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Combination of ondansetron and dexamethasone in the prophylaxis of postoperative nausea and vomiting

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Summary

We studied 100 ASA I–II females undergoing general anaesthesia for major gynaecological surgery, in a prospective, double-blind, placebo-controlled, randomized study. Patients received one of four regimens for the prevention of postoperative nausea and vomiting (PONV): ondansetron 4 mg ($n = 25$), dexamethasone 8 mg ($n = 25$), ondansetron with dexamethasone (4 mg and 8 mg, respectively, $n = 25$) or placebo (saline, $n = 25$) There were no differences in background factors or factors related to operation and anaesthesia, morphine consumption, pain or side effects between groups. The incidence of nausea and emetic episodes in the ondansetron with dexamethasone group was lower than in the placebo ($P < 0.01$), ondansetron ($P < 0.05$) and dexamethasone ($P = 0.057$) groups. There were no differences between ondansetron and dexamethasone, and both were more effective than placebo ($P < 0.05$ and $P < 0.01$, respectively). Dexamethasone appeared to be preferable in preventing nausea than emetic episodes. Fewer patients in the ondansetron with dexamethasone group needed antimetic rescue ($P < 0.01$ *vs* placebo and $P < 0.05$ *vs* ondansetron). We conclude that prophylactic administration of combined ondansetron and dexamethasone is effective in preventing PONV. (*Br. J. Anaesth*. 1996; **76**: 835–840).

Key words

Surgery, gynaecological. Vomiting, nausea. Vomiting, antimetics. Pharmacology, ondansetron. Pharmacology, dexamethasone.

Recent reviews have reported that the incidence of postoperative nausea and vomiting (PONV) is 30 % [1, 2], with little improvement in recent years, but it may be higher because of the influence of preoperative patient characteristics, factors related to operation and anaesthesia, and the intensity of pain and its management in the postoperative period [3, 4].

The introduction into clinical practice of the 5-HT_3 receptor antagonist, ondansetron, has provided effective antiemesis in surgical patients without significant drug-related side effects [5, 6]. Dexamethasone has been used as an antiemetic for more than 10 yr in patients receiving chemotherapy, with limited side effects [7–11]. The mechanism of action of dexamethasone as an antiemetic is not known.

None of the available antiemetics is entirely effective in all patients, perhaps because there is no single stimulus for PONV. The combination of drugs currently used in the treatment of nausea and vomiting in patients receiving chemotherapy [8], could be a solution to control situations with severe, frequent PONV. Recently, the combination of ondansetron and dexamethasone has been shown to be a highly effective prophylactic measure for patients receiving high-dose cisplatin chemotherapy [8].

In this prospective, double-blind, randomized study, we assessed the safety and efficacy of a single i.v. dose of ondansetron 4 mg, dexamethasone 8 mg, ondansetron with dexamethasone (4 mg and 8 mg, respectively) or placebo (2 ml of saline) in females undergoing elective major gynaecological surgery.

Patients and methods

After obtaining local Ethics Committee approval and written informed consent, we studied 100 ASA I – II women, aged 18–65 yr, weighing 45–90 kg, undergoing major elective gynaecological surgery. Patients who had received opioids, NSAID, steroids or antiemetic agents during the previous month or who had hypersensitivity to either ondansetron or steroids were excluded.

Patients were allocated randomly to one of four groups: P (placebo), O (ondansetron), D (dexamethasone) and O + D (ondansetron with dexamethasone). The study was prospective, conducted in a double-blind manner, with a stratified randomization to ensure an equal number of patients of the same age and weight undergoing the same type of surgery in each group (Table 1).

The night before surgery we recorded the following variables: age, weight and height, previous general anaesthesia and abdominal surgery, history

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Table 1 Patient data (number of patients)

	Group			
	P	O	D	O and D
n	25	25	25	25
Age (yr)				
< 40	5	5	5	5
40—60	17	17	17	17
> 60	3	3	3	3
Weight (kg)				
< 60	9	9	9	10
60–80	15	16	15	14
> 80	1	0	1	1
Type of surgery				
Hysterectomy	20	20	20	20
Adnexectomy	2	2	2	2
Second look laparotomy	2	2	2	2
Myomectomy	1	1	1	1

of motion sickness or headache, history of PONV after previous surgery, phase of menstrual cycle and grade of anxiety. All patients were taught to use the patient-controlled analgesia (PCA) pump for self-administration of morphine and were told to call the nurse as soon as they felt nausea or had any emetic episode in the postoperative period.

