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Premedication with H_1 and H_2 blocking agents reduces the incidence of postoperative nausea and vomiting

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Abstract. *Objective:* Patients undergoing anaesthesia and surgery frequently complain about postoperative nausea and vomiting (PONV). Whether pretreatment with H_1 and H_2 blocking agents reduces the incidence of PONV remains controversial. To answer this question, we performed a randomised, prospective, placebo-controlled clinical study to evaluate the efficacy of a premedication with H_1 and H_2 receptor antagonists.
Material and subjects: 1149 patients (both sexes) undergoing surgery were randomly assigned to three treatment groups and one control group.
Patients in the treatment groups were premedicated with the following H_1 + H_2 receptor antagonists:

- Group 1 (n = 335): 5 mg/kg cimetidine i.v. + 0.1 mg/kg dimetindene i.v.
  20 min before induction of anaesthesia
- Group 2 (n = 337): 1.25 mg/kg ranitidine i.v. + 0.1 mg/kg dimetindene i.v.
  20 min before induction of anaesthesia
- Group 3 (n = 316): 300 mg ranitidine p.o. + 0.1 mg/kg dimetindene i.v.
  1 to 2 h before induction of anaesthesia
- Group 4 (n = 161): 20 ml saline solution i.v.
  20 min before induction of anaesthesia

Patients from the treatment groups 1, 2 and 3 received regional or general anaesthesia depending on the clinical decision. All control patients received general anaesthesia consisting of fentanyl, a thiobarbiturate, enflurane, nitrous oxide, oxygen, and vecuronium.
Results: The incidence of nausea and vomiting was 8.5%, 6.8% and 5.4% in patients from the treatment groups (1, 2 and 3) who underwent general anaesthesia (n = 545), with no statistically significant differences between groups. The incidence of nausea and vomiting in the control group (n = 161) was 28.3% (nausea) and 27.5% (vomiting), respectively. In patients who underwent regional anaesthesia (n = 443), the incidence of nausea and vomiting was 2.5% and 1.1%, respectively.
Conclusions: Premedication with H_1 and H_2 blocking agents significantly reduces the incidence of postoperative nausea and vomiting.

Key words: Antihistamines – Ranitidine – Cimetidine – Nausea – Vomiting – General anaesthesia

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Introduction

Prior to surgery, many patients worry about postoperative nausea and vomiting (PONV) [1, 2]. Nausea and vomiting in the post-operative phase (PONV) are the most frequent side effects of anaesthesia with an incidence of 20–30% [2–4]. PONV is therefore described as the 'big little problem' of anaesthesia [5]. PONV is unpleasant for the patient and has negative effects on the patient's satisfaction. Indeed when patients are asked about their preferences for the immediate postoperative period, the first choice is no nausea or vomiting, this is above freedom from pain or any other postoperative complications [2, 6]. Major medical complications caused by aspiration, ruptured sutures, liquid and electrolyte-imbalance in children and deaths from 'Boerhaave syndrome' although described in the literature are relatively rare [7]. Thus a safe and effective treatment to prevent PONV would benefit patients. Indeed patients would even pay the costs from their own pockets for a guaranteed PONV free anaesthesia [2, 8].

The aetiology of PONV is complex and multifactorial. Several patient-, anaesthesia- and surgery-related factors are known to influence an individual's risk of PONV [2, 9–11]. There are at least four different types of pharmacological receptors, which are involved in the process of vomiting. Drugs that are presently used for prophylaxis and/or treatment of PONV can be classified with respect to their sites of action and include dopaminergic, histaminergic, muscarinic

The efficacy of the combined use of H_1- and H_2-receptor antagonists for prevention of PONV was previously demonstrated and suggested a role for histamine in the pathogenesis of PONV [16, 17]. More recently, cyclizine (H_1 receptor antagonist) proved to be at least as effective as ondansetron in preventing PONV after gynaecological laparoscopy and was even superior to ondansetron concerning the use of rescue antiemetics in patients undergoing diagnostic laparoscopy [18]. A recently published study investigating changes in the mediator levels of histamine and serotonin metabolites after gynaecological laparoscopy demonstrate an association between these changes in mediator levels and PONV [19, 20]. In accordance with these results, a recently published metaanalysis showed that dimenhydrinate, another H_1 antagonist with some antimuscarinic activity, has a similar efficacy with respect to the prophylaxis of PONV when compared to more common antiemetics such as $5HT_3$ antagonists and droperidol [2, 21].

