British Journal of Anaesthesia 1998; **80**: 764–766

Granisetron in the prevention of nausea and vomiting after middle-ear surgery: a dose-ranging study

Y. FUJII, H. TOYOOKA, H. TANAKA

Summary

This study was undertaken to determine the minimum effective dose of granisetron, a selective 5-hydroxytryptamine type 3 receptor antagonist, for the prevention of postoperative nausea and vomiting (PONV) after middle-ear surgery. In a randomized, double-blind, placebo-controlled trial, 120 women (ASA I) received placebo (saline) or granisetron at three different doses (20 $\mu g\,kg^{-1}$, 40 $\mu g\,kg^{-1}$, 100 $\mu g\,kg^{-1}$) i.v. immediately before the induction of anaesthesia ($n=30$ for each group). A standard general anaesthetic technique was used throughout. A complete response, defined as no PONV and no need for another rescue antiemetic during 0–3 h after anaesthesia, occurred in 40 %, 43 %, 83 % and 87 % of patients who had received placebo, granisetron 20 $\mu g\,kg^{-1}$, granisetron 40 $\mu g\,kg^{-1}$ or granisetron 100 $\mu g\,kg^{-1}$, respectively; the corresponding incidence during 3–21 h after anaesthesia was 47 %, 47 %, 87 % and 87 % ($P<0.05$, overall Fisher's exact probability test). Granisetron 40 $\mu g\,kg^{-1}$ appears to be the minimum effective dose for preventing PONV in women undergoing middle-ear surgery. (*Br. J. Anaesth.* 1998; **80**: 764–766)

Keywords: pharmacology granisetron; vomiting nausea antiemetics; surgery ear

The incidence of nausea and vomiting after middle-ear surgery varies from 62 % to 80 % with no antiemetic treatment.[1–3] Granisetron, like ondansetron, is a selective antagonist of the 5 hydroxytryptamine type 3 (5-HT_3) receptor, and is effective for the treatment of emesis in patients receiving cytotoxic drugs.[4] Granisetron has a more potent and longer activity than ondansetron against emesis associated with chemotherapy.[5] We have recently shown that it reduces the incidence of nausea and vomiting after middle-ear surgery.[6] The present study was undertaken to determine the minimum effective dose of granisetron for the prevention of postoperative nausea and vomiting (PONV), in a randomized, double-blind comparison with placebo, in women undergoing middle-ear surgery.

Patients and methods

After obtaining institutional review board approval and informed consent, we studied 120 female patients (ASA I, aged 25–60 yr) undergoing middle-ear surgery (tympanoplasty or mastoidectomy). Patients with gastrointestinal disease, those with a history of motion sickness or previous PONV or both, those who were pregnant or menstruating, or who had taken antiemetics within 24 h before surgery were excluded from the study.

Patients received no preanaesthetic medication and, in a randomised, double-blind manner, a single dose of placebo (saline) or granisetron at three different doses (20 $\mu g\,kg^{-1}$, 40 $\mu g\,kg^{-1}$, 100 $\mu g\,kg^{-1}$) i.v. over 2–5 min immediately before the induction of anaesthesia. Anaesthesia was induced with thiopentone 5 mg kg^{-1} i.v., and vecuronium 0.2 mg kg^{-1} i.v. was used to facilitate tracheal intubation. After tracheal intubation, anaesthesia was maintained with 1.0–3.0 % (inspired concentration) isoflurane and nitrous oxide 66 % (which was replaced by air before closing of the tympanic membrane) in oxygen. No patient received opioids before tracheal intubation or during the maintenance of anaesthesia. Ventilation was mechanically controlled and was adjusted to maintain an end-tidal concentration of carbon dioxide between 4.6 kPa and 5.2 kPa througout surgery with an anaesthetic/respiratory analyser (Ultima, Datex, Helsinki, Finland). Muscle relaxation was achieved with vecuronium and antagonized by a combination of atropine 0.02 mg kg^{-1} i.v. and neostigmine 0.04 mg kg^{-1} i.v. at the end of surgery. The trachea was extubated when the patient was awake. Placement of a nasal or oral gastric tube during surgery was not permitted. Rectal temperature was monitored and maintained at 37 ± 1 °C throughout surgery. If two or more episodes of vomiting occurred during the first 24 h after anaesthesia, a rescue antiemetic (for example, metoclopramide 0.2 mg kg^{-1}) was given. After operation, patients received indomethacin 50 mg as required when they complained of pain. After operation, all episodes of PONV (nausea, retching, vomiting) during the first 24 h after anaesthesia (that is, 0–3 h in the post-anaesthetic unit and 3–24 h in the ward) were recorded by nursing staff unaware of which treatment patients had received. A complete response was defined as no PONV and no need for a rescue

