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Effects of Ondansetron in the Prevention of Postoperative Nausea and Vomiting in Children

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Background: **Postoperative nausea and vomiting (PONV) is a commonly observed adverse effect of general anesthesia. Recently, ondansetron, a new serotonin$_3$ (5-hydroxytryptamine$_3$) receptor antagonist was shown to be effective in the prophylaxis and prevention of chemotherapy-induced nausea and vomiting in children and adults as well as of PONV in adults. The aim of the current study was to evaluate the capacity of ondansetron to prevent PONV in pediatric patients.**

Methods: **Two hundred children (132 boys and 68 girls) 2–10 yr of age received general inhalational anesthesia for surgical procedures (the extremities; ear, nose, and throat; inguinal hernia and phimosis; and dentistry) of an expected duration of less than 90 min. This study was divided into two phases: prophylaxis and rescue treatment. For prophylaxis, patients were randomly assigned to two groups: one group received an intravenous injection of 0.1 mg/kg ondansetron, and the other group received a placebo before surgical incision under double-blind conditions. For rescue treatment, only placebo patients were included; as a rescue medication they received an intravenous injection of 0.1 mg/kg ondansetron or 0.02 mg/kg droperidol according to a prestudy randomization under double-blind conditions. Incidence and severity of PONV (PONV score 0 = no nausea and no retching; 1 = complaining of sickness and retching; 2 = vomiting one or two times in 30 min; 3 = vomiting more than two times in 30 min) was recorded over a 4-h period in the postanesthesia care unit. Within 72 h of the procedure, a follow-up nurse interviewed the parents for late-onset nausea in the children.**

Results: **With regard to prophylaxis, 10% of patients receiving ondansetron had PONV during the 4-h observation period *versus* 40% of those receiving placebo ($P < 0.001$). The incidence of vomiting alone (PONV score ≥2) was 5% and 25%, respectively ($P < 0.001$). There were no significant differences between ondansetron and droperidol in the treatment of PONV. However, at the end of the 4-h period, ondansetron patients were less sedated than were patients who had received droperidol ($P < 0.01$). Interviews with parents could be performed for 143 of 200 children (76 ondansetron and 67 placebo). Twenty-four children (15 ondansetron and 9 placebo) showed late-onset PONV after the 4-h observation period but within 24 h of the procedure (19.7% *vs.* 13.4%; *P* not significant).**

Conclusions: **Ondansetron is effective in the prevention of PONV in pediatric patients for the first 4 h after general anesthesia. Lower sedation scores with ondansetron compared with droperidol may be an advantage, especially in ambulatory surgery. However, the incidence of late-onset PONV (>4–24 h) was not influenced by prophylactic treatment with one dose of ondansetron preoperatively. (Key words: Anesthesia: pediatric. Antagonists, serotonin: ondansetron. Complications, postoperative: nausea; vomiting. Vomiting: antiemetic therapy.)**

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IN children, postoperative nausea or vomiting (PONV) are important adverse effects of general anesthesia,[1] resulting in prolonged recovery room stays and, on occasion, unanticipated admission after outpatient surgery.[2]

A variety of different pharmacologic approaches (anticholinergics, antihistamines, butyrophenones, dopamine receptor antagonists) has been investigated in the prevention and treatment of PONV,[3,4] but undesirable side effects such as excessive sedation, hypotension, dry mouth, dysphoria, hallucinations, and extrapyramidal reactions have been noted.[5,6]

Recently, a selective 5-hydroxytryptamine$_3$ receptor antagonist, ondansetron (1,2,3,9-tetrahydro-methyl-3-[(2-methylimidazol-1)methyl] carbazole-4-one hydrochloride hydrate) has been shown to be effective in

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preventing and treating nausea and vomiting associated with emetogenic cancer chemotherapy[7,8] and PONV in adults.[9–12] It has also been proven to be effective in pediatric cancer treatment.[13–15]

This study was designed to determine whether intravenous bolus injections of ondansetron are effective in preventing PONV in children, and to compare the efficacy and adverse effects of ondansetron with those of droperidol, which is currently used to treat PONV in this patient population.