All patients had their last oral intake at least 8 h before the start of anaesthesia and were premedicated with bromazepam 0.1 mg kg^{-1} administered orally the night before surgery and atropine 0.01 mg kg^{-1} i.m., 30 min before induction of anaesthesia.

Each patient received two syringes with 2 ml of solution before induction of anaesthesia. Patients in group P received 0.9 % saline, those in group O, ondansetron 4 mg and 0.9 % saline, those in group D, dexamethasone 8 mg and 0.9 % saline, and those in group O and D, ondansetron 4 mg and dexamethasone 8 mg.

Anaesthesia was induced with thiopentone 5 mg kg^{-1}, atracurium 0.5 mg kg^{-1} and fentanyl 5 μg kg^{-1}. The trachea was intubated 3 min after administration of atracurium. A nasogastric tube and a urinary catheter were placed in all patients. Anaesthesia was maintained with 50 % nitrous oxide in oxygen supplemented with isoflurane (0.5–1 % expired concentration). Ventilation was adjusted to maintain end-tidal carbon dioxide pressure at 4.7 kPa. Neuromuscular blocking agents and fentanyl were used as required. All patients received morphine 0.1 mg kg^{-1} when it was predicted that surgery would end in 30 min. It was not necessary to antagonize residual neuromuscular block in any patient. No other sedative, analgesic or antiemetic drug was administered. The nasogastric tube and urinary catheter were left in place.

The variables recorded during the operative period included: type of incision (Pfannenstiel or midline laparotomy), type of surgery (hysterectomy, adnexectomy, reassessment laparotomy (second look) for ovarian cancer or myomectomy), total amount of atracurium and fentanyl administered, and duration of surgery and anaesthesia.

Postoperative analgesia was provided with i.v. ketorolac 30 mg/8 h and PCA (Pain Management Provider TM, Abbott, North Chicago, IL, USA) morphine 1 mg ml^{-1} (demand dose = 1 mg; lockout interval = 10 min; and maximum dose in 4 h = 0.25 mg kg^{-1}).

In the recovery room (2 h) and in the ward (12, 24 and 48 h after recovery from anaesthesia) we studied the following variables: in (1) incidence of PONV—we asked patients if they felt nauseated or sick in each period, with only two possible answers, "yes" if they did for at least 10 min, or "no". Retching and vomiting were grouped together under the common term "emetic episode" and were assessed as present or absent. The primary end-point was a complete response, as defined by no nausea or emetic episodes during the 48-h postoperative period. (2) Number of patients who needed rescue antiemetic treatment—if patients experienced nausea for 30 min or more than one emetic episode in 15 min, rescue antiemetic treatment was available with metoclopramide 10 mg/8 h. (3) Pain intensity scores, with and without active movement, were obtained with the VAS test. They were classified into three categories to allow easier statistical analysis. The pain categories were: severe if VAS score was greater than 7, moderate if VAS score was 3–7 and light if VAS score was less than 3. (4) Total amount of morphine consumed. (5) Sedation five-point scale: 4 = completely awake, open eyes; 3 = drowsy, closed eyes; 2 = asleep, responds to oral call; 1 = asleep, responds to touch or pain; 0 = does not respond). (6) Other side effects.

All observations were made by the same previously trained nurses as soon as the symptoms appeared. Nausea, retching and vomiting were also assessed by the same anaesthetist by questioning the patient 2, 12, 24 and 48 h after recovery from anaesthesia. Both the nurses and the anaesthetist were unaware of which antiemetic the patient had received.

We also recorded the following variables: postoperative comfort, postoperative analgesia and night rest (rated as bad, fair, good and very good), postoperative comfort compared with previous experiences (rated as worse, similar, better and not comparable), time before first postoperative oral intake, time before standing up and moment at which nasogastric tube and urinary catheter were removed (rated as less than 12 h, at 12–24 h, at 24–36 h, at 36–48 h and more than 48 h).

