Single dose i.v. tropisetron in the prevention of postoperative nausea and vomiting after gynaecological surgery


Summary

In a prospective, randomized, multicentre, double-blind, placebo-controlled study, we have compared the efficacy of a single i.v. dose of tropisetron 0.5 mg, 2 mg and 5 mg in the prevention of postoperative nausea and vomiting (PONV). We studied 385 ASA class I and II female patients undergoing abdominal or vaginal gynaecological surgery, including laparoscopy. Tropisetron or placebo were administered before a standardized general anaesthetic. The frequency of vomiting in the 24-h period after entry into the recovery room was reduced from 44 % after placebo to 31 %, 26 % and 30 % after tropisetron 0.5 mg, 2 mg and 5 mg, respectively \( (P = 0.06, P = 0.009 \text{ and } P = 0.043; \text{ unadjusted}) \). Compared with placebo, nausea was reduced from 55 % to 46 %, 34 % and 46 % \( (P = 0.25, P = 0.003, P = 0.22) \), and need for rescue treatment from 39 % to 29 %, 23 % and 35 % \( (P = 0.13, P = 0.017 \text{ and } P = 0.59) \) for the same groups. Tropisetron 2 mg appeared to be the optimal dose for prophylaxis against PONV with a side-effect profile similar to that of placebo. \( (Br. J. Anaesth. 1996; 76: 54–60) \)

Key words

Vomiting, nausea. Vomiting, antiemetics. Serotonin antagonist, tropisetron.

Postoperative nausea and vomiting (PONV) remain among the most common of anaesthesia-related adverse effects [1]. The aetiology of PONV is multifactorial and includes factors related to the characteristics of the patient, the type of surgery, type of anaesthetic and postoperative factors [2–5]. Antiemetic prophylaxis may be justified in patients who are at greater risk of developing postoperative nausea and/or vomiting [2]; these include patients with a history of previous postoperative emesis and women undergoing gynaecological procedures, e.g. laparoscopy.

Antiemetics with an antidopaminergic action such as metoclopramide and droperidol are often used in the control of PONV but their use is limited by side-effects including sedation, hypotension, extrapyramidal symptoms and dysphoria [6].

Tropisetron (Navoban, ICS 205-930, Sandoz Pharma Ltd, Switzerland) is a selective competitive 5-HT\(_3\) receptor antagonist, which has low affinity for 5-HT\(_4\) receptors [7] and little or no activity at the non-5-HT\(_3\) receptors, such as \(\alpha_1, \alpha_2\) and \(\beta\). adrenoceptors, muscarinic and nicotinic cholinergic receptors, histamine H\(_1\) and H\(_2\) receptors and dopamine D\(_2\) receptors [8]. At a dose of 5 mg once daily, tropisetron has been shown to be an effective and well tolerated agent for the prevention of chemotherapy-induced emesis [9]. The metabolism of tropisetron in humans is linked to the polymorphically expressed cytochrome P-450 IID6 enzyme system. The elimination half-life of tropisetron is 8 h in fast metabolisers and even longer in slow metabolisers [10], which could make this agent suited to prevention of PONV using a single dose. A single i.v. dose of tropisetron 5 mg has been shown to reduce significantly the incidence of PONV after gynaecological surgery under general anaesthesia [11]. The aim of the present study was to determine if smaller doses of tropisetron would be effective compared with placebo in the prevention of PONV.

Patients and methods

This randomized, multicentre, placebo-controlled, double-blind study was carried out in eight hospitals in Belgium and was conducted with the approval of the local Ethics Committees. The study was explained to each patient and written or oral witnessed informed consent was obtained. We studied ASA grade I and II women, between 18 and 75 yr, undergoing abdominal or vaginal gynaecological surgery, including laparoscopy, under general anaesthesia. Patients were expected to remain in hospital for at least 6 h after surgery. Patients were excluded if they had vomited during the 24 h before surgery or if they had received antiemetics during...
The duration of anaesthesia and the awakening time, i.e. the time between the end of administration of anaesthesia and the time of eye opening on request, were recorded with the level of consciousness after 30 min in the recovery room. The occurrence of emetic episodes in the operating room was also recorded. Postoperative analgesia was standardized. Patients could receive propacetamol, paracetamol or piritramide, an opioid analgesic. If the patient experienced PONV, the choice of the rescue treatment was at the discretion of the investigator. The first routine measurement of heart rate and systolic and diastolic arterial pressure after arrival in the ward was also recorded. In a single centre, electrocardiographic (ECG) recordings were obtained before surgery (baseline ECG), and 2 h (2-h ECG), 4 h (4-h ECG) and 24-h (24-h ECG) after administration of the study drug. Patients at that centre stayed in the recovery room for the 2-h and 4-h ECG.

