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ORIGINAL ARTICLE

Safety of ondansetron loading doses in children with cancer

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Abstract
Introduction In highly emetogenic chemotherapy, the recommended dose of the serotonin-receptor antagonist ondansetron (5 mg/m^2 q8h) may be insufficient to prevent chemotherapy-induced nausea and vomiting. In adults, ondansetron-loading doses (OLD) of 32 mg are safe. We aimed to evaluate in children the safety of an OLD of 16 mg/m^2 (top, 24 mg) i.v., followed by two doses of 5 mg/m^2 q8h.
Materials and methods This retrospective single-center study included all pediatric oncology patients having received ≥1 OLD between 2002 and 2005. Adverse events (AE) definitely, probably, or possibly related to OLD were studied, excluding AE not or unlikely related to the OLD. Associations between potential predictors and at least moderate AE were analyzed by mixed logistic regression.
Results Of 167 patients treated with chemotherapy, 37 (22%) received 543 OLD. The most common AE were hypotension, fatigue, injection site reaction, headache, hot flashes/flushes, and dizziness. At least mild AE were described in 139 OLD (26%), at least moderate AE in 23 (4.2%), and severe AE in 5 (0.9%; exact 95% confidence interval [CI], 0.4–2.1). Life-threatening or lethal AE were not observed (0.0%; 0.0–0.6). At least moderate AE were significantly more frequent in female patients (odds ratio [OR] 3.5; 95% CI 1.4–8.8; p=0.010), after erroneously given second OLD (17.0; 1.9–154; p=0.012) and higher 24 h cumulative surface corrected dose (1.26 per mg/m^2; 1.06–1.51; p=0.009). OLD given to infants below 2 years were not associated with more frequent AE.
Conclusions Ondansetron-loading doses of 16 mg/m^2 (top, 24 mg) i.v. seem to be safe in infants, children, and adolescents.

Keywords Chemotherapy · Children · Ondansetron loading dose · Nausea · Emesis

Introduction

Nausea and vomiting remain one of the three most distressing side effects of chemotherapy [8]. Specific serotonin (5-HT) receptor antagonists are generally accepted as the standard of care for prophylaxis of emesis [9, 12]. In highly emetogenic chemotherapy, the recommended doses are often insufficient, however. Optimal pediatric dosing and scheduling of antiemetics remain uncertain, and large robust trials are needed [1]. Due to variation of pharmacokinetic parameters in children, higher weight-based doses of 5-HT$_3$ antagonists than those used in adults may be required for antiemetic protection [12]. The question is whether higher doses are also safe.

The standard dose of ondansetron, a selective 5-HT$_3$ receptor antagonist, is 5 mg/m^2 (top dose, 8 mg) given intravenously or orally every 8 h. In adults, ondansetron loading doses (OLD) of 32 mg applied intravenously have been shown to be safe and well tolerated [19], while comparable data in children are rare. One prospective, random-

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ized, double-blind study found no clinical or laboratory toxicity after application of 16 ondansetron doses of 0.6 mg/kg in children, corresponding to about 18 mg/m^2, top dose 32 mg [18].

The aim of this retrospective single center study was to determine whether an OLD of 16 mg/m^2 (top dose, 24 mg), administered intravenously before chemotherapy and followed by doses of 5 mg/m^2 (top dose, 8 mg) every 8 h, was safe in children and adolescents.

Materials and methods

Patients

Since 2002, all patients diagnosed with a malignancy treated with severely emetogenic chemotherapy at the Division of Pediatric Hematology/Oncology, Department of Pediatrics, University of Bern, Switzerland routinely received OLD. Patients receiving moderately emetogenic chemotherapy in whom nausea and emesis was not controlled by the standard dose of ondansetron, i.e., 5 mg/m^2 (top, 8 mg) given orally or intravenously every 8 h, received OLD as well.

Eligible for this retrospective single-center study were all patients up to the age of 17 years, who had received at least one OLD between January 1, 2002 and December 31, 2005. This study had been approved by the institutional review board.

