

Prophylactic antiemetic therapy with granisetron in women undergoing thyroidectomy

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Summary

We have evaluated the efficacy and safety of granisetron, a selective 5-hydroxytryptamine type-3 receptor antagonist, for the prevention of postoperative nausea and vomiting (PONV) in women undergoing thyroidectomy. In a prospective, randomized, placebo-controlled, double-blind study, 100 ASA I patients, aged 30–57 yr, received placebo or granisetron at three different doses (20, 40 or 100 $\mu\text{g kg}^{-1}$) ($n=25$ each), i.v., immediately before induction of anaesthesia. A standard general anaesthetic technique was used. A complete response, defined as no PONV and no need for another rescue antiemetic during the first 3 h after anaesthesia, was seen in 36%, 44%, 92% and 92% of patients who received placebo, granisetron 20 $\mu\text{g kg}^{-1}$, 40 $\mu\text{g kg}^{-1}$ and 100 $\mu\text{g kg}^{-1}$, respectively; corresponding values during the next 21 h after anaesthesia were 40%, 44%, 88% and 88% ($P<0.05$; overall Fisher's exact probability test). There were no clinically important adverse events in any group. We conclude that granisetron 40 $\mu\text{g kg}^{-1}$ was an effective antiemetic for the prevention of PONV after thyroidectomy. Increasing the dose to 100 $\mu\text{g kg}^{-1}$ provided no further benefit. (*Br. J. Anaesth.* 1998; 81: 526–528).

Keywords: vomiting, nausea; vomiting, antiemetics; vomiting, nausea, surgical factors; pharmacology, granisetron; surgery, thyroidectomy

Postoperative nausea and vomiting (PONV) are common and unpleasant complications after surgery performed under general anaesthesia.¹ The reported incidence of PONV in patients undergoing thyroidectomy is 60–65% when no prophylactic antiemetic is given.^{2,3} Most of the currently used antiemetics, antihistamines (e.g. hydroxyzine), butyrophenones (e.g. droperidol) and dopamine receptor antagonists (e.g. metoclopramide) have undesirable adverse effects, such as excessive sedation, hypotension, dry mouth, dysphoria, restlessness and extrapyramidal symptoms.¹ Granisetron, in common with ondansetron, is a selective antagonist of the 5-hydroxytryptamine type-3 (5-HT₃) receptor, and is also effective for the treatment of emesis in patients receiving cytotoxic drugs.⁴

Granisetron has a more potent and longer acting activity against cisplatin-induced emesis than ondansetron.⁵ We have demonstrated recently that it

reduces the incidence of PONV after gynaecological surgery.^{6,7} We conducted a prospective, randomized, placebo-controlled, double-blind study to evaluate the efficacy and safety of granisetron for the prevention of PONV in women undergoing general anaesthesia for thyroidectomy.

Patients and methods

After obtaining approval from the Institutional Review Board and informed consent, we studied 100 ASA I female patients, aged 30–57 yr, undergoing general anaesthesia for thyroidectomy. Patients who had gastrointestinal disease, those who had a history of motion sickness or previous PONV, or both, those who were menstruating, or those who had received antiemetic medication within 24 h before surgery were excluded.

Patients were allocated randomly to one of four groups ($n=25$ for each) to receive placebo or granisetron 20, 40 or 100 $\mu\text{g kg}^{-1}$ i.v. before induction of anaesthesia according to a randomization list generated by a random number function in a computer spreadsheet. According to this list, identical syringes containing each drug were prepared by personnel not involved in the study.

Premedication comprised diazepam 5 mg orally, 60 min before induction of anaesthesia. Anaesthesia was induced with thiopental (thiopentone) 5 mg kg^{-1} i.v. and fentanyl 2 $\mu\text{g kg}^{-1}$ 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 66% nitrous oxide in oxygen, with controlled ventilation adjusted to maintain an end-tidal concentration of carbon dioxide of 4.2–5.3 kPa. Neuromuscular block was achieved with vecuronium, as required. At cessation of surgery, atropine 0.02 mg kg^{-1} i.v. and neostigmine 0.04 mg kg^{-1} i.v. were administered for antagonism of neuromuscular block, and the trachea was extubated. Rectal temperature was monitored and maintained at $37\pm1^\circ\text{C}$ using hot water warming pads. If two or more episodes of PONV occurred during the first

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Table 1 Patient characteristics, surgical and anaesthetic details, and postoperative analgesia, (mean (SD or range) or number). Patients who had experienced the menopause were excluded. No significant differences

