

Antiemetic and analgesic-sparing effects of diphenhydramine added to morphine intravenous patient-controlled analgesia

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Background. This study was designed to examine the analgesic and dose-related antiemetic efficacy of diphenhydramine–morphine mixture for intravenous patient-controlled analgesia (PCA).

Methods. Healthy women, undergoing abdominal total hysterectomy were recruited to this double-blinded randomized placebo-controlled study. Patients were randomly allocated to one of three groups ($n=40$ each). In group 1, patients received saline at induction and morphine 1 mg ml^{-1} alone for postoperative PCA. Patients in groups 2 and 3 received diphenhydramine 30 mg i.v. at induction and were given a 1.2:1 or a 4.8:1 ratio, respectively, of diphenhydramine–morphine mixture for postoperative PCA.

Results. A total of 112 patients completed the study. The incidence of postoperative nausea (31.6% vs 67.6%, $P<0.01$) and vomiting (15.8% vs 40.5%, <0.05) was significantly lower in group 3 than in group 1. Furthermore, the incidence of severe nausea was significantly lower in group 3 than in group 1 (2.6% vs 24.3%, $P<0.05$). The rescue antiemetic requirements were also significantly less in group 3 than in group 1 (5.3% vs 24.3%, $P<0.05$). However, there was no significant difference between group 2 and group 1 in any of the comparisons. Pain intensity, 24-h morphine consumption and diphenhydramine-related side-effects, such as sedation or dry mouth, did not differ among the three groups.

Conclusion. An initial bolus of diphenhydramine 30 mg at anaesthetic induction followed by postoperative PCA with a 4.8:1, but not 1.2:1, diphenhydramine–morphine mixture provides an effective antiemetic efficacy without morphine-sparing effects.

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Intravenous patient-controlled analgesia (PCA) has been extensively used to provide effective analgesia,¹ but the use of morphine is associated with postoperative nausea and vomiting (PONV). An incidence as high as 80% has been quoted with the use of PCA morphine in patients after gynaecological procedures.² The high incidence of PONV has frequently led to the abandonment of PCA despite its analgesic efficacy.³ Various antiemetic agents, such as promethazine,⁴ cyclizine,⁵ ondansetron,^{6–8} metoclopramide,^{9–11} and droperidol,^{5,6,12} have been added to PCA opioids to reduce PCA-related PONV. However, diphenhydramine, an inexpensive H₁ receptor antagonist frequently used to treat nausea and vomiting,¹³ has not been investigated in this manner.

In the randomized double-blind placebo-controlled study, we evaluated whether an initial bolus of diphenhydramine

at anaesthetic induction followed by postoperative PCA with diphenhydramine–morphine mixture could reduce morphine-related PONV in women undergoing abdominal total hysterectomy. Two different ratios of diphenhydramine–morphine mixture were investigated.

Methods

This randomized double-blinded placebo-controlled study was approved by the Hospital Committee for Human Investigation. Written informed consent was obtained from all patients. A total of 120 women (18–65 yr; ASA I or II) scheduled for elective abdominal total hysterectomy under general anaesthesia and postoperative analgesia with a PCA device were assessed for inclusion in the study. Exclusion criteria included pregnancy or lactation, underlying

gastrointestinal diseases, a documented allergic reaction to any of the medications used, concurrent use of any antiemetic, antipsychotic medications, or a history of previous PONV and motion sickness.

According to a computer-generated random number table, patients were allocated to one of three groups ($n=40$ per group). Each patient was assigned one 1-ml induction syringe as the loading dose and one 100-ml non-polyvinylchloride plastic PCA container for postoperative pain management. The control group (group 1) received an induction syringe containing 0.9% saline as placebo and a PCA container containing morphine 1 mg ml^{-1} alone. The two treatment groups each received an induction syringe containing diphenhydramine 30 mg and PCA containers containing diphenhydramine–morphine mixtures with a ratio of diphenhydramine to morphine of 1.2:1 or 4.8:1 (groups 2 and 3, respectively). All patients were blinded to the nature of the drug administered. A specially trained nurse anaesthetist, not involved in any subsequent assessments, was in charge of preparing the study medication and group assignment.