In agreement with a study using a similar design [12] the main 24-h evaluation period for nausea and emesis began after the patient entered the recovery room and was capable of responding to a verbal command. This 24-h period was divided further into three assessment periods. The first period corresponded to the stay in the recovery room. The second period started when the patient left the recovery room and ended when 6 h of the 24-h period had passed. The third period covered the next 18 h. For the purpose of data collection no distinction was made between vomiting and retching. An emetic episode was defined as a single vomit or retch, or multiple vomits or retches separated in time by less than 1 min. Presence or absence of nausea was also recorded together with rescue treatment, if given. The patients were given diary cards on which to record the occurrence of emetic episodes, nausea and administration of antiemetic drugs. For the assessment of safety and efficacy the investigator used the patient’s diary card and the observations of the nursing staff and questioned the patient directly. Day-case surgery patients remained in hospital during the first two assessment periods and were questioned by phone at the end of the 24-h observation period. In addition, a diary card completed by the patient was sent by mail to the study centre. Day-case surgery patients could be enrolled only in those centres where follow-up for the 6–24-h period could be guaranteed by the investigator.

**ENDPOINTS AND STATISTICAL ANALYSIS**

The primary efficacy variable of the study was the proportion of patients defined by the presence or absence of any emetic episodes over the 24-hour period regardless of rescue treatment given. A minimum sample size of 360 patients in four groups of 90 patients was selected to detect a 50 % reduction in the frequency of emetic episodes, from 40–50 % with placebo to 20–25 % with the optimal dose of tropisetron at the 5 % significance level with 80 % power. No interim analyses were planned or conducted.

For the primary efficacy variable the differences in proportions between treatment groups were tested by means of chi-square tests without continuity correction. A global test of all treatment groups against placebo was followed by pairwise tests comparing placebo with each dose of tropisetron. A closed-test procedure was used in order to ensure that the nominal level of significance was kept at 0.05 [13]. All tests were two-sided. Statistical analyses were performed using SAS version 6.08 under licence from SAS Institute (Cary, NC, USA).

Both the adjusted P values obtained using this closed test procedure and the unadjusted P values...
are reported. Secondary efficacy variables were the occurrence of nausea over the 24-h postoperative period, the administration of rescue treatment over the same period and the occurrence of emetic episodes over the 24-h period including events in the operating room. *P* values of the comparisons based on these secondary efficacy variables are reported with the caveat that their significance level must be adjusted to account for multiple testing.

Further exploratory analyses of possible prognostic factors were performed using logistic regression models. The following factors were considered: treatment group, centre, age, weight, history of PONV, motion sickness, days since last menses (<8, 8–40, ≥40 days), use of a benzodiazepine as premedication, type of surgery (laparoscopy, laparotomy), duration of anaesthesia, use of an anticholinergic before or during anaesthesia, use of postoperative opioids, and use of rescue treatment for nausea. Each factor was considered alone in the model, and then the final model was built by taking the most significantly related factor and adding the remaining factors not yet in the model until all significantly related factors had been included. The odds ratio and 95 % confidence intervals (CI) were calculated for the variables in the final model, both unadjusted, and adjusted for the other factors.

**Results**

**Characteristics of the Patients and the Anaesthesia**

Informed consent was obtained and study medication was prepared for a total of 391 sequential patients. The number of patients enrolled per centre varied between 33 and 70. Three patients withdrew their consent before administration of the study drug. Three ineligible patients were withdrawn from the study before administration of study medication because of a history of angioneurotic oedema, an ovarian carcinoma with metastases and a positive pregnancy test. The study medication was administered to a total of 385 patients in the 1-h period before the start of induction. In a single patient, induction followed 125 min after study drug administration because of unexpected delay in the surgery schedule. All 385 female patients were included in the analysis.

In this study 381 of 385 patients (99 %) were white. The groups were comparable in age, weight, height, days since last menstrual cycle and proportion of patients with a history of general anaesthesia and PONV or motion sickness (table 1).

The mean time between administration of study drug and the start of induction was 9 min and this was similar for all groups. In all four groups laparoscopy was the most common type of surgery (in 56 % of the patients), followed by abdominal hysterectomy (table 2).