Definitions

The OLD was given intravenously, 16 mg/m^2 (top dose, 24 mg) over 15 min, half an hour before starting chemotherapy. It was followed by two intravenous or oral doses of ondansetron (5 mg/m^2; top dose, 8 mg) every 8 h. Data on adverse events (AE) was collected for 24 h after administration of the OLD.

The Common Terminology Criteria for Adverse Events (CTCAE; Version 3.0) were used to specify and quantify AE [23]. Severity of AE was divided into five grades: mild, moderate, severe, life-threatening, and death due to AE. Furthermore, it was described whether AE were definitely, probably, possibly, unlikely, or not related to the OLD [14].

Chemotherapy was classified into four levels of emetogenic risk, i.e., minimal (emesis in <10%) like vincristine, low (10 to 30%) like etoposide, moderate (30 to 90%) like ifosfamide, and high (>90%) like cisplatin [12].

Data assessment

Patient characteristics (sex, age at diagnosis, diagnosis, and relapse status), emetogenic risk of chemotherapy, and information on AE including quality, severity, and relation to OLD were extracted retrospectively from patient records.

Statistical analysis

Because of non-normally distributed data, median, interquartile range (IQR), and range were calculated. Exact Blyth–Still–Casella 95% confidence intervals (CI) were calculated for proportions. The exact Fisher–Freeman Halton test was used for comparing proportions, and mixed logistic regression (penalized quasi-likelihood method) for comparison of AE risks between different groups. Two-sided tests were applied throughout, and p values below 0.05 were considered significant. The softwares used were StatXact 6 (Cytel Software, Cambridge, MA, USA) and R 2.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients

In the 4 years studied, 167 patients were diagnosed with cancer requiring chemotherapy, with 37 (22%) of them receiving at least one OLD. The proportion of children receiving OLD was significantly lower in those with leukemia or lymphoma vs those with solid tumor within or outside the central nervous system, while there were no differences as to age at diagnosis, gender, and relapse status (Table 1). The median age of the 37 children studied here was 6.9 years when receiving their first OLD (range, 0.4 to 15.7). The smallest child weighed 4.4 kg, with a calculated body surface area of 0.26 m^2.

Ondansetron-loading doses

During the study period, these 37 patients received 543 OLD (median per patient, 12; range, 1 to 46) during 231 cycles of chemotherapy. As intended, 508 (94%) OLD were administered intravenously, while 35 (6%) were given orally. Only four (0.7%) OLD were given as antiemetic therapy, while the remaining 539 (99.3%) doses were applied prophylactically. As additional antiemetic medication, dexamethasone (2 mg/m^2 q8h) was given in 454 (84%) of the OLD, dexamethasone together with lorazepam in 12 (2.2%), and lorazepam in 1 (0.2%), while the OLD was administered without concurrent antiemetic medication 76 (14%) times.

The median OLD was 16 mg (IQR, 12 to 24; range, 4 to 25). The intended top dose of 24 mg, corresponding to a body surface area of at least 1.5 m^2, was given 175 times (32%), while it was exceeded once (0.2%; 25 mg). The median surface-corrected dose was 15.6 mg/m^2 (IQR, 14.8 to 16.2; range, 10.7 to 20.5). The OLD was dosed as in-

Table 1 Patient characteristics

Characteristic	All patients	Patients receiving at least one OLD		
	Number	Number (proportion)	OLD per patient: median (range)	OLD in total (proportion)
Total	167	37 (22%)	12 (1 to 46)	543 (100%)
Diagnosis ($p<0.001$)				
Leukemia	77	5 (6%)	2 (1 to 18)	26 (5%)
Lymphoma	24	2 (8%)	11 (5 to 16)	21 (4%)
CNS tumor	25	13 (52%)	11 (4 to 18)	133 (24%)
Solid tumor outside CNS	41	17 (41%)	18 (4 to 46)	363 (67%)
Age at diagnosis ($p=0.63$)				
<2 years	33	6 (18%)	9 (4 to 14)	52 (10%)
≥2 and <6 years	47	11 (23%)	13 (4 to 46)	173 (32%)
≥6 and <12 years	49	9 (18%)	8 (1 to 36)	103 (19%)
≥12 years	38	11 (29%)	18 (1 to 44)	215 (40%)
Gender ($p=0.85$)				
Female	81	17 (21%)	9 (1 to 46)	220 (41%)
Male	86	20 (23%)	14 (1 to 44)	323 (59%)
Relapse status* ($p=1.00$)				
Initial diagnosis	159	34 (21%)	12 (1 to 44)	479 (88%)
Relapse	20	4 (20%)	17 (8 to 22)	64 (12%)

