Ondansetron compared with metoclopramide in the treatment of established postoperative nausea and vomiting†

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Summary
We have studied 746 males and females undergoing general anaesthesia for any type of surgical procedure in a double-blind, controlled, randomized study. After experiencing at least one nausea and/or one emetic episode in the 6 h after recovery from anaesthesia, patients received either ondansetron 4 mg i.v. or metoclopramide 10 mg i.v. Patients were observed for postoperative nausea and vomiting (PONV) for 24 h after drug administration. Complete control of PONV was achieved more frequently in the ondansetron-treated patients compared with the metoclopramide-treated patients during the 24-h period (59% vs 41% (P<0.001) and 44% vs 34% (P=0.006) for emetic episodes and nausea, respectively). Furthermore, ondansetron was associated with greater patient satisfaction than metoclopramide (P<0.001) with 49% and 32% of patients, respectively, very satisfied. The overall incidence of adverse events was similar in the ondansetron (7%) and metoclopramide (8%) groups. Ondansetron was as well tolerated and more effective than metoclopramide for all assessment criteria in the treatment of established PONV.

Key words

Postoperative nausea and vomiting (PONV) is a troublesome phenomenon after general anaesthesia. PONV is also a major concern for patients undergoing outpatient surgery under general anaesthesia and may complicate and delay discharge from hospital. In some cases, for example ophthalmic surgery, PONV can compromise surgery. Ondansetron has been shown to be effective and well tolerated in the prevention and treatment of PONV. For prevention, it seems logical to use ondansetron for some procedures known to be associated most commonly with PONV.

In the treatment of established PONV, therapeutic practices differ from one country to another and agents such as metoclopramide and droperidol are often administered. Droperidol has been demonstrated to be effective at low doses but its haemodynamic and sedative effects limit its use, particularly when rapid awakening is sought. Metoclopramide is also used widely as an antiemetic. It was for these reasons that we compared ondansetron with metoclopramide.

In the treatment of established PONV, Claybon compared i.v. ondansetron 1, 4 or 8 mg with placebo in 2812 male and female patients in three different studies. The combined results showed that ondansetron 4 mg was the optimal dose for treating established PONV.

In this study we have compared, under routine clinical conditions, the efficacy and safety of ondansetron 4 mg i.v. with metoclopramide 10 mg i.v. in the treatment of established PONV in patients receiving general anaesthesia.

Patients and methods
This randomised, double-blind, parallel-group comparative study was carried out in 60 French centres. The study was approved by the local Ethics Committee and written informed consent was obtained from each patient.

We studied male and female inpatients, aged 18–75 yr, having undergone surgery under general anaesthesia and scheduled to be hospitalized for at least 30 h after recovery. The main exclusion criteria were patients who had received an antiemetic drug in the 24 h before anaesthesia and during the study, patients who experienced nausea, vomiting, or both, in the 24 h before anaesthesia, and patients who were scheduled to have a nasogastric tube in situ after operation. A balanced general anaesthetic technique was used for all patients and the use of propofol was permitted only for induction of anaesthesia.

The following concurrent medications were defined for the purpose of the study: premedication with any benzodiazepine, if required; induction of anaesthesia with i.v. agents such as thiopentone, P. DIEMUNSCH, MD, Hôpital Civil, 67091 Strasbourg Cedex, France. C. CONSEILLER, MD, Hôpital Cochin, 75014 Paris Cedex, France. N. CLYTI, PHD, J. P. MAMET, PHD, Laboratoire Glaxo Wellcome, 75016 Paris Cedex, France. Accepted for publication: April 22, 1997.

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propofol; analgesia with any i.v. opioid, as required; maintenance of anaesthesia with inhaled nitrous oxide in oxygen and supplemented with halothane, enflurane or isoflurane, as required; neuromuscular block and antagonism with any agent, as required; and postoperative analgesia with opioid or non-opioid analgesics, or combinations of the two, administered parenterally, rectally or orally.

Other concurrent medications (e.g. antibiotics) administered to the patient during the study were also recorded.

Patients who experienced one episode of nausea (duration at least 5 min) or one emetic episode (defined as a single vomit or retch or any number of continuous vomits separated by at least 1 min), or both, during the 6 h after recovery from anaesthesia were allocated randomly to receive either ondansetron 4 mg i.v. or metoclopramide 10 mg i.v. as a slow i.v. injection administered over at least 5 min in a double-blind study (the study drug was administered by a third person, nurse or anaesthetist, who did not participate in the study).

Rescue antiemetic medication was given to patients in case of severe nausea, if an emetic episode occurred at least 15 min after drug administration or at any time at the patient’s request. Any licensed antiemetic could be used as rescue medication.