	Placebo (n = 25)	20 µg kg ⁻¹ (n = 25)	40 µg kg ⁻¹ (n = 25)	100 µg kg ⁻¹ (n = 25)
Age(yr)	46.3(31–57)	47.2(30–57)	45.3(31–57)	46.0(30–57)
Height(cm)	156.7(6.4)	157.2(7.0)	157.5(7.4)	156.7(7.7)
Weight(kg)	52.3(5.0)	55.8(7.7)	52.6(6.5)	55.2(10.7)
Last menstrual cycle(days)[n]	15.3(3.2)[17]	16.2(2.9)[16]	16.1(3.6)[17]	15.4(3.8)[16]
Duration of operation(min)	142.9(47.4)	151.5(38.9)	146.6(38.0)	140.0(41.4)
Duration of anaesthesia(min)	178.1(54.3)	179.8(37.4)	175.8(40.7)	170.8(41.0)
Clinical status				
Euthyroidism(n)	20	21	20	20
Hyperthyroidism treated(n)	5	4	5	5
Postoperative analgesia				
Indomethacin(n)	15	15	16	15
Buprenorphine(n)	5	4	4	5

Table 2 Number (%) of patients with a complete response (no PONV, no rescue), nausea, retching or vomiting and those who required rescue antiemetic during the first 3 h (0–3 h) and the next 21 h (3–21 h) after anaesthesia. P values vs Placebo

	Placebo (n = 25)	20 µg kg ⁻¹ P(n = 25)	40 µg kg ⁻¹ P(n = 25)	100 µg kg ⁻¹ P(n = 25)	P
0–3 h after anaesthesia					
Complete response	9(36%)	11(44%)	0.387 23(92%)	0.001 23(92%)	0.001
Vomiting	8(32%)	6(24%)	0.377 1(4%)	0.012 1(4%)	0.012
Retching	2(8%)	1(4%)	0.5 0(0%)	0.245 0(0%)	0.245
Nausea	8(32%)	8(32%)	1.0 2(8%)	0.037 2(8%)	0.037
Rescue	7(28%)	5(20%)	0.371 0(0%)	0.048 0(0%)	0.048
3–24 h after anaesthesia					
Complete response	10(40%)	11(44%)	0.5 22(88%)	0.001 22(88%)	0.001
Vomiting	7(28%)	6(24%)	0.5 1(4%)	0.024 1(4%)	0.024
Retching	2(8%)	2(8%)	1.0 1(4%)	0.5 1(4%)	0.5
Nausea	8(32%)	7(28%)	0.5 2(8%)	0.037 2(8%)	0.037
Rescue	7(28%)	5(20%)	0.371 0(0%)	0.048 0(0%)	0.048

24 h after anaesthesia, another rescue antiemetic (e.g. metoclopramide) was given. Postoperative analgesia was provided with indomethacin 50 mg, as required, for moderate pain, and buprenorphine 0.2 mg i.m. for severe pain.

All episodes of PONV (nausea, retching and vomiting) were recorded during the first 24 h after anaesthesia (i.e. 0–3 h in the post-anaesthesia unit and 3–24 h in the ward) by direct questioning by specifically trained nurses without knowledge of which drugs the patients had received, or by spontaneous complaint by the patients. The nurses asked the patients if retching or vomiting had occurred and if they felt nauseated, with only two possible answers (yes/no). Nausea was defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit; retching was defined as the laboured, spasmodic, rhythmic contractions of the respiratory muscles; vomiting was defined as the forceful expulsion of gastric contents from the mouth.¹ Complete response (i.e. emesis-free) was defined as no PONV and no need for rescue antiemetic medication. Details of other adverse events throughout the study were recorded by follow-up nurses who interviewed the patients and recorded spontaneous complaints.

Statistical analyses of the data between the treatment groups were performed by ANOVA with Bonferroni correction for multiple comparison, chi-square test or Fisher's exact probability test, as appropriate. *P* < 0.05 was considered significant. All values are expressed as

mean (SD, range) or number (%). Twenty-five patients per group were sufficient to detect a difference with *a* = 0.05 and power (1–*β*) = 0.8.

Results

Patient characteristics and details of anaesthesia are summarized in table 1. There were no significant differences between groups.