OLD indicates ondansetron loading dose
p p value resulting from exact Fisher–Freeman–Halton tests; *CNS* central nervous system
*Of the 12 patients treated for both initial diagnosis and relapse during the study period, one received at least one OLD

tended, i.e., 16 mg/m^2±15% (13.6 to 18.4 mg/m^2), with a top dose of 24 mg, 503 (93%) times, while doses were too low 10 (1.8%) times and too high 30 (5.5%) times (Fig. 1).

Of the 543 OLD, 528 (97%) were followed as intended by two conventional ondansetron doses every 8 h, while 9 (1.7%) times only one conventional dose, and 6 (1.1%) times no further ondansetron dose was administered. After three (0.6%) OLD, a second OLD was administered erroneously within 3.5 to 6.5 h. The median cumulative ondansetron dose over 24 h was 31 mg. The median cumulative surface corrected dose, aiming at 26 mg/m^2, was 26.1 mg/m^2 (IQR, 24.7 to 27.8; range, 13.5 to 36.1).

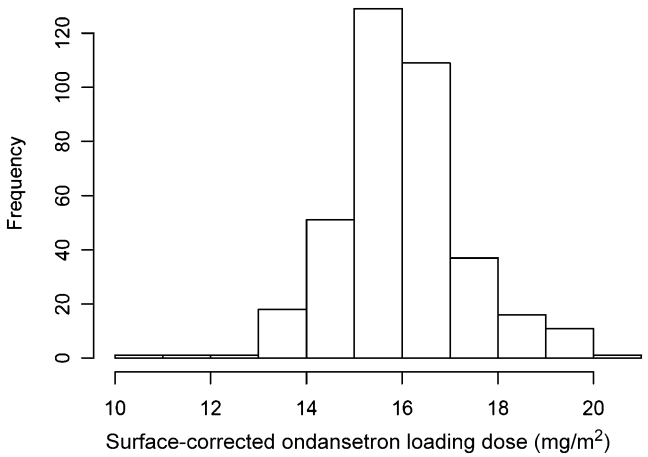

Fig. 1 Ondansetron-loading doses given to patients with a body surface area of 1.5 m^2 at most (total, 375). Children with a higher surface area received the top dose of 24 mg

Observed adverse events

In total, 356 AE were reported. There were 298 mild AE, 45 moderate AE, and 13 severe AE, while there were no life-threatening or lethal AE. As 190 AE were considered not or unlikely to be related to the OLD, only the remaining 166 AE at least possibly related were further studied. Of these, 140 (84%) AE were mild, 21 (13%) moderate, and 5 (3.0%) severe. The most common AE were hypotension and fatigue (31 each), injection site reaction (16), headache (15), hot flashes/flushes (14), and dizziness (11; Table 2).

In 139 OLD (25.6%; exact 95% CI 22.0 to 29.4), at least one AE at least possibly related to the OLD was observed. In 23 (4.2%; 2.8 to 6.3) of these OLD, an AE was at least moderate, and in 5 (0.9%; 0.4 to 2.1) of these OLD, the AE was severe. See Table 3 for details and for the respective numbers when the three OLD that were followed erroneously by a second OLD were excluded from analysis.

Of interest, OLD given to infants below 2 years were not associated with more AE than in older children: In infants, at least one mild AE at least possibly related to the OLD was recorded in 6 of 52 OLD (12%; 5 to 23), while there were no moderate or severe AE recorded in OLD in these infants.

