TROPISETRON FOR POSTOPERATIVE NAUSEA AND VOMITING IN PATIENTS AFTER GYNAECOLOGICAL SURGERY

P. J. W. ZOMERS, C. J. M. LANGENBERG AND K. M. DE BRUIJN

SUMMARY

In a double-blind study, we have compared the prophylactic antiemetic effect of tropisetron 5 mg (Navoban, a 5-HT₃ receptor antagonist) with that of placebo, both given as a short i.v. infusion approximately 15 min before wound closure in patients undergoing gynaecological surgery. Perioperative anaesthetic care was standardized and patients were observed for at least 24 h after operation. The 35 patients given tropisetron and 34 given placebo treatment were well matched for characteristics. Vomiting occurred in 26% of tropisetron-treated patients, compared with 59% of placebo-treated patients (P = 0.006); 69% of tropisetron-treated patients suffered nausea, compared with 88% of placebo-treated patients (P = 0.05). In addition, patients judged the antiemetic treatment with tropisetron as more effective than the placebo treatment (visual analogue score 71 vs 51 mm (P = 0.003)).

KEY WORDS

Vomiting: nausea, tropisetron.

Postoperative nausea or vomiting occur frequently after surgery under general anaesthesia. Abdominal and gynaecological surgery are particularly associated with postoperative nausea or vomiting, the reported incidence ranging from 1 to 80%, with an estimated 20-40% average [1, 2]. In a pilot study to determine the overall incidence of nausea and vomiting in the recovery ward, including all patients (n = 446) undergoing all types of anaesthetic techniques and surgery, it became clear that the greatest incidence of vomiting and nausea occurred in the gynaecological patients under general anaesthesia [Langenberg and Zomers, unpublished data]. Furthermore, postoperative nausea or vomiting are the most frequent factors preventing patients returning home at the end of the day after day-case surgery [3] or necessitating readmission to hospital [4], and this emphasizes the need for an effective antiemetic [5].

Tropisetron, a selective 5-HT₃ receptor antagonist, proved effective against nausea and vomiting induced by chemotherapy when administered as an optimal once-daily dose of 5 mg [6]. The success of this and other 5-HT₃ receptor antagonists [7] in preventing chemotherapy-induced nausea and or vomiting, led to study of their efficacy in treating postoperative nausea and vomiting [8-10]. In this study we have compared the efficacy of tropisetron with that of placebo for the prevention of postoperative nausea and vomiting in patients undergoing a gynaecological operation under standardized anaesthetic conditions.

PATIENTS AND METHODS

After obtaining informed consent and approval from the local Ethics Committee, we studied 70 consecutive non-pregnant women aged 18-75 yr undergoing gynaecological surgery under general anaesthesia (tables I, II). Day-case patients, those with confounding co-existing medical conditions and those receiving concomitant medications that could...
haemoglobin concentration, leucocytes and platelet counts and measurements of serum concentrations of electrolytes, creatinine and liver enzymes ALAT, ASAT and alkaline phosphatase. These tests were repeated at 24–48 h after the administration of the study drug. The operations were performed with standard anaesthetic monitoring, including arterial pressure, heart rate (ECG) and pulse oximetry. The attending anaesthetist recorded all adverse events, including any unusual symptoms which the patient mentioned during the interview on the day after the operation. The time between end of anaesthesia and opening the eyes was noted.

Statistical evaluation and end-points
We examined the hypothesis that at least 40% of the patients in the placebo group would suffer from nausea and vomiting and that tropisetron would reduce the incidence of nausea and vomiting to approximately 10%. A sample size of 38 patients per treatment group would provide 80% power to detect a difference of treatment success of 60% in the placebo group and 90% in the tropisetron group at the $\alpha = 0.05$ significance level [10]. Grouped data were analysed by means of $z$ tests or Wilcoxon tests and contingency tables by means of chi-square tests. Two-sided values of probability $P$ were added as appropriate.

Primary efficacy end-points were the number of episodes of vomiting and nausea recorded by the nurses and the patients. Secondary efficacy end-points were the frequency of alternative antiemetic therapy and the subjective ratings of the patient VAS score. Tolerance and safety were assessed from the adverse event recordings and the anaesthesia records.

Data were analysed with “Biomedical Computer-programmes (BMPD) Statistical Software Manual” version 1988, on a Compac PC, Dos version 3.31.

RESULTS
We studied 70 patients; one patient given placebo was excluded because of missing data. The results are presented for 35 patients who received tropisetron and 34 who received placebo. The groups were comparable (table I). The most common co-existing diseases are shown in table IV for the two groups. Approximately 50% of the patients in each group who previously underwent general anaesthesia had suffered nausea or vomiting on those occasions.

Anaesthesia and postoperative analgesic medications were comparable in the two groups.

### TABLE III. Doses of sufentanil and naloxone administered

<table>
<thead>
<tr>
<th></th>
<th>Tropisetron ($n = 15$)</th>
<th>Placebo ($n = 18$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufentanil (µg)</td>
<td>10–70</td>
<td>10–80</td>
<td>0.42</td>
</tr>
<tr>
<td>Naloxone (µg)</td>
<td>20–70</td>
<td>20–80</td>
<td>0.78</td>
</tr>
</tbody>
</table>

interfere with the evaluation of the study drug, in particular phenothiazines and prokinetic drugs, were excluded.

Antiemetic treatment was randomized in a double-blind, placebo-controlled study with two parallel groups. The study adhered to the conditions laid down in the Declaration of Helsinki and its amendments and was carried out in accordance with the "Guidelines of Good Clinical Practice".

