Prophylaxis for vomiting by children after tonsillectomy: ondansetron compared with perphenazine

W. M. SPLINTER AND E. J. RHINE

Summary
We have compared the effects of ondansetron and perphenazine on vomiting after tonsillectomy in 216 healthy children, aged 2–12 yr. The study was randomized, stratified, blocked and double blind. Anaesthesia was induced with propofol i.v. or by inhalation of halothane and nitrous oxide. Ondansetron 150 μg kg⁻¹ or perphenazine 70 μg kg⁻¹ was administered i.v. after induction of anaesthesia in a double-blind manner. Perioperative management of emesis, pain, fluids and patient discharge were standardized. Ondansetron and perphenazine had similar effects on postoperative vomiting (44% vs 41%; ondansetron vs perphenazine P=0.77). By logistic regression analysis, the only significant predictor of postoperative vomiting was age, that is males had a greater incidence of vomiting (49% vs 35%; P=0.016). In-hospital vomiting was associated with a prolongation of stay in the day-care surgical unit of 7 min per episode of vomiting (P=0.015). We conclude that ondansetron and perphenazine had similar effects on vomiting in children after tonsillectomy in a day-case setting. (Br. J. Anaesth. 1998; 80: 155–158)

Keywords: anaesthesia, paediatric; surgery, otolaryngological; vomiting, antiemetics, ondansetron; vomiting, antiemetics, perphenazine

Vomiting is a common, unpleasant sequel to surgery and anaesthesia and may result in dehydration, important electrolyte disturbances, delayed discharge from hospital and unscheduled admission to hospital.1-3 Children undergoing tonsillectomy are at particular risk of vomiting, with as many as 71–73% of children vomiting after tonsillectomy.4 Anaesthetists are searching for cost-effective techniques that may minimize this problem.

Ondansetron and perphenazine are antiemetics that decrease vomiting after tonsillectomy in children.5-7 For many, ondansetron has become the "gold standard" antiemetic because of its efficacy and minimal side effects compared with alternatives. Unfortunately, ondansetron is expensive. Perphenazine is a phenothiazine with moderate anticholinergic effects, weak to moderate sedative effects and potent antiemetic effects. Compared with ondansetron, perphenazine had similar antiemetic effects and fewer side effects in adults after hysterectomy.6 We have evaluated the hypothesis that ondansetron and perphenazine have similar effects on vomiting in children after tonsillectomy.

Patients and methods
Healthy children, aged 2–12 yr, undergoing elective tonsillectomy or adenotonsillectomy were enrolled in this randomized, stratified, blocked, double-blind study after obtaining approval from our Ethics Committee. Within the balanced study design, blocks of five patients were stratified according to use of premedication and technique for induction of anaesthesia so that a similar number of patients in each study group received premedication and the two available induction techniques. The children were allocated randomly to receive ondansetron or perphenazine in a double-blind manner. Exclusion criteria included allergy to a study drug, history of sleep apnoea or ASA III or greater.

Patients were permitted to drink clear fluids for up to 3 h before anaesthesia, but did not ingest solid food on the day of surgery. Those children requiring premedication received midazolam 0.5 mg kg⁻¹ (maximum dose 15 mg) orally, 20–30 min before induction of anaesthesia. General anaesthesia was induced by inhalation of nitrous oxide and halothane or propofol 2.5–3.5 mg kg⁻¹ i.v. Mivacurium 0.25 mg kg⁻¹ was administered if a neuromuscular blocking agent was indicated to facilitate tracheal intubation. Ondansetron 150 μg kg⁻¹ (maximum dose 8 mg) or perphenazine 70 μg kg⁻¹ (maximum dose 5 mg) was administered i.v. in a double-blind manner immediately after induction of anaesthesia. The dose for perphenazine was extrapolated from the adult dose of 5 mg. Anaesthesia was maintained with 0.75–2.0% halothane and 70% nitrous oxide in oxygen. Midazolam 50 μg kg⁻¹ (maximum dose 3 mg) i.v. was given if the child had not received it for premedication. (Midazolam was given to all patients because it has been shown to have antiemetic effects in children undergoing tonsillectomy.)7 All patients received codeine 1.5 mg kg⁻¹ i.m. in the right thigh before commencement of surgery. Intraoperative i.v. fluid comprised lactated Ringer’s solution at half the calculated deficit during the first hour, plus main-
tenance fluids, in addition to replacement of four times the estimated blood loss with crystalloids.

