

Epidural Meperidine after Cesarean Section A Dose-Response Study

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Background: Epidural meperidine is effective for postoperative analgesia, but the optimum dose has not been evaluated.

Methods: Five doses of epidural meperidine (12.5, 25, 50, 75, and 100 mg) given at the first request for analgesia after cesarean section were compared. Visual analog pain scores, duration of analgesia as defined by time to first patient-controlled epidural analgesia demand, plasma concentrations of meperidine, side effects, and subsequent 24-h consumption of meperidine were evaluated.

Results: All doses were effective, but patients took longer to become pain-free after 12.5 mg (median 30 min) compared with 25 mg (median 12 min, $P = 0.038$), and duration of analgesia was shorter after 12.5 mg (median 83 min) compared with 25 mg (median 165 min, $P = 0.0005$). Increasing dose to more than 25 mg did not improve onset or duration of analgesia. Plasma concentrations of meperidine were less than minimum effective analgesia concentration for all doses except 100 mg. There was more frequent nausea ($P = 0.004$) and dizziness ($P = 0.0002$) after 100 mg compared with smaller doses.

Conclusions: Epidural meperidine provides effective postoperative analgesia, although of relatively short duration. A single dose of 25 mg is superior to 12.5 mg, but there is no benefit from increasing the dose to 50 mg or greater. (Key words: Analgesia, epidural; postcesarean section. Analgesics: meperidine.)

Meperidine hydrochloride is an opioid of intermediate lipid solubility (octanol/pH 7.4 buffer partition coefficient 38.8, compared with morphine sulfate 1.42),¹ and unlike more lipid-soluble agents, such as fentanyl^{2,3} (partition coefficient 813), and sufentanil⁴ (partition coefficient 1,778), it has been shown consistently to provide superior analgesia with smaller dose requirements and lower plasma concentrations compared with those required for systemic administration.⁵⁻⁸ Meperidine has been used safely for postcesarean section analgesia for longer than a decade in some countries.^{5,6} However, the dose-response relationship for epidural meperidine has not been described. Therefore, we performed a randomized, double-blind comparison of five doses of meperidine given as a single epidural bolus for pain relief after cesarean section. Analgesic efficacy, duration, side effects, and systemic absorption were evaluated to determine the optimum dose.

Materials and Methods

After obtaining approval from the local Clinical Research Ethics Committee, we studied 75 ASA physical status 1 or 2 women undergoing cesarean section under epidural anesthesia. Women undergoing elective and nonelective operations were enrolled. All patients gave written informed consent and were instructed on the use of a 100-mm visual analog scale and a patient-controlled analgesia device (Abbott Pain Management Provider, Abbott Laboratories, North Chicago, IL). Elective cases received 150 mg ranitidine orally the night before and the morning of surgery and 0.3 M sodium citrate 30 ml on arrival in the operating room, whereas nonelective cases received 0.3 M sodium citrate 30 ml when the decision for surgery was made. An epidural catheter was inserted into the L2-3 or L3-4 vertebral interspace and lidocaine 2% with adrenaline 1:200,000 was injected to establish sensory anesthesia to the T4 dermatome. The existing catheter was used in patients

THERE is controversy whether epidural administration of highly lipid-soluble opioids has advantages over intravenous or intramuscular routes of administration.

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Received from the Department of Anaesthesia and Intensive Care, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong. Submitted for publication January 3, 1996. Accepted for publication April 3, 1996. Presented in part at the New York State Society of Anesthesiologists, Inc., 49th Postgraduate Assembly in Anesthesiology, New York, New York, December 11, 1995.

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with an epidural catheter already *in situ* for labor analgesia. Intraoperative analgesia, if required, was provided by nitrous oxide *via* face mask or 10 mg intravenous increments of ketamine and hypotension was treated with intravenous boluses of ephedrine. The epidural catheter and filter were cleared of local anesthetic by flushing with 2 ml normal saline after completion of surgery.