The two mixture ratios were chosen according to two rationales. First, among Taiwanese women undergoing abdominal total hysterectomy, an average of 25 mg PCA morphine has been shown to provide adequate analgesia in the first 24 h postoperatively.¹⁴ Our institutional experience also suggests that a bolus injection of diphenhydramine 30 mg at 6-h intervals, a total of 120 mg in the first 24 h postoperatively, can relieve the coexisting PCA morphine-induced emesis. Thus the ratio of diphenhydramine to morphine in group 3 (4.8:1) was derived by dividing 120 mg diphenhydramine by 25 mg morphine. This combination ratio, a direct conversion from effective bolus dose, can be anticipated to produce a greater efficacy–safety profile than conventional bolus injection because of the distinct pharmacokinetic advantages associated with the PCA-based drug delivery system.¹ Secondly, 25% of the calculated ratio (1.2:1) was chosen for group 2 to disclose whether a minimal diphenhydramine concentration would still be potent enough to protect against PCA-induced emesis. This ratio was chosen on the basis of the results of two previous studies using promethazine–morphine⁴ and droperidol–morphine¹² showing that the antiemetic effect was still demonstrable even at 20–25% of the typical corresponding drug dosage for emesis. Collectively, the aims of these two different and separate ratios are to explore whether the novel diphenhydramine–morphine combination is an effective regimen and to serve as a prerequisite for future dose-finding studies.

Anaesthesia

Before surgery, all patients were instructed on the operational use of the PCA system and a 0–10 visual analogue scale (VAS), where 0 represented no pain and 10 the worst pain imaginable. All patients fasted for at least 8 h before surgery. A standard general anaesthetic was given, comprising thiopental $3\text{--}5\text{ mg kg}^{-1}$, fentanyl $1.5\text{--}3\text{ }\mu\text{g kg}^{-1}$,

and atracurium $0.5\text{--}0.8\text{ mg kg}^{-1}$. Anaesthesia was maintained by isoflurane 0.8–1.5% in oxygen. The assigned induction syringe was administered immediately after induction. The last dose of fentanyl had to be given 30 min before the end of surgical procedures. Edrophonium $0.5\text{--}1\text{ mg kg}^{-1}$ and atropine 0.015 mg kg^{-1} were given to antagonize residual neuromuscular block at the end of surgery.

Postoperative analgesia was provided in the recovery room immediately after the patient complained of pain. At the discretion of the nursing staff or the attending anaesthesiologist, the assigned PCA solution was administered in 1- to 2-mg increments until the patient was comfortable. When the patient was stable and sufficiently alert, PCA was initiated. One millilitre of PCA solution was administered on demand with a 5-min lockout and no background infusion was set. Patients were continuously monitored with a three-lead electrocardiogram, digital pulse oximetry, and non-invasive blood pressure during the stay in the postoperative recovery room. All the patients were made aware that rescue antiemetic (prochlorperazine 10 mg i.v.) would be available on request. The rescue antiemetic treatment was repeated if necessary. After a 1-h stay in the recovery room, patients were transferred to the ward when the vital signs were stable.

Data obtained for each patient included age, weight, type of surgery, and duration of anaesthesia. Assessments of pain, nausea, vomiting, pruritus, dry mouth, sedation, PCA morphine, and rescue antiemetic requirements, as well as any noted side-effects, were recorded by an independent clinical investigator at 1, 2, 4, and 24 h postoperatively. Patients were instructed to report the intensity of pain at rest using VAS and to use PCA to maintain $\text{VAS} \leq 3$. We asked patients to categorize the severity of nausea, vomiting, pruritus, and dry mouth at the end of the study period as none, mild, moderate, or severe. The level of sedation was assessed by the investigator by using a five-point scoring scale: 0=fully awake; 1=drowsy, closed eyes; 2=asleep, easily aroused with light tactile stimulation or simple verbal command; 3=asleep, arousable only by strong physical stimulation; 4=unarousable.¹⁵ A sedation score ≥ 3 was regarded as unacceptable in this context, and was to be assessed and reported by any health care personnel with the subject then being switched to an alternate analgesic modality. Urinary retention could not be assessed because of the routine use of indwelling catheters in all patients. Respiratory depression was defined as bradypnoeic episodes (a ventilatory frequency $<8\text{ bpm}$) lasting $>10\text{ min}$. Respiratory depression was treated with naloxone $40\text{ }\mu\text{g i.v.}$

