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Original Paper

An Increased Loading Dose of Ondansetron: a North European, Double-blind Randomised Study in Children, Comparing 5 mg/m^2 with 10 mg/m^2*

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A North European, randomised, double-blind study, comparing a loading-dose of ondansetron of 5 mg/m^2 with 10 mg/m^2, administered intravenously before highly emetogenic chemotherapy, was carried out in 187 chemotherapy-naïve children. In the first 24 h, both groups received further ondansetron intravenously at a dose of 5 mg/m^2 8-hourly. Thereafter, ondansetron was given at an oral dose of 4 or 8 mg depending on the surface area of the child, three times a day and continued for at least 3 days after the last day of chemotherapy. There was no difference in the control of emesis between the two groups. Ondansetron provided good control of emesis and nausea on day 1 with 71–72% of patients experiencing two or fewer emetic episodes (complete or major responders) and 90–86% of patients reporting nausea as none or mild. There was also no difference in the efficacy of the treatment arms in the control of emesis and nausea on subsequent days of the study period. Both anti-emetic regimens were well-tolerated.

Key words: highly emetogenic, emesis, ondansetron, 5-HT$_3$ receptor antagonist, cisplatin, ifosfamide
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INTRODUCTION

ONDANSETRON, the first highly selective 5-HT$_3$ (5-hydroxytryptamine$_3$) receptor antagonist available for use in children, has been shown to be effective in the prevention of nausea and emesis induced by emetogenic chemotherapy [1, 2]. The introduction of ondansetron along with other 5-HT$_3$ receptor antagonists has been a major advance in emesis control, particularly in children receiving aggressive chemotherapy regimens, where satisfactory control of nausea and vomiting with traditional anti-emetics, such as metoclopramide or chlorpromazine, is only obtained with doses that are accompanied by undesirable side-effects [3–10].

The objectives of this North European, multicentre, randomised, double-blind, parallel group study were to increase primarily the anti-emetic efficacy of ondansetron by increasing the initial intravenous loading-dose from 5 mg/m^2 (maximum 8 mg) (regimen A) to 10 mg/m^2 (maximum 16 mg) (regimen B) in children receiving highly emetogenic chemotherapy. The hypothesis behind the potentially beneficial increased loading-dose was that children are known to have a shorter serum half-life of ondansetron and, when receiving highly emetogenic chemotherapy regimens, i.e. containing cisplatin or ifosfamide, children are given a high level of hydration that could increase the clearance of ondansetron and reduce the initial saturation of 5-HT$_3$ receptors. The second aim of the study was to evaluate if the addition of an initial dose of 10 mg/m^2

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of dexamethasone (with a maximum of 16 mg) could improve the anti-emetic response in children considered to be treatment failures with ondansetron as a single agent.

PATIENTS AND METHODS

The study was carried out in 18 oncology units throughout Belgium, The Netherlands, Denmark, Sweden and Finland. Guidelines from the Declaration of Helsinki (1964), modified by the 41st World Medical Assembly in Hong Kong in September 1989, were adhered to. The protocol received approval from the regulatory authorities and local ethical committees appropriate for the countries involved. Informed consent was obtained from a parent or guardian by the local study investigator.

Patients

Children between 2 and 16 years old, who had not received prior chemotherapy and who were scheduled to receive highly emetogenic chemotherapy (Table 1) were eligible for inclusion. The study ran from November 1992 to June 1994. Patients with severe concurrent illness, gastrointestinal obstruction, brain tumours, cerebral metastases or meningeal leukaemia were excluded, along with children who had received anti-emetics 24 h prior to the start of the trial. However, those receiving benzodiazepines only for night sedation were eligible.

