Optimal anti-emetic dose of granisetron for preventing post-operative nausea and vomiting

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In order to determine the optimal effective dose of granisetron for preventing postoperative nausea and vomiting, the drug was administered in doses of either 20, 40 or 60 $\mu g \cdot kg^{-1}$. The efficacy of granisetron was evaluated in a randomized, double-blind comparison with placebo in 100 patients undergoing general anaesthesia for major gynaecological surgery. The patients received a single dose of either granisetron or placebo (saline) iv immediately after recovery from anaesthesia. The effects were assessed during the 24 hr after recovery from anaesthesia by means of a nausea and vomiting score; 0 = no emetic symptoms, 1 = nausea, 2 = vomiting. The treatment groups were similar for patient characteristics, surgical procedures and anaesthetics administered. The mean scores were 0.7, 0.6, 0.2 and 0.2 after administration of placebo, granisetron 20, 40 and 60 $\mu g \cdot kg^{-1}$, respectively. Granisetron 40 $\mu g \cdot kg^{-1}$ was as effective as 60 $\mu g \cdot kg^{-1}$ and both resulted in reduction of the scores compared with placebo and granisetron 20 $\mu g \cdot kg^{-1}$ ($P < 0.05$). In conclusion, granisetron 40 $\mu g \cdot kg^{-1}$ is considered to be the appropriate dosage for preventing postoperative emesis after anaesthesia.

Dans le but de déterminer la dose optimale efficace de granisetron pour prévenir les nausées et vomissements postopératoires, ce médicament est administré à des doses différentes de 20, 40 ou 60 $\mu g \cdot kg^{-1}$. Chez 100 patientes soumises à une anesthésie générale pour une chirurgie gynécologique majeure, on compare l'efficacité du granisetron avec un placebo aléatoirement et à double aveugle. Les patients reçoivent une dose unique soit de granisetron soit de placebo (soluté physiologique) iv immédiatement au réveil de l'anesthésie. Les effets sont mesurés 24 heures plus tard grâce à un score de nausées et vomissements: 0 = aucun symptôme, 1 = nausées, 2 = vomissements. Les caractéristiques des patientes, les interventions chirurgicales et les anesthésiques administrés ne diffèrent pas entre les groupes. Les scores moyens ont été de 0,7, 0,6, 0,2 et 0,2 après l'administration du placebo et du granisetron 20, 40 et 60 $\mu g \cdot kg^{-1}$ respectivement. Le granisetron 40 $\mu g \cdot kg^{-1}$ est aussi efficace que 60 $\mu g \cdot kg^{-1}$ et les deux doses produisent une baisse des scores comparativement au placebo et au granisetron 20 $\mu g \cdot kg^{-1}$ ($P < 0,05$). Pour conclure, on considère que le granisetron 40 $\mu g \cdot kg^{-1}$ constitue une posologie adéquate pour prévenir les nausées et vomissements postopératoires.

Key words
COMPLICATIONS: nausea, vomiting;
VOMITING: anti-emetics; granisetron, incidence, nausea;
SURGERY: gynaecological.

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Granisetron (Kytril®), a selective 5-hydroxytryptamine type 3 ($5\text{-}HT_3$) receptor antagonist, has potent anti-emetic effects for the treatment of cisplatin-induced nausea and vomiting.[1] Recently, we demonstrated that administration of granisetron reduced the incidence of postoperative nausea and vomiting.[2] However, the optimal effective dose of granisetron has not been reported. This study was performed to determine the optimal dose of granisetron for preventing postoperative emesis in a randomized, double-blind comparison with placebo in patients undergoing general anaesthesia for major gynaecological surgery.

Methods

After obtaining approval from our institutional ethics committee, 100 female patients undergoing general anaesthesia for major gynaecological surgery were studied. Informed consent was obtained from each patient. All patients were between 25 and 65 yr and were ASA physical status I or II. No patient had cardiovascular, respiratory, renal, hepatic or neurological disease. In addition, none had received any anti-emetic drug within 24 hr of surgery.

