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High-dose ondansetron regimen *vs* droperidol for morphine patient-controlled analgesia

M. DRESNER, S. DEAN, A. LUMB AND M. BELLAMY

Summary

We have performed a randomized, double-blind study comparing droperidol and high-dose ondansetron mixed with morphine for patient-controlled analgesia (PCA). To detect a reduction in the incidence of postoperative nausea and vomiting from 55% to 20% with a power of 80% at the $P<0.05$ level, 29 patients per group were required. We studied 60 healthy women undergoing abdominal hysterectomy, anaesthetized using a standard technique. Group D received a bolus dose of droperidol 1.25 mg at induction followed by droperidol 0.1 mg per 1 mg of morphine from the PCA system. Group O received a bolus dose of ondansetron 4 mg at induction followed by ondansetron 0.32 mg per 1 mg of morphine. This dose of ondansetron is more than double that studied previously. Mean nausea and vomiting scores at 4, 8, 12 and 24 h, mean time to first vomit, sedation scores, incidence of side effects, and doses of prochlorperazine did not differ between the groups. In group D, 24 patients did not vomit compared with 23 in group O. The only significant difference between the groups was increased morphine consumption in the ondansetron group up until 12 h after operation ($P<0.05$), but by 24 h this difference was not significant. The ondansetron regimen was more expensive (at local prices) by a factor of 27, and our results suggested no clinical advantage over droperidol. (*Br. J. Anaesth*. 1998; **81**: 384–386).

Keywords: vomiting, incidence; vomiting, antiemetics; pharmacology, ondansetron; pharmacology, droperidol; analgesia, patient-controlled

Patient-controlled analgesia (PCA) is an effective, safe and labour-saving technique for providing postoperative pain relief.[1] However, its use does not solve the problem of postoperative nausea and vomiting (PONV).[2,3] Droperidol,[4–7] ondansetron[8] and combinations of the two[9] have been shown to reduce the incidence of PONV when added to morphine in a patient-controlled analgesia system (PCAS). In this study, we have compared the efficacy, side effects and cost of a high-dose ondansetron regimen with droperidol.

Patients and methods

A previous study showed that the incidence of postoperative vomiting associated with morphine and droperidol PCAS was 51%[8] To detect a reduction in the incidence of PONV from 55% to 20% with a power of 80% at the $P<0.05$ level, 29 patients per group were required. After obtaining approval from the Clinical Research (Ethics) Committee, written informed consent was obtained from all patients. Patients with allergies to any of the drugs or history of severe PONV were excluded. We studied 60 ASA I–II women undergoing abdominal hysterectomy via a Pfannenstiel incision for benign disease.

All parents were anaesthetized by one of the authors using a standard anaesthetic technique. Premedication comprised oral diazepam 10 mg, 1 h before surgery. The induction sequence consisted of fentanyl 4 $\mu g\ kg^{-1}$, an induction dose of propofol 2–3 mg kg^{-1} with lidocaine 1 mg ml^{-1}, atracurium 0.5 mg kg^{-1} and intubation with a 7.5-mm tracheal tube. Patients' lungs were ventilated to normocapnia with 0.6–1.2% isoflurane (end-expiratory) and 70% nitrous oxide in oxygen, and antagonized with glycopyrrolate 7 $\mu g\ kg^{-1}$ and neostigmine 40 $\mu g\ kg^{-1}$.

Patients were allocated randomly to one of two groups after induction of anaesthesia. Each patient received a loading dose of the appropriate antiemetic and the PCAS mixture was prepared. The drug combination for group D was a loading dose of droperidol 1.25 mg, and a mixture of morphine 1 mg ml^{-1} with droperidol 0.1 mg ml^{-1} in the PCAS. Group O received a loading dose of ondansetron 4 mg and a PCAS mixture of morphine 1 mg ml^{-1} with ondansetron 0.32 mg ml^{-1}. Graseby PCAS pumps (Graseby Medical Ltd, Watford, Herts, UK) were used, set to deliver a loading dose of morphine 5 mg on the first request, followed by 1-mg bolus doses of morphine with a 5-min lockout period. All patients received oxygen, and vital signs, ventilatory frequency and conscious level were monitored throughout PCAS therapy. Prochlorperazine 12.5 mg i.m. was prescribed at the discretion of nursing staff.

PONV, prochlorperazine usage, pain, sedation, antiemetic side effects and morphine consumption were recorded by ward nurses blinded to the treatment group at 4, 8, 12 and 24 h after operation, using the verbal rating scores shown in table 1. PCAS syringes were refilled when appropriate by an on-call

M. DRESNER*, MB, BS, FRCA, S. DEAN, MB, CHB, FRCA, A. LUMB, MB, BS, FRCA, M. BELLAMY, MA, MB, BS, FRCA, Department of Anaesthetics, St James's University Hospital, Beckett Street, Leeds LS9 7TF. Accepted for publication: March 11, 1998.

*Present address for correspondence; Department of Anaesthetics, Leeds General Infirmary, Great George Street, Leeds LS1 3EX.