Materials and Methods

The study was performed in 200 pediatric patients of ASA physical status 1 or 2. The study protocol was approved by the Institutional Ethical Committee of the University of Basel Children's Hospital; written informed consent was obtained from the parents of each child.

Inclusion criteria were age >2 yr, body weight ≤40 kg, and extraabdominal surgery: procedures on the extremities; ear, nose, and throat surgery; surgery for inguinal hernia and phimosis; and dental procedures of an expected duration of less than 90 min. Patients were not excluded if they had a history of motion sickness or previous PONV. Exclusion criteria were missing informed consent or preexisting hepatic disorders.

This study was divided into two phases: prophylaxis and rescue medication. In the prophylaxis phase, 200 patients were prospectively randomized into the following groups using computer generated random numbers: 100 patients each received an intravenous injection of 0.1 mg/kg ondansetron or placebo. As a rescue medication in case of PONV, all ondansetron patients received 0.02 mg/kg droperidol as an intravenous bolus injection. Only placebo patients were included in the rescue part of the study. They received an intravenous injection of 0.1 mg/kg ondansetron or 0.02 mg/kg droperidol as rescue medication according to a randomization plan. All drugs were administered under double-blind conditions.

Medication

Ondansetron was obtained from Glaxo AG, Schöhnbühl/Bern, Switzerland, and 4 mg of the drug was placed into 2-ml ampules. Droperidol (Janssen Pharmaceutica AG, Baar, Switzerland) was dissolved in 0.9% sodium chloride solution and 0.8 mg was placed in 2-ml ampules. For placebo administration, 2-ml ampules of 0.9% sodium chloride solution were used. For each patient, the medication set contained one ampule for prophylactic treatment (labeled "ampule 1") and another ampule as a rescue medication in case of PONV (labeled "ampule 2") according to the randomization list. The test medications, labeled for blind administration, was prepared by the hospital pharmacy staff.

Dietary Restrictions

Patients did not consume milk or solids for at least 6 h before operation; clear fluids were allowed until 2 h before induction. Postoperatively, clear fluids were offered in small quantities if desired but not earlier than 2 h after arrival in the recovery room.

Anesthetic Procedure

Patients were premedicated with 0.5 mg/kg midazolam rectally 20 min before surgery or 0.4 mg/kg midazolam orally 1 h before surgery. General anesthesia was induced with halothane and 60% nitrous oxide in oxygen administered by mask or with thiopental (5 mg/kg) intravenously. When tracheal intubation was necessary (ear, nose, and throat and dentistry groups), the children received 0.1 mg/kg vecuronium, and, before extubation, their stomachs were emptied *via* a gastric tube. Anesthesia was maintained with halothane (0.4–1.0%) and nitrous oxide (60% in oxygen). Children in whom the trachea was not intubated, breathed spontaneously or received assisted ventilation administered *via* face mask or laryngeal mask to achieve an end-tidal CO_2 partial pressure of 35–50 mmHg. In the inguinal hernia and phimosis patients, additional caudal (0.19–0.25% bupivacaine) or inguinal (0.5% bupivacaine) blockade was performed. In rare cases, the halogenated agent was changed to isoflurane because of ventricular ectopy. Intravenous fluid management consisted of administration of Ringer's lactate, correcting half of the preoperative deficit within the 1st h and maintaining fluid requirements according to body weight. Intraoperatively, no opioids were administered.

Administrations

To achieve a standardized dosage, at the beginning of induction or in case of PONV each 2-ml ampule was diluted with 8 ml 0.9% sodium chloride solution and thus contained 0.4 mg/ml ondansetron, 0.08 mg/ml droperidol, or normal saline (placebo) in a final volume of 10 ml.

In the prophylaxis part of the study, patients then received 0.25 ml/kg body weight of ampule 1 equiv-

alent to 0.1 mg/kg ondansetron or saline, as a slow intravenous injection over 3 min after induction of anesthesia and before surgical incision. Blood pressure and heart rate were recorded before and 1, 3, and 5 min after drug administration.

