EFFECT OF TROPISETRON, A 5-HT$_3$ RECEPTOR ANTAGONIST, ON ANALGESIA AND NAUSEA AFTER INTRATHecal MORPHINE

M. T. PITKÄNEN, L. NIEMI, M. K. TUOMINEN AND P. H. ROSENBERG

SUMMARY

We have studied the effect of tropisetron, a 5-HT$_3$ receptor antagonist, on postoperative nausea, vomiting and pain in 54 patients, aged 50–83 yr, after major hip or knee surgery. The patients were given subarachnoid injection of plain 0.5% bupivacaine, mixed with preservative-free morphine 0.3 mg, for surgical and postoperative analgesia. In a double-blind fashion, either tropisetron 5 mg (1 mg ml$^{-1}$) or saline 5 ml was injected i.v. 30 min after spinal administration of bupivacaine and morphine. The number of patients needing i.m. oxycodone for pain relief, the total number of oxycodone doses or the mean time to the first i.m. oxycodone administration did not differ significantly between the two groups. The number of patients who became nauseated or vomited during the observation period did not differ significantly between groups. Seventeen patients had nausea and 11 vomited in the tropisetron group, compared with 20 and 13, respectively, in the control group during the first 24 h.

KEY WORDS


Intrathecal morphine provides good pain relief after orthopaedic surgery of the lower extremities [1–3]. Unfortunately, the use of spinal morphine, even in small doses, is often associated with unpleasant side effects such as urinary retention, pruritus and nausea and vomiting [4]. Specific 5-HT$_3$ receptor antagonists are beneficial in attenuating nausea and vomiting induced by chemotherapeutic agents in cancer patients [5–7]. Recently, two 5-HT$_3$ antagonists, ondansetron [8–10] and tropisetron [11] have been introduced for the prevention and treatment of emesis after general anaesthesia.

It is important to consider that 5-HT receptor antagonists may influence pain perception in addition to nausea and vomiting. In the spinal cord, 5-HT is involved in antinociception mechanisms [12, 13]. 5-HT$_3$ increases nociceptive thresholds and tropisetron has been shown to antagonize 5-HT$_3$-induced antinociception, suggesting an important role for 5-HT$_3$ receptors in modulating spinal nociceptive responses [14]. On the other hand, 5-HT$_3$ receptor antagonists, including tropisetron, have been found to reduce certain types of pain (chemical and inflammatory) by peripheral 5-HT$_3$ receptor mechanisms [15, 16].

The efficacy of 5-HT$_3$ antagonists for prevention of nausea and vomiting after intrathecal administration of morphine has not been investigated. The present study was designed to see if a prophylactic 5-mg dose of i.v. tropisetron influences the incidence of nausea and vomiting, and the quality of postoperative analgesia in patients undergoing hip or knee operations (arthroplasty or osteotomy) under bupivacaine–morphine spinal anaesthesia.

PATIENTS AND METHODS

The study was approved by the Ethics Committee of Surgical Hospital/Helsinki University Central Hospital, and the patients gave informed consent.

We studied 54 ASA I–III patients, undergoing major orthopaedic hip or knee surgery in this randomized, double-blind study (table I). All patients were premedicated with oral diazepam 5 mg (weight 60 kg or less), 10 mg (61–80 kg) or 15 mg (weight greater than 80 kg). Patients older than 75 yr were given diazepam 5 mg (80 kg or less) or 10 mg (>80 kg). The subarachnoid puncture was performed...
formed in the midline of the L3–4 interspace (25- or
27-gauge needle), with the patient in the lateral
position. Preservative-free morphine 0.3 mg was
mixed with plain 0.5% bupivacaine 20 mg (a 15-mg
dose was used in two patients in the tropisetron
and one patient in the saline group) before injection. The
level of analgesia to pinprick 60 min after the
injection was recorded.

Within 30 min after subarachnoid injection of
bupivacaine with morphine, one of the investigators
injected either tropisetron 5 mg (3α-tropanyl-1H-
indole-3-carboxylic acid ester; Sandoz Ltd, Basel,
Switzerland) or an equivalent volume of saline i.v.
over 2–3 min using a coded syringe. The syringe was
filled with the test solution by a trained nurse,
according to a note in a sealed envelope. The investi-
gators were unaware of the agent injected.

Non-invasive arterial pressure (oscillotonometry),
ECG, heart rate and \( S_{O_2} \) were monitored in the
operating room and in the postanaesthesia care unit.
I.v. fluids (Ringer’s acetate, hydroxyethyl starch)
and erythrocyte concentrate transfusions were given
on an individual basis, according to our clinical
routines. Oxygen 2–3 litre min\(^{-1}\) was delivered via a
nasal catheter during surgery. During operation,
fentanyl 50 μg i.v. for analgesia and diazepam
2.5–5 mg i.v. for sedation were administered, if
required. Pain and the need for medication were
assessed on an arbitrary scale: 0 = no pain; 1 = mild
pain (opioids not needed); 2 = pain (opioids
needed); 3 = severe pain (opioids needed immedi-
ately) after operation, for 24 h. Ketoprofen 100 mg
orally for mild pain (score 1) or oxycodone
0.1–0.14 mg kg\(^{-1}\) i.m. for more severe pain was given
on request. The patients were confined to bed for
24 h. On the ward, they were allowed to drink and
eat light meals.