We used the chi-square test and Fisher's exact test for non-parametric analysis. Parametric data were analysed using analysis of variance (Fisher's PLSD correction was also applied), Kruskal–Wallis and Mann–Whitney tests. $P < 0.05$ was considered significant.

Results

The incidence of background factors and factors related to operation and anaesthesia, which may modify PONV, did not differ between groups (table 2).

A complete response (no nausea and no emetic episodes during the 48-h postoperative period) occurred in 84 % of patients in the ondansetron with dexamethasone group and in only 20 % of patients in the placebo group ($P < 0.01$). In the ondansetron

Table 2 Background factors and those related to operation and anaesthesia (mean (SD or range) or number of patients)

	Group			
	P	O	D	O and D
n	25	25	25	25
Age (yr)	47 (22–65)	47 (21–63)	46 (26–65)	46 (19–65)
Weight (kg)	63 (8)	62 (10)	62 (8)	64 (8)
Height (cm)	160 (5)	159 (6)	160 (5)	160 (5)
Motion sickness (*n*)	4	8	7	6
Headache (*n*)	2	2	3	4
Anxiety (*n*)				
Calm	7	3	4	6
Nervous	9	15	16	15
Very nervous	9	7	5	4
Menstrual cycle (*n*)				
Days 1–6	4	5	3	7
Days 7–16	5	5	4	4
Days 17–(–1)	4	5	3	5
Postmen.–Amenorr.	12	10	15	9
Previous general anaesthesia	10	12	11	16
Previous abdominal surgery	6	11	9	8
History of PONV	3	4	4	6
Type of incision				
Pfannenstiel	20	15	19	20
Midline laparotomy	5	10	6	5
Atracurium (mg kg^{-1})	0.7 (0.1)	0.7 (0.1)	0.7 (0.2)	0.8 (0.2)
Fentanyl (μg kg^{-1})	5.9 (0.9)	6.0 (1.2)	5.7 (0.8)	5.6 (0.6)
Duration of surgery (min)	109 (24)	116 (31)	111 (46)	117 (30)
Duration of anaesthesia (min)	132 (25)	137 (33)	137 (47)	136 (30)

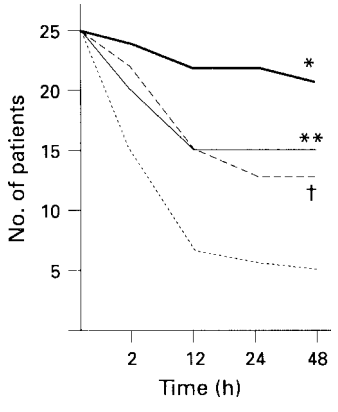

Figure 1 Number of patients without PONV from the end of surgery until the moment of each evaluation. Number and percentage of patients with a complete response: group O + D (——) (n = 21, 84 %); group D (——) (n = 15, 60 %); group O (– – –) (n = 13, 52 %) and group P (. . . . .) (n = 5, 20 %). *P < 0.05 *vs* group O and P < 0.01 *vs* group P; **P < 0.01 *vs* group P; †P < 0.05 *vs* group P.

Table 3 Number of patients (%) with nausea and emetic episodes (EE) from the end of surgery until the moment of each evaluation. Significant difference (P < 0.05) compared with: *group P; †group O; ‡group D

	Group			
	P	O	D	O and D
n	25	25	25	25
2 h				
Nausea	10 (40)	3 (12)*	5 (20)	1 (4)*
EE	6 (24)	0 (0)*	3 (12)	0 (0)*
12 h				
Nausea	18 (72)	10 (40)*	10 (40)*	3 (12)*†‡
EE	11 (44)	3 (12)*	8 (32)*	1 (4)*‡
24 h				
Nausea	19 (76)	12 (48)*	10 (40)*	3 (12)*†‡
EE	11 (44)	6 (24)	8 (32)	1 (4)* †‡
48 h				
Nausea	20 (80)	12 (48)*	10 (40)*	4 (16)*†
EE	12 (48)	6 (24)	8 (32)	1 (4)*†‡

group, it occurred in 52 % of patients and in 60 % of patients in the dexamethasone group (fig. 1).

