

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 prevention, however, 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 common cause of postoperative morbidity.¹ If severe, vomiting may result in bleeding at the operative site, aspiration of vomitus, fluid and electrolyte imbalance, oesophageal tears, gastric herniation, muscular rib fractures and wound dehiscence. Raised intracranial, intraocular or intra-abdominal pressure during PONV can lead to the rupture of delicate suture lines, resulting in the need for additional surgery. The variable efficacy and potential adverse reaction to traditional antiemetic agents have made routine prophylaxis of postoperative nausea and vomiting unnecessary, but may be justified in identified high-risk groups. Factors associated with an increased risk of PONV include age, gender, obesity, menstrual period, history of motion sickness, anxiety, gastroparesis, and type of surgical procedure (e.g. laparoscopic, gynaecologic, strabismus and middle ear surgery). Therapeutic intervention via the use of antiemetic drugs forms the basis of the prevention and treatment of postoperative nausea and vomiting. The discovery and development of drugs that selectively antagonise the action of 5-hydroxytryptamine (serotonin) at 5HT₃ receptors has given more reliable clinical options for the prevention and treatment of PONV.²⁻⁸ Traditional antiemetic drugs (e.g. promethazine, metoclopramide, droperidol) are generally less expensive than ondansetron when used for prophylaxis. However, their tendency to cause undesirable side-effects is seen as a major disadvantage. Ondansetron is a serotonin receptor antagonist known to be effective in the prophylaxis and treatment of postoperative nausea and vomiting.^{9,10} Promethazine is a phenothiazine derivative that is an effective antagonist of muscarinic, cholinergic, histaminergic and partially dopaminergic receptors.¹¹ Its major site of antiemetic action has been identified as the chemoreceptor trigger zone, and it may cause excessive sedation. Drug cost is of importance in a developing country's health care delivery system because of limited resources. Promethazine is a drug that is affordable and readily available in most countries in the African sub-region. This study examined the efficacy of this agent in comparison to ondansetron and placebo.

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 scheduled to have a nasogastric tube in situ postoperatively, weighed less than 45 kg or more than 90 kg, and 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

hours). 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).

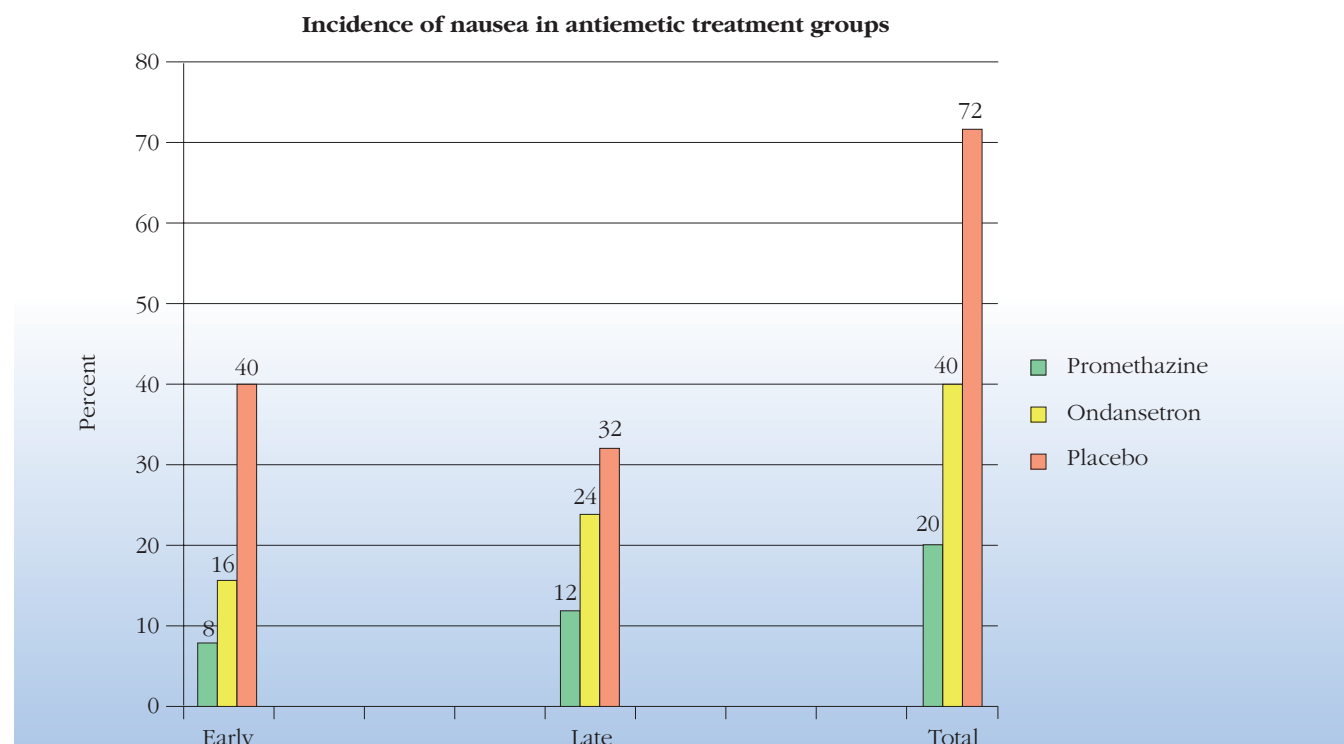
Figure 1 is a comparison of the frequencies of nausea in the three study groups. Early nausea was observed in 8% of the promethazine group, 16% of the ondansetron group and 40% in the placebo group ($p = 0.016$). Late nausea was found to be 12% in the promethazine group, 24% in the ondansetron group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