TABLE I Patient characteristics and surgical procedures

Group	Placebo ($n = 25$)	Granisetron 20 $\mu g \cdot kg^{-1}$ ($n = 25$)	Granisetron 40 $\mu g \cdot kg^{-1}$ ($n = 25$)	Granisetron 60 $\mu g \cdot kg^{-1}$ ($n = 25$)
Age (yr)	46.7 ± 7.7	46.3 ± 11.8	44.1 ± 9.0	45.4 ± 7.9
Height (cm)	152.9 ± 5.4	154.4 ± 4.9	153.8 ± 4.8	152.8 ± 5.1
Weight (kg)	54.2 ± 7.1	56.3 ± 10.1	55.3 ± 7.3	53.9 ± 5.5
Duration of operation (min)	80 ± 34	80 ± 24	82 ± 31	81 ±32
Duration of anaesthesia (min)	104 ± 32	105 ± 25	106 ± 30	105 ± 31
Types of operation performed				
- Abdominal hysterectomy	19	18	20	19
- Vaginal hysterectomy	0	1	0	1
- Salpingo-oophorectomy	4	3	3	2
- Others	2	3	2	3

All values are expressed as mean ± SD.

All patients were premedicated with atropine sulphate 0.5 mg *im* 30 min before the induction of anaesthesia. In the operating room, patients were placed in the lateral decubitus position. A 17-gauge Tuohy needle was inserted at either L_{2-3} or L_{3-4} interspace with a loss of resistance technique and an 18-gauge epidural catheter was placed cephalad (approximately 5 cm) through the needle. Correct placement was confirmed by administration of a test dose of 2 ml lidocaine 1.5%. After catheter placement, the patients were placed in the supine position. Anaesthesia was induced with thiopentone 4–5 $mg \cdot kg^{-1}$ *iv*, and succinylcholine 1.5–2 $mg \cdot kg^{-1}$ *iv* was used to facilitate tracheal intubation after precurarization with pancuronium 0.02 $mg \cdot kg^{-1}$ *iv*. After tracheal intubation, anaesthesia was maintained with N_2O/O_2 (2:1) and isoflurane 0.5–2%. Ventilation was controlled mechanically and was adjusted to keep an end-tidal $P_{ET}CO_2$ between 35 and 40 mmHg with an anaesthetic/respiratory gas analyzer (Capnomac Ultima, Datex, Finland). When haemodynamic variables were stable, 10–15 ml lidocaine 1.5% were injected through the epidural catheter. Neuromuscular blocking drugs were used as required. Rectal temperature was monitored and maintained at 37±1°C using a heating pad. At the end of surgery, reversal of muscle relaxation was achieved with atropine sulphate 0.02 $mg \cdot kg^{-1}$ *iv* and neostigmine 0.04 $mg \cdot kg^{-1}$ *iv*, and then the trachea was extubated. The patients received, in a randomized, double-blind manner, a single *iv* dose of either granisetron (20, 40 and 60 $\mu g \cdot kg^{-1}$) or placebo (saline) immediately after emergence from general anaesthesia. If two or more episodes of vomiting occurred for 24 hr after anaesthesia, standard anti-emetic therapy (e.g., metoclopramide) was given. Postoperative analgesia was provided by indomethacin (50 mg, *pr*) for moderate pain and buprenorphine (0.2 mg, *im* or epidural) for severe pain as needed.

Postoperatively, episodes of nausea and vomiting experienced by each patient were recorded during the 24 hr after recovery from anaesthesia by direct questioning by other anaesthetists who did not know which anti-emetics patients had received. These were assessed by means of a nausea and vomiting score; 0 = no emetic symptoms, 1 = nausea, 2 = vomiting. Retching was not assessed as a separate entity, and patients who experienced retching were classified as nauseous. The details of any side effect experienced by the patients were also recorded throughout the study.

Patient demographic data were analyzed with one-way analysis of variance (ANOVA) and Student's t test. The scores of postoperative nausea and vomiting were compared with χ^2 test followed by Kruskal-Wallis test. A P value of < 0.05 was considered significant. All values were expressed as mean ± SD.

Results

Patient characteristics and surgical procedures were summarized in Table I. No difference existed among the four groups.

During the 24 hr after recovery from anaesthesia, the scores for postoperative nausea and vomiting in patients who had received granisetron 40 $\mu g \cdot kg^{-1}$ (0.2) and 60 $\mu g \cdot kg^{-1}$ (0.2) were lower than those who had received placebo (0.7) ($P < 0.05$). However, no difference in the scores were observed between patients who received placebo and granisetron 20 $\mu g \cdot kg^{-1}$ (0.6) Table II.

No additional anti-emetics were administered and no patients required buprenorphin postoperatively, whereas the frequency of use of indomethacin was approximately 30% in each group. No side effects considered to be related to the anti-emetics were reported.