The severe AE reported to be at least possibly related to five OLD included dizziness, headache, and abdominal pain. There were two patients experiencing severe AE probably or definitely related to an OLD: First, a girl aged 16 years, treated for medulloblastoma, developed severe dizziness plus moderate injection site reaction immediately after receiving erroneously a second OLD after 3.5 h, leading to a cumulative

Table 2 Adverse events

Type of AE	Grade of Adverse Events			
	Mild	Moderate	Severe	Total
Hypotension	31 (5.7%)	0	0	31 (5.7%)
Fatigue	30 (5.5%)	1 (0.2%)	0	31 (5.7%)
Injection site reaction	12 (2.2%)	4 (0.7%)	0	16 (2.9%)
Pain–head/headache	8 (1.5%)	5 (0.9%)	2 (0.4%)	15 (2.8%)
Hot flashes/flushes	12 (2.2%)	2 (0.4%)	0	14 (2.6%)
Dizziness	9 (1.7%)	0	2 (0.4%)	11 (2.0%)
Pain–abdomen	8 (1.5%)	0	1 (0.2%)	9 (1.7%)
Constipation	7 (1.3%)	2 (0.4%)	0	9 (1.7%)
Allergic reaction	7 (1.3%)	1 (0.2%)	0	8 (1.5%)
Pain–extremity-limb	6 (1.1%)	1 (0.2%)	0	7 (1.3%)
Mood alteration–agitation	1 (0.2%)	2 (0.4%)	0	3 (0.6%)
Ocular–other (impaired vision)	1 (0.2%)	2 (0.4%)	0	3 (0.6%)
Pruritus	2 (0.4%)	0	0	2 (0.4%)
Edema: head and neck	2 (0.4%)	0	0	2 (0.4%)
Diarrhea	2 (0.4%)	0	0	2 (0.4%)
Dysphagia	0	1 (0.2%)	0	1 (0.2%)

Indicated are the number of adverse events reported, and the respective proportion of OLD in parentheses

ondansetron dose of 28 mg/m^2. Second, a 5-year-old girl treated for osteosarcoma developed severe abdominal pain 2 h after receiving a correctly dosed OLD.

Factors associated with the risk of adverse events

Table 4 displays that double OLD, a higher 24 h cumulative surface corrected dose, and female gender all were significantly associated with an increased frequency of moderate or severe AE. This was the case as well for a higher surface-corrected loading dose and age above 2 years for mild, moderate, or severe AE. The other factors examined were not significantly associated with AE.

Antiemetic efficacy

Although the efficacy was not a primary endpoint, data on frequency of emesis and nausea were collected in the chart review. Complete or major control of emesis, i.e., not exceeding one episode in 24 h, was achieved in 472 (87%) OLD. In 393 (72%) OLD, no nausea or emesis at all was noted in the charts.

Discussion

The results of this study indicate that OLD applied as described to prevent or treat chemotherapy induced nausea and vomiting in infants, children, and adolescents seem to be safe and well tolerated. In 404 of 543 (74%) loading doses, no adverse events at least possibly related to ondansetron were reported. Side effects were usually mild in nature (116 OLD, 23%), while moderate (18, 3.3%) and severe (5, 0.9%) adverse events occurred in few OLD only.

The most commonly reported adverse events at least possibly related to the OLD in our study were fatigue and

Table 3 Adverse events at least possibly related to ondansetron-loading doses

Type of AE	Number of OLD with at least 1 AE of the specified type (proportion; exact 95% confidence interval)	
	540 single OLD as intended*	All 543 OLD
At least mild AE	138 (25.6%; 21.9 to 29.4)	139 (25.6%; 22.0 to 29.4)
At least probably related to OLD	39 (7.2%; 5.2 to 9.7)	40 (7.4%; 5.3 to 9.9)
At least moderate AE	22 (4.1%; 2.6 to 6.0)	23 (4.2%; 2.8 to 6.3)
At least probably related to OLD	4 (0.7%; 0.3 to 1.8)	5 (0.9%; 0.4 to 2.1)
At least severe AE	4 (0.7%; 0.3 to 1.8)	5 (0.9%; 0.4 to 2.1)
At least probably related to OLD	1 (0.2%; 0.0 to 1.0)	2 (0.4%; 0.1 to 1.3)
At least life-threatening AE	0 (0.0%; 0.0 to 0.6)	0 (0.0%; 0.0 to 0.6)
Death as an AE	0 (0.0%; 0.0 to 0.6)	0 (0.0%; 0.0 to 0.6)