YOSHITAKA FUJII, MD, HIDENORI TOYOOKA, MD, Department of Anaesthesiology, University of Tsukuba Institute of Clinical Medicine, Tsukuba City, Ibaraki, Japan. HIROYOSHI TANAKA, MD, Department of Anaesthesiology, Toride Kyodo General Hospital, Toride City, Ibaraki, Japan. Accepted for publication: January 14, 1998.

Correspondence to: Yoshitaka Fujii, Department of Anaesthesiology, University of Tsukuba Institute of Clinical Medicine, 2–1–1, Amakubo, Tsukuba City, Ibaraki 305, Japan.

Table 1 Patient characteristics and surgical details. Values are mean (SD or range) or number. No significant differences

	Placebo ($n=30$)	Granisetron 20 μg kg^{-1} ($n=30$)	Granisetron 40 μg kg^{-1} ($n=30$)	Granisetron 100 μg kg^{-1} ($n=30$)
Age (yr)	44.6 (22–65)	43.8 (23–68)	44.0 (22–65)	42.0 (22–66)
Height (cm)	157.0 (6.8)	157.6 (7.0)	156.4 (5.5)	155.9 (6.3)
Weight (kg)	54.9 (7.3)	55.9 (6.6)	56.2 (8.2)	53.7 (8.0)
Duration of operation (min)	211.7 (38.1)	216.5 (43.1)	214.8 (38.1)	214.4 (39.9)
Duration of anaesthesia (min)	243.5 (40.4)	247.2 (44.9)	243.2 (38.2)	240.5 (39.2)
Indomethacin used postoperatively (*n*)	17	17	16	16
Types of operation performed (*n*)				
Tympanoplasty	23	22	22	22
Mastoidectomy	7	8	8	8

Table 2 Number (%) of patients having complete response (no PONV, no rescue antiemesis), and also nausea, retching, vomiting or requiring rescue antiemetic during the first 3 h (0–3 h) and the next 21 h (3–21 h) after anaesthesia. PONV = postoperative nausea and vomiting. *P* values *vs* placebo

	Placebo ($n=30$)	Granisetron 20 μg kg^{-1} ($n=30$)	*P*	Granisetron 40 μg kg^{-1} ($n=30$)	*P*	Granisetron 100 μg kg^{-1} ($n=30$)	*P*
0–3 h after anaesthesia							
Complete response (no PONV, no rescue antiemesis)	12 (40)	13 (43)	0.5	25 (83)	0.001	26 (87)	0.001
Nausea	9 (30)	8 (27)	0.5	3 (10)	0.052	3 (10)	0.052
Retching	1 (3)	2 (7)	0.5	0 (0)	0.5	1 (3)	1.0
Vomiting	8 (27)	7 (23)	0.5	2 (7)	0.04	1 (3)	0.013
Rescue antiemesis	6 (20)	5 (17)	0.5	0 (0)	0.012	0 (0)	0.012
3–24 h after anaesthesia							
Complete response (no PONV, no rescue antiemesis)	14 (47)	15 (50)	0.5	26 (87)	0.001	26 (87)	0.001
Nausea	7 (23)	7 (23)	1.0	2 (7)	0.073	2 (7)	0.073
Retching	1 (3)	1 (3)	1.0	0 (0)	0.5	1 (3)	1.0
Vomiting	8 (27)	7 (23)	0.5	2 (7)	0.04	1 (3)	0.013
Rescue antiemesis	5 (17)	5 (17)	1.0	0 (0)	0.026	0 (0)	0.026