Benzodiazepine premedication was administered to 72 % of all patients with the majority of these (60 %) receiving diazepam. Other benzodiazepines given included alprazolam (21 %), lorazepam (16 %), midazolam (2 %) and lorazepam (in one patient). The mean doses were similar for all groups (diazepam 8.5 mg, alprazolam 0.8 mg, lorazepam 3.3 mg). Anticholinergic premedication was used in five (5 %), three (3 %), six (6 %) and six (6 %) patients in the placebo, tropisetron 0.5-mg, 2-mg and 5-mg groups, respectively, and consisted of glycopyrronium (n = 15, mean dose 0.2 mg) or atropine 0.3 mg (n = 5).

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**Table 1** Characteristics of the four groups (mean (range or SD) or number (%))

<table>
<thead>
<tr>
<th>Tropisetron</th>
<th>Placebo (n = 97)</th>
<th>0.5 mg (n = 97)</th>
<th>2 mg (n = 96)</th>
<th>5 mg (n = 96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>41 (22–74)</td>
<td>38 (19–69)</td>
<td>38 (24–67)</td>
<td>41 (18–74)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66 (13)</td>
<td>63 (11)</td>
<td>66 (15)</td>
<td>65 (12)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163 (7)</td>
<td>164 (6)</td>
<td>164 (6)</td>
<td>163 (7)</td>
</tr>
<tr>
<td>Days since last menstrual cycle</td>
<td>12.5</td>
<td>16.2</td>
<td>13.8</td>
<td>14.0</td>
</tr>
<tr>
<td>n</td>
<td>59</td>
<td>71</td>
<td>63</td>
<td>64</td>
</tr>
<tr>
<td>Motion sickness</td>
<td>14 (14 %)</td>
<td>19 (20 %)</td>
<td>10 (11 %)</td>
<td>8 (8 %)</td>
</tr>
<tr>
<td>Previous general anaesthesia</td>
<td>73 (75 %)</td>
<td>73 (75 %)</td>
<td>71 (75 %)</td>
<td>72 (75 %)</td>
</tr>
<tr>
<td>General anaesthesia with PONV</td>
<td>21 (22 %)</td>
<td>17 (18 %)</td>
<td>22 (23 %)</td>
<td>22 (23 %)</td>
</tr>
</tbody>
</table>

**Table 2** Types of operations performed (number (%)). *Laparoscopic surgery included laparoscopic tubal ligation (15 % of all patients), dilatation and curettage with laparoscopic tubal ligation (5 %), diagnostic laparoscopy (10 %), laparoscopy for ovarian cyst (10 %), laser laparoscopy (6 %), repermeabilization of fallopian tubes (3 %), laparoscopy for endometriosis (3 %) or other (3 %)

<table>
<thead>
<tr>
<th>Tropisetron</th>
<th>Placebo (n = 97)</th>
<th>0.5 mg (n = 97)</th>
<th>2 mg (n = 95)</th>
<th>5 mg (n = 96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparoscopic surgery*</td>
<td>52 (54 %)</td>
<td>58 (60 %)</td>
<td>55 (58 %)</td>
<td>49 (51 %)</td>
</tr>
<tr>
<td>Abdominal hysterectomy</td>
<td>21 (22 %)</td>
<td>17 (18 %)</td>
<td>17 (18 %)</td>
<td>14 (15 %)</td>
</tr>
<tr>
<td>Other gynaecological laparotomy</td>
<td>6 (6 %)</td>
<td>5 (5 %)</td>
<td>7 (7 %)</td>
<td>9 (9 %)</td>
</tr>
<tr>
<td>Vaginal hysterectomy</td>
<td>9 (9 %)</td>
<td>5 (5 %)</td>
<td>11 (12 %)</td>
<td>11 (11 %)</td>
</tr>
<tr>
<td>Other vaginal surgery</td>
<td>9 (9 %)</td>
<td>11 (11 %)</td>
<td>5 (5 %)</td>
<td>13 (14 %)</td>
</tr>
<tr>
<td>Breast surgery</td>
<td>0 (0 %)</td>
<td>1 (1 %)</td>
<td>0 (0 %)</td>
<td>0 (0 %)</td>
</tr>
</tbody>
</table>
The duration of anaesthesia (overall mean 77 min), the use of anaesthetics and postoperative opioids are detailed in table 3. All patients had induction of anaesthesia with thiopentone and received nitrous oxide supplemented with isoflurane. Atracurium or vecuronium was used as neuromuscular blocking agent. One patient undergoing breast surgery did not receive a neuromuscular blocker. In 111 patients (29% of cases) the neuromuscular blocking agent was antagonized using neostigmine at a mean dose of 1.6 mg, in all but two patients associated with an anticholinergic agent consisting of glycopyrronium (n = 102, mean dose 0.4 mg) or atropine (n = 7, mean dose 0.3 mg). All patients received opioids during anaesthesia and these consisted of sufentanil (in 55% of cases) or fentanyl. One patient received both agents. Opioids were antagonized using naloxone (mean dose of 73 μg) in four (4%) patients, two (2%) and five (5%) patients in the placebo, tropisetron 0.5-mg, 2-mg, and 5-mg groups, respectively. Postoperatively, opioids were given to 70% of patients in each of the groups and consisted primarily of piritramide. Pethidine was used for three patients. Other postoperative analgesics consisted of propacetamol or paracetamol. Intraoperative bradycardia was treated with atropine in eight patients (mean dose 0.4 mg) and with glycopyrronium in seven patients (mean dose 0.4 mg). Eleven patients (3%) received a gastric tube during anaesthesia.