Statistical analysis

Based on our preliminary data, the sample size was predetermined using a power analysis as follows: the overall incidence of nausea in the first 24 h after surgery in the placebo-controlled group was 70%; a 50% reduction in the incidence of nausea (from 70% to 35%) was of clinical relevance; $\alpha=0.05$ (two-tailed) and $\beta=0.2$. It indicated that 36 patients per group would be sufficient. Data were

analysed using SPSS 10.0 (SPSS Inc., Chicago, IL). A series of one-way analyses of variance was conducted to examine differences among the three groups with respect to continuous variables. If a significant difference was found, the Tukey post hoc comparisons were used to detect intergroup differences. The Kruskal–Wallis test was used to determine differences among the three groups with respect to ordinal variables, and post hoc comparisons between groups were made using the Mann–Whitney *U*-test. Categorical variables were analysed using 2×2 χ^2 -tests to determine the differences between group 1 and group 2 and the difference between group 1 and group 3. All follow-up analyses were corrected for the number of simultaneous contrasts using the Bonferroni's adjustments. A *P*-value <0.05 was considered statistically significant.

Results

A total of 120 patients were enrolled in the study over a 6-month period. Eight patients were subsequently excluded for a variety of reasons: two had difficult intubation, two were reoperated within 24 h of surgery because of continuous haemorrhage, one had her PCA machine replaced twice because of pump malfunction and data collection was incomplete in the remaining three. Thus 112 patients completed the study: 37 in group 1, 37 in group 2 and 38 in group 3. Patient characteristics and intraoperative variables were comparable in all groups (Table 1).

Pain intensities were not significantly different among the groups during the 24 h of observation (Fig. 1). The total dose of PCA morphine (Fig. 2) did not differ between groups at each observational time point. The overall dose of diphenhydramine, including the initial loading bolus, was 60.8 (SD 14.8) mg in group 2 and 140.9 (43.7) mg in group 3. The maximum morphine consumption during the first 24 h after surgery was 51 mg in a patient in group 2, while the maximum dose of diphenhydramine (including the initial loading bolus) was 222 mg in a patient in group 3. There was no report of morphine-related respiratory depression or diphenhydramine-related somnolence (sedation score ≥ 3) in this study.

The incidence and severity of nausea, vomiting, and rescue antiemetic requirements are reported in Table 2. Compared with the control group, the overall incidence of postoperative nausea and vomiting was significantly reduced in group 3 ($P < 0.05$). Furthermore, the incidence

Table 1 Patient characteristics and intraoperative data. Values are mean (range), mean (SD) or number. The three groups were similar for all variables tested

	Group 1	Group 2	Group 3
Number	37	37	38
Age (yr)	45.1 (21–62)	43.7 (23–66)	42.7 (23–65)
ASA (I/II)	17/20	19/18	18/20
Weight (kg)	56.4 (8.4)	58.1 (9.1)	56.4 (9.0)
Duration of anaesthesia (min)	113 (42)	125 (46)	119 (39)
Intraoperative fentanyl used (μ g)	131.8 (34.7)	129.1 (26.0)	134.2 (32.1)

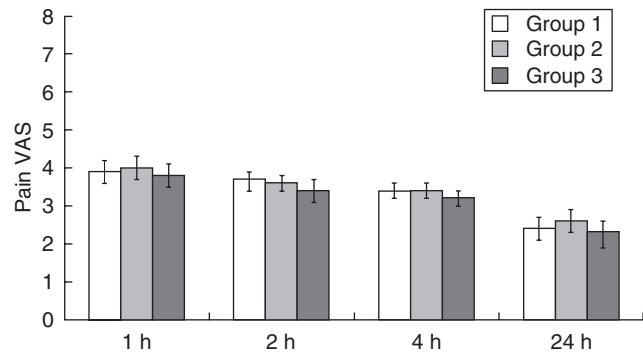


Fig 1 VAS pain intensity at rest (mean and 95% confidence interval). No significant differences.

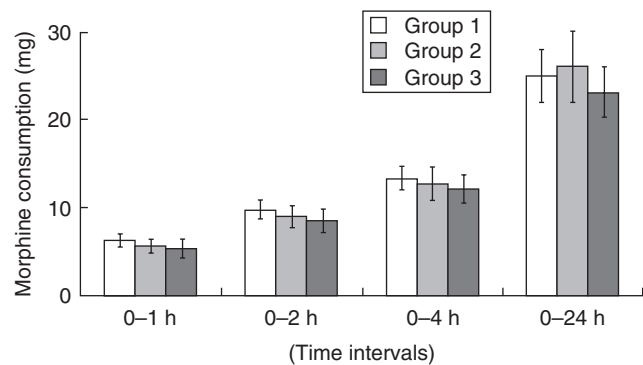


Fig 2 Morphine consumption (mean and 95% confidence interval). No significant differences were observed.