Table 3 Adverse events. Values are number (%). No significant differences

	Placebo ($n=30$)	Granisetron 20 μg kg^{-1} ($n=30$)	Granisetron 40 μg kg^{-1} ($n=30$)	Granisetron 100 μg kg^{-1} ($n=30$)
0–3 h after anaesthesia				
Any adverse effects	6 (20)	6 (20)	5 (17)	5 (17)
Headache	2 (7)	2 (7)	2 (7)	2 (7)
Dizziness	2 (7)	2 (7)	2 (7)	2 (7)
Others (constipation, muscle pain)	2 (7)	2 (7)	1 (3)	1 (3)
3–24 h after anaesthesia				
Any adverse efects	6 (20)	5 (17)	5 (17)	6 (20)
Headache	3 (10)	2 (7)	2 (7)	3 (10)
Dizziness	2 (7)	2 (7)	2 (7)	2 (7)
Others (constipation, muscle pain)	1 (3)	1 (3)	1 (3)	1 (3)

antiemetic. Details of any adverse effects throughout the study were also recorded by a follow-up nurse who interviewed the patients.

Statistical analyses of data obtained were performed by one-way analysis of variance (ANOVA) with Bonferroni correction for multiple comparison, the chi-square test or Fisher's exact probability test, as appropriate. $P<0.05$ was considered significant. All values were expressed as mean (SD), median (ranges) or number (%). We set $\alpha=0.05$ and $\beta=0.8$, and used a large magnitude of effect (effective size 0.8) to estimate a sufficient sample size. The analysis showed that 30 patients per group would be sufficient.

Results

The treatment groups were comparable with regard to patient characteristics and types of operation (table 1).

During 0–3 h after anaesthesia, a complete response occurred in 12 of 30 patients (40 %) who had received placebo *vs* 13 of 30 patients (43 %) who had received granisetron 20 μg kg^{-1} ($P=0.5$), 25 of 30 (83 %) who had received granisetron 40 μg kg^{-1} ($P=0.001$), and 26 of 30 (87 %) who had received granisetron 100 μg kg^{-1} ($P=0.001$). During 3–24 h after anaesthesia, these data were 14 of 30 (47 %) with placebo *vs* 15 of 30 (50 %) with granisetron 20 μg kg^{-1} ($P=0.5$), 26 of 30 (87 %) with granisetron 40 μg kg^{-1} ($P=0.001$), and 26 of 30 (87 %) with granisetron 100 μg kg^{-1} ($P=0.001$) (table 2).

The most common adverse events in the four groups were headache and dizziness (table 3). There were no differences in the incidence of these events during the first 3 h and the next 21 h after anaesthesia among the treatment groups (that is, the incidence was 17–20 % in each group).

Discussion

Middle-ear surgery (tympanoplasty or mastoidectomy) is associated with a relatively high incidence of PONV.[1–3] Previous studies found the incidence of PONV to be between 62 % and 80 % in patients undergoing general anaesthesia for middle-ear

surgery.[1–3] The incidence of PONV (no complete response) in this study was approximately 60 % in patients who had received placebo, and was in accordance with our previous study in this population.[6]

The aetiology of PONV after middle-ear surgery is complex and depends on several factors, which include patient characteristics, types of surgery, anaesthetic technique and postoperative pain.[7] Patient-related factors are age, sex, obesity and a history of motion sickness or previous PONV or both. Surgical factors include an increased middle-ear pressure caused by nitrous oxide.[3] In the present study, however, the treatment groups were comparable with respect to patient characteristics, surgical procedure, anaesthetics administered and analgesics used after operation. In addition, no pressure was generated in the middle-ear from diffusion of nitrous oxide, which was replaced by air before closing of tympanic membrane. Therefore, the difference in the incidence of PONV among the groups can be attributed to the difference in dose of granisetron administered. Granisetron has been reported to be effective for the treatment of emesis induced by cancer chemotherapy.[4] In previous studies we have demonstrated that granisetron 40 $\mu g\ kg^{-1}$ reduces the incidence of PONV after middle-ear surgery and gynaecological surgery.[6,8]