The occurrence of nausea and vomiting was
recorded continuously during the patient’s stay in
the postanaesthesia care unit and on the ward.
Pruritus and micturition problems (need for bladder
catheterization) and other observations were noted.
Patients were assessed for pain, sedation and head-
ache at 6-h intervals: at 15:00 on the ward (by
investigator), at 21:00 (by a trained nurse), at 03:00
(by a trained nurse) and at 09:00 (by investigator)
and once more if the 24-h observation period was
incomplete at 09:00. For analyses, analgesia re-
quirement and episodes of nausea or vomiting were
grouped at 6-h intervals. In the case of persistent
vomiting, droperidol 1.25 mg i.m. was given. In the
recovery room, metoclopramide 10–20 mg i.v. was
given. The characteristics of the patients and perioperative
data in the two groups were comparable (table I).

Two patients in the saline group and three in the
tropisetron group were given ketoprofen. The
patients in the tropisetron group and one in the
saline group who were given ketoprofen also needed
oxycodone (table II). There were no differences
between the groups in the number of patients
requiring supplementary oxycodone, the total num-
ber of doses or the time from the injection of
intrathecal morphine to the first administration of
i.m. oxycodone. The number of patients who were
completely pain-free (score 0) decreased over time at
a similar rate in both groups (table III).

There was no statistically significant difference
between the number of patients in the two groups
who became nauseated or vomited during the
observation period (table IV). In the tropisetron
group, there were 11 patients who had no nausea
and seven who had nausea on only one occasion;
the respective numbers of patients in the saline
group were six and 11 (ns). The total number of episodes of
nausea, or vomiting, or both, occurring during
7–18 h from the injection of the test drug was greater
in the saline group (fig. 1) (ns). Two patients in the
tropisetron and one patient in the saline group
needed metoclopramide, and eight patients in the
tropisetron and six in the saline group required
droperidol.

| TABLE II. Postoperative requirement for oxycodone and mean (sd)
time to first dose. No significant difference between groups |
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<tr>
<td>No. patients</td>
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<tr>
<td>Tropisetron</td>
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<td>Saline</td>
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<th>TABLE III. Pain scores (no significant differences between groups)</th>
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<tr>
<td>Number of patients</td>
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<tr>
<td>Post-anaesthesia care unit</td>
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<tr>
<td>Tropisetron</td>
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<tr>
<td>Score 1 1 3 6 6 10</td>
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<tr>
<td>Score 2 0 0 3 4 1</td>
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<tr>
<td>Score 3 0 0 1 0 2</td>
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<td>Saline</td>
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<tr>
<td>Score 1 1 4 7 5 8</td>
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<td>Score 2 0 1 1 2 4</td>
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<td>Score 3 0 0 1 1 2</td>
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<tr>
<th>TABLE IV. Number of patients experiencing nausea/vomiting, urinary retention requiring catheterization or pruritus. No significant difference between groups</th>
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<tbody>
<tr>
<td>Nausea/vomiting</td>
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<td>Tropisetron</td>
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Statistical analysis

Sample size was established using a sample size
calculation to compare the prevalence of nausea in
these patients. For this analysis, we used the
prevalence published from similar groups of subjects
[17–19] and set critical error levels at \( \beta = 0.25 \) and
\( \alpha = 0.05 \).

Statistical significance between the mean values
was evaluated using Student’s \( t \) test and between
frequencies using Fisher’s exact test. The Mann–
Whitney \( U \) test was used for level of spinal analgesia.
Pruritus and urinary retention occurred in almost the same number of patients in the two groups (table IV). No postdural puncture headache or ventilatory frequencies less than 10 b.p.m. were observed.

DISCUSSION

Our data indicate that prophylactic i.v. tropisetron had no observable influence on intrathecal morphine analgesia after major hip and knee surgery. Only a small, non-significant reduction in the number of episodes of nausea could be detected after operation for 7–18 h (fig. 1). The timing and dose of the tropisetron administration were based on experience in the prevention of chemotherapy-induced emesis [5] and the relatively long elimination half-life (approximately 8 h) of the drug in man (production information, Sandoz Ltd, Basel, Switzerland). Tropisetron was administered 30 min after intrathecal morphine. However, this may be considered as prophylactic, since intrathecally administered morphine reaches the respiratory centre (which is close to the chemoreceptor trigger zone and vomiting centre) by 60 min [4].

The incidence of nausea in the present study (59% and 74%) was greater than in two of our recent studies in orthopaedic patients: when bupivacaine spinal anaesthesia without addition of intrathecal morphine was given, the postoperative incidence of nausea was 37.5% [17] and when morphine 0.1 mg 24 h 

Fig. 1. Incidence of nausea in the tropisetron (□) and saline (■) groups. No significant difference between groups.

683

Side effects such as headache and sedation, which occur in cancer patients during tropisetron treatment [5], were not observed in our patients.

The lack of significant effect of tropisetron on nausea and vomiting after subarachnoid morphine in the present study is not suggestive of an important role of 5-HT3 receptor involvement in this particular type of nausea. The nausea associated with cisplatin therapy is at least in part caused by the release of 5-HT from the viscera and activation of 5-HT3 receptors [7] and it can therefore be attenuated to a clinically significant degree with specific 5-HT3 antagonists. There are also suggestions that the 5-HT3 receptor antagonists may act on peripheral receptors found in abdominal visceral afferent neurones [26], which could explain the poor antiemetic effect of the 5-HT3 antagonist in the present study. Metoclopramide, one of the rescue antiemetics used in our study, might be better suited for the prevention and treatment of nausea induced by subarachnoid morphine [27]. Metoclopramide increases lower oesophageal sphincter tone and enhances gastric and bowel motility and has antidopaminergic [28] and, in large doses, also an anti-5HT receptor action [29].

REFERENCES