The aim of our study was to compare the potential of two H_2-receptor antagonists, cimetidine and ranitidine, each in combination with the H_1-receptor antagonist dimetindene, in preventing postoperative nausea and vomiting.

Patients and methods

After ethical approval and with written informed consent from each patient, patients were recruited at the University Hospital Munich for this open, prospective, randomised, placebo-controlled clinical study.

Study design

Patients undergoing surgery from different disciplines (general surgery, orthopaedic surgery and urology) were randomly assigned to either one of three treatment groups or the placebo group. Exclusion criteria for study participation were: age <18 years; pregnancy or lactation; emergency patient; allergy or intolerance to study medication; intake of study medication prior to study participation; oral administration of study medication not possible; planned discharge during observation period; operation outside normal h.

Course for the individual patient

Patients in the treatment groups received either general or regional anaesthesia, depending on the clinical decision. All patients in the control group received general anaesthesia (Table 1).

Induction of general anaesthesia consisted of thiopental, fentanyl, and vecuronium followed by nitrous oxide/oxygen and enflurane. Nausea and vomiting were documented after surgery with a patient-completed questionnaire indicating 'present' or 'none' over a time period of 24 h after operation (observation period). Patients with severe postoperative nausea and vomiting were treated with a rescue medication consisting of 10 mg metoclopramide.

Patients in the four study groups were premedicated with the following $H_1 + H_2$ receptor antagonist combinations or placebo (saline):

- Group 1 (n = 335): 5 mg/kg cimetidine i. v. + 0.1 mg/kg dimetindene i. v.
  20 min before induction of anaesthesia
- Group 2 (n = 337): 1.25 mg/kg ranitidine i. v. + 0.1 mg/kg dimetindene i. v.
  20 min before induction of anaesthesia
- Group 3 (n = 316): 300 mg ranitidine p. o. + 0.1 mg/kg dimetindene i. v.
  1 to 2 h before induction of anaesthesia
- Group 4 (n = 161): 20 ml saline solution i. v.
  20 min before induction of anaesthesia

Statistical analysis

Data are presented as number or the mean (range). Comparisons of mean values between the groups were performed using the Kruskal-Wallis test. Incidences (frequencies, rates) were compared using Chi^2-test. Treatment differences were considered significant at $p \leq 0.05$.

Results

Of 1438 patients enrolled in this study, 1149 were included in the analysis of efficacy (Table 1). Of the 289 patients excluded from the statistical evaluation, surgery had to be rescheduled in 172 patients because of incoming emergency cases. In 38 patients, surgery was delayed for more than 2 h after premedication; 5 patients allocated to group 3 had not received oral ranitidine according to the protocol; and 66 patients withdrew consent to participate in the study before induction of anaesthesia.

The patients enrolled in this study belonged to the following ASA physical status groups: I (21.8%), II (37.8%), III (35.5%) and IV (4.9%). There were no statistically significant differences between the four groups in terms of ASA classification of physical status, age (mean 42 y), height (mean 171 cm), weight (mean 71 kg), or gender (approx. 65% male/35% female in all groups). There were no significant demographic differences between patients who completed the study and those who did not.

Table 1. Premedication with H1/H2 blocking agents. Subjects enrolled in the study.

	Group 1	Group 2	Group 3	Group 4	Total
Premedication	Cim/Dim i. v.	Ran/Dim i. v.	Ran/Dim p. o.	Saline	
General anaesthesia	181	197	167	161	706
Regional anaesthesia	154	140	149		443
Total	335	337	316	161	1149

Treatment groups were premedicated 20 min before induction of anaesthesia.
Group 1: 5 mg/kg cimetidine i. v. (Cim) + 0.1 mg/kg dimethindene i. v. (Dim)
Group 2: 1.25 mg/kg ranitidine i. v. (Ran) + 0.1 mg/kg dimethindene i. v. (Dim)
Group 3: 300 mg ranitidine p. o. (Ran) 1 to 2 h before induction of anaesthesia
Group 4: Placebo (20 ml saline solution i. v.) 20 min before induction of anaesthesia