Management of postoperative emesis, pain and fluids was standardized. Vomiting was defined as the forceful expulsion of liquid gastric contents. Retching and nausea were not considered vomiting. Nursing staff and parents were aware of this definition of vomiting. Nursing staff recorded vomiting in the charts, which is standard practice in our hospital. Patients who vomited twice in hospital received dimenhydrinate 1 mg kg\(^{-1}\) i.v. Parents were contacted 24 h after surgery by a research assistant to ascertain the number of times their child vomited after discharge from hospital and what the parents had done in response to the vomiting. Pain in the post-anaesthesia recovery room (PAR) was treated with morphine 50 μg kg\(^{-1}\) i.v., while subsequent pain was treated with acetaminophen or codeine, or both, in the day-case surgical unit (DCSU) and at home. i.v. fluid comprised lactated Ringer’s solution at twice maintenance rates in the PAR and DCSU. Patients were encouraged, but not coerced, to drink clear fluids in the DCSU before discharge. Patients were discharged following a recommended hospital policy of a minimum 4-h stay in the DCSU and after ingestion of clear fluids.

Continuous, normally distributed data, such as patient age, were compared using one-way ANOVA, and continuous, non-normally distributed data, such as length of stay in the DCSU, were compared using the Mann–Whitney U test. Binomial data, such as incidence of vomiting, were compared using chi-square analysis and Fisher’s exact test, where appropriate. Logistic regression analysis was used to detect if factors such as study drug, age, weight, in-hospital analgesics, premedication, use of neuromuscular blocking agents, operative time, estimated intraoperative blood loss and induction technique were significant predictors of vomiting. Stepwise linear regression analysis was used to assess the effect of study group, in-hospital vomiting, age, premedication and induction technique on length of stay in the DCSU. Sample size was determined by assuming that the acceptable difference in vomiting was 20%. The alpha error was set at 0.05 (two-sided) and type II error was at 0.20. The projected sample size was 110 patients per group after consideration of potential dropouts.

Results

Over a period of 6 months, 220 patients were enrolled. Four patients were subsequently excluded because of major study violations. The groups were similar after stratification and blocking of patients (table 1) and they had similar characteristics (table 2). Mivacurium was administered to 86 patients in the ondansetron group and to 83 patients in the perphenazine group. No patient required antagonism of neuromuscular block. Duration of stay in the PAR was similar in the two groups (mean 46 min vs 47 min for the ondansetron and perphenazine groups, respectively) but in the DCSU, ondansetron-treated patients had a briefer stay (median 235 (range 165–305) min vs 240 (175–430) min; ondansetron vs perphenazine, \(P=0.007\)). Analgesic use in hospital was similar. In the ondansetron group, four patients received morphine in the PAR and 108 patients received codeine in the DCSU, while in the perphenazine group, seven patients received morphine in the PAR and 107 patients received codeine in the DCSU.

Episodes of vomiting per patient ranged from 0 to 11. Fifteen patients in the ondansetron group vomited three or more times, while 19 patients in the perphenazine group vomited three or more times. The study groups had a similar incidence of vomiting (table 3). By logistic regression analysis, the sex of the child was a significant (\(P=0.013\)) predictor of postoperative vomiting, with 49% of males and 35% of females vomiting. Other potential predictors (study group, age, weight, induction technique, premedication, duration of anaesthesia, estimated intraoperative blood loss, use of neuromuscular blocking agents and use of in-hospital postoperative opioids) of vomiting were not significant (table 4). Patients who vomited twice while in hospital received a rescue antiemetic (dimenhydrinate) which was given to four patients in the ondansetron group and to seven patients in the perphenazine group.

Six patients were admitted or readmitted to hospital after discharge, five of whom were in the ondansetron group. Four of these patients were admitted for surgical reasons: bleeding (\(n=3\) or

### Table 1
Confounding variable distribution (number of patients)

<table>
<thead>
<tr>
<th>Group</th>
<th>Premedication</th>
<th>Propofol induction</th>
<th>Inhalation induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron</td>
<td>21</td>
<td>55</td>
<td>54</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>19</td>
<td>55</td>
<td>52</td>
</tr>
</tbody>
</table>

### Table 2
Patient and surgical data (mean (sd), median (range) or number)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age (yr) (mean (range))</th>
<th>Weight (kg)</th>
<th>Length of anaesthesia (min)</th>
<th>Blood loss (ml)</th>
<th>Sex (M/F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron</td>
<td>109</td>
<td>7.1 (2–12.5)</td>
<td>29 (15)</td>
<td>31 (11)</td>
<td>15 (0–225)</td>
<td>49/60</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>107</td>
<td>6.8 (2–12.8)</td>
<td>26 (12)</td>
<td>32 (13)</td>
<td>15 (0–220)</td>
<td>49/58</td>
</tr>
</tbody>
</table>

### Table 3
Incidence of postoperative vomiting. PAR = post-anaesthetic recovery room, DCSU = day-case surgical unit, Day 0 = day of surgery, Day 1 = day after surgery

<table>
<thead>
<tr>
<th>Group</th>
<th>PAR</th>
<th>DCSU</th>
<th>Day 0</th>
<th>Day 1</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron</td>
<td>2%</td>
<td>11%</td>
<td>20%</td>
<td>26%</td>
<td>44%</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>2%</td>
<td>15%</td>
<td>22%</td>
<td>25%</td>
<td>41%</td>
</tr>
</tbody>
</table>