Table 2 Main adverse effects and rescue antiemetic requirements. Values are shown as number or number (%). Sedation scores: 0, fully awake; 1, drowsy, closed eyes; 2, asleep, easily aroused with light tactile stimulation or simple verbal command; 3, asleep, arousable only by strong physical stimulation; 4, unarousable. Respiratory depression is defined as bradypnoeic episodes (ventilatory frequency <8 bpm) lasting >10 min. * $P < 0.05$ and ** $P < 0.01$, group 3 versus group 1

	Group 1	Group 2	Group 3
No. of patients	37	37	38
Nausea			
Total	25 (67.6)	21 (56.8)	12 (31.6)**
Mild	7	7	8
Moderate	9	8	3
Severe	9 (24.3)	6 (16.2)	1 (2.6)*
Vomiting			
Total	15 (40.5)	12 (32.4)	6 (15.8)*
Mild	3	2	3
Moderate	4	5	1
Severe	8 (21.6)	5 (13.5)	2 (5.3)
Patients requiring prochlorperazine	9 (24.3)	7 (18.9)	2 (5.3)*
Total no. of doses	15	10	3
Pruritus	7 (18.9)	8 (21.6)	2 (5.3)
Dry mouth	3	5	9
Sedation (0/1/2/3/4)			
1 h	24/8/5/0/0	23/7/7/0/0	21/9/8/0/0
2 h	29/5/3/0/0	28/5/4/0/0	25/8/5/0/0
4 h	32/2/3/0/0	30/5/2/0/0	28/6/4/0/0
24 h	35/2/0/0/0	35/2/0/0/0	34/4/0/0/0
Respiratory depression	0	0	0

of severe nausea was significantly lower in group 3 than in group 1 (2.6% vs 24.3%, $P<0.05$). The incidence of severe vomiting was lower in group 3 than in group 1 (5.3% vs 21.6%, $P=0.094$); however, the difference was not statistically significant. The number of patients requiring prochlorperazine was also significantly less in group 3 than in group 1 (5.3% vs 24.3%, $P<0.05$). Furthermore, the total number of doses of prochlorperazine was least in group 3. In contrast, there were no significant differences between group 2 and group 1 with regard to the incidence and severity of nausea and vomiting, and the antiemetic requirements.

There was no statistically significant difference in the level of sedation between the groups at each of the observation time points. No patient had a sedation score ≥ 3 (Table 2). The incidence and severity of pruritus and dry mouth were similar among the groups. None of the adverse effects warranted terminating PCA use.

Discussion

This study shows that the addition of diphenhydramine to PCA morphine, following an initial bolus dose given at induction of anaesthesia, significantly reduces morphine-related nausea and vomiting and the need for further antiemetic treatment without additional sedative effect. With the lack of a morphine-sparing effect, our result clearly demonstrates that the profound antiemetic efficacy does not occur as a result of reduced morphine consumption. We also showed that a diphenhydramine-to-morphine ratio of 4.8:1, but not 1.2:1, provides sufficient protection against nausea and vomiting. The concentration-dependent efficacy demonstrates that the ratio of diphenhydramine–morphine mixtures plays a critical role in the prophylaxis of PCA morphine-related PONV.

Diphenhydramine, an active ingredient of dimenhydrinate, has been widely used as an antiemetic agent. In comparison, 30 mg of diphenhydramine is equivalent to about 60 mg of dimenhydrinate (a combination of diphenhydramine and 8-chlorotheophylline in equal proportions) in potency. Diphenhydramine has a faster onset of action than dimenhydrinate because dimenhydrinate is the prodrug of diphenhydramine and must be broken down in the body before it is active. Both drugs block muscarinic–cholinergic receptors located in the vestibular pathways and vomiting centre.¹³ In female inpatients, Eberhart and colleagues¹⁶ used an i.v. dose of dimenhydrinate given after induction followed by three further rectal doses of the drug postoperatively. They found that dimenhydrinate reduced the incidence and severity of PONV, but an unacceptably large number of patients still experienced it. While repeating dimenhydrinate may be associated with increased benefit in adults, Kranke and colleagues¹⁷ concluded in a recent meta-analysis that the dose–response and the optimal time of administration still remain unclear.