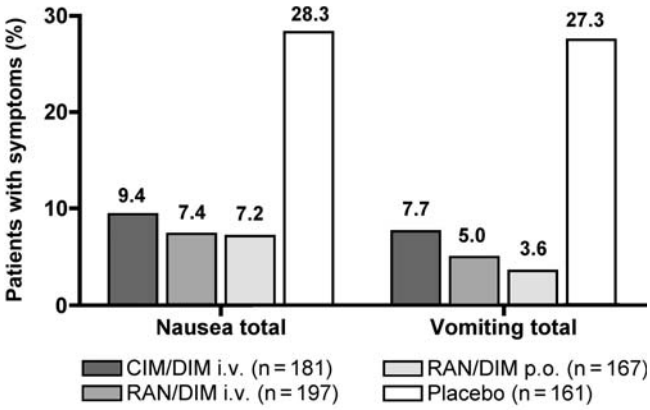

Fig. 1. Incidence of nausea and vomiting within 24 h after general anaesthesia. CIM = cimetidene; RAN = ranitidine; DIM = dimetindene; i.v. = intravenous; p.o. = peroral; Placebo = saline.

The average duration of surgery for patients in *group 1* was 78 min (range: 10 to 465 min); 80 min (range: 10 to 395 min) for *group 2*; 75 min (range: 10 to 395 min) for *group 3*; and 114 min (range: 25 to 480 min) for *group 4* (control group). The duration of surgery in the control group differed significantly from those in each of the treatment groups ($p \leq 0.05$). In the three treatment groups, 443 patients received regional anaesthesia and 545 patients underwent general anaesthesia. All 161 patients of the control group received general anaesthesia according to the study protocol.

The other agents given to patients who underwent general anaesthesia with isoflurane or enflurane were: N_2O_2 (99.8% of patients), vecuronium (98% of patients), fentanyl (95% of patients), thiopental (95% of patients) and etomidate (5% of patients). Patients undergoing regional anaesthesia received bupivacaine, mepivacaine, or prilocaine depending on the expected duration of surgery.

The incidence of nausea and vomiting was significantly lower ($p \leq 0.01$) in patients who received regional anaesthesia: 1.9% of patients in group 1 (n = 154); 2.9% in group 2 (n = 140); and 2.7% in group 3 (n = 149) suffered from nausea, and 1.3%, 1.4%, and 0.7%, respectively, suffered from vomiting. In all treatment groups, the mean incidence of nausea (8%) and vomiting (5.4%) was significantly lower after general anaesthesia compared to the placebo group (28.3% and 27.5%, respectively; $p \leq 0.01$ and $p \leq 0.001$) (Fig. 1). The three different treatment groups were not statistically significantly different. However, the incidence of PONV in the treatment groups receiving Ran/Dim i.v. and Ran/Dim p.o. was slightly lower than in the Cim/Dim i.v. group.

Comparing the gender of the patients, there was a high incidence of nausea in females in the placebo group (36.6%) compared to the treatment groups (12.8%). In male patients 19.6% suffered from nausea in the placebo group and 5.2% in the treatment groups. In female patients, vomiting occurred in 9.8% of the treated patients compared to 45.4% in the placebo group; 13.8% of the male individuals vomited in the placebo group but only 2.9% after H_1/H_2 pretreatment.

Discussion

The reported incidence of postoperative nausea and vomiting varies, ranging from 19.4% to 55% and even higher after gynaecological surgery, causing problems during the recovery period [2–4, 15, 22, 23]. The incidence in our control group (28.3%), was consistent with previously published papers [2, 12, 15, 16]. The incidence of vomiting reported in the literature is ca. 20% in male patients treated with ondansetron [2, 12, 15, 22].