### Table 4
Incidence of vomiting over 24 h by subgroup (number %)

<table>
<thead>
<tr>
<th>Ondansetron</th>
<th>Perphenazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral midazolam</td>
<td>8/21 (39)</td>
</tr>
<tr>
<td>No premedication</td>
<td>40/88 (45)</td>
</tr>
<tr>
<td>Propofol induction</td>
<td>26/55 (47)</td>
</tr>
<tr>
<td>Inhalation induction</td>
<td>22/54 (40)</td>
</tr>
<tr>
<td>All cases</td>
<td>47/109 (59)</td>
</tr>
</tbody>
</table>
refusing to drink \( (n = 1) \). One patient in the ondansetron group required in-hospital management of emesis and one patient was admitted for management of exacerbation of asthma.

Duration of stay in the DCSU was affected significantly by two factors: (1) in-hospital vomiting \((P = 0.01)\) and (2) study drug \((P = 0.02)\). Each episode of in-hospital vomiting prolonged DCSU stay by 7 min. Patients in the perphenazine group stayed in the DCSU for an average of 7 min longer than patients in the ondansetron group. No adverse events, such as extrapyramidal symptoms or allergic reactions, possibly attributable to ondansetron or perphenazine, were observed or reported by the nursing staff or parents.

**Discussion**

Ondansetron and perphenazine were observed to have similar effects on the incidence of vomiting in children after tonsillectomy. These similarities in the antiemetic effect were noted in hospital and after discharge. The incidence of vomiting after tonsillectomy was similar to that observed in previous investigations, but greater than that reported by van den Berg. Although both drugs decreased the incidence of vomiting compared with placebo, the incidence of emesis after prophylactic treatment was still high in this study. Ideally, the incidence of vomiting should be less than the 41% rate noted. Also, a decrease in the use of rescue antiemetics and elimination of the instances where children have numerous episodes of vomiting would be desirable. In addition, the incidence of vomiting on the day after surgery \((25–26\%)\) is of concern.

We used a blocked, stratified design to permit both control and flexibility. Patients were enrolled into this study before the parents and their child’s anaesthetist had come to a decision as to premedication and the anaesthesia induction technique. The blocked and stratified approach leads to a balanced design, which simplifies inter-group comparisons, while flexibility in choice of premedication and induction technique optimizes clinical management.

Adverse effects with a single, therapeutic dose of ondansetron or perphenazine are extremely rare and generally minor. In Desilva and colleagues’ study in adults, only patients who received perphenazine were free of adverse side effects. Perphenazine is a phenothiazine, a class of drugs which have a high therapeutic index and “are remarkably safe agents.” Major adverse side effects after a single dose of ondansetron are rare, and there is only one report of dyskinesia after a single dose of perphenazine. Although there were no adverse events caused by perphenazine during this and previous studies, much larger sample sizes would be required to evaluate accurately the incidence of adverse effects after perphenazine in children.

The prophylactic antiemetics used in this study were dissimilar with respect to cost. The ondansetron dose for a 20-kg child (3 mg) costs $12.90 Canadian, while perphenazine costs only $0.81 Canadian for the treatment of a 20-kg patient. Treatment of emesis by nursing staff and family, delayed hospital discharge, unscheduled admission and mental costs to the patient and family also add to the cost of care. Of note, in this study those patients in the perphenazine-treated group had a slight delay in discharge (7 min) from the day-case surgical unit compared with the ondansetron group. Unfortunately, we are not able to calculate the cost of such delays within our health care system.

The dose of perphenazine was based on the 5-mg dose used in adult investigations. A larger dose \((8 \text{ mg})\) has been noted to increase drowsiness among adult oncology patients. There are, to the best of our knowledge, no dose–response curves for the antiemetic effect of this drug in the perioperative setting in adults or children. While the dose used in our study has been shown previously to be effective, it is not necessarily the optimal dose. The ondansetron dose is based on previous studies in children in a perioperative setting.

The aetiology of vomiting after tonsillectomy is unknown and probably multifactorial in origin. Surgical techniques which minimize blood loss may be as effective as the use of antiemetics in attempting to decrease vomiting after tonsillectomy.

The sex of the child was identified as a significant predictor of postoperative vomiting by logistic regression analysis. This is, to the best of our knowledge, the first report that male children vomit more than female children after anaesthesia–surgery and is probably a spurious finding. It is not expected that future studies will support this observation. With almost identical male to female ratios in the two study groups, the difference in vomiting according to the child’s sex had no effect on our results.

In summary, ondansetron and perphenazine had similar effects on vomiting in children after tonsillectomy. However, the observed incidence of vomiting was unacceptably high \((41–44\%)\), especially on the day after surgery \((25–26\%)\).

**Acknowledgments**

We thank research assistants Marilyn Parkin, BA and Lydia Komocar, RN.

**References**