Table 1 Observation record, repeated at 4, 8, 12 and 24 h after surgery

Nausea since surgery	0	None
	1	Mild, intermittent nausea
	2	Constant, moderate nausea
	3	Severe nausea
Vomiting since surgery	0	None
	1	One vomit only
	2	Several vomits
	3	Repeated retching/vomiting
Prochlorperazine given?	Yes/No	
Pain score	0	No pain
	1	Slight pain
	2	Moderate pain
	3	Severe pain
Sedation level	0	Alert
	1	Drowsy
	2	Sleeping, but rousable
	3	Unrousable
Side effects		Extrapyramidal sign
		Restlessness/anxiety
		Headache
PCAS morphine used	mg	

Table 2 Patient characteristics (median (range))

	Group D (droperidol, $n=30$)	Group O (ondansetron, $n=30$)
Age (yr)	46 (29–60)	45 (28–57)
Weight (kg)	64 (48–84)	63 (46–88)

anaesthetist who was aware of the patient's treatment group.

Results were analysed using SPSS. Chi-square with Yates' correction and the Mann–Whitney *U* test were used as appropriate; time to first episode of vomiting was analysed by Kaplan–Meier plotting and the log rank test. $P<0.05$ was regarded as significant.

Results

There was no difference between the groups in age or weight (table 2).

The results are shown in table 3. Apart from morphine use in die first 12 h, there were no significant differences between the groups.

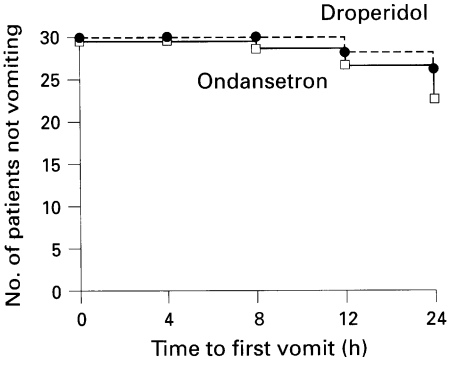

Figure 1 Time to first episode of vomiting in the ondansetron and droperidol groups.

Table 3 Nausea and vomiting, pain and sedation scores and morphine consumption in the two groups. Values in parentheses refer to the number of patients affected by any nausea or vomiting scores at that time

	Group D	Group O
Mean nausea score at:		
4 h	0.47 (12)	0.5 (12)
8 h	0.4 (11)	0.63 (14)
12 h	0.37 (9)	0.43 (12)
24 h	0.37 (4)	0.57 (7)
Mean vomiting score at:		
4 h	0 (0)	0 (0)
8 h	0 (0)	0.03 (1)
12 h	0.1 (2)	0.1 (3)
24 h	0.23 (4)	0.33 (7)
No. who never vomited	24	23
Doses of prochlorperazine given?	14	14
Mean pain score at:		
4 h	1.53	1.8
8 h	1.33	1.2
12 h	0.97	1.07
24 h	0.23	1.3
Mean sedation score at:		
4 h	1.13	1.13
8 h	0.93	0.7
12 h	0.97	0.77
24 h	0.3	0.23
Headaches	3	6
Anxiety/restlessness	0	0
Extrapyramidal symptoms	0	0
PCAS morphine used by:		
4 h	18.87	28.93 ($P<0.0086$)
8 h	26.47	38.63 ($P<0.0033$)
12 h	32.9	44.77 ($P<0.0376$)
24 h	43.6	56.67

Table 4 Cost per patient of the antiemetic regimens

	Group D	Group O
Cost per 50 mg of morphine	£0.93	£24.74
Cost per patient	£1.27	£34.72

Time to first vomit is shown in figure 1 .There were no significant differences between the groups.

Mean cost per patient of the two antiemetic regimens, at local prices, is shown in table 4, and takes into account the greater need for second syringes in group O. Droperidol costs assume taking the bolus and infusion doses from a single ampoule. Prices include value added tax.

Discussion

Droperidol, a butyrophenone, acts primarily as a dopamine (D_2) antagonist. In the prevention of PONV, several studies have demonstrated its superiority over placebo, either as a bolus dose before PCA therapy[4] or mixed with morphine in ratios of 0.05 mg:1 mg[5,6] to 0.17 mg: 1 mg.[10] Despite the improvements, nausea was still seen in 30–50% of patients treated with droperidol.

Ondansetron is a highly selective 5-hydroxytryptamine type 3 receptor antagonist which acts peripherally on vagus nerve endings and centrally on the chemoreceptor trigger zone. Given in two 4-mg boluses, it has been shown to be similar to placebo

during PCA.[9] After loading with 4 mg, a concentration of ondansetron 0.13 mg per 1 mg of morphine has been shown to be as good, but not better than droperidol.[8 11] Our study showed that increasing the infused concentration of ondansetron to 0.32 mg per 1 mg of morphine failed to improve on the efficacy of droperidol. The only study in which ondansetron performed better than droperidol using a PCA involved droperidol 0.1 mg *and* ondansetron 0.13 mg per 1 mg of morphine.[11] Even then, the combination proved superior to droperidol or ondansetron alone only for the first 12 h.

The only difference between the two groups was lower morphine consumption in the first 12 h in the droperidol group. This could be related to the sedative effect of droperidol. However, there was no resultant difference in pain scores.

Our results and those of other studies support the use of droperidol as the first-line drug in preventing PONV associated with PCA. Ondansetron may have a role in patients for whom droperidol is unsuitable, but this study did not support the use of high-dose ondansetron in terms of efficacy or economics. The literature suggests a role for a combination regimen in patients with a history of severe PONV. Given the multifactorial causes, multiple receptors and diverse neural pathways involved in PONV, research into other multiple drug combinations would appear to be the logical way forward.

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