AE Adverse event; *OLD* ondansetron-loading dose
*After three (0.6%) OLD, a second OLD had been erroneously administered within 8 h

Table 4 Influence of characteristics of patients and of loading doses on the risk of at least moderate adverse events

Characteristic	Loading doses	OLD with at least moderate AE at least possibly related to OLD		
	Number	Number (proportion)/*median (interquartile range)	Odds ratio (95% CI)	*p* value
Gender				
Female	220	16 (7.3%)	3.54 (1.43–8.77)	0.010
Male	323	7 (2.2%)	reference	
Age at administration				
<2 years	52	0 (0%)	0.00 (0.00-?)	1.00
≥2 and <6 y	155	10 (6.5%)	1.62 (0.56–4.67)	0.37
≥6 and <12 y	87	3 (3.4%)	0.73 (0.19–2.82)	0.65
≥12 years	249	10 (4.0%)	reference	
Diagnosis				
Leukemia	26	2 (7.7%)	2.74 (0.53–14.2)	0.24
Lymphoma	21	2 (9.5%)	3.58 (0.66–19.5)	0.15
CNS	133	9 (6.8%)	2.55 (0.99–6.58)	0.062
Solid tumors	363	10 (2.8%)	reference	
Relapse status				
Relapse	64	4 (6.3%)	1.33 (0.38–4.63)	0.66
No relapse	479	19 (4.0%)	reference	
Emetogenic risk of chemotherapy				
Minimal (<10%)	2	0 (0%)	0.00 (0.00-?)	1.00
Low (10% to 30%)	20	2 (10%)	reference	
Moderate (30 to 90%)	316	12 (3.8%)	0.34 (0.08–1.39)	0.13
High (>90%)	205	9 (4.4%)	0.34 (0.08–1.46)	0.15
Loading dose (mg)*	16.0 (12.0–24.0)	16.0 (12.0–20.0)	1.00 (0.92–1.08)	0.91
Loading dose, surface-corrected (mg/m^2)*	15.6 (14.8–16.2)	15.6 (14.8–16.4)	0.90 (0.65–1.25)	0.52
Cumulative dose (mg/24 h)*	31.0 (20.0–40.0)	26.0 (20.0–37.0)	1.03 (0.98–1.09)	0.22
Cumulative dose, surface-corrected (mg/m^2/24 h)*	26.1 (24.7–27.8)	27.3 (25.5–28.6)	1.26 (1.06–1.51)	0.009
Application form of OLD				
Intravenous	508	22 (4.3%)	Reference	
Oral	35	1 (2.9%)	0.70 (0.12–4.14)	0.69
Double loading dose				
No	540	22 (4.1%)	Reference	
Yes	3	1 (33.3%)	17.0 (1.88–154)	0.012
Additional medication				
Dexamethasone or Lorazepam	467	20 (4.3%)	1.15 (0.37–3.57)	0.81
None	76	3 (3.9%)	Reference	

*Indicates median (interquartile range) are indicated for continuously measured variables

hypotension (6% of OLD each), headache, injection site reaction, hot flashes/flushes (3% each) and constipation, abdominal pain, and dizziness (2% each). Both the incidence and spectrum of adverse events reported were similar to those of adults receiving an intravenous OLD of 32 mg [16, 17, 19] and to those of children after a standard dose of 5 mg/m^2 ondansetron, where headache was noted in 2 to 8%, constipation in 1 to 3.5% and diarrhea in 2% besides rarer adverse effects like dizziness, warm feeling, somnolence, rash, and urticaria [5, 6, 13, 21].

