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Prophylactic antiemetic therapy with a combination of granisetron and dexamethasone in patients undergoing middle ear surgery

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Summary

We have compared the efficacy of granisetron in combination with dexamethasone with each drug alone in the prevention of postoperative nausea and vomiting (PONV) after middle ear surgery. In a randomized, double-blind study, 120 patients (85 females) received granisetron 3 mg, dexamethasone 8 mg or granisetron 3 mg with dexamethasone 8 mg i.v. ($n=40$ in each group), immediately before induction of anaesthesia. A standardized 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 recorded in 83%, 50% and 98% of patients who had received granisetron, dexamethasone and granisetron–dexamethasone, respectively. The corresponding incidences during the next 21 h after anaesthesia were 80%, 55% and 98% ($P<0.05$; overall Fisher's exact probability test). In summary, prophylactic use of combined granisetron and dexamethasone was more effective than each antiemetic alone for the prevention of PONV after middle ear surgery. (*Br. J. Anaesth*. 1998; **81**: 754–756).

Keywords: vomiting, nausea; vomiting, antiemetics, granisetron; vomiting, antiemetics, dexamethasone; surgery, otolaryngological

Postoperative nausea and vomiting (PONV) occur frequently after middle ear surgery, with incidences as high as 80% when no prophylactic antiemetic is given.[1–3] We have demonstrated recently that granisetron, a selective 5-hydroxytrypatamine type 3 (5-HT_3) receptor antagonist, reduces the incidence of PONV in patients undergoing general anaesthesia for middle ear surgery.[4] However, this antiemetic cannot entirely control PONV after middle ear surgery. Dexamethasone has been used as an antiemetic in patients receiving chemotherapy, with limited side effects,[5] and has also been reported to decrease chemotherapy-induced emesis when added to an antiemetic regimen.[6] In this study, we have compared the efficacy of granisetron with dexamethasone with each antiemetic alone for the prevention of PONV in patients undergoing middle ear surgery.

Patients and methods

After obtaining approval from the Institutional Review Board and informed consent, we studied 120 ASA I patients (85 females), aged 25–60 yr, undergoing middle ear surgery (tympanoplasty or mastoidectomy). Patients with gastrointestinal diseases, those who had received any antiemetic medication within 24 h before surgery, and those who were pregnant or menstruating were excluded.

Patients were allocated randomly to receive one of three treatment regimens ($n=40$ each): granisetron 3 mg, dexamethasone 8 mg or granisetron 3 mg with dexamethasone 8 mg. The drugs were administered i.v. immediately before induction of anaesthesia. A randomization list was prepared by a random number function in a computer spreadsheet and indentical syringes containing each drug were prepared by personnel not involved in the study.

Patients received no preanaesthetic medication. Anaesthesia was induced with thiopental 5 mg kg^{-1} and fentanyl 2 μg kg^{-1} i.v., and vecuronium 0.2 mg kg^{-1} i.v. was used to facilitate tracheal intubation. Anaesthesia was maintained with 1.0–3.0% isoflurane (inspired concentration) and 66% nitrous oxide (which was replaced by air before closing the tympanic membrane) in oxygen. Ventilation was controlled mechanically and adjusted to maintain end-tidal carbon dioxide concentration at 4.6–5.2 kPa throughout surgery using an anaesthetic–respiratory analyser (Ultima, Datex, Helsinki, Finland). Patients were not given opioids during surgery. A nasogastric tube was inserted and suction applied to empty the stomach of air and other contents. Before tracheal extubation, the nasogastric tube was again suctioned and removed. Neuromuscular block was achieved with vecuronium and antagonized by 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. 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, rescue antiemetic (e.g. metoclopramide 0.2 mg kg^{-1}) was given. After operation, patients received indomethacin 50 mg rectally if they complained of moderate to severe pain.

During the first 24 h after anaesthesia (i.e. 0–3 h in the post-anaesthetic unit and 3–24 h on the ward), all episodes of PONV (nausea, retching, vomiting) were recorded every 3 h by blinded nursing staff. The nurses asked the patients if retching or vomiting had

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Table 1 Patient characteristics (mean (SD or range) or number). Combination = Granisetron with dexamethasone. No significant differences

	Granisetron ($n=40$)	Dexamethasone ($n=40$)	Combination ($n=40$)
Age (yr)	45 (25–60)	42 (25–60)	44 (25–60)
Sex (F/M)	29/11	28/12	28/12
Height (cm)	158 (8)	159 (8)	158 (7)
Weight (kg)	56 (8)	56 (8)	58 (8)
History of motion sickness (*n*)	3	3	3
History of previous PONV (*n*)	2	2	2
Duration of operation (min)	217 (40)	214 (42)	218 (39)
Duration of anaesthesia (min)	247 (40)	243 (44)	247 (41)
Indomethacin used after operation (*n*)	22	23	22
Types of operation performed (*n*)			
Tympanoplasty	30	30	29
Mastoidectomy	10	10	11

occurred and if they felt nauseated, with only two possible answers (yes/no). Nausea was defined as the unpleasant sensation associated with awareness of the urge to vomit; retching was defined as laboured, spasmodic, rhythmic contraction of the respiratory muscles without expulsion of gastric contents; and vomiting was defined as the forceful expulsion of gastric contents from the mouth.[7] A complete response was defined as no PONV and no need for rescue antiemetic medication. Details of adverse events throughout the study were recorded by follow-up nurses who asked patients general questions and also recorded spontaneous complaints.