ASSESSMENTS

The number of recurrent emetic episodes during the 15 min to 24 h after the end of drug administration and the time to the first recurrent emetic episode were recorded. The highest nausea grade using a four-point scale (none, mild, moderate, severe) was recorded during the same period. Global satisfaction with the study medication experienced by the patient was assessed using a five-point scale, 24 h after the end of drug administration, as very satisfied, quite satisfied, neither satisfied nor unsatisfied, rather unsatisfied or very unsatisfied. The safety of the study drug was assessed by monitoring adverse events throughout the 24-h period. The investigators recorded any unexpected adverse events, irrespective of their potential relation to the study drug.

All concomitant treatments were recorded over the same period.

STATISTICAL ANALYSIS

The study sample size (n=768) was based on the assumption that complete control of emetic episodes at 24 h would be achieved in 50% of patients in the ondansetron group and in 40% of patients in the metoclopramide group, using a two-sided test with a significance level of 5% and a power of 80%. Nine hundred patients were planned to be included in order to take into account non-evaluable patients.

The number of patients took into account the fact that an interim analysis of the primary end-point was planned on the first 450 patients included in the study. Statistical analysis was performed on the intent-to-treat population, that is all patients who were randomized and received medication.

The primary end-point was the proportion of patients experiencing no emetic episode (no retches and/or no vomits) and without rescue or withdrawal during the 15 min to 24 h after drug administration. Patients who were rescued or withdrawn from the study were considered to be treatment failures from that time onwards. Comparisons were made between the two treatment groups using the chi-square test.

Secondary end-points were the number of recurrent emetic episodes, time to first recurrent emetic episode, emesis by gender, incidence and severity of nausea, global satisfaction of the patient, percentage of patients who were rescued, and incidence and severity of adverse events.

Time to first recurrent emetic episode was compared between the two groups using the log-rank test, and associated curves were obtained according to the Kaplan–Meier method. Statistical tests used were either the Wilcoxon rank sum test for the number of emetic episodes, severity of nausea and rescue medication, or the Mantel–Haenszel test for patient global satisfaction. Incidence of nausea was assessed by the two-sided chi-square test.

Patients who received rescue antiemetic medication were regarded as treatment failures. Patients experiencing more than five emetic episodes or who were rescued or withdrawn were assigned the value of five episodes for the purpose of analysis. In addition, rescued patients were assigned a severe nausea grade (data adjusted for rescue).

Results

INTERIM ANALYSIS

Interim analysis of the primary end-point was performed on the first 450 patients (235 ondansetron-treated patients and 215 metoclopramide-treated patients).

Results of the interim analysis showed that the percentage of patients with no emetic episodes and who were not rescued or withdrawn from the study between 15 min and 24 h after drug administration was significantly higher in the ondansetron group than in the metoclopramide group (60% vs 42%, P<0.001). It was therefore decided to terminate recruitment into the study at this point and perform the final analysis on all recruited patients. By the time these results were obtained the total number of recruited patients was 746.

FINAL ANALYSIS

A total of 2032 patients who gave written informed consent were screened; 746 of these experienced one episode of nausea or emetic episode, or both, and were allocated randomly to receive ondansetron 4 mg i.v. (n = 380) or metoclopramide 10 mg i.v. (n = 366). Patient characteristics (table 1), type of surgery performed (table 2), medical conditions and concurrent treatments were well matched in the two groups. However, there was a large proportion of women (91%). The main types of operations performed were gynaecological (52%) and gastrointestinal (12%). Also, duration of anaesthesia and
time to recovery from anaesthesia were similar in the two groups (table 3).

A similar proportion of patients in both groups received opioid analgesics (176 in the ondansetron group, 159 in the metoclopramide group), non-opioid analgesics (150 in the ondansetron group, 152 in the metoclopramide group) or no analgesics (54 in the ondansetron group, 55 in the metoclopramide group).

Other prognostic factors for emesis were well matched in the two groups, that is previous history of PONV (150 patients in the ondansetron group and 147 in the metoclopramide group), previous history of motion sickness (61 patients in the ondansetron group and 65 in the metoclopramide group), use of propofol (172 patients in the ondansetron group and 168 in the metoclopramide group) and use of atropine (22 patients in the ondansetron group and 26 in the metoclopramide group).

PRIMARY END-POINT

The percentage of patients with no emetic episode and who were not rescued or withdrawn from the study between 15 min and 24 h after the end of drug administration was significantly higher in the ondansetron group (59%; 223 of 380) than in the metoclopramide group (41%; 151 of 366) (P<0.001; chi-square test).

SECONDARY END-POINTS

Number of emetic episodes

The number of emetic episodes in the ondansetron group was significantly smaller than that in the metoclopramide group (P<0.001) (table 4).