A complete response 0–3 h after anaesthesia was seen in 36% of patients who received placebo, 44% with granisetron 20 µg kg⁻¹, 92% with granisetron 40 µg kg⁻¹ and 92% with granisetron 100 µg kg⁻¹; corresponding values for 3–24 h after anaesthesia were 40%, 44%, 88% and 88%. Thus significantly more patients had a complete response within the first 24 h after anaesthesia in the granisetron 40 µg kg⁻¹ and 100 µg kg⁻¹ groups compared with placebo (*P* < 0.05). There was no difference between placebo and granisetron 20 µg kg⁻¹ (table 2).

Seven of 25 patients who had received placebo and five of those who had received granisetron 20 µg kg⁻¹ required rescue antiemetic for severe PONV during the first 3 h and the next 21 h after anaesthesia (i.e. two or more episodes of PONV), compared with none who received granisetron 40 µg kg⁻¹ or 100 µg kg⁻¹ (*P* < 0.05) (table 2).

The most common adverse events were headache and dizziness, which were relatively mild. There were no differences in the incidence of adverse effects (table 3).

Table 3 Adverse events. Values are number (%). There were no significant differences

	Placebo (n = 25)	20 µg kg ⁻¹ (n = 25)	40 µg kg ⁻¹ (n = 25)	100 µg kg ⁻¹ (n = 25)
0–3 h after anaesthesia				
Any adverse effects	5(20%)	4(16%)	4(16%)	5(20%)
Headache	2(8%)	2(8%)	2(8%)	2(8%)
Dizziness	2(8%)	1(4%)	1(4%)	2(8%)
Others(constipation, muscle pain)	1(4%)	1(4%)	1(4%)	1(4%)
3–24 h after anaesthesia				
Any adverse effects	4(16%)	4(16%)	4(16%)	4(16%)
Headache	2(8%)	2(8%)	2(8%)	2(8%)
Dizziness	1(4%)	1(4%)	1(4%)	1(4%)
Others (constipation, muscle pain)	1(4%)	1(4%)	1(4%)	1(4%)

Discussion

Postoperative nausea and vomiting (PONV) are distressing side effects of anaesthesia and surgery, with a high incidence after thyroidectomy.^{2,3} The aetiology of PONV remains unclear, but is probably related to several factors, including age and sex of the patient (mostly middle-aged women), and intense peroperative vagal stimulation (surgical handling of neck structures).³ Several factors, including obesity, anaesthetic technique and postoperative pain, are considered to increase the incidence of PONV.¹ However, in our study the groups were similar in patient characteristics, surgical procedure, anaesthetic administered and analgesics used after operation. Therefore, the difference in complete response can be attributed to the study drug.

We found a high incidence of PONV during the first 24 h after anaesthesia (64% for 0–3 h after anaesthesia and 60% for 3–24 h after anaesthesia) in patients who had received placebo. This is comparable with an incidence of nearly 60% reported previously.^{2,3}

Granisetron has already been reported to be effective for the treatment of vomiting in patients receiving cytotoxic drugs.⁴ It has also been reported that granisetron is effective in the prevention of PONV after gynaecological surgery.^{6,7} We have demonstrated that there was a complete response (no PONV, no rescue) in significantly more patients who received granisetron 40 µg kg⁻¹ or 100 µg kg⁻¹ compared with those who had received placebo. The exact mechanism of granisetron in preventing PONV is not known, but it has been suggested that it may act on sites containing 5-HT₃ receptors with demonstrated antiemetic effects.⁸

The effective dose of granisetron is between 40 and 80 µg kg⁻¹ for the treatment of cancer therapy-induced emesis.⁹ We could find no report to determine the minimum effective dose for the prevention of PONV in patients undergoing thyroidectomy. We have demonstrated that the efficacy of granisetron 40 µg kg⁻¹ was similar to that of 100 µg kg⁻¹ for the prevention of PONV, and that there was no difference between placebo and granisetron 20 µg kg⁻¹. In

addition, the severity of PONV was also reduced with granisetron 40 or 100 µg kg⁻¹, as no patient required rescue medication for the treatment of two or more episodes of PONV, compared with several patients who received placebo or granisetron 20 µg kg⁻¹. These data suggest that granisetron in a minimum dose of 40 µg kg⁻¹ was effective for the prevention of PONV after thyroidectomy.

The most frequent adverse events were headache and dizziness but there were no differences in the incidence of these symptoms between groups.

In summary, granisetron 40 µg kg⁻¹ was an effective antiemetic for the prevention of PONV in female patients undergoing thyroidectomy. Increasing the dose to 100 µg kg⁻¹ provided no further benefit.

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