Among the reports on OLD in pediatric patients, this is the first study with safety as primary end point. In a prospective, double-blind, randomized study, Sandoval et al. [18] compared the antiemetic efficacy of a single high-dose (0.6 mg/kg, corresponding to about 18 mg/m^2, maximum dose 32 mg) with a repeated standard dose (0.15 mg/kg, maximum dose 8 mg, every 4 h) in 31 pediatric oncology patients. The study suggested that single high-dose ondansetron was as efficacious as the multiple standard-dose regimen and was well tolerated. No patient experienced any clinical or laboratory toxicity (16 high doses of ondansetron applied; toxicity in 0%; exact 95% CI, 0 to 20%). Brock et al. [5] conducted a randomized, double-blind study, comparing a standard dose of 5 to 10 mg/m^2, i.e., a medium dose of ondansetron, in 187 chemotherapy-naive children. There was no difference in the control of emesis or nausea,

and both anti-emetic regimens were tolerated well. Four adverse events (headache in two episodes, dizziness, and warm feeling) were considered to be at least probably related to the standard dose (5 mg/m^2) compared to one AE (headache) probably related to the medium dose of 10 mg/m^2. In a randomized, double-blind, placebo-controlled trial, Parker et al. [15] had applied 48 OLD of 0.45 mg/kg, corresponding to about 14 mg/m^2. No analysis of adverse events was performed.

Surprisingly, girls appeared to suffer more AE than boys. Although female patients are known to have a higher incidence of chemotherapy-induced nausea and vomiting than male patients [11, 19, 20], we do not know of any data on gender-related differences of adverse effects of ondansetron or of perceiving them.

Three times (0.6%) a second loading dose had erroneously been given. As expected, this led to a significantly higher risk of at least moderate adverse events, as was a higher surface-corrected cumulative dose. These results show that OLD must not be arbitrarily increased. The top dose in our patients had been set to 24 mg, clearly below the OLD of 32 mg established in adult oncology. This top dose had been exceeded only once (0.2%). Generally, the adherence to dosing instructions was high with 93% of doses lying within the accepted range of 16 mg/m^2±15%.

A limitation of the present study is the retrospective design, which can lead to missing data, especially on AE. Both the physician and nurse's chart records, however, were searched through for AE to minimize this risk. The fact that in infants no excess of AE was recorded might reflect that either they are not more susceptible to side effects of OLD or that an important part of the side effects in this age group were recorded with a smaller probability than in older children better able to communicate. As might be anticipated when considering the severity of illness of this patient population, it was sometimes difficult to determine whether the adverse event was due to the underlying malignancy itself, to chemotherapy, other medication, or ondansetron. This problem, however, would remain as well in a prospectively designed study. For dexamethasone as a very frequent co-medication, potentially linked to hot flashes, dizziness, mood alteration, and edema, we did not find an increased frequency of AE.

An advantage of this study was the large sample size with 543 OLD, which allowed to calculate 95% CI for AE that are clearly smaller than those published before [5, 18]. Even for infants below 2 years, sample size was acceptable with 52 OLD. Remarkably, few data about the use of serotonin 5-HT3 receptor antagonists in infants have been published [4]. One placebo-controlled study demonstrated that standard ondansetron dose (0.1 mg/kg, corresponding to 3 mg/m^2) is well tolerated and effective in preventing postoperative nausea and vomiting in patients younger than 2 years of age [10]. In our study, OLD given to infants were not associated with more frequent AE described.

Chemotherapy-induced nausea and vomiting is still an important problem both in adult [2, 3, 7, 22] and pediatric oncology [9]. Besides approaches using new substances like neurokinin antagonists [22] and new ways of application like patient-controlled dosing of antiemetic drugs [9], higher than standard doses of established substances, like OLD, may help to reduce this problem.

In conclusion, we report that an ondansetron-loading dose of 16 mg/m^2 (maximum, 24 mg) i.v. to prevent chemotherapy-induced nausea and vomiting in infants, children, and adolescents with cancer seems to be safe and well tolerated. In three quarters of OLD, no adverse event possibly due to the OLD occurred at all. A severe AE at least possibly related to the OLD occurred after five doses (0.9%; exact 95% CI, 0.4 to 2.1%). However, an upper dose limit exists, and OLD must not be increased arbitrarily. Despite the fact that this is a retrospective study, its results seem to be well-founded and clinically applicable. However, they cannot directly be applied to other 5-HT inhibitors.

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