The patients stayed in the recovery room for a mean of 140 min. Patients having day-case surgery...
represented 6% of all patients (22 of 385) and were distributed evenly over the four treatment groups. All other patients remained in hospital for the full 24-h observation period.

Efficacy results
In one patient the efficacy could not be assessed because of postoperative intragastric suction following intraoperative perforation of the intestinal wall by a laparoscope. The results for the primary endpoint and the secondary endpoints are listed in table 4. Both tropisetron 2 mg and 5 mg resulted in significant reduction in the incidence of vomiting compared with placebo. Vomiting or retching when the patient was still in the operating room after surgery occurred in three (3%), three (3%), three (3%) and seven patients (7%) in the placebo, tropisetron 0.5-mg, 2-mg and 5-mg groups respectively. When this incidence of vomiting is included in the 24-h period results, a significant decrease compared with placebo occurred only for the 2-mg dose. Compared with placebo the reduction in incidence of nausea and the use of rescue treatment were also significant for the 2-mg dose but not for the other doses of tropisetron tested.

Rescue treatment was administered to 19% of all patients in the recovery room and to 18% of all patients on the ward and consisted most frequently of alizapride (50 mg to 250 mg i.v.), followed by metoclopramide (10 mg to 40 mg i.v.). Six patients received droperidol 1.25 mg i.v. The mean doses of these agents given in the recovery room and on the ward were similar for all groups.

The frequency of first emetic episodes per assessment period are presented in figure 1, together with the frequency of recurrences of emesis that had started in a previous period. Fewer recurrences were seen in the second and third period for both the tropisetron 2-mg and 5-mg groups whereas the effect on first occurrence of vomiting in the first, second and third observation period was most pronounced for the tropisetron 0.5-mg, 2-mg and 5-mg doses, respectively.

The analysis of the subgroup of patients with a positive history of PONV revealed a frequency of vomiting in the placebo treatment group of 71% (15 of 21 patients), which was reduced to 44% (7 of 16 patients), 36% (8 of 22 patients) and 41% (9 of 22 patients) for the 0.5-mg, the 2-mg and the 5-mg doses, respectively. Furthermore, the subgroup analyses based on the use of a benzodiazepine as premedication, the duration of anaesthesia, the type of surgery, the presence or absence of motion sickness, the number of days since last menses, the use of an anticholinergic before or during anaesthesia and the use of postoperative opioids suggested that the efficacy of tropisetron was not restricted to a single subgroup.

The prognostic factors were included in a logistic model to find which ones were related most significantly to the primary outcome variable. The factors treatment, previous PONV and motion sickness were significant in the univariate models. The only factors which remained significant when considering combinations of factors were treatment, previous history of PONV and use of anticholinergics. There were no significant interactions. The adjusted odds ratio (95% CI) of treatment compared with placebo were 0.53 (0.29, 1.0), 0.40 (0.21, 0.76) and 0.51 (0.27, 0.95) for tropisetron 0.5 mg, 2 mg and 5 mg, respectively. The adjusted odds ratio (95% CI) associated with previous PONV was 2.41 (1.43, 4.07) and with use of anticholinergics 0.53 (0.32, 0.87).

Safety results
The recovery from anaesthesia measured by the waking time and the level of consciousness assessed 30 min after arrival in the recovery room was very similar in all four groups (table 5). All adverse events

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Recovery from anaesthesia (mean; median (range) or number (%)). *Time between end of administration of anaesthetics and eye opening on request</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>(n = 97)</td>
</tr>
<tr>
<td>Waking time (min)*</td>
<td>12.3 (10 (2–75))</td>
</tr>
<tr>
<td>Level of consciousness 30 min after arrival in recovery</td>
<td></td>
</tr>
<tr>
<td>Awake</td>
<td>75 (77 %)</td>
</tr>
<tr>
<td>Reacts to verbal command</td>
<td>19 (20 %)</td>
</tr>
<tr>
<td>Reacts to physical stimuli</td>
<td>2 (2 %)</td>
</tr>
<tr>
<td>Not arousable</td>
<td>1 (1 %)</td>
</tr>
</tbody>
</table>
are listed in table 6. There were no allergic reactions or other adverse events in the period between study drug administration and start of induction of anaesthesia. Most adverse events occurred only once. With perhaps the exception of headache, there was no increased frequency of adverse events in patients who received a higher dose of tropisetron.