In the rescue part of the study, medication was administered if PONV occurred (PONV score ≥ 1). According to the study design, all ondansetron patients received droperidol as a rescue medication, whereas placebo patients were given ondansetron or droperidol in case of PONV. The 2-ml ampule 2 was diluted with 8 ml sodium chloride 0.9% and thus contained 0.4 mg/ml ondansetron or 0.08 mg/ml droperidol. As in the prophylaxis group, children then received 0.25 ml/kg body weight intravenously, equivalent to 0.1 mg/kg ondansetron or 0.02 mg/kg droperidol.

Postoperative Pain Treatment

When older children complained of pain or younger children, not able to communicate verbally, cried, paracetamol (acetaminophen, 15–25 mg/kg) was given by rectal route as an analgetic of the first choice and, if necessary, pentazocine (0.3 mg/kg) intravenously as the analgetic of second choice.

Observations and Data Handling

Postoperatively, all children were transported to the postanesthesia care unit. The patients were evaluated by numeric rank scores for PONV, pain, and sedation (table 1). The observations were performed by one of three trained postanesthesia care nurses who had been instructed as to the study design and score system and who were unaware of the children's group assignments. Observations were recorded when the child arrived in the postanesthesia care unit (transport period) and at 30-min intervals until 240 min post-arrival. The severity of PONV was scored as follows: 0 = no nausea and no retching; 1 = complaining of sickness and retching; 2 = vomiting one or two times in 30 min; and 3 = vomiting more than two times in 30 min. PONV data after rescue medication were not considered for further analysis in the prophylaxis part of the study.

Intensity of postoperative pain was assessed every 30 min over the 4-h observation period. To account for severity and duration of pain, the sum of all these values was calculated for each patient (cumulative pain score) and used for statistical analysis.

For the rescue part of the study, sedation scores at the end of the 4-h period were compared between the two treatment groups.

Table 1. Recovery Room Scoring System

Factor	Score
PONV	
No nausea, no retching	0
Complaining of sickness, retching	1
Vomiting 1–2 times/30 min	2
Vomiting >2 times/30 min	3
Sedation	
Awake, responsive	0
Sleepy, but awake most of the time	1
Sleeping more than half of the time	2
Sleeping all the time	3
Pain	
No pain at all	0
Mild pain	1
Moderate pain	2
Severe pain	3

When possible, a designated follow-up nurse interviewed the parents by telephone for late-onset PONV (4–24 h postoperatively).

Statistics

Statistical analyses of data between two patient groups were performed by analysis of variance, Kruskal-Wallis test, chi-squared test, or Fisher's exact test, as appropriate. Age dependence of incidence of PONV was assessed by logistic regression. All tests were performed using SPSS for Windows (Release 6.0, SPSS Inc., Chicago, IL). The level of significance was $P = 0.05$.

Results

Patient characteristics, types of surgery, and anesthetic or postoperative management were comparable between groups (table 2).

With regard to prophylaxis of PONV, a statistically significant effect of ondansetron on incidence and severity of nausea was demonstrated: during the postanesthesia care unit stay, 10% of the ondansetron patients showed signs of mild, moderate, or severe PONV compared with 40% in the placebo patients (tables 3 and 4). Except for the transport period and the >3–4 h observation period, ondansetron group patients showed significantly lower incidence and severity of PONV than placebo patients (table 3). If only the incidence of vomiting (PONV score ≥ 2) was compared, the difference was still statistically significant during the 4-h observation period ($P < 0.001$).

Table 2. Patient Characteristics

Characteristic	Ondansetron		Placebo	
	Mean	Range	Mean	Range
Age (yr)	5.0	2.0–10.0	5.5	2.0–10.9
Height (cm)	111	85–150	112	80–145
Weight (kg)	18.5	11.0–30.0	19.0	10.0–40.0
Duration of anesthesia (min)	91.5	30–310	92.5	50–205
Duration of surgery (min)	47.9	10–260	43.9	10–135
No. of patients				
Sex (M/F)	65/35		67/33	
Type of surgery*				
EXT	5		4	
ENT	51		46	
ING	33		40	
DENT	11		10	
Combined GA + RA	32		31	
PACU analgetic treatment				
Paracetamol	52		56	
Pentazocine	42		41	

* Procedures on extremities (EXT); ear, nose, and throat (ENT); inguinal hernia and phimosis (ING); and dentistry (DENT).

