Antiemetic prophylaxis with promethazine or ondansetron in major gynaecological surgery

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ABSTRACT

Background: Postoperative nausea and vomiting remain a significant cause of morbidity among patients undergoing general anaesthesia. The optimal strategy for prophylaxis remains controversial. This study evaluated the efficacy of ondansetron 8 mg compared with promethazine 25 mg or placebo for the prevention of nausea and vomiting in patients undergoing elective major gynaecological surgery.

Methods: Seventy-five patients received intravenous injection of the study medication (ondansetron-25, promethazine-25 or placebo-25) immediately before the induction of anaesthesia. Nausea and vomiting were assessed over a 24-hour postoperative period.

Results: Nausea occurred in 20%, 40% and 72% of the promethazine, ondansetron and placebo groups respectively (p = 0.001). The overall incidence of vomiting was 12%, 16%, and 60% (p = 0.000) for promethazine, ondansetron and the placebo respectively. Postoperative drowsiness was prominent in the promethazine group. There was no significant difference in effectiveness between promethazine and ondansetron.

Conclusions: Promethazine 25 mg was significantly more effective than ondansetron 8 mg in the prevention of postoperative nausea and vomiting. Promethazine is inexpensive and the cost of drugs is of importance in developing African countries. Drowsiness was a significant side-effect with promethazine, and this will be a disadvantage in ambulatory surgery.

Introduction

Postoperative nausea and vomiting (PONV) remain a significant cause of morbidity among patients undergoing general anaesthesia. The optimal strategy for prophylaxis remains controversial. This study evaluated the efficacy of ondansetron 8 mg compared with promethazine 25 mg or placebo for the prevention of nausea and vomiting in patients undergoing elective major gynaecological surgery.

Methods

Seventy-five patients received intravenous injection of the study medication (ondansetron-25, promethazine-25 or placebo-25) immediately before the induction of anaesthesia. Nausea and vomiting were assessed over a 24-hour postoperative period.

Results

Nausea occurred in 20%, 40% and 72% of the promethazine, ondansetron and placebo groups respectively (p = 0.001). The overall incidence of vomiting was 12%, 16%, and 60% (p = 0.000) for promethazine, ondansetron and the placebo respectively. Postoperative drowsiness was prominent in the promethazine group. There was no significant difference in effectiveness between promethazine and ondansetron.

Conclusions

Promethazine 25 mg was significantly more effective than ondansetron 8 mg in the prevention of postoperative nausea and vomiting. Promethazine is inexpensive and the cost of drugs is of importance in developing African countries. Drowsiness was a significant side-effect with promethazine, and this will be a disadvantage in ambulatory surgery.

Materials and methods

Institutional approval from the ethics committee and informed patient consent were obtained. Seventy-five patients who were American Society of Anaesthesiologists Risk Classification I to III, aged between 18 and 65 years and scheduled for major gynaecological surgery under general anaesthesia were studied.

Patients were excluded from the study if they showed evidence of uncontrolled clinically important neurological, renal, hepatic, cardiovascular, metabolic or endocrine dysfunction, and if they were pregnant or breast-feeding. The patients were premedicated with diazepam (5 to 10 mg). Patient and investigator blinding was ensured. The study drugs were drawn and labelled A, B or C (A – promethazine 25 mg, B – ondansetron 8 mg, and C – placebo) in sterile 20 ml syringes and made to equal volumes of 20 ml with normal saline. All the drugs were colourless. On arrival in the theatre, the patients were randomly assigned by computer-generated balloting to one of three groups (A, B, C). The study medication was given immediately before the induction of anaesthesia with sodium thiopentone and maintained with nitrous oxide in oxygen supplemented with halothane. Neuromuscular blockade was provided with pancuronium and pentazocine administered for analgesia. Reversal of the blockade was achieved with atropine and neostigmine. Postoperatively, the patients were evaluated for nausea and vomiting by a senior registrar blinded to the designated agent.

