mg h^{-1} (n = 182)*	*32 mg (n = 180)*	*8 mg (n = 173)*	*Total (n = 535)*
Headache	16 (9)	25 (14)	20 (12)	61 (11)
Diarrhoea	3 (2)	5 (3)	5 (3)	13 (2.5)
Constipation	3 (2)	3 (2)	–	6 (1)
Flushing	2 (1)	2 (1)	–	4 (0.8)
Xerostomia	1 (0.5)	3 (2)	–	4 (0.8)
Laboratory changes	4 (2)	7 (4)	2 (1)	13 (2.5)
Miscellaneous	11 (6)	14 (8)	10 (6)	35 (7)

tinuous infusion regimen of ondansetron (de Mulder *et al.*, 1990; Marty *et al.*, 1990), and a recent trial where complete control of emesis was reported in 58% of patients with a single intravenous dose of 32 mg and in 57% with the continuous infusion schedule (Marty & d'Allens, 1990).

The patterns of emesis over the 24 h period in patients who experienced emesis provide further evidence that the three dose schedules are equally efficacious. The half-life of elimination of ondansetron is approximately 3.5 h in healthy volunteers (Blackwell & Harding, 1989) and young patients (Lazarus *et al.*, 1990) but may be up to 7 h in elderly patients (Priestman *et al.*, 1990). Following a single bolus dose of 8 mg of ondansetron, plasma levels fall to below 5 ng ml^{-1} at 12 h, compared to consistent levels of 30–50 ng ml^{-1} with the continuous infusion schedule used in this study (Colthup & Palmer, 1989; Seynaeve *et al.*, 1990). The similar degree of anti-emetic control and pattern of emesis experienced by patients in the three treatment groups indicates that the constant plasma levels afforded by the continuous infusion regimen confer no additional benefit during the acute phase of emesis. This emphasises that the period up to 12 h following the cisplatin infusion may be the critical period for acute anti-emetic control. During this period, elevations in urinary levels of 5-HIAA, a urinary metabolite of 5HT, have been observed (Cubeddu *et al.*, 1990). The plasma levels afforded by the 8 mg single dose are probably adequate for antagonising 5HT-mediated emesis at $5HT_3$ receptors, providing protection in the majority of patients. Continuous antagonism at $5HT_3$ receptors in the 24 h following cisplatin may not be necessary for conferring any additional benefit, hence the similar efficacies observed with the 8 mg single dose and constant infusion schedules.

Several prognostic factors (Tonato *et al.*, 1991) such as previous exposure to chemotherapy, patient age, gender, chronic alcohol use, and dose of cisplatin administered are known to affect the control of chemotherapy-induced nausea and vomiting. This large parallel group study was designed to include chemotherapy-naive patients only and all the important prognostic factors were well balanced within the three groups. The comparable efficacy observed with the 8 mg single dose, in particular, cannot therefore be attributed to a chance selection of patients who were likely to have a more favourable response into this treatment group.

Some interesting points emerged from the retrospective stratifications of response based on gender and the concurrent use of cytotoxic agents. It is known that emesis in women is more difficult to control than in men (Tonato *et al.*, 1991), but it is not clear whether this is due to an underlying mechanism(s) or the more frequent use of moderately emetogenic agents such as cyclosphosphamide or doxorubicin with cisplatin in women. In this study, the degree of control of emesis (complete response) was significantly lower in female patients. This difference was consistently observed in further retrospective stratifications to determine the effect of cisplatin dose or concurrent chemotherapy on treatment outcome in men and women. Our results suggest that although the use of concurrent cytotoxics affect treatment outcome in women, they are not an influencing factor on their own and that other factor(s) therefore may be involved. Humoral factors (Carl *et al.*, 1989) are unlikely to explain the observed differences between men and women. Whole blood and plasma 5-HT levels are higher in healthy women than men but no data are available on the fluctuation in levels of the neurotransmitter in patients of different gender receiving chemotherapy (Ortiz *et al.*, 1988). It is known that anticipatory nausea and vomiting in chemotherapy-induced emesis are associated with a susceptibility to motion sickness and anxiety in addition to other characteristics (Morrow & Dobkin, 1988). It may also be that these factors are particularly relevant to women in the control of chemotherapy-induced emesis. Further attempts to elicit the physiological mechanism should be encouraged. Moreover, further studies should utilise prospective stratifications based on patient gender and cisplatin doses and include a pre-trial history about anxiety, motion sickness and vomiting during pregnancy (Martin & Diaz-Rubio, 1990) to determine the effect of these factors on treatment outcome and to optimise the most suitable prophylactic anti-emetic regimens for women.

In the population studied, the majority of patients (80%) received cisplatin at doses < 100 mg m^{-2} and the continuous infusion of 1 mg h^{-1} or a higher single dose of 32 mg conferred no additional benefits over a single 8 mg dose. It is known that the degree of emesis experienced by cisplatin-treated patients is related to the dose of cisplatin administered (Tonato *et al.*, 1991) and complete control of emesis was achieved in a significantly lower proportion of the 107 patients who received cisplatin at doses $\geqslant 100$ mg m^{-2}. Within this group of 107 patients (20% of patients) there were no statistically differences in response rates between the three treatment schedules. However, the power of the comparisons was lower than that carried out for the response rates between treatment groups for patients who received cisplatin at doses < 70 mg m^{-2}.

Although serotonin is a significant mediator of acute emesis (Cubeddu *et al.*, 1990), failure to completely protect all patients indicates that other mechanism(s) may also be involved. The addition of dexamethasone to ondansetron has been shown to significantly improve anti-emetic control (Roila *et al.*, 1991). As the mechanism and site of action of dexamethasone are not yet known, it is possible that dexamethasone contributes to overall efficacy by suppressing one or more of these additional mechanism(s).

The adverse events considered to be related to ondansetron were generally mild in nature, and the incidences were similar between the treatment schedules. As previously observed, headache was the most common event.

In conclusion, this study shows that a single intravenous dose of 8 mg of ondansetron is as efficacious as a 32 mg daily dose in the prophylaxis of acute cisplatin-induced emesis. In the population studied, a continuous infusion of 1 mg/hour for 24 h conferred no additional benefit in anti-emetic protection. The efficacy of single dose anti-emetic prophylaxis is likely to improve patient and nursing staff acceptance of ondansetron; moreover, it should allow out-patient treatment where appropriate.

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