The H_1 and H_2 receptor antagonists used in this study significantly reduced the incidence of nausea and vomiting, with oral ranitidine being as effective as the intravenous formulation. The combination of ranitidine/dimethindene did not differ from cimetidine/dimetindene in its ability to reduce nausea and vomiting. Cimetidine binds reversibly to cytochrome P450 isoenzymes and inhibits hepatic oxidative drug metabolism of agents like theophylline, phenytoin, lidocaine, and the benzodiazepines [24, 25]. Thus cimetidine may cause higher plasma levels of these drugs, an undesired effect in drugs that have a narrow therapeutic range [26]. Ranitidine, however, does not affect the pharmacokinetics of these drugs [24, 25]. In addition to previously published data on the efficacy of a $H_1 + H_2$ antihistamine prophylaxis for PONV [16, 17], a recently published study using a $H_1 + H_2$ antihistamine prophylaxis (cimetidine and dimetindene) clearly demonstrated a marked reduction in the incidence of PONV in patients undergoing general anaesthesia and surgery compared to patients without prophylaxis [27].

Often, the question for the anaesthetist is not whether an antiemetic should be given but rather which antiemetic by which route (i.v. or p.o.). Although studies investigating the effect of ondansetron on postoperative nausea and vomiting are interesting (Table 2) [22], most studies report superiority of ondansetron in doses of 4–8 mg over placebo [2, 12, 15, 28]. Outcome studies comparing ondansetron with other therapies showed it was significantly better than metoclopramide, but not better than droperidol [12, 15, 22, 28].

Antiemetics may not only increase patient's satisfaction with anaesthesia, but may also decrease the incidence of aspiration pneumonia. Hypnotics, anaesthetics and muscle relaxants appear to increase acidity and volume of gastric juice during the induction phase via histamine receptors in the stomach [29]. Drugs given throughout the course of anaesthesia may also stimulate histamine release which, in turn, stimulates the production of gastric juice and leads to cardiovascular instabilities due to histamine release during anaesthesia and surgery [29, 30]. H_2 receptor antagonists

Table 2. Incidence of nausea and vomiting within 24 h post general anaesthesia.

	Group 1	Group 2
Symptoms	Ondansetron i.v.	Placebo i.v.
Nausea female	60% (n = 259)	70% (n = 269)
Nausea male	42% (n = 204)	51% (n = 223)
Vomiting female	31% (n = 272)	55% (n = 282)
Vomiting male	37% (n = 204)	70% (n = 223)

such as ranitidine and cimetidine may decrease nausea and vomiting by inhibiting secretion of gastric acid; the central antiemetic properties of the H_1 blocker dimetindene may contribute to the overall effect.

Oral administration of H_1/H_2 antihistamines 1 to 2 h before the beginning of anaesthesia was as effective as intravenous administration 20 min before anaesthesia. We hypothesize that ranitidine (300 mg p.o.) may have a specific effect on the H_2 receptors of the stomach, thus reducing the excretion of gastric juice before anaesthetics are given. Prophylaxis with H_1/H_2 receptor antagonists lessens the amount of histamine release after administration of hypnotics, analgesics and muscle relaxants and also reduces cutaneous reactions and changes in blood pressure [30–32]. For example, oral premedication with H_1 and H_2 antagonists prevents the haemodynamic and cutaneous adverse effects caused by mivacurium [33].

The newest class of antiemetics used for the prevention and treatment of PONV are the serotonin receptor antagonists. These have been shown to reduce the incidence of PONV [34, 35]. The 5-HT_3 receptor antagonists are superior to conventional antiemetic agents for the prevention of PONV [36], however, they are relatively expensive. In contrast, it has been reported that ondansetron and cyclizine show equal effectiveness for the prevention of PONV [18]. Furthermore, the combined use of ondansetron and cyclizine was shown to be more effective in preventing PONV than just using ondansetron [37].

An optimal antiemetic efficacy may be achieved with a combination of different receptor antagonists in order to block various emetic stimuli acting at different receptor sites suggested by Kovac [2, 10, 15] and others. Thus for patients at high risk for PONV, a combination of antiemetics acting at different receptors should be considered. Accordingly a combined antiemetic prophylaxis has been shown to improve results in high-risk patients [12, 15, 28, 38, 39]. These strategies include: providing routine therapy with antiemetics and using rescue agents for postoperative nausea and vomiting. The reduction of both nausea and vomiting in our study by more than two-thirds (treatment compared with placebo) may have benefits: shorter stays in the post-anaesthesia care unit, use of fewer nursing resources, and decreased expenses are possible advantages of this preventive treatment as well as improved patient's satisfaction.

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