Anti-emetic dose schedule

The initial intravenous loading-dose of ondansetron, either 5 mg/m^2 (maximum 8 mg) or 10 mg/m^2 (maximum 16 mg) according to the randomisation code, was administered immediately prior to chemotherapy as a 15-min infusion. Two additional intravenous doses of ondansetron of 5 mg/m^2 were administered 8 and 16 h after the initial dose. Thereafter, on subsequent days when chemotherapy was given, ondansetron was administered orally three times a day at a dose according to the surface area of the child: 4 mg $<$ 1 m^2, 8 mg $\geq$ 1 m^2. The first oral intake was given 24 h after the start of chemotherapy and it was continued for 3 days after the last day of chemotherapy or 5 days if nausea or vomiting persisted. The anti-emetic loading dose of ondansetron was blinded to the clinicians, the patients, the parents and the nurses. Patients were categorised as treatment failures during the first course of chemotherapy if they suffered more than five emetic episodes in any 24-h period and/or they received rescue anti-emetic medication and/or there was any change in anti-emetic drug treatment. These patients entered the second part of the study and were given dexamethasone at a dose of 10 mg/m^2 (maximum 16 mg) as an intravenous infusion over 15 min, 30 min prior to the chemotherapy, in addition to ondansetron. The loading-dose of ondansetron was the same as in the first course of chemotherapy, either 5 mg/m^2 or 10 mg/m^2 according to the initial randomisation code.

Table 1. Definition of highly emetogenic chemotherapy

Chemotherapy	Dose
Actinomycin D	$\geq$15 μg/kg; $\geq$0.45 mg/m^2
Carboplatin	$\geq$400 mg/m^2
Cisplatin	$\geq$20 mg/m^2
Cyclophosphamide	$\geq$500 mg/m^2
Cytosine arabinoside	$\geq$500 mg/m^2
Dacarbazine	$\geq$250 mg/m^2
Daunorubicin	$\geq$40 mg/m^2
Doxorubicin	$\geq$40 mg/m^2
Ifosfamide	$\geq$1 g/m^2
Methotrexate	$\geq$5 g/m^2
Mitoxantrone	$\geq$8 mg/m^2
Nitrogen Mustard	$\geq$6 mg/m^2
Epirubicin	$\geq$45 mg/m^2

Efficacy data collection

The number of episodes of vomiting or retching (emetic episodes) were recorded on diary-cards by the patient, their parents or nurse. An emetic episode was defined as a single vomit or retch or any number of continuous vomits or retches. Each emetic episode would, by definition, be separated by the absence of vomiting or retching for at least 1 min. Nausea was defined as the feeling of wanting to be sick without retching and was graded as none (not feeling sick at all), mild (feeling sick) or severe (feeling very sick). Appetite was assessed by means of a graded scale as being better than usual, as usual or worse than usual. During the intravenous ondansetron treatment period, patients were monitored as in-patients and assessed after the first 24-h period (study day 1). The timing and number of episodes of vomiting or retching were recorded on a diary-card during this period by the nursing staff and/or parents as was the grade of nausea and the child's appetite. After the first 24-h period, it was possible for the child to be managed on an out-patient basis and the parents or the patients themselves completed the diary-card for each further 24-h period. The same information as for day 1 was recorded on the diary-card in addition to the number of tablets of ondansetron taken and/or the use of rescue medication. At the next hospital visit, after completing the oral ondansetron treatment, the diary-cards were collected and checked for completeness. Any points arising were discussed with the patient or parent.

Efficacy analysis

The anti-emetic efficacy of the two loading doses of ondansetron was analysed during the first 24 h of chemotherapy by comparing:

(1) the percentage of complete or major responders in both groups;
(2) the mean number of vomiting episodes in both groups; and
(3) the grade of nausea.

The difference between the two groups during the subsequent chemotherapy treatment period was analysed by comparing the proportion of emesis-free days. No emetic episode was recorded as a 'complete' response, 1–2 episodes was a 'major' response, 3–5 episodes was a 'minor' response and more than 5 emetic episodes in any 24-h period and/or the administration of rescue medication and/or any change in anti-emetic drug treatment was recorded as a failure.