The incidence of nausea and emetic episodes in patients in group O + D was lower than in those in groups P, O and D during the whole study. There were significant differences between groups O + D and P at all times (P < 0.01), and between group O + D and groups O and D at some times only (table 3). There were no differences in the frequencies of nausea and emetic episodes between patients who received ondansetron or dexamethasone.

Only two patients (8 %) in group O + D required antiemetic rescue (P < 0.01 *vs* group P and P < 0.05 *vs* group O), compared with seven patients (28 %) in group D (P < 0.01 *vs* group P), nine patients (36 %) in group O (P < 0.05 *vs* group P) and 17 patients (68 %) in group P.

There were no significant differences in pain intensity between groups at any time. At the end of the study only two patients at rest and 21 with movement had a VAS score greater than 3 (table 4).

Opioid requirements did not differ between groups, although in groups D and O + D, requirements were greater from 12 h after the end of operation. Mean total consumption of morphine at 48 h from the end of surgery was 32 (SD 14.8), (range 5–63) mg in group P, 32 (18.7), (4–68) mg in group O, 39 (22.4), (8–79) mg in group D and 38 (24.6), (4–94) mg in group O + D.

There were no significant differences in sedation. There was no patient with category 0, 1 or 2 at any

Table 4 Number of patients (%) in the different pain categories in each treatment group and period. The pain categories were: light (VAS 0 < 3), moderate (VAS 3–7) and severe (VAS > 7–10)

	Group			
	P (n = 25)	O (n = 25)	D (n = 25)	O and D (n = 25)
2 h				
Light	16 (64)	11 (44)	13 (52)	16 (64)
Moderate	9 (36)	13 (52)	12 (48)	9 (36)
Severe	—	1 (4)	—	—
12 h rest				
Light	18 (72)	19 (76)	14 (56)	13 (52)
Moderate	7 (28)	6 (24)	11 (44)	12 (48)
Severe	—	—	—	—
12 h mov.				
Light	5 (20)	2 (8)	6 (24)	4 (16)
Moderate	16 (64)	19 (76)	13 (52)	14 (56)
Severe	4 (16)	4 (16)	6 (24)	7 (28)
24 h rest				
Light	23 (92)	25 (100)	22 (88)	23 (92)
Moderate	2 (8)	—	3 (12)	2 (8)
Severe	—	—	—	—
24 h mov.				
Light	11 (44)	16 (64)	10 (40)	9 (36)
Moderate	13 (52)	9 (36)	12 (48)	14 (56)
Severe	1 (4)	—	3 (12)	2 (8)
48 h rest				
Light	24 (96)	25 (100)	25 (100)	24 (96)
Moderate	1 (4)	—	—	1 (4)
Severe	—	—	—	—
48 h mov.				
Light	22 (88)	21 (84)	19 (76)	17 (68)
Moderate	3 (12)	4 (16)	6 (24)	8 (32)
Severe	—	—	—	—

time during the study. At 12 h after the end of surgery, there were only seven patients with category 3, and all patients were in category 4 by 24 h (table 5).

The percentage of adverse events was similar between groups (table 4). The most commonly reported adverse event was headache. Perineal itching was reported during administration of a solution in groups that received dexamethasone, but disappeared spontaneously in 30 s. Itching was the only adverse effect associated with a high consumption of morphine.

No patient scored postoperative comfort as bad. Comfort was found to be greater in group O + D than group P at 24 h ($P < 0.05$) (Fig. 2). There were no differences between groups at 48 h and only 11 % of patients defined postoperative comfort as fair, most because of PONV.

Night rest was similar between groups. No patient considered night rest as bad. Four patients in group P, one patient in group O, one in group D and two in group O + D defined the first night's rest as fair mainly because of PONV. Fourteen patients (five patients in group P, three patients in group O, two in group D and four in group O + D) described rest as fair on their second night mainly because of lack of their usual hypnotics at home (10 patients) and PONV.

Postoperative comfort was similar to previous surgical experiences in 8 % of patients, not comparable in 20 % and better in 72 %. There were no significant differences between groups.

