Effect of tropisetron on vomiting during patient-controlled analgesia in children

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Patient-controlled analgesia (PCA) is associated with a high incidence of vomiting which is distressing and interferes with postoperative recovery. Tropisetron, a long-acting selective 5-HT3 receptor antagonist, has been shown to be effective in preventing nausea and vomiting associated with PCA use in adults and chemotherapy in children. We assessed the efficacy of prophylactic intraoperative administration of tropisetron on the incidence of vomiting in children using morphine PCA. We studied 58 patients, allocated randomly to receive tropisetron 0.1 mg kg\(^{-1}\) to a maximum of 5 mg, or normal saline. Children who received tropisetron had an incidence of vomiting during the first 24 h after operation of 22% compared with 66% in the control group (\(P<0.001\)). In addition, the severity of vomiting was less in the tropisetron group with only one child (4%) vomiting more than twice compared with nine (31%) in the control group (\(P=0.01\)). We conclude that tropisetron is efficacious in reducing the incidence and severity of postoperative vomiting in children using PCA.

Keywords: analgesia, paediatric; children; analgesia, patient-controlled; vomiting, nausea; vomiting, incidence; vomiting, antiemetics

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Patient-controlled analgesia (PCA) is an effective and popular method for the control of pain after surgery in children more than 7 yr of age.\(^1\) Nausea and vomiting occur in 40–60% of patients using PCA.\(^2\) Tropisetron is a serotonin (5-HT\(_3\)) receptor antagonist proved to be effective in the treatment of nausea and vomiting in children receiving cytotoxic chemotherapy as a once-daily dose.\(^3\) \(^4\) It has a half-life 2–3 times longer than ondansetron.\(^5\)

Tropisetron has been shown to reduce the incidence of vomiting during PCA in adults from 48% to 22% in the first 18 h after surgery.\(^2\) In this study, we have determined the efficacy of prophylactic administration of tropisetron on the incidence of vomiting after surgery and during the use of PCA in children.

Patients and methods

After obtaining approval from the Hospital Ethics Committee and written parental consent, we studied children aged 7 yr or more, undergoing surgery for which PCA was planned for postoperative pain relief. Patients were excluded if they had received an antiemetic before presentation for surgery.

The type of operation and perioperative anaesthetic management were not controlled. After induction of anaesthesia, patients were allocated randomly to receive a single dose of tropisetron 0.1 mg kg\(^{-1}\) to a maximum dose of 5 mg or an equivalent volume of normal saline. Random allocation was performed using sealed envelopes and block randomization with a block size of 10. The anaesthetist was not aware of which solution was being administered. No other antiemetic agents were administered during anaesthesia.

At the end of surgery, postoperative analgesia was provided by morphine PCA, delivered by a Graseby PCA pump system. Morphine 0.5 mg kg\(^{-1}\) was diluted to 50 ml with normal saline, and the PCA pump was programmed to deliver a bolus dose of 20 µg kg\(^{-1}\) with a lockout time of 5 min. A background infusion of 5 µg kg\(^{-1}\) h\(^{-1}\) was added at the discretion of the anaesthetist.

The incidence of vomiting was determined at 0–2, 2–6, 6–12, 12–18 and 18–24 h after arrival in the recovery room. Recovery room and ward nurses, who were blinded to the treatment, collected the data. Vomiting in theatre at the time of tracheal extubation was not included. Vomiting was defined as the forceful expulsion, or attempted expulsion, of gastric contents. Patients were offered rescue antiemetic therapy (metoclopramide 0.15 mg kg\(^{-1}\)) if they suffered from vomiting or were distressed by nausea.
The chi-square test was used to compare the frequency of vomiting in each time period and the need for rescue antiemetic therapy in the two groups. Levene’s test for the equality of variances was used to contrast total morphine consumption. We required 40 patients in each group to achieve a result with a power of 80% and an alpha error of 0.05. These numbers assumed a frequency of vomiting of 50% in the control group and 20% in the tropisetron group.

Results

Fifty-eight children were enrolled in the study but data for two children in the tropisetron group were incomplete and therefore excluded. The two groups were comparable in age, sex, weight, type of surgical procedure, intraoperative morphine dose, use of neostigmine and atropine to reverse the effects of neuromuscular block, and the use of propofol or thiopental for induction of anaesthesia (Table 1). All patients received i.v. induction, and anaesthesia was maintained with a volatile agent in nitrous oxide and oxygen.

In the control group, 19 (66%) patients had one or more emetic episodes compared with six (22%) in the tropisetron group during the 24-h observation period (P=0.001). The incidence of vomiting increased with time in the tropisetron group and was not significantly different at the 18–24-h interval compared with the control group (Fig. 1). Nine patients (31%) in the control group had more than two emetic episodes compared with six (22%) in the tropisetron group, but this was not statistically significant.