Sample size statement

It was estimated from the results of our previous open multicentre trial of ondansetron treatment in children, that approximately 50% of the patients receiving ondansetron at a loading dose of 5 mg/m^2 would be complete or major responders on the first day of chemotherapy [11]. For the present study to detect a true difference of 15% between both

groups, with a power of 80% at the 0.05 significance level, 169 patients were to be included in each arm (uncorrect χ^2 statistic). To allow for the inclusion of at least 10% of unevaluable patients, it was planned to enrol 368 children in the study. However, an interim analysis was to be performed on the first 187 patients included in the trial (50% of the total sample size). All comparative analyses were two-sided with a 5% significance level and results were considered significant at *P*-values below or equal to 0.025.

RESULTS

The scheduled interim analysis was performed when 187 patients had been recruited and clearly showed no differences in response rate on day 1 between regimen A and regimen B. In agreement with all the participating centres, it was therefore decided to stop the trial.

Efficacy

The overall efficacy analysis was carried out on the 160 children who had followed the protocol correctly; 27 were excluded due to protocol violation. Protocol violation included the following: at least 1 of the i.v. doses differed by more than 25% of that stated in the protocol (9), no data were available (6), chemotherapy was other than that considered highly emetogenic and listed in Table 1 (5), no zero baseline nausea was confirmed (2), the in-/exclusion criteria were not adhered to (2), no dose data were available (2), and 1 oral dose was given in place of the required i.v. dose (1). Overall efficacy was analysed for 79 patients in regimen A and 81 patients in regimen B—88 boys and 72 girls. There were missing data on nausea on day 1 for 1 patient in regimen A and therefore this analysis was carried out on 159 patients, 79 in regimen A and 80 in regimen B. The data on vomiting were missing for 2 patients on day 1 and therefore this analysis was carried out on 158 patients, 79 in regimen A and 79 in regimen B. The two treatment arms were well-balanced with respect to patient demography (Table 2). No efficacy differences between the two groups was seen. Ondansetron provided good control of emesis and nausea on day 1 with 71–72% of patients experiencing two or fewer emetic episodes and 90–86% of patients reporting no or only mild nausea (Figure 1). Appetite was reported on day 1 as 'as usual' or 'better' in 44–45% of patients. There was also no difference in the efficacy between the treatment arms in the control of emesis and nausea on subsequent days of the study period. The efficacy of ondansetron (5 mg/m^2 or 10 mg/m^2 loading-dose) on the worst day of chemotherapy treatment is shown in Figure 2. Appetite on the worst day of the chemotherapy treatment period was reported as 'as usual' or 'better' in 27–28% of patients.

Table 2. Patient demography

	5 mg/m^2 group	10 mg/m^2 group
Number of patients	93	94
Age range	2.0–16.7	1.9–16.3
Mean age	8.4	8.5
Gender		
Male	50 (54%)	52 (55%)
Female	43 (46%)	42 (45%)
Mean surface area (m^2)	1.1	1.1

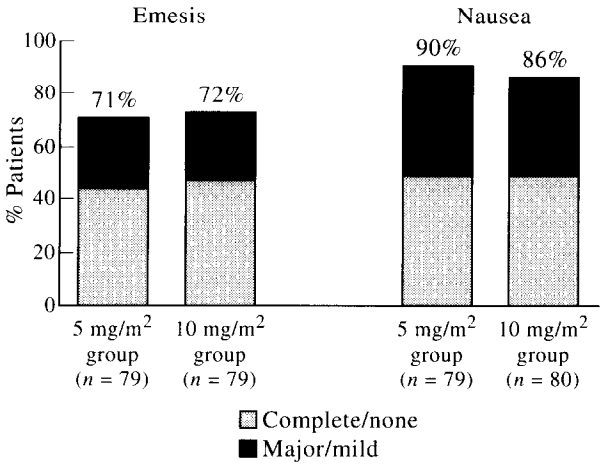

Figure 1. The efficacy of ondansetron (5 mg/m^2 or 10 mg/m^2 loading dose) over the first 24 h following chemotherapy.