Statistical analysis was by ANOVA with Bonferroni correction for multiple comparison, chi-square test or Fisher's exact probability test, as appropriate (Stat View 4.0; Macintosh). $P<0.05$ was considered significant. All values are expressed as mean (SD, range) or number (%). We set $\alpha=0.05$ and $\beta=0.2$, and used a large magnitude of effects (effective size 0.8) to estimate a sufficient sample size. The analysis showed that 40 patients per treatment group would be sufficient.

Results

Patient characteristics and surgical procedures were similar in each group (table 1).

A complete response during the first 3 h (0–3 h) after anaesthesia was recorded in 83%, 50% and 98% of patients who had received granisetron, dexamethasone and granisetron–dexamethasone, respectively. The incidences during the next 21 h (3–24 h) after anaesthesia were 80%, 55% and 98%, respectively. Thus a complete response within the first 24 h after anaesthesia was achieved significantly more often in patients who had received a combination of granisetron and dexamethasone than in those who had received granisetron or dexamethasone alone (table 2).

The most frequently reported adverse events were headache and dizziness, but there were no differences between groups (table 3).

Discussion

Postoperative nausea and vomiting (PONV) are among the most common complications after anaesthesia and surgery, with a relatively high incidence after middle ear surgery (tympanoplasty or mastoidectomy).[1–3] Our previous study found that the incidence of PONV was as high as 60% in patients undergoing general anaesthesia for middle ear surgery.[4,8] This incidence may justify the use of prophylactic antiemetics for the prevention of PONV after middle ear surgery.

The aetiology of PONV after middle ear surgery performed under general anaesthesia is not known, but is probably multifactorial.[7] Several factors, including age, sex, obesity, history of motion sickness and/or previous PONV, menstruation, surgical procedure, anaesthetic technique and postoperative pain are considered to affect the incidence of PONV. In this study, however, these factors were well balanced between groups. An increased middle ear pressure by nitrous oxide is also one of the surgical factors contributing to PONV.[3] As middle ear pressure was measured in this study, no pressure was generated in the middle ear from diffusion of nitrous oxide, which was replaced by air before closing the tympanic membrane. Therefore, the difference in complete response between the groups may be attributed to differences in the antiemetic drugs administered.

We have demonstrated recently that granisetron 40 $\mu g\ kg^{-1}$ reduced the incidence of PONV in patients undergoing middle ear surgery,[3] and also that the efficacy of granisetron 40 $\mu g\ kg^{-1}$ was similar to that of granisetron 100 $\mu g\ kg^{-1}$ for the prevention of PONV in this population.[8] The dose chosen for this study was 3 mg (approximately 55 $\mu g\ kg^{-1}$). It has been reported that dexamethasone 8 mg decreased chemotherapy-induced emesis when added to an antiemetic regimen.[6] Therefore, in this study, the same dose of dexamethasone was added to granisetron 3 mg.

The precise mechanism of action of granisetron–dexamethasone in the augmentation of a complete response remains unclear, but granisetron antagonizes 5-HT_3 receptors in sites associated with antiemetic activity[9] and dexamethasone may also inhibit stimulation of 5-HT_3 receptors.[10] Dexamethasone did not increase the incidence of adverse events when added to granisetron.

We conclude that prophylactic therapy with a combination of granisetron and dexamethasone was more effective than each antiemetic alone for the prevention of PONV after middle ear surgery. This suggests that dexamethasone may be used as a

Table 2 Number (%) of patients with a complete response (no PONV, no rescue) and incidence of nausea, retching, vomiting and rescue antiemetic during the first 3 h (0–3 h) and the next 21 h (3–21 h) after anaesthesia. Combination = granisetron with dexamethsaone; P_1 values = granisetron vs dexamethasone; P_2 values = granisetron vs combination; and P_3 values = dexamethasone vs combination

	Granisetron ($n=40$)	Dexamethasone ($n=40$)	Combination ($n=40$)	P_1	P_2	P_3
0–3 h after anaesthesia						
Complete response (no PONV, no rescue)	33(83%)	20(50%)	39(98%)	0.002	0.028	0.001
Nausea	4(10%)	10(25%)	1(3%)	0.069	0.179	0.003
Retching	1(3%)	2(5%)	0(0%)	0.5	0.5	0.247
Vomiting	3(8%)	10(25%)	1(3%)	0.033	0.308	0.003
Rescue	0(0%)	5(13%)	0(0%)	0.027	1.0	0.027
3–24 h after anaesthesia						
Complete response (no PONV, no rescue)	32(80%)	22(55%)	39(98%)	0.015	0.014	0.001
Nausea	4(10%	9(23%)	1(3%)	0.112	0.179	0.007
Retching	2(5%)	2(5%)	0(0%)	1.0	0.247	0.247
Vomiting	3(8%)	9(23%)	1(3%)	0.057	0.308	0.007
Rescue	0(0%)	5(13%)	0(0%)	0.027	1.0	0.027

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

	Granisetron ($n=40$)	Dexamethasone ($n=40$)	Combination ($n=40$)
0–3 h after anaesthesia			
Headache	3(8%)	3(8%)	3(8%)
Dizziness	2(5%)	2(5%)	2(5%)
Others(constipation, muscle pain)	2(5%)	1(3%)	2(5%)
3–24 h after anaesthesia			
Headache	3(8%)	3(8%)	3(8%)
Dizziness	2(5%)	2(5%)	2(5%)
Others (constipation, muscle pain)	1(3%)	1(3%)	1(3%)

component of combined prophylaxis for the control of PONV in patients undergoing other surgical procedures.

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