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CLINICAL INVESTIGATIONS

Dose requirements, efficacy and side effects of morphine and pethidine delivered by patient-controlled analgesia after gynaecological surgery

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Summary

We have compared the dose requirements and side effects of morphine with those of pethidine when administered by patient-controlled analgesia in 40 patients (ASA I–II, 20–65 yr) after elective total abdominal hysterectomy. Patients were allocated randomly, in a double-blind manner, to receive either morphine (bolus dose 2 mg, lockout time 10 min) or pethidine (bolus dose 20 mg, lockout time 10 min) for postoperative pain relief. Mean 24-h morphine and pethidine consumption was 70 (SEM 6.2) mg and 660 (67.8) mg, respectively (ratio 1 : 9.4). There were no significant differences in postoperative sedation, nausea, pain relief and patient satisfaction (VAS 0–100 mm), and requirements for antiemetics. Four patients receiving pethidine were withdrawn because of postoperative confusion and one receiving morphine because of intractable nausea and vomiting. The 95 % confidence interval for this difference between the groups for VAS scores of sedation, nausea and pain were approximately 30 mm. (*Br. J. Anaesth*. 1996; **76**: 484–486)

Key words

Analgesia, postoperative. Analgesia, patient-controlled. Analgesics opioid, morphine. Analgesics opioid, pethidine.

Morphine and pethidine are used commonly for patient-controlled analgesia (PCA). There are some clinical situations where pethidine may be preferred to morphine, for example in asthmatics (anticholinergic action of pethidine) and after bowel anastomoses (dehiscence with morphine [1]) but the choice is often based on other perceived differences in efficacy and side effects such as quality of analgesia and tendency to nausea and vomiting. However, there are few data in the literature to enable proper comparison.

PCA enables comparison of the potency, efficacy and side effects of opioids in the treatment of pain after surgery [2, 3]. Therefore, we have examined, in a prospective, randomized, double-blind study, the relative efficacy and side effects of morphine and pethidine.

Patients and methods

We studied 40 patients, ASA I–II, aged 20–65 yr, undergoing total abdominal hysterectomy. All patients gave written informed consent to the study which was approved by the local Ethics Committee.

Patients were instructed in the use of the PCA machine (Graseby) on the day before surgery. A visual analogue scale (VAS) for assessment of nausea, pain and satisfaction was also explained. Each VAS comprised a 100-mm unmarked line, the ends of which denoted extremes of the variables in question, that is no nausea—extreme nausea; no pain—worst pain imaginable; very unhappy—delighted with everything.

All patients were premedicated with temazepam 10–20 mg orally, 1 h before surgery. Anaesthesia was induced with propofol 2 mg kg^{-1} and tracheal intubation and positive pressure ventilation were facilitated by the use of vecuronium 0.1 mg kg^{-1}. Anaesthesia was maintained with 1 % isoflurane and 66 % nitrous oxide in oxygen, and fentanyl 2–4 $\mu g\ kg^{-1}$.

Patients were allocated randomly (sealed envelopes) to receive morphine or pethidine by PCA (morphine 2 mg bolus, lockout 10 min; pethidine 20 mg bolus, lockout 10 min). The drug solution was prepared such that 1 ml contained either morphine 2 mg or pethidine 20 mg. The anaesthetist and nurse investigators were blinded to the contents of the PCA syringe. Operation of the PCA device was recorded by a printer (Hewlett–Packard Thermal Printer).

During the immediate recovery period, opioid was administered i.v. in a double-blind fashion in either 1-mg (morphine) or 10-mg (pethidine) increments in the recovery room. Increments were given every 2–4 min by the anaesthetist conducting the study, until pain control was judged to be comfortable and satisfactory by the patient. PCA was then commenced.

VAS scores for pain, nausea and satisfaction were made at 4, 8 and 24 h after commencing PCA. Sedation (wide awake—unable to stay awake) was also assessed at 4, 8 and 24 h by the blinded observers using a VAS scoring system. At the end of the 24-h study period, patients were asked to describe their appreciation of overall pain, nausea and vomiting which was assessed on a three-point verbal scale

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(none/slight, moderate, severe). Patient satisfaction was assessed in a similar manner. All measurements were made by a blinded investigator. Prochlorperazine 12.5 mg i.m. was given for nausea on patient request by the nursing staff who were also blinded to the opioid used.

Data were analysed by Student's *t*-test, Mann–Whitney *U* test and chi-square test with Yates' correction, as appropriate. MANOVA for repeated measures was used for visual analogue scores.

Results

There were no significant differences in age, weight, temazepam premedication, duration of surgery and dose of fentanyl administered during surgery (table 1).

Mean 24-hour postoperative opioid consumption by PCA was morphine 70 (SEM 6.2) and pethidine 660 (67.8) mg (ratio 1 : 9.4). There were no significant differences between the groups in the VAS scores for pain, nausea, sedation or satisfaction, and these data, with 95 % confidence intervals (CI) for the differences, are shown in table 2. There was no difference also in the number of doses of prochlorperazine administered (table 3).

Overall pain, nausea and vomiting, and satisfaction scores obtained at the end of the study are shown in table 4. These data include those patients (see below) who were withdrawn from the study. There were no significant differences between the two groups.

Four patients in the pethidine group became disorientated and confused, 2–3 h after commencing PCA. They were withdrawn from the study and symptoms disappeared 2–3 h after removing PCA. There were no signs of respiratory depression, the maximum total amount of incremental pethidine received by these patients in the recovery room was 30 mg and overall no patient received more than 50 mg of pethidine in total.