GA = general anesthesia; RA = regional anesthesia; PACU = postanesthesia care unit.

Incidence and severity of PONV were not influenced by gender in the ondansetron or placebo patients (difference not statistically significant). However, in the placebo patients, the incidence of PONV increased with age (table 4). In the ondansetron patients, this relation could not be documented because of the small number of patients who had PONV. Due to the small number of patients in the dentistry group and the procedures on extremities group, no significance could be demonstrated. The other groups (inguinal hernia and phimosis group and ear, nose, and throat group), representing 85% of the patients, showed a significant decrease in incidence of PONV when receiving ondansetron prophylaxis (fig. 1).

After bolus administration of ondansetron, blood pressure and heart rate remained unchanged intra- and postoperatively after 1, 3, and 5 min in both ondansetron and placebo patients compared with the base line. In each group, no extrapyramidal adverse events such as torticollis, dystonia, or restlessness and anxiety were observed.

Forty placebo patients developed PONV and were, therefore, eligible for the rescue part of the study. In eleven children, the intravenous catheter was nonfunctional postoperatively for various reasons and these patients were excluded. Of the remaining 29 patients, 13 received droperidol and 16 ondansetron; there were no differences between these two treatment groups with respect to demographic data and severity of PONV. Comparison of PONV scores (only PONV scores after rescue medication) showed no difference between the two groups: 12 of 16 children recovered completely from PONV in the ondansetron therapy group *versus* 11 of 13 children in the droperidol therapy group. However, ondansetron patients were less sedated: sedation scores at the end of the 4-h period were significantly higher in the droperidol- than in the ondansetron-treated children (median 1.5 *vs.* median 0.0; 25%/75% interquartile range 0/3 *vs.* 0/0.5, respectively; $P < 0.01$).

No child had to be admitted overnight because of severe PONV. Two patients (both placebo) developed protracted PONV within the 4-h observation period and did not respond to rescue medication within 30 min; one had received ondansetron and one droperidol.

The postoperative intake of clear fluids (tea or water) did not influence the incidence of PONV. In the placebo patients, 22 of the 40 children with PONV had drunk water or tea before symptoms of nausea occurred, whereas in the children receiving ondansetron, 5 of 10 had been drinking water or tea before signs of PONV were observed.

For analgesic treatment, 15–25 mg/kg paracetamol (acetaminophen) was given rectally (n = 108) and 0.3 mg/kg pentazocine intravenously (n = 83) as a second-choice drug. Compared with placebo, ondansetron patients showed a similar incidence (n = 34 and n = 32, respectively) and identical severity of postoperative pain (median cumulative pain score 2.0). The need for postoperative analgesic therapy was comparable in ondansetron and placebo patients: 52 and 56 children received paracetamol (acetaminophen), 42 and 41 pentazocine, respectively. Although an opioid, the administration of pentazocine did not significantly increase the incidence of PONV (23 of 83 children) compared with those who did not receive this drug (27 of 117 children).

In 143 of the 200 children (76 ondansetron, 67 placebo), interviews with parents could successfully be performed by a follow-up nurse. Twenty-four children (15 ondansetron, 9 placebo) developed PONV between 4 and 24 h after the procedure (19.7% *vs.* 13.4%; *P* not significant).

Discussion

Vomiting is an unpleasant experience for children and, though rare, the main reason for overnight hospital

Table 3. Severity of PONV and Time Interval of Occurrence

	PONV Score*	TP†	0–1 h	>1–2 h	>2–3 h	>3–4 h	Total (0–4 h)
Placebo	0	94	83	72	64	60	60
	1	2	5	4	1	3	15
	2	4	5	5	7	1	22
	3		1	2			3
	Score ≥ 1	6	11	11	8	4	40
Ondansetron	0	96	93	93	92	90	90
	1	2	1			2	5
	2	2	2				4
	3				1		1
	Score ≥ 1	4	3		1	2	10
P‡		NS	<0.05	<0.001	<0.001	NS	<0.001

Values are no. of patients.