Nausea and vomiting were assessed by direct questioning of the patient after recovery from anaesthesia. Recovery was defined as the first response to spoken command. Nausea was defined as a subjectively unpleasant sensation associated with the awareness of the urge to vomit and was evaluated by the patient being interviewed. Vomiting was defined as the forceful expulsion of gastric contents from the mouth. The number of episodes of vomiting was documented. The postoperative period was divided into an early phase (0 to 6 hours) and a late phase (6 to 24
Nausea was graded as mild if it lasted less than two hours and severe if it lasted more than two hours. The data collected from each patient included the age, weight, height, gender, previous history of postoperative nausea and vomiting, phase of menstrual cycle, type of surgical procedure and pain scores. The duration of anaesthesia and the time required for the patients to recover from anaesthesia agents (defined as the first response to spoken command), as well as adverse reactions, were documented.

The patient's demographic data were analysed with one way analysis of variance (ANOVA) and student's t-test. The chi square test was used for non-parametric assessment. EPI-INFO 6.04 software was used for the above statistical analysis. A p value < 0.01 was considered as statistically significant.

**Results**

Seventy-five patients were evaluated in three treatment groups (promethazine – 25, ondansetron – 25 and placebo – 25). The patients' characteristics, last menstrual period, pain scores, duration of anaesthesia and awakening time were not significantly different in the three groups (see Table I).

Figure 1 is a comparison of the frequencies of nausea in the three study groups. Early nausea was observed in 8% of the promethazine group, 16% of the ondansetron group and 40% in the placebo group (p = 0.016). Late nausea was found to be 12% in the promethazine group, 24% in the ondansetron group and 32% in the placebo group (p = 0.236). The overall incidence of nausea was 20% in the promethazine group, 40% in the ondansetron group and 72% in the placebo group (p = 0.001).

**Table I: Patients' characteristics**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Promethazine (Mean ± SD)</th>
<th>Ondansetron (Mean ± SD)</th>
<th>Placebo (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36.60 ± 6.07</td>
<td>35.56 ± 7.33</td>
<td>36.16 ± 7.09</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67.80 ± 10.07</td>
<td>65.28 ± 11.99</td>
<td>66.28 ± 11.85</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.63 ± 0.07</td>
<td>1.63 ± 0.08</td>
<td>1.64 ± 0.08</td>
</tr>
<tr>
<td>Lmp (days)</td>
<td>17.88 ± 7.10</td>
<td>17.79 ± 5.56</td>
<td>21.21 ± 8.16</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>141.00 ± 28.76</td>
<td>155.40 ± 28.06</td>
<td>159.40 ± 28.52</td>
</tr>
<tr>
<td>Awakening time (min)</td>
<td>13.24 ± 2.84</td>
<td>6.96 ± 1.46</td>
<td>6.13 ± 2.53</td>
</tr>
<tr>
<td>Procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myomectomy</td>
<td>5</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Total abdominal hysterectomy</td>
<td>7</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Exploratory laparotomy</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Tuboplasty</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
</tbody>
</table>

Lmp = last menstrual period

**Figure 1:** Incidence of nausea in antiemetic treatment groups
Early vomiting was observed in 4% of the ondansetron group, 8% of the promethazine group and 44% of the placebo group \((p = 0.003)\). Late vomiting was at 4% in the promethazine group, 12% in the ondansetron group and 16% in the placebo group \((p = 0.575)\).

The overall occurrence of vomiting in the promethazine group was 12%, in the ondansetron group it was 16% and in the placebo group it was 60% \((p = 0.001)\) (see Figure 2).

Table II shows the severity of nausea in the antiemetic groups.