One patient in the morphine group was withdrawn because of intractable nausea and vomiting. This patient became severely nauseated after receiving morphine 3 mg i.v. in the recovery room and was withdrawn from the study 3 h later. Her symptoms remained for several hours despite the use of prochlorperazine and ondansetron.

Table 1 Patient characteristics (mean (SD or range)). No significant differences

	Morphine ($n = 20$)	Pethidine ($n = 20$)
Age (yr)	43 (20–65)	39 (25–49)
Weight (kg)	69.58 (13.16)	61.53 (7.43)
Temazepam (mg)	18.4 (3.8)	18.5 (4.8)
Duration of surgery (min)	65.79 (24.51)	66.00 (21.72)
Fentanyl (μg)	242 (53.40)	231 (43.30)

Table 2 Mean (SEM) and 95 % confidence intervals for the differences in visual analogue scores for pain, nausea, sedation and satisfaction at 4, 8, 24 h

	Morphine (mm) ($n = 19$)	Pethidine (mm) ($n = 16$)	95 % CI of difference
Pain			
4 h	45.2 (6.8)	55.9 (4.8)	(−6.9, 28.4)
8 h	42.4 (5.5)	44.4 (6.9)	(−15.7, 19.9)
24 h	39.7 (5.4)	40.3 (4.1)	(−13.5, 14.8)
Nausea			
4 h	14.7 (4.9)	11.9 (5.2)	(−17.4, 11.8)
8 h	31.0 (7.2)	37.1 (8.0)	(−15.8, 27.9)
24 h	33.1 (6.2)	27.1 (7.8)	(−26.0, 13.9)
Sedation			
4 h	67.2 (6.7)	65.3 (5.8)	(−20.2, 16.4)
8 h	50.2 (6.9)	55.7 (8.4)	(−16.4, 27.4)
24 h	55.8 (6.2)	48.2 (6.8)	(−26.3, 10.9)
Satisfaction			
4 h	52.1 (6.5)	69.2 (6.5)	(−34.9, 0.6)
8 h	48.2 (6.8)	61.1 (6.5)	(−28.8, 8.7)
24 h	69.3 (5.0)	63.1 (5.4)	(−21.1, 8.7)

Table 3 Number (%) of patients requiring prochlorperazine. No significant differences

Prochlorperazine doses (*n*)	Morphine ($n = 20$)	Pethidine ($n = 16$)
0	8 (40)	2 (13)
1	8 (40)	9 (56)
2	2 (10)	5 (31)
3	2 (10)	0 (0)

Table 4 Three-point verbal scoring at 24 h. No significant differences

	Morphine ($n = 20$)	Pethidine ($n = 20$)
Pain		
Severe	2	2
Moderate	8	10
Slight/none	10	8
Nausea		
Unbearable/severe	7	5
Moderate	8	9
Slight/none	5	6
Satisfaction		
Unhappy/miserable	9	5
Moderately happy	9	9
Happy/delighted	2	6

Discussion

We found no significant differences between morphine and pethidine PCA over a 24-h period in pain, nausea and vomiting, sedation and patient satisfaction. The 95 % CI for the differences between the groups for VAS scores of pain, nausea and sedation were approximately 30 mm. The clinical importance of this difference is uncertain but we believe that it is unlikely to be significant. However, one patient was severely nauseated after a small dose of morphine and was withdrawn from study.

Our data are similar to those obtained in patients receiving morphine, pethidine or oxymorphone via PCA after elective Caesarean section during extradural anaesthesia [4]. Also, there were no differences between morphine and pethidine after open cholecystectomy [5]. The comparison in this study was less clear as its primary purpose was to investigate the efficacy and side effects of nalbuphine. However, there may be significant differences between morphine and pethidine when delivered via PCA in

children [6]. Morphine was associated with better analgesia and greater sedation, with no other differences in side effects.

Morphine : pethidine potency ratios of between 1 : 10 and 1 : 12 have been described in the postoperative period [5 7, 8]. Our ratio of 1 : 9.4 is consistent with these data.

While we did not intend to study postoperative confusion, it was interesting to note that four relatively young, healthy patients in our study became confused and disorientated in the early postoperative period after small doses of pethidine. This was not relieved by administration of oxygen, although there were no signs of respiratory depression, but improved rapidly after cessation of pethidine administration. Postoperative confusion with pethidine has been described previously. For example, in a recent well designed study of 245 postoperative patients, pethidine was associated significantly with postoperative delirium (odds ratio 2.7) [9]. However, these patients tended to be older than those in our study (> 50 yr) and psychological measurements were obtained from day 2 to day 5 after operation.

Confusion may be caused by norpethidine, a metabolite of pethidine [10]. However, in our study, significant plasma concentrations of this metabolite were unlikely as relatively small doses of pethidine were administered before symptoms commenced (maximum 50 mg). Many drugs with a central anticholinergic action are associated with deranged function of the central nervous system [11] and it may be that the anticholinergic action of pethidine was significant in our patients.

In conclusion, we have shown little difference in the pharmacodynamics of pethidine and morphine with respect to analgesia, nausea and vomiting, sedation and patient satisfaction using PCA with the regimen described in relatively healthy patients undergoing elective hysterectomy. However, our work gives further evidence to the view that pethidine may be associated with an increased incidence of postoperative confusion.

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