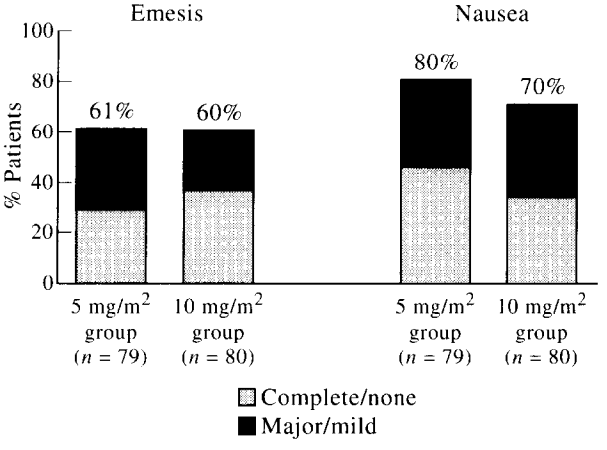

Figure 2. The efficacy of ondansetron (5 mg/m^2 or 10 mg/m^2 loading dose) on the worst day during the chemotherapy treatment.

On day 1, there were 31 patients who received cisplatin-containing chemotherapy. The dose ranged from 20 mg/m^2/day for 5 days to 102 mg/m^2/day on day 1. The median dose on day 1 was 100 mg/m^2. Of these children, 14 received regimen A. Patients who received chemotherapy containing cisplatin did not have as good a control of nausea and vomiting as patients who received other types of highly emetogenic chemotherapy. On day 1, 50% (7/14) of patients in regimen A and 53% (9/17) in regimen B who received cisplatin-containing chemotherapy experienced two or fewer emetic episodes as compared to 71% (56/79) of patients in regimen A and 72% (57/79) in regimen B in the total population. However nausea was well-controlled on day 1 in patients receiving cisplatin, 79% (11/14) in regimen A and 77% (13/17) in regimen B had no or mild nausea, compared with 90% (71/90) in regimen A and 86% (69/80) in regimen B in the total population. The data were also analysed separately on day 1 for the 28 patients who had received ifosfamide as part of their chemotherapy regimen, 14 in regimen A and 14 in regimen B. There were two or fewer emetic episodes in 79% (11/14) in regimen A patients versus 64% (8/14) in regimen B patients. Nausea was reported as none or mild in 100% (14/14) in regimen A and 86% (12/14) in regimen B.

There was no statistical difference between the results in the two regimens; if anything there was a trend towards better results in the 5 mg/m^2 arm, regimen A.

An analysis was carried out for each group of patients, those who had received cisplatin, ifosfamide and the remaining group, comparing the results between regimen A and B on each day of the study (day 1–9). No significant difference was found on any day.

Late control of emesis was poor in patients who received cisplatin. On the worst day of chemotherapy only 21% (3/14) in regimen A and 18% (3/17) in regimen B had two or fewer emetic episodes as compared to 61% (48/79) in regimen A and 60% (48/80) in regimen B of the total population.

Results were available from 34/41 patients who were classified as treatment failures (15 on day 1, 11 on day 2, 7 on day 3 and 1 on day 6) and who were given ondansetron plus dexamethasone for the second course of chemotherapy. There were 15 patients who received a loading dose of 5 mg/m^2 and 19 patients who received a loading dose of 10 mg/m^2. Complete and major responses were found on 60% (9/15) and (16/19), respectively, and appetite was 'as usual' or 'better' in 60% (9/15) and 72% (13/18), respectively.

Tolerability

The safety analysis included the whole population ($n = 187$). Ten serious adverse events were reported (seven cases of hyperthermia and infection secondary to neutropenia, one ulcerative oesophagitis induced by continuous vomiting, one left iliaca thrombus and one pneumothorax). None of these were considered by the investigator possibly, probably or almost certainly to be related to the study drug. In regimen A, two adverse events were considered almost certainly related to the study drug (headache, dizziness) and another two adverse events were considered probably related to the study drug (headache, warm feeling). In regimen B, one adverse event was considered probably related to the study drug (headache).