Table 5 Number of patients with different categories of sedation in each group and period (categories of sedation: 4 = completely awake, open eyes; 3 = drowsy, closed eyes; 2 = asleep, answer to oral call; 1 = asleep, answer to touch or pain; 0 = does not respond)

	Group			
	P (n = 25)	O (n = 25)	D (n = 25)	O and D (n = 25)
2 h				
4	14 (56)	16 (64)	18 (72)	13 (52)
3	11 (44)	9 (36)	7 (28)	12 (48)
2	—	—	—	—
1	—	—	—	—
0	—	—	—	—
12 h				
4	22 (88)	24 (96)	22 (88)	25 (100)
3	3 (12)	1 (4)	3 (12)	—
2	—	—	—	—
1	—	—	—	—
0	—	—	—	—
24 h				
4	25 (100)	25 (100)	25 (100)	25 (100)
3	—	—	—	—
2	—	—	—	—
1	—	—	—	—
0	—	—	—	—
48 h				
4	25 (100)	25 (100)	25 (100)	25 (100)
3	—	—	—	—
2	—	—	—	—
1	—	—	—	—
0	—	—	—	—

Table 6 Adverse events. Number of patients in each treatment group

	Group			
	P	O	D	O and D
n	25	25	25	25
Headache	2	3	1	3
Sp_{O_2} < 94 % after 2 h in recovery room with Fi_{O_2} = 0.21	2	1	1	2
Perineal itching	—	—	3	2
Abdominal distension	1	—	2	1
Urinary retention	—	2	1	—
Itching	1	—	1	—

There were no differences between groups in time before removal of the urinary catheter and nasogastric tube, time before standing up and time before oral intake.

Discussion

We found that during the 48 h period after recovery from anaesthesia, ondansetron 4 mg and dexamethasone 8 mg were more effective than placebo in preventing nausea, although there were no significant differences in vomiting, perhaps because the groups were small. Moreover, there were no significant differences between dexamethasone and ondansetron and both drugs offered adequate control of PONV. But the major finding was that in the 48-h period, the combination of ondansetron and dexamethasone was more effective than placebo and ondansetron alone for nausea and vomiting, and better than dexamethasone for vomiting but not for nausea. No

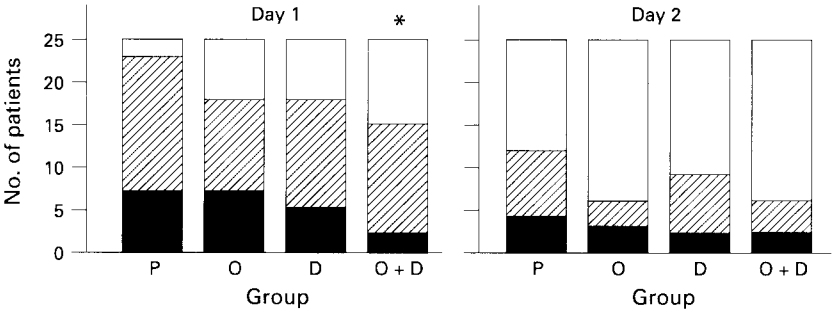

Figure 2 Grade of comfort after surgery. Number of patients who felt bad (none), fair (■), good (▨) or very good (□) in each treatment group. $*P < 0.05$ *vs* group P.

patient had vomiting in the recovery room (first 2 h) in the ondansetron with dexamethasone group, and only one patient during the 48-h postoperative period. Moreover, there was only one patient with nausea in the recovery room and only four had nausea during the 48-h postoperative period.

We chose patients at high risk of PONV: women aged 18–65 yr, in whom the incidence of PONV is three times higher [1, 2], undergoing major gynaecological surgery, a type of surgery associated with the highest incidence of PONV [2–4, 12]. We analysed factors that have been shown to affect the incidence of PONV such as patient weight [1, 2], history of motion sickness [3] or PONV after previous anaesthesia [12], grade of anxiety [1, 2] and phase of menstrual cycle [13]. In our study all of these factors were well balanced between groups. All patients underwent the same preoperative fasting and premedication, the same standardized balanced anaesthesia, without antagonism of neuromuscular block, and the same postoperative care, including the techniques and drugs used for postoperative analgesia. Type of incision, total amount of atracurium and fentanyl administered and duration of operation (none for more than 4 h) were similar in all groups. All of these factors also increase the incidence of PONV [1–4]. Postoperative factors involved in PONV [1–4], such as intensity of postoperative pain, morphine consumption, time to oral intake, time to stand up and time to remove nasogastric tube, were matched equally between groups.