In the postanesthesia care unit, patients were randomized by drawing of shuffled coded envelopes to receive one of five doses of preservative-free meperidine epidurally at the first request for analgesia: 12.5, 25, 50, 75, or 100 mg. All doses were diluted to 10 ml with normal saline and injected through the epidural filter over 30 s. The epidural catheter and filter were then flushed with 1 ml normal saline. Patient assessments were made immediately before the dose of meperidine and at 3, 6, 9, 12, 15, 30, and 60 min after the dose. At each assessment, patients were asked to grade pain, nausea, dizziness, and pruritus using the visual analog scale, arterial hemoglobin saturation was recorded with a pulse oximeter (Biox 3700e, Ohmeda, Louisville CO 80027), arterial pressure and pulse rate were recorded with a noninvasive blood pressure monitor (Dinamap, Critikon, Tampa, FL), and sedation was assessed on a 4-point scale (1 = alert; 2 = awake but drowsy; 3 = asleep, easy to rouse; 4 = asleep, difficult to rouse).

After 30 min, patient-controlled epidural analgesia (PCEA) was made available using 10 mg/ml meperidine

(dose 20 mg, lockout interval 10 min, 4-h maximum 200 mg). Patients were observed in the postnatal ward according to our standard protocol for PCEA, which consists of hourly measurement of respiratory rate and level of consciousness. The time of first PCEA demand, and total meperidine consumption in the first 24 h were obtained subsequently from the electronic memory of the PCEA device.

An intravenous cannula for blood sampling was inserted into a forearm vein on the side opposite to the intravenous infusion. Blood samples for subsequent measurement of plasma concentration of meperidine were taken before administration of the dose and at 15, 30, and 60 min after the dose. Blood sampling was omitted in patients who had received intramuscular meperidine during labor and the 60 min sample was omitted in patients who made a PCEA demand between 30 and 60 min. Samples were immediately centrifuged and the plasma was stored at -70°C before assay using a modified gas chromatography method.^{9,10} The calibration curves for the assay were linear over the range 50–3000 ng/ml with coefficients of variation for between-day variation of 7.73% and 3.35% at 50 and 500 ng/ml, and coefficients of variation for within-day variation of 7.22% and 4.27% at 50 and 500 ng/ml. The lower limit of detection was 20 ng/ml.

Patient characteristics were analyzed using one-way analysis of variance followed by Scheffé's F test. Pain scores, time to first request for analgesia, time to first PCEA demand, 24-h meperidine consumption, and side

Table 1. Patient Characteristics and Details of Anesthesia

	Dose of Epidural Meperidine (mg)				
	12.5 (n = 15)	25 (n = 15)	50 (n = 15)	75 (n = 15)	100 (n = 15)
Age (yr)	32 ± 4.2	32 ± 7.4	31 ± 4.0	31 ± 5.5	30 ± 5.9
Weight (kg)	64 ± 8	61 ± 10	73 ± 5	66 ± 16	62 ± 6
Height (cm)	154 ± 4	155 ± 6	158 ± 4	155 ± 6	157 ± 6
Elective (n)	10	10	11	12	12
Nonelective (n)	5	5	4	3	3
Epidural analgesia in labor (n)	0	1	0	1	0
Im meperidine in labor (n)	1	2	0	2	1
Lidocaine 2% dose (ml)	20 ± 5	19 ± 3	22 ± 5	20 ± 5	20 ± 5
Intraoperative analgesic supplement required (n)	4	2	4	5	5
First request for analgesia (min)	122 (82–138)	104 (90–165)	123 (111–138)	122 (110–141)	120 (80–172)
Patients having blood samples (n)	13	13	14	13	13

Values are mean ± SD or number except time to request for analgesia, which is shown as median and interquartile range. Weight was significantly different among groups ($P = 0.01$, one-way analysis of variance) and greater in the 50-mg group compared with the 25-mg group (Scheffé's test). There were no differences between groups.

EPIDURAL MEPERIDINE: DOSE-RESPONSE

effects were analyzed using Kruskal-Wallis analysis of variance with comparisons between individual pairs of groups made using the Mann-Whitney *U* test. Frequency data were analyzed using the chi-squared test. Spearman's rank correlation was used to examine the association between patient weight and height and pain relief. $P < 0.05$ was considered statistically significant.