Intraoperative bradycardia, reported as adverse event or treated with an anticholinergic, did not occur more frequently in any of the tropisetron groups compared with placebo, nor did heart rate, systolic and diastolic arterial pressure show a differential pattern of response to the anaesthesia for the four study groups. There were five cases of intraoperative hypertension documented as adverse event, distributed over all treatment groups, and one case of postoperative hypotension, which occurred 12 h after administration of tropisetron 5 mg in a patient suffering from severe nausea.

Four ECG recordings per patient were obtained in a single centre for 47 patients. There were no ECG abnormalities other than a single case of a transient first degree AV block and a transient QTc prolongation in another patient, both observed in the immediate postoperative period. The patient showing a transient first degree AV block already had a PQ/PR interval at baseline of 0.18 s after a history of complete thyroidectomy for Hashimoto thyroiditis with treatment-resistant hyperthyroidism. This patient had received tropisetron 2 mg. The patient with the transient prolongation of the QTc for the 2-h ECG and the 4-h ECG had received tropisetron 0.5 mg and had a ‘double hump’ aspect of the T wave at baseline.

Discussion

In accordance with the recommendations published by Korttila [14] we conducted a double-blind, placebo-controlled, comparative study with a sample size large enough to detect small differences and permit an even distribution of confounding factors that affect emesis among the study groups.

Our data show that a single dose of tropisetron 2 mg was effective in the prophylaxis of PONV and that the results for the high-risk subgroup of patients with a positive history of PONV are consistent with the overall results. Both tropisetron 2 mg and 5 mg resulted in a significant reduction in vomiting compared with placebo for the main 24-h period. The differences between the results for the three doses of tropisetron tested would perhaps have indicated a clearer dose response relationship.

Although the numbers are small, the retching and vomiting associated with the removal of the tracheal tube in the operating room at the end of anaesthesia was clearly not suppressed by tropisetron. As more of these events occurred in the 5-mg dose group, the difference between placebo and the 5-mg dose was non-significant when these events were added to the main 24-h results (table 4). Figure 1 suggests that the efficacy of tropisetron was sustained beyond the first 6 h after surgery. This is in agreement with the relatively long half-life of tropisetron and supports the use of a single dose of tropisetron to cover the full 24-h period.

5-HT₃ receptor antagonists are not general anti-
emetics. Although 5-HT3 receptor antagonists are beneficial in abdominal procedures, because these procedures may release 5-HT and activate visceral afferent pathways or the area postrema in a similar way to that proposed for anticancer therapies, it has been suggested that 5-HT3 antagonists might be less effective in ear, nose and throat or ocular surgery [15]. Clinical trials with tropisetron are required to test this hypothesis.

As PONV is a multifactorial problem we have used logistic regression models to estimate factors predictive of response. Of interest was the composition of the final logistic regression model, in which use of an anticholinergic was retained as associated with a lower incidence of PONV, independent of the effect of tropisetron and thus suggesting that the combination of both type of drugs could be more effective in preventing PONV than each drug alone.

In this study we administered tropisetron before induction in the hope of blocking the effect of serotonin released during surgery. This is in contrast with a previous study [11] where tropisetron was administered shortly before wound closure, when most of the serotonin that activates the receptors, implicated in nausea and vomiting reflexes, may already have been liberated. In retrospect, and considering that the anaesthetic technique used was not identical in the two studies, the timing of administration of tropisetron did not seem to be a major determinant of efficacy.

Dose comparative studies in the prevention of PONV have been reported for ondansetron [12] and recently also for granisetron [16], two other 5-HT3 antagonists. These studies were also conducted mainly in female patients undergoing abdominal gynaecological surgery. As was the case for tropisetron in this study, the minimum dose of ondansetron and granisetron found to be effective for prevention of PONV was lower than the dose used in the setting of cancer chemotherapy. Although the frequency of emesis in the placebo group was slightly lower in our study compared with a study with ondansetron [12], the extent of reduction of PONV for postoperative nausea and vomiting. European Journal of Anaesthesiology 1992; 9 (Suppl. 6): 25–31.