Ondansetron is a selective 5-HT_3 receptor antagonist, effective in preventing PONV [6, 12, 13, 14–17]. The effectiveness of i.v. ondansetron as a prophylactic postoperative antiemetic was evaluated by McKenzie and colleagues in a dose ranging study [15], and it was demonstrated that a single 4-mg i.v. dose appeared to be the lowest acceptable dose to prevent PONV. Since then, most authors have agreed that this i.v. dose before induction is effective antiemetic prophylaxis [6, 18].

Dexamethasone was first reported to be an effective antiemetic agent in patients undergoing cancer chemotherapy in 1981 [7]. Since then randomized, placebo-controlled studies have shown that dexamethasone and other steroids are significantly better than other agents (metoclopramide, prochlorperazine, droperidol, domperidone) in preventing nausea and vomiting associated with chemotherapy. The mechanism of dexamethasone-induced antiemetic activity is not fully understood, but may involve central inhibition of prostaglandin synthesis [19]. Another theory involves a decrease in 5-HT turnover in the central nervous system [20] or changes in the permeability of the blood CSF barrier to serum proteins [21]. However, there is no experimental proof to support these hypotheses. The plasma elimination half-life of dexamethasone is approximately 4–4.5 h, similar to that of other antiemetics usually administered in a single dose [22] (for instance, ondansetron has a plasma half-life of approximately 3 h) [23]. A dose ranging study by Drapkin and Sokl [9] evaluated the effectiveness of i.v. dexamethasone in patients undergoing chemotherapy. An 8-mg i.v. dose appeared to be as effective as 32 mg in preventing nausea and vomiting in cancer chemotherapy. These are reasons why we chose dexamethasone as an antiemetic in a single 8-mg dose. A retrospective study by Mataruski and colleagues [24] showed that 34 patients who received intraoperative steroids were less likely to experience PONV than 27 who did not. Recently, Yoshitaka, Hiroyoshi and Hidenori [25] found no differences between placebo, granisetron and dexamethasone in women undergoing general anaesthesia for major gynaecological surgery. The lack of differences between the groups could be because of the low incidence of PONV and the small number of patients in the study.

McKenzie and colleagues [26] studied ondansetron and ondansetron with dexamethasone in women undergoing major gynaecological surgery and the results showed that the combination was more effective than ondansetron alone, as our results confirmed. More recently, Yoshitaka, Hiroyoshi and Hidenori [25] found differences between granisetron with dexamethasone and placebo, granisetron and dexamethasone alone, in women undergoing general anaesthesia for major gynaecological surgery.

All groups had a similar percentage of patients reporting adverse events. Perineal itching was present only in groups who received dexamethasone, and it appears to be related to the vehicle [11]. Chronic treatment with large doses of steroids has been implicated in postoperative complications such as infection and delayed or poor wound healing [27]. Many complications are dose related, and with low dose or discontinuation of steroids, their frequency decreases rapidly [28]. Furthermore, we did not find that giving a single large dose of steroid interfered with wound healing after surgery or produced other major side effects.

There were no significant differences between groups in sedation. The small number of patients with grade 3 sedation at 12 h had a higher consumption of morphine.

Pain and PONV are the most common, unpleasant postoperative events. As pain was similar in all groups, the lower incidence of PONV in our study was the main reason for the better results in group O + D compared with group P at 24 h. Both ondansetron and dexamethasone provided adequate control of PONV. If our results are confirmed in larger studies, dexamethasone will be more advantageous than ondansetron in terms of cost and resource allocation. The combination of ondansetron with dexamethasone was the most effective in reducing PONV. This combination could be useful in day-case surgical procedures because of the absence of side effects and sedation.

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