Time to first emetic episode

Analysis of the median time to the first emetic episode showed that patients in the ondansetron group remained free of emesis for longer than patients in the metoclopramide group (P<0.001) (fig. 1). The median time to the first emetic episode was 5 h in the metoclopramide group compared with more than 24 h in the ondansetron group (39% of ondansetron treated-patients were still free of emesis at 24 h).

Incidence and severity of nausea

The percentage of patients with no nausea adjusted

![Figure 1](https://example.com/figure1.png)
Comparing the distribution of nausea grade:

*Rescued patients were assigned a severe nausea grade.*

Distribution of the worst nausea grade adjusted for rescue between 15 min and 24 h after drug administration was significantly higher in the metoclopramide group (44% vs 34%; \( P = 0.006 \)).

Distribution of the worst nausea grade adjusted for rescue between 15 min and 24 h after drug administration was significantly lower in the ondansetron group (\( P < 0.001 \)) (fig. 2).

Global satisfaction of the patient

Distribution of patient global satisfaction was significantly different between the two groups (\( P < 0.001 \)). There were more very satisfied patients in the ondansetron group than in the metoclopramide group (49% vs 32%) (fig. 3).

Rescue medication

More patients received rescue medication in the metoclopramide group than in the ondansetron group (39% vs 26%; \( P < 0.001 \)).

Safety

A similar proportion of patients experienced adverse events in both treatment groups (ondansetron 7%, metoclopramide 8%). The majority of adverse events were assessed as non-drug-related; 1% of patients in the ondansetron group and 2% of patients in the metoclopramide group experienced a drug-related adverse event. The most frequently reported adverse event was headache, which was assessed as drug-related in four patients (one in the ondansetron group, three in the metoclopramide group). Six patients experienced a serious adverse event during the study; none was assessed as related to study medication.

A total of four patients withdrew because of adverse events, none being related to the study treatment.

Discussion

PONV is a common postoperative problem with an overall incidence of approximately 25%. The type of surgery influences the occurrence of PONV: gynaecological surgery is associated with the highest incidence of PONV\(^7^9\) followed by abdominal surgery.\(^10\) Our study population was in accordance with this incidence (746 patients experienced PONV from a total of 2032 patients screened).

A combined analysis of two different studies published by Claybon\(^4\) showed that a single i.v. dose of ondansetron 4 mg was superior to placebo for complete control of emetic episodes (45% vs 21%) and complete control of nausea (38% vs 20%). Moreover, results of these studies showed that a higher dose of ondansetron (8 mg) had no additional benefit in terms of efficacy:safety ratio.

The results of our study showed that ondansetron was significantly superior to metoclopramide for the control of recurrent emetic episodes (59% vs 41%; \( P < 0.001 \)) and for the control of nausea (44% vs 34%; \( P = 0.006 \)). The median time to the first emetic episode after drug administration was greater than 24 h in the ondansetron group compared with 5 h in the metoclopramide group (\( P < 0.001 \)). Moreover, severity of nausea was less important in the ondansetron group than in the metoclopramide group (\( P < 0.001 \)). Finally, our study evaluated patient global satisfaction which had not previously been routinely investigated in PONV: patients in the ondansetron group reported higher satisfaction scores than those in the metoclopramide group (\( P < 0.001 \)).

Comparative studies in the prevention of PONV showed that ondansetron was superior to metoclopramide\(^11^12\) and droperidol,\(^13^14\) or both.\(^15^16\) Moreover, the reduced requirement for further rescue antiemetics\(^13^17\) may suggest that ondansetron provides greater benefit. Ondansetron has further advantages compared with droperidol: it is not associated with extrapyramidal effects and sedation.\(^18\) Metoclopramide is also known to induce extrapyramidal side effects, especially when used for chemotherapy-induced emesis.\(^19\)

In the treatment of established PONV, there are some data comparing ondansetron with other antiemetics.\(^4^20^21\) These three studies showed that there was no significant difference between ondansetron and droperidol. However, the results could be criticized because of the small study population. In addition, evaluation of patients was followed for only a short period of time after treatment.

To date, this is the largest study comparing
ondansetron with an active comparator in the treatment of established PONV. Our results showed that ondansetron was more effective than metoclopramide. The incidence of adverse events was low and similar in both the ondansetron and metoclopramide groups. The majority of adverse events were assessed as non-drug-related. In addition, the nature of adverse events was consistent with previous experience.3 5 11

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References

1. Lee PJ, Pandit SK, Green CR. Postanesthetic side effects in the outpatient. Which are the most important? *Anaesthesia and Analgesia* 1995; 80 (Suppl.): S271.