Twelve patients (41%) in the control group received at least one rescue dose of metoclopramide compared with six (22%) in the tropisetron group, but this was not statistically significant.

Mean cumulative PCA morphine consumption in the 24-h period was 0.68 (SD 0.38) mg kg⁻¹ day⁻¹ in the tropisetron group and 0.52 (0.32) mg kg⁻¹ day⁻¹ in the control group. The greater morphine consumption in the tropisetron group was not statistically significant (P=0.19).

Failure to recruit 80 patients to the study was a result of 0.05. These numbers assumed a frequency of vomiting of 50% in the control group and 20% in the tropisetron group.

Discussion

Vomiting during PCA therapy in children is very common, and the incidence of postoperative vomiting in our control group (66%) was similar to that reported previously. Our study showed that tropisetron reduced the incidence and severity of vomiting in children using PCA. The need for rescue antiemetics was less and total morphine consumption was greater in children who received tropisetron, but these trends did not reach statistical significance. Our findings on the efficacy of tropisetron in preventing vomiting in children were similar to those found in children after tonsillectomy, and in adults receiving PCA. In the latter study, tropisetron reduced the incidence of postoperative nausea and vomiting (PONV) from 48% to 22% during the first 18 h after surgery. However, the antiemetic effect did not last beyond 18 h and the incidence of PONV increased at 19–36 h after operation.

We found that there was a tendency for the incidence of vomiting in the tropisetron group to increase in the 18–24-h interval, whereas the incidence of vomiting in the control group was higher at all times and without a discernible pattern. Although this is suggestive of a decrease in the effectiveness of tropisetron after 18 h, the difference was not significant. Tropisetron has a longer elimination half-life than ondansetron but this may not produce a longer duration of action. Interactions at the receptor level, and not plasma pharmacokinetics, are more important for defining the efficacy of 5-HT₃ receptor antagonists.

The impression that PCA produces more PONV than other methods of analgesia is widespread, although not supported by research. In a recent quality assurance study, 17% of patients stated that the worst thing about PCA was that it made them feel sick. 21% of patients said they restricted pressing the button because of this side effect. We believe that the greater morphine consumption by the tropisetron group in both our study and that of others (where it achieved

Table 1 Patient data (mean (sd or range), and surgical and anaesthetic characteristics. n=number of patients

<table>
<thead>
<tr>
<th>Patient data</th>
<th>Control group (n=29)</th>
<th>Tropisetron group (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>11.8 (8.0–15.4)</td>
<td>11.5 (8.4–15.5)</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>17:12</td>
<td>16:11</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>40.1 (9.6)</td>
<td>42.7 (14.9)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendicectomy (n)</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>Orthopaedic (n)</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Other (n)</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Anaesthetic induction agent</td>
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<td></td>
</tr>
<tr>
<td>Thiopental (n)</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>Propofol (n)</td>
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<td>8</td>
</tr>
<tr>
<td>Use of neostigmine (n)</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>Intraoperative morphine dose (mg kg⁻¹)</td>
<td>0.1 (0.03)</td>
<td>0.1 (0.02)</td>
</tr>
<tr>
<td>PCA ceased &lt; 24 h after operation (n)</td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>

Fig 1 Incidence of vomiting in the control and tropisetron groups, measured at 0–2, 2–6, 6–12, 12–18 and 18–24 h after arrival in the recovery room. *P<0.05
statistical significance) was because of the reduced PONV in association with tropisetron use. An alternative explanation for the greater morphine consumption in the tropisetron group is that 5-HT3 antagonists have an anti-analgesic effect. Tropisetron has been shown to reverse the analgesic effects of intrathecally administered serotonin in animal studies. However, a study in patients receiving intrathecal morphine after orthopaedic surgery failed to demonstrate a difference in analgesic requirements in those patients who had also received tropisetron. Similarly, ondansetron did not alter the perception of experimental pain in human volunteers who received alfentanil.

The absence of an anaesthetic protocol for the study meant that the tropisetron and control groups were different in terms of anaesthetic induction agent. More patients in the control group received propofol than thiopental, although this was not statistically significant ($P = 0.06$). This does not detract from our conclusions on the efficacy of tropisetron, as a meta-analysis has shown that propofol as an induction agent has a likely antiemetic effect and thus advantaged the control group.

The dose of tropisetron used in our study was 0.1 mg $kg^{-1}$, to a maximum of 5 mg, which is similar to the dose used in adult studies of postoperative nausea and vomiting, but smaller than that used in paediatric chemotherapy studies. Investigators of tropisetron use with cancer chemotherapy have found few side effects attributable to the drug; headache and bowel habit disturbance have been reported. The lack of adverse effects is very appealing, as it is the perceived high incidence of side effects of other antiemetics in children that has made clinicians cautious about prescribing these drugs. Our study has shown tropisetron to be an efficacious drug for the prophylaxis of PONV in association with PCA.

References
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