For the treatment of emesis induced by cancer therapy, the effective dose of granisetron is between 40 $\mu g\ kg^{-1}$ and 80 $\mu g\ kg^{-1}$.[9] We demonstrated in the present study that granisetron 40 $\mu g\ kg^{-1}$ was as effective as granisetron 100 $\mu g\ kg^{-1}$ in the prevention of PONV, and that antiemetic efficacy of each dose was superior to that of placebo during the periods 0–3 h and 3–24 h ($P = 0.001$). No difference in a complete response (no PONV, no rescue) was observed between patients who had received placebo and those who had received granisetron 20 $\mu g\ kg^{-1}$. These results suggest that granisetron 40 $\mu g\ kg^{-1}$ is the minimum effective dose for the prevention of PONV after middle-ear surgery. Adverse events observed in this study were relatively mild, and there was no difference in the incidence of adverse effects, such as headache and dizziness, among the four groups.

The use of new antiemetics (for example, 5-HT_3 receptor antagonists) has been recently criticized because of its high cost.[10] Our hospital pharmacy pays $103 for granisetron 3 mg, and the drug is much more expensive than other antiemetics (for example, $1.8 for droperidol 2.5 ma, $0.6 for metoclopramide 10 mg). However, use of these cheaper antiemetics has been limited because of their side effects, which include excessive sedation and extra pyramidal symptoms.[7] Furthermore, on the basis of our results, the use of a lower dose (40 $\mu g\ kg^{-1}$) would reduce the cost of granisetron. In conclusion, granisetron 40 $\mu g\ kg^{-1}$ is an effective antiemetic for the prevention of PONV after middle-ear surgery. Increasing the dose to 100 $\mu g\ kg^{-1}$ provides no demonstrable benefit in reducing the incidence of PONV.

References

1. Honkavaara P, Saarinvaara L, Klemola U-K. Prevention of nausea and vomiting with transdermal hyocine in adults after middle ear surgery during general anaesthesia. *British Journal of Anaesthesia* 1994; **73**: 763–766.
2. Honkavaara P. Effect of ondansetron on nausea and vomiting after middle ear surgery during general anaesthesia. *British Journal of Anaesthesia* 1996; **76**: 316–318.
3. Reinhart DJ, Klein KW, Schroff E. Transdermal scopolamine for the reduction of postoperative nausea in outpatient ear surgery: a double-blind, randomized study. *Anaesthesia and Analgesia* 1994; **79**: 281–284.
4. Bermudez J, Boyle EA, Minter WD, Sanger GJ. The antiemetic potential of the 5-hydroxytryptamine, receptor antagonist BRL 43694. *British Journal of Cancer* 1988; **58**: 644–650.
5. Andrews PLR, Bhandari P, Davey PT, Bingham S, Marr HE, Blower PR. Are all $5HT_3$ receptor antagonists the same? *European Journal of Cancer* 1992; **28**: S2–S6.
6. Fujii Y, Toyooka H, Tanaka H. Granisetron reduces the incidence of nausea and vomiting following middle ear surgery. *British Journal of Anaesthesia* 1997; **79**: 539–540.
7. Watcha MF, White PF. Postoperative nausea and vomiting. Its etiology, treatment, and prevention. *Anesthesiology* 1992; **77**: 162–184.
8. Fujii Y, Tanaka H, Toyooka H. Reduction of postoperative nausea and vomiting with granisetron. *Canadian Journal of Anaesthesia* 1994; **41**: 291–294.
9. Furue H, Oota K, Taguchi T, Niitani H. Clinical evaluation of granisetron against nausea and vomiting induced by anticancer drugs: optimal dose-finding study. *Journal of Clinical Therapy and Medicine* 1990; **6**: 49–61.
10. White PF, Watcha MF. Are new drugs cost-effective for patients undergoing ambulatory surgery? *Anesthesiology* 1993; **78**: 2–5.