Our study is the first to show that an adequate diphenhydramine–morphine mixture ratio is an ideal meas-

ure for protecting against morphine-related PONV. The particular advantage of this study is the use of the PCA device to deliver diphenhydramine and morphine simultaneously on demand for postoperative pain relief. Considering the application of the PCA concept to antiemetic therapy, diphenhydramine is superior to dimenhydrinate because of its faster onset of effect. As the elimination half-life of both diphenhydramine and morphine is 2.5–4 h, their similar pharmacokinetic profiles allow simultaneous titration of both drugs to achieve a balance between analgesia and antiemesis. The predetermined on-demand bolus injection provided by PCA is able to minimize delay in obtaining efficacy and thus is able to reduce side-effects associated with larger bolus doses. We believe that the antiemetic efficacy of diphenhydramine in morphine PCA is mainly attributed to the drug administration timed to provide adequate blood concentrations during the first 24-h postoperative period. Considering the duration of the uncomplicated surgical procedures in our study (<4 h), the initial loading bolus of diphenhydramine administered immediately after induction of anaesthesia ensures an adequate plasma concentration before the initiation of PCA. By adding diphenhydramine to morphine PCA, a small prophylactic dose of diphenhydramine is administered with each morphine bolus, further extending the antiemetic effects beyond the period covered by a single bolus dose.

The most interesting finding in this study is the lack of additional sedative effect by diphenhydramine throughout the first 24-h postoperative period. One potential drawback of the use of diphenhydramine is profound drowsiness and delayed arousal after general anaesthesia.^{13,18} As sedation is a shared common side-effect associated with both diphenhydramine and morphine, co-administration of diphenhydramine and morphine theoretically precipitates patients' sedation. In view of the likelihood of delayed emergence from anaesthesia or the susceptibility of patients to additional sedation from the subsequent PCA usage, the initial loading bolus of diphenhydramine was administered immediately after induction of anaesthesia followed by intermittent titration of morphine and diphenhydramine via PCA settings. Thus the minidose titration of diphenhydramine–morphine admixture (4.8 mg diphenhydramine on each demand with 5 min lockout) can minimize the level of sedation. In contrast, sedation could have been more pronounced if diphenhydramine had been administered separately in set intervals at 30 mg every 6–8 h. The antiemetic mechanism of our results cannot be simply explained by the common observation that sedation or drug-induced drowsiness often makes nausea more bearable by allowing the patient to 'sleep it off'.¹⁹ Thus the coexisting sedative effect of minidose diphenhydramine titration attributed little, if any, to its antiemetic effect.

Delivering an analgesic–antiemetic combination by PCA systems has been widely accepted as a successful and sensible approach to reducing PCA opioid-related emesis.²⁰ Droperidol is the best-documented drug that has shown

consistent antiemetic efficacy, with greater antinausea than antiemetic effects.^{12,20} However, concern about the potential droperidol-related cardiac toxicity has led to a cessation of droperidol following a 'black box' warning issued by US Food and Drug Administration in 2001.²¹ Ondansetron, a serotonin-selective antagonist, has been shown to be as effective as, but not better than, droperidol in combination with morphine PCA.⁶⁻⁸ However, limited antiemetic efficacy even under a high-dose ondansetron regimen suggests the limited effectiveness of the drug itself.^{6,7} Metoclopramide does not appear to be an effective antiemetic in combination with morphine PCA.^{10,11} In a recent trial,⁹ metoclopramide was found to exhibit potent antiemetic efficacy against PCA tramadol-induced PONV, but at the cost of increased sedation. Interventions with promethazine⁴ and cyclizine⁵ are encouraging, but were based on very limited numbers of patients or did not have placebo control. Compared with the antiemetics mentioned above, diphenhydramine is favoured by most clinicians for its cost-effectiveness, simplicity and safety. As multiple antiemetic combinations for PONV prophylaxis have shown promising results,^{22,23} diphenhydramine, with its demonstrable efficacy and a good safety profile, can be accepted as a useful co-medication drug in combination with other antiemetics for PCA-related PONV.

Another concern with the use of the morphine-diphenhydramine mixture is the potential incompatibility of this combination. Although chemical compatibility data between diphenhydramine and morphine are lacking, our preclinical laboratory study proved that this combination appeared to be stable as both drugs remained clinically active and no precipitate was visible after 24 h.

In conclusion, we have attested to the satisfactory antiemetic efficacy and postoperative pain relief achieved by a 4.8:1, but not a 1.2:1, ratio of diphenhydramine to morphine for postoperative PCA in women undergoing abdominal total hysterectomy without additional sedative effect. The lack of a morphine-sparing effect suggests that diphenhydramine does not potentiate morphine-produced analgesic effect. However, the optimal ratio of diphenhydramine-morphine admixture for the prophylaxis of PCA morphine-related PONV still needs to be evaluated by future studies.

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