Premedication was with diazepam 10 mg. Anaesthesia was induced with etomidate 0.2 mg kg$^{-1}$, atracurium 0.3 mg kg$^{-1}$ and sufentanil 0.3 µg kg$^{-1}$ and the trachea was intubated. After induction, a gastric tube was inserted to avoid gastric dilatation. Anaesthesia was maintained with 70% nitrous oxide and isoflurane (preferred concentration 0.5%) in 30% oxygen, supplemented with atracurium and sufentanil as necessary (table III). At the end of the anaesthesia, residual neuromuscular block was antagonized with prostigmine 1 mg and atropine 0.5 mg i.v.; small doses of naloxone (20–40 µg) were given only if necessary. The nasogastric tube was removed in the operating room. For postoperative analgesia, paracetamol 500 mg 6-hourly and piritramide 20 mg as required were prescribed. Two patients in the ICS group and five patients in the placebo group received extradural 0.25 % bupivacaine at their own request. The extradural infusion of 0.25 % bupivacaine was commenced when the patient left the recovery room.

As antiemetic prophylaxis, patients received either placebo or tropisetron 5 mg given as a short infusion approximately 15 min before wound closure. A 5-mg dose of tropisetron was chosen because it had proved to be optimal for treatment of nausea and vomiting induced by various highly emetic chemotherapy regimens [6]. For rescue antiemetic treatment, the patient was given a suppository containing domperidone 60 mg. If nausea or vomiting persisted for more than 1 h thereafter, another domperidone suppository was given.

Information on postoperative nausea and vomiting over the 24-h period after administration of the study medication was obtained from three sources: nursing observation in the recovery room and on the ward; the attending anaesthetist interviewed the patient on the day after the operation and completed a checklist; the patient completed a VAS score for self-assessment of nausea and vomiting and well-being on the day after surgery (VAS score: 0 mm = severe complaints of nausea and vomiting—not satisfied; 100 mm = no complaints of nausea and vomiting—completely satisfied).

Patients underwent physical examination, blood tests and an ECG. The laboratory tests consisted of haemoglobin concentration, leucocytes and platelet counts and measurements of serum concentrations of

### TABLE IV. Co-existing medical conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo ($n = 10$)</th>
<th>Tropisetron ($n = 13$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Ventricular extrasystole</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Anaemia</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Spastic colon</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Carotid artery insufficiency</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Twenty-six percent of tropisetron-treated patients vomited during the 24-h observation period, compared with 59% of placebo-treated patients (\(P = 0.006\)). In the recovery room, only three (8%) tropisetron-treated patients vomited, compared with 10 (29%) placebo-treated patients (\(P < 0.001\)). On the ward, eight (23%) tropisetron-treated patients vomited, compared with 19 (56%) placebo-treated patients (\(P < 0.001\)). Sixty-nine percent of tropisetron-treated patients experienced nausea, compared with 88% of placebo-treated patients (\(P = 0.05\)). When the patients with postoperative extradural analgesia were excluded, the frequencies of nausea and vomiting were unchanged.

The time between discontinuing nitrous oxide and the patient opening the eyes was 3.6 (SD 3.2) min in the tropisetron group and 3.4 (2.4) min in the placebo group (\(P = 0.87\)). Overall, patients in the tropisetron group were significantly more satisfied with their treatment than those in the placebo group. The overall satisfaction score correlated well with the frequency of vomiting \((r = -0.64; P < 0.001)\) and the frequency of episodes of nausea \((r = -0.55; P < 0.001)\) (table V).

There were no changes in biochemical tests after operation compared with before operation. Postoperative changes in hemoglobin concentration and PCV could be explained on the basis of blood loss and haemodilution.

**DISCUSSION**

The incidence of vomiting and especially that of nausea in our placebo group were greater than those reported previously \([1, 2, 5, 7–9]\). The choice of patient and period of observation on the ward may explain this finding. Women are known to experience a greater incidence of postoperative nausea and vomiting than men. Gynaecological operations particularly predispose to postoperative nausea and vomiting. In addition, the interaction between the patients, nursing staff and anaesthetist for data collection may have influenced the high incidence of nausea reported in this study. However, the data were consistent between the two groups and we believe that the extent of postoperative nausea has been underestimated in the past.

Tropisetron, in common with ondansetron \([7, 8]\), controlled vomiting more effectively than nausea. This finding corresponds with data for tropisetron used to treat chemotherapy-induced nausea and vomiting \([6]\). However, the pathogenesis of nausea may differ from that of vomiting; for example, severe pain and anxiety may have contributed to nausea, but not to vomiting. It is not likely, therefore, that one drug will be equally effective in treating both nausea and vomiting.

There were no differences between the groups in the time between the end of operation and opening the eyes on request or the duration of stay in the recovery room. Tropisetron did not prevent nausea and vomiting in all patients and, in retrospect, the timing of its administration may be judged not to have been ideal. Shortly before wound closure, most of the anaesthetic medication had been given and this may already have liberated the serotonin that activates the receptors implicated in nausea and vomiting reflexes. At the time of planning the study, however, we did not know if tropisetron would interfere with haemodynamic stability during induction and crucial events during the operation.

The possibility that the antiemetic medication may have interfered with anaesthetic care was examined by comparing the vital signs, recovery times, the incidence of postoperative amnesia and the analgesic requirements during and after operation. However, there were no significant differences between the two groups in these variables. Also, tropisetron did not affect laboratory variables or the ECG, and no side effects were detected. We conclude that the prophylactic administration of tropisetron 5 mg before the end of the operation effectively reduced the incidence of postoperative nausea and vomiting, without any ill effects.

**ACKNOWLEDGEMENT**

Sandoz Pharma Ltd provided the tropisetron and matching placebo.

**REFERENCES**