TP = transport period.

* PONV Score: 0 = no nausea, no retching; 1 = complaining of sickness, retching; 2 = vomiting 1–2 times/30 min; 3 = vomiting >2 times/30 min.

† *P* value = chi-square test or Fisher's exact test as appropriate.

admissions.[2] In adults, the incidence of PONV is 20–40%,[16] for children, no consistent data are available.[17] One study reported a low incidence of 8.9% in pediatric ambulatory surgery,[2] but tonsillectomies were not included. Another study of children over 5 yr of age found about one third of patients experienced PONV.[1] In high-risk cases of children undergoing strabismus surgery, approximately 80% of the patients not receiving any antiemetic prophylactic treatment vomit postoperatively.[18] Our overall incidence was 40% in the untreated group (placebo), who had various types of surgery. In agreement with reported data,[19] the incidence of PONV in placebo patients increased with age for all types of surgery (table 4).

An effective antiemetic that could be used prophylactically for a patient population at higher risk and therapeutically to treat PONV, when it occurred, would be a valuable asset to pediatric anesthesia management, especially if it is devoid of significant adverse effects such as sedation or extrapyramidal movement.

Previous studies in adults have shown the effectiveness of ondansetron in the prevention and treatment of PONV.[9,10,20,21] In most of these studies, an oral premedication or treatment as well as an intravenous pretreatment before the induction of anesthesia has been shown to be effective.[22] However, a clear dose–effect relation of ondansetron for pediatric patients has not been established. We decided to give 0.1 mg/kg ondansetron intravenously, which is effective in the control of chemotherapy-induced emesis.[8]

Our study documents the efficacy of ondansetron in the prevention of PONV during the first 4 h postoperatively. Detailed analysis of our data, however, shows that ondansetron did not prevent the occurrence of

Table 4. Incidence of PONV in Different Age Groups

	Placebo			Ondansetron			
		Patients with PONV			Patients with PONV		
Age (yr)	No. of Patients	n	%	No. of Patients	n	%	*P* Value*
2–4	37	12	32.4	38	4	10.5	<0.05
>4–6	31	12	38.7	33	1	3.0	<0.001
>6–8	19	8	42.1	20	2	10.0	<0.05
>8–10	13	8	61.5	9	3	33.3	NS
Total	100	40	40	100	10	10	<0.001

* Incidences of PONV were compared by chi-square test or Fisher's exact test as appropriate.

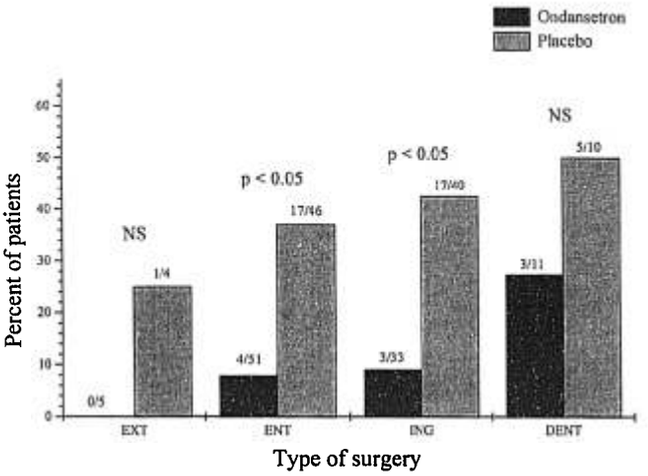

Fig. 1. Incidence of postoperative nausea or vomiting (PONV) for various types of surgery: procedures on extremities (EXT); ear, nose, and throat (ENT); inguinal hernia and phimosis (ING); and dentistry (DENT). Numbers above bars = patients with PONV. Except for EXT and DENT, data show significant reduction of the incidence of PONV in the patients receiving ondansetron (chi-squared test or Fisher's exact test as appropriate).