Discussion

This study was designed to determine the optimal effective dose of granisetron for prevention of postoperative nausea

TABLE II Postoperative nausea and vomiting scores during the 24 h after anaesthesia

		No. of patients		
Group	*Mean score*	*Score 0*	*Score 1*	*Score 2*
Placebo ($n = 25$)	0.7	13	8	4
Granisetron				
- 20 $\mu g \cdot kg^{-1}$ ($n = 25$)	0.6	14	7	4
- 40 $\mu g \cdot kg^{-1}$ ($n = 25$)	0.2	22	2	1
- 60 $\mu g \cdot kg^{-1}$ ($n = 25$)	0.2	23	1	1

Scores scale: 0 = no emetic symptoms; 1 = nausea, 2 = vomiting.

and vomiting in patients undergoing major gynaecological surgery. The major findings were that during the 24 hr after recovery from anaesthesia, the anti-emetic efficacy of granisetron 40 $\mu g \cdot kg^{-1}$ and 60 $\mu g \cdot kg^{-1}$ was superior to that of granisetron 20 $\mu g \cdot kg^{-1}$ and placebo ($P < 0.05$), but there was no difference between granisetron 40 $\mu g \cdot kg^{-1}$ and 60 $\mu g \cdot kg^{-1}$.

The incidence of nausea and vomiting after gynaecological surgery performed under general anaesthesia varies considerably.[3] A number of factors including age, obesity, operative procedure, anaesthetic technique and postoperative pain are thought to increase the incidence of these postoperative symptoms. In this study, however, the treatment groups were similar for patient characteristics, surgical procedures, anaesthetics administered and analgesics used postoperatively. Therefore, the differences in the scores among the groups can be attributed to the differences in doses of granisetron administered.

The results of this study showed the effectiveness of granisetron 60 $\mu g \cdot kg^{-1}$ compared with placebo in the prevention of postoperative nausea and vomiting. This was in accordance with out previous study.[2]

Granisetron has already been proved to be an effective treatment for preventing emesis induced by cancer chemotherapy.[1] Our previous study provided evidence that it was also effective in reducing the incidence of these symptoms after surgery.[2] The exact mechanism of action of granisetron in preventing postoperative emesis is not known, but it has been suggested that its site of action is on the 5-HT_3 receptor with demonstrated anti-emetic effects.[4]

It has been reported that effective doses of granisetron are between 40 and 80 $\mu g \cdot kg^{-1}$ for the treatment of cancer therapy-induced emesis.[5] As previously demonstrated, granisetron 3 mg which approximated 60 $\mu g \cdot kg^{-1}$, reduced the occurrence of postoperative nausea and vomiting.[2] The present study also demonstrated that granisetron 40 $\mu g \cdot kg^{-1}$ was as effective as 60 $\mu g \cdot kg^{-1}$, and that both doses had potent anti-emetic effects compared with granisetron 20 $\mu g \cdot kg^{-1}$. Furthermore, there was no difference in efficacy between placebo and granisetron 20 $\mu g \cdot kg^{-1}$. This suggests that granisetron 40 $\mu g \cdot kg^{-1}$ can be regarded as the minimal appropriate dose in the prevention of postoperative nausea and vomiting.

It has been reported by Falkson *et al.*[6] that mild headache occurs in patients receiving granisetron to prevent chemotherapy-induced nausea and vomiting. In this study, however, no side effects, including headache, considered to be related to this agent were observed. This was in agreement with our previous study.[2] The reason for this difference is unknown, but may be attributed to the difference in patient characteristics. Therefore, on the basis of our results, the use of granisetron for preventing postoperative emesis appears to be safe.

In the present study, granisetron was administered upon emergence from general anaesthesia as described previously.[2] As the appropriate timing of administration of granisetron remains unclear, further studies are needed to elucidate the optimal timing for administering granisetron. Our hospital pharmacy pays 10,020 yen ($100 US) for 3 mg (approximately 60 $\mu g \cdot kg^{-1}$) of granisetron. The use of lower dose, 40 $\mu g \cdot kg^{-1}$, would decrease the cost of this drug.

In conclusion, this study suggests that granisetron 40 $\mu g \cdot kg^{-1}$ is the optimal effective dose to prevent postoperative nausea and vomiting, especially when the anaesthetic technique avoids opioids.

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