	Promethazine (Mean \pm SD)	Ondansetron (Mean \pm SD)	Placebo (Mean \pm SD)
Age (years)	36.60 \pm 6.07	35.56 \pm 7.33	36.16 \pm 7.09
Weight (kg)	67.80 \pm 10.07	65.28 \pm 11.99	66.28 \pm 11.85
Height (m)	1.63 \pm 0.07	1.63 \pm 0.06	1.64 \pm 0.08
Lmp (days)	17.88 \pm 7.10	17.79 \pm 5.56	21.21 \pm 8.16
Duration of anaesthesia (min)	141.00 \pm 28.76	135.40 \pm 28.06	139.40 \pm 28.32
Awakening time (min)	13.24 \pm 2.84	6.96 \pm 1.46	6.13 \pm 2.53
Procedure			
Myomectomy	5	15	13
Total abdominal hysterectomy	7	6	8
Exploratory laparotomy	2	4	4
Tuboplasty	1	0	0
Total	25	25	25

Lmp – last menstrual period

Figure 1: Incidence of nausea in antiemetic treatment groups

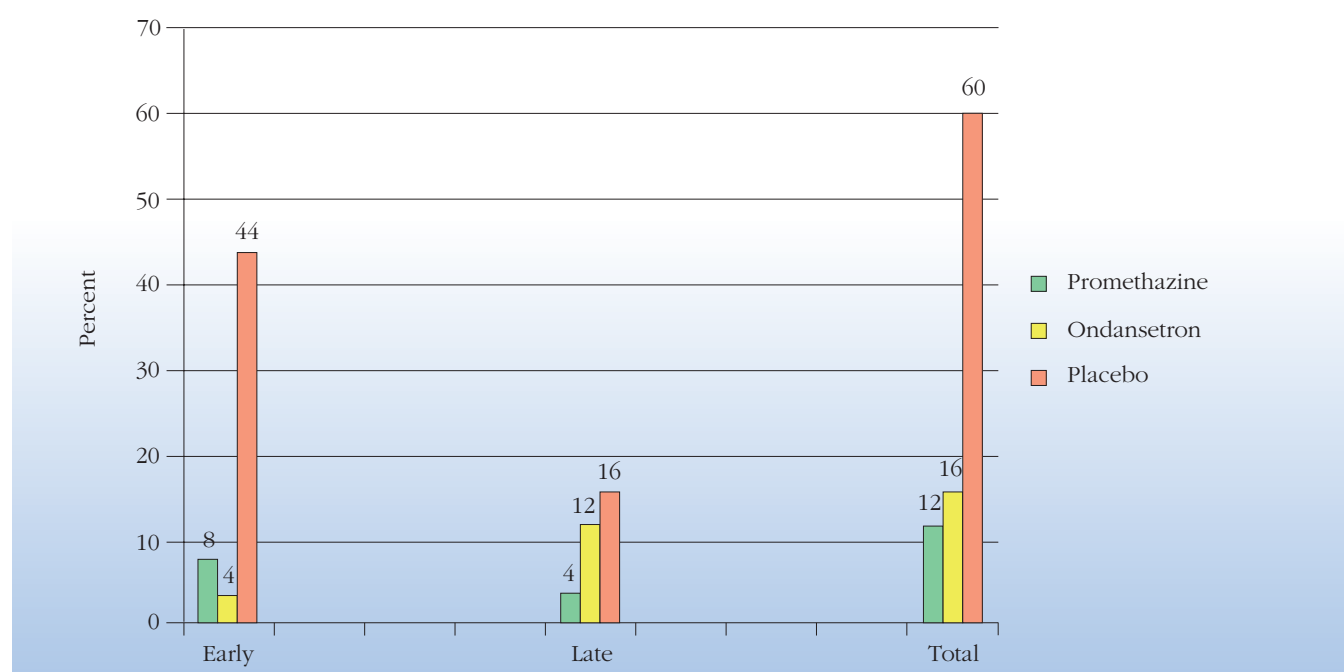


Early vomiting was observed in 4% of the ondansetron group, 8% of the promethazine group and 44% of the placebo group ($p = 0.003$). Late vomiting was at 4% in the promethazine group, 12% in the ondansetron group and 16% in the placebo group ($p = 0.375$).

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.

Figure 2: Incidence of vomiting in antiemetic treatment groups



Four patients (16%) experienced mild nausea in the ondansetron and placebo groups, while two patients (8%) experienced mild nausea in the promethazine group ($p = 0.630$). There were three patients (12%) who developed severe nausea in the promethazine group, eleven (44%) in the ondansetron group and fourteen (56%) in the placebo group ($p = 0.002$). Eight patients (32%) in the placebo group experienced severe vomiting (more than two episodes), one patient (4%) in the promethazine group, and no patients in the ondansetron group ($p = 0.001$) (see Table III).

Table IV shows the various adverse effects observed.

Table II: Severity of nausea

	Promethazine – 25	Ondansetron – 25	Placebo – 25	p value
Severity	N	N	N	
Mild	2	4	4	0.630
Severe	3	6	14	0.004*

*p value < 0.01

Table III: Severity of vomiting

	Promethazine – 25	Ondansetron – 25	Placebo – 25	p value
Severity	N	N	N	
Mild	2	4	7	0.171
Severe	1	0	8	0.001*

*p value < 0.01

Table IV: Adverse reactions to antiemetic prophylaxis

Side effect	Promethazine – 25	Ondansetron – 25	Placebo – 25	p value
Drowsiness	8(32%)	0	1(4%)	0.008*
Headache	0	2(8%)	1(4%)	0.017