PONV before arrival in the postanesthesia care unit. This may be due to mechanical stimulation and changing positions. At the <0–1 h, <1–2 h, and <2–3 h observations, ondansetron patients showed a low incidence of PONV (fig. 1) and low PONV scores (table 3) and the differences from the placebo patients were significant. There was no significant difference during the <3–4 h observation period and during the >4–24 h recovery period. This might be related to the pharmacokinetic profile of ondansetron: the plasma elimination half-life in adults is 2.8 ± 0.6 h after intravenous and 3.2 ± 0.7 h after oral administration of an 8-mg dose.[23] In children receiving cancer chemotherapy, the half-life of oral ondansetron was reduced in children between 4–12 yr (2.47 h) compared with children > 12 yr (3.84 h).[24] Therefore repeated (iv or oral) administration of ondansetron may decrease the incidence of PONV during the 4–24 h period and further studies should be implemented to investigate this hypothesis.

We do not know if ondansetron alters the overall incidence of PONV, because our telephone interview recovery data were incomplete. But a response rate of 71.5% for the telephone follow-up by our special staff nurses corresponds favorably to the 50% rate in another investigation[2] and the 33% rate when using a mailed questionnaire method.[25] With our study design, we concentrated on the 4-h observation period, as we expected it to be problematic to compare well assessed in-hospital data with the telephone interviews. Furthermore, circumstances differ with concern to distance for riding home, mobilization or resting at home, and amount and type of food or liquids ingested at home. If, by calculation, the incidence of PONV in 143 completed interviews was projected to 200 patients, the number of children experiencing PONV between 4–24 h postoperatively would be 21 and 13 in the ondansetron and placebo patients, respectively. Adding the number of PONV patients of both time periods (0–4 h, >4–24 h) yields an overall incidence of PONV of 31% *versus* 53% ($P < 0.01$).

There was a consensus between the authors that it was ethically not acceptable to include a placebo group in the rescue part of the study. This decision, however, limited the interpretation of the results. The lack of a difference in the incidence of PONV between the two rescue groups may be the result of a comparable efficacy for the two drugs or of no efficacy at all. As droperidol 0.02 mg/kg has been shown to be effective in the treatment of PONV in pediatric patients,[26,27] we suggest that ondansetron had a comparable therapeutic effect to that of droperidol, although a type II error cannot be excluded. The droperidol-treated patients showed a significant increase in sedation score compared with ondansetron during the 4-h observation period. Because our protocol did not permit discharge before 4 h postoperatively, we could not demonstrate a shortened recovery room stay for the ondansetron-treated patients.

For assessment of PONV, sedation, and pain, we decided to use a rank score rather than analog scales. As recently reviewed,[28] most researchers use numeric scores and the character of sedation is usually assessed by themselves rather than by the patient. Many of our patients were uncooperative or unable to communicate verbally, and we expected to obtain the most objective results using the judgment of a small group of experienced postanesthesia care nurses. Assessment of nausea measurements revealed substantial equivalence of visual analogue scales and numeric rank scores.[29]

Ondansetron has not been found to have significant side effects on hematologic or cardiorespiratory functions.[9,10] In cancer patients, the common adverse events were headache, diarrhea, and transient increase in the plasma activities of alanine aminotransferase and aspartate aminotransferase.[30] In our investigation, no influence on heart rate or blood pressure was observed and no observation was recorded, that could have been attributed to ondansetron.

During the postanesthesia care unit observation, children were allowed but not forced to drink clear fluids starting 2 h postoperatively, as it has been shown that drinking is not a prerequisite for discharging pediatric patients after day surgery.[19]

Our study shows that one dose of intraoperatively administered ondansetron is effective in the prevention of PONV during the first 4 h postoperatively, and has no undesirable adverse effects such as sedation or hemodynamic depression. Further investigations should address the questions of whether repeated doses decrease the incidence of PONV during the remaining recovery period, and whether therapeutic administration is as effective as prophylactic. Regarding the benefit of ondansetron prophylaxis or treatment, it is important that further studies should be devoted to investigate the overall outcome of patients: potential reduction in recovery room stay and readmission rate as well as improved patient satisfaction. This information may then allow us to judge whether the increased costs outweigh these potential benefits.

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