Table II: Severity of nausea

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>0.650</td>
</tr>
<tr>
<td>Severe</td>
<td>5</td>
<td>6</td>
<td>14</td>
<td>0.004*</td>
</tr>
</tbody>
</table>

*p value < 0.01

Table III: Severity of vomiting

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>2</td>
<td>4</td>
<td>7</td>
<td>0.171</td>
</tr>
<tr>
<td>Severe</td>
<td>1</td>
<td>0</td>
<td>8</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

*p value < 0.01

Table IV: Adverse reactions to antiemetic prophylaxis

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness</td>
<td>8(32%)</td>
<td>0</td>
<td>1(4%)</td>
<td>0.008*</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>20(80%)</td>
<td>1(4%)</td>
<td>0.017</td>
</tr>
</tbody>
</table>

*p value < 0.01
**Discussion**

Ondansetron is a highly potent and selective 5HT3 receptor antagonist. High-risk patients were selected for this study – females, in whom the incidence of vomiting is three times higher and who were undergoing major gynaecological surgery, a procedure associated with a very high incidence of vomiting. Standardised premedicant, anaesthetic technique and postoperative analgesic regimen were used. The study demonstrated the efficacy of promethazine in reducing the overall incidence of postoperative nausea and vomiting. However, ondansetron influenced postoperative vomiting more than its effect on nausea. This observation was consistent with the findings of Gan et al, who found no difference in the incidence of nausea between ondansetron and placebo. Hindle et al subsequently suggested the possibility that neuronal pathway mediating nausea and vomiting are distinct, the former having a partial 5HT3 component and the latter having a predominant 5HT3 component. Dundee and McMillan reported their observations of the use of ondansetron in oncology patients, in whom drug-induced nausea and vomiting are major problems. They found that ondansetron was much more effective in reducing vomiting than in reducing nausea. In a double-blind comparison of ondansetron with droperidol and metoclopramide in 60 patients undergoing general anaesthesia for dilatation and curettage, Alon and Himmelheber found no significant difference among the groups for nausea. However, they found that ondansetron was more significantly effective for vomiting. The incidence of vomiting in the early postoperative period was lower in the ondansetron group (4%) compared to the promethazine group (8%). This was reversed in the late postoperative period, when promethazine was associated with a lower incidence of vomiting (4%) compared with ondansetron (12%). This suggests that ondansetron is more effective in reducing the incidence of vomiting in the early postoperative period, but that it could not sustain this superiority over promethazine in the late postoperative period. A possible explanation for this observation is that the half life of ondansetron (E = 3-5 hours), whereas the half life of the antiemetic action of promethazine is longer (E = 9.73 ± 3.4 hours). Nausea was significantly less severe in the promethazine group. It is possible that the severity of nausea may be influenced by sedation. Since nausea is a subjective symptom, patients who are sedated or drowsy may not reliably report the occurrence of this symptom.

Ondansetron had a good safety profile, with only two (8%) patients who had an adverse event (headaches), similar to that seen in the placebo group. This study did not measure bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase and gamma glutamyltranspeptidase. Asymptomatic increases in transaminase have been reported during the use of ondansetron and are included in the existing prescribing information for this drug. Drowsiness was significantly higher in the promethazine group. This will be a major disadvantage in the ambulatory surgical setting, where delayed discharge and consequent overnight hospital stay may increase patient and hospital costs. Nevertheless, it may still be a distressing adverse event in the in-patient population and may affect the patient's overall satisfaction with the anaesthetic experience.

Costs will continue to feature prominently in the decision of drug pharmacy committees. Drug committees worldwide increasingly demand evidence that a new drug be either more effective than existing drugs or be associated with a reduction in the incidence of adverse effects. Limitations in the availability of funding for the health sector in Nigeria demand that the economic implications of new drugs be examined before the replacement of old, existing agents. Promethazine (pharmacy cost of intravenous promethazine 25 mg is 20 Naira) is inexpensive and is a readily available antiemetic in our hospital. Its demonstrated efficacy compared with ondansetron (pharmacy cost of ondansetron 4 mg ondansetron is 1800 Naira) in this study suggests that it will be very economical for antiemetic prophylaxis in selected high-risk patients coming for surgical procedures.

**References**

12. Watcha MF, McMillan CM, Analgesia & Analgesia 1995;77:938–.