DISCUSSION

The majority of clinical trial experience with ondansetron has been obtained in adults. The first pilot dose-ranging studies in children were carried out in Australia [12] and the United Kingdom [13]. Clinical trial experience with ondansetron in children has been obtained from four European multicentre studies including over 400 patients [11, 14–16]. In these studies, ondansetron was given intravenously at a dose of 5 mg/m^2 (maximum 8 mg) immediately before chemotherapy followed by intravenous or oral treatment (2, 4 or 8 mg) three times a day for up to 5 days. These studies showed that ondansetron is an effective and well-tolerated anti-emetic in the control of emesis and nausea induced by a wide variety of chemotherapy regimens. However, lower response rates were associated with highly emetogenic chemotherapy such as cisplatin and ifosfamide. Clinical trial experience with ondansetron in adults suggests that patients receiving highly emetogenic chemotherapy may benefit from receiving a higher dose of ondansetron [17]. Another study has shown that the half-life of ondansetron is shorter in children than in adults [18]. There is also evidence that 5-hydroxytryptamine plays a rôle in triggering acute emesis [19]. It was, therefore, postulated that increasing the loading-dose of ondansetron in children would produce better anti-emetic control in children receiving highly emetogenic chemotherapy, in particular, those whose treatment included cisplatin.

The results of our study show that an increased loading dose of 10 mg/m^2 does not improve the control of vomiting or nausea in children receiving highly emetogenic chemotherapy. However both regimen A and regimen B provided good control of chemotherapy-induced emesis, on day 1, in all children (71–72% complete or major control and 86–90% no or mild nausea). The results from day 2 onwards in children who received cisplatin were not as good. Acute emesis following the administration of cisplatin, when no anti-emetic prophylaxis is provided, is known to be severe, and delayed emesis, occurring between 24 and 120 h after the administration of cisplatin, is extremely common. However, it has been suggested that cisplatin-induced delayed emesis is less severe if acute emesis is controlled. A study by Kris and collegues [20], including 86 patients receiving 120 mg/m^2 of cisplatin for the first time and who received good anti-emetic cover, showed that 62% experienced no vomiting in the first 24 h, but 93% of the patients experienced some degree of delayed nausea or vomiting. The patients included in the Kris study were those who would be expected to have the least severe delayed emesis as only patients who had less than three episodes of emesis in the first 24 h were included. There is also evidence to support the hypothesis that 5-hydroxytryptamine$_3$, may not be the major mediator of cisplatin-induced delayed emesis in adults and children [21–23]. A report by Gandara [23] on the control of delayed emesis in patients who received cisplatin and who were randomised to ondansetron or placebo on day 2 to day 5 only showed a statistically significant difference in favour of ondansetron on day 3.

Although the mechanism involved in cisplatin-induced delayed emesis is not understood, a number of studies have demonstrated that the efficacy of ondansetron can be enhanced by the addition of dexamethasone [24–27]. There is also evidence from the literature that, in adult patients who received cisplatin, the addition of dexamethasone to ondansetron prior to chemotherapy [28] might be more cost-effective than starting with ondansetron alone. In the second part of the present study, where regimen A plus dexamethasone was compared to regimen B plus dexamethasone, there was no significant difference between the results of the two arms. However the results of both arms with the addition of dexamethasone were encouraging, considering that these patients were previous treatment failures. The study design and small number of treatment failures did not permit a comparison of the results between the first and the second part of the study.

In conclusion, this study did not demonstrate a difference in the efficacy or tolerability of ondansetron given as a 5 mg/m^2 or a 10 mg/m^2 loading-dose on the first day of chemotherapy in patients who received highly emetogenic chemotherapy. The results from the patients who were considered treatment failures and who received a second course of treatment with additional dexamethasone were good, but numbers were small. Future studies on anti-emetic treatment in children should focus on those receiving repeated courses of chemotherapy containing cisplatin and on the mechanisms behind delayed emesis.

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