*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.¹² 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.¹³ 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.¹⁴ Dundee and McMillan reported their observations of the use of ondansetron in oncology patients, in whom drug-induced nausea and vomiting are major problems.¹⁵ 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 66 patients undergoing general anaesthesia for dilatation and curettage, Alon and Himmelseher found no significant difference among the groups for nausea.¹⁶ 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 the short half life of ondansetron ($E_{1/2}$ = 3-5 hours),¹⁷ whereas the half life of the antiemetic action of promethazine is longer ($E_{1/2}$ = 9.73 ± 3.4 hours).¹⁸ 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 assessment, patients that are asleep 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 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 intravenous 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.

This study cannot claim to have rigorously assessed the financial implications of ondansetron compared with promethazine. The increased cost of ondansetron may need to be balanced against its potential for a lower incidence of the side-effects associated with promethazine (e.g. drowsiness and extra-pyramidal reaction). Indirect costs resulting from a delay in the resumption of normal activities by a drowsy patient also require assessment. A cost analysis of the study drugs will be important, since the practice of anaesthesia will increasingly require the allocation of limited resources among competing demands. Promethazine is effective in the prophylaxis of postoperative nausea and vomiting and is recommended for in-patients, because of its low cost and its availability, especially in the poor, developing countries of Africa. Drowsiness is a major concern regarding the side-effects of promethazine. In a retrospective analysis, Habib et al found that there was no difference in efficacy or sedation between 6.25 mg promethazine and the higher doses used for the treatment of established postoperative nausea and vomiting.¹⁹ A dose-ranging study with a view to retaining the efficacy of promethazine without undesirable side-effects in a prophylactic setting will be beneficial.

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Conflict of interest

The authors hereby declare that there is no conflict of interest regarding this study.

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