Results

Fifty-five elective and 20 nonelective cases completed the study. Three cases of breach of protocol occurred before randomization; these patients were rejected and three further patients were enrolled as replacements. Nonelective cases included two patients who had received epidural infusion of 0.1% bupivacaine and 0.0002% fentanyl and six patients who had received a single dose of intramuscular meperidine for labor analgesia. Time to first PCEA demand could not be obtained for one patient in the 75-mg group because of technical problems with the PCEA device. Patient characteristics and details of anesthesia are shown in table 1. Weight was different between groups ($P = 0.01$) and greater in the 50 mg group compared with the 25 mg group. Other patient characteristics were similar. There were no differences between groups in lidocaine dose, time to initial request for analgesia, or requirement for supplementation by ketamine or nitrous oxide.

Blood sampling was omitted from nine patients: six because they had received intramuscular meperidine before surgery and three because blood samples could not be obtained for technical reasons (table 1). There were no blood samples at 60 min from ten patients: four owing to technical reasons (one in each of the 12.5-mg and 100-mg groups and two in the 25-mg group) and six because patients made PCEA demands before 60 min (four in the 12.5-mg group and one in each of the 25-mg and 100-mg groups).

Pain scores in the first 60 min after the dose of epidural meperidine are shown in figure 1. Median time for patients to become pain-free (pain score zero) was greater after 12.5 mg meperidine (30 min) compared with 25 mg (12 min; $P = 0.038$, Mann-Whitney *U* test); there was no difference between 25 mg and any of the other doses. Seven patients failed to achieve pain score zero in the 12.5-mg group compared with one patient in each of the 25-mg, 50-mg, and 75-mg groups and no patients in the 100-mg group ($P = 0.001$, chi-squared test).

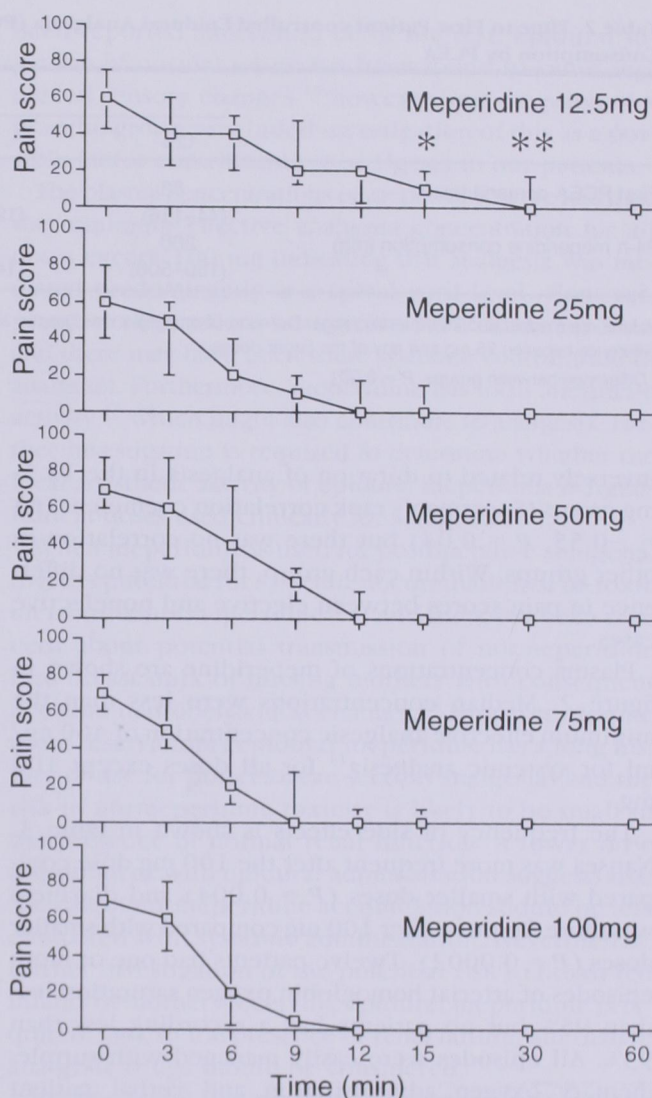


Fig. 1. Visual analog pain scores (mm) after epidural injection of five different doses of meperidine (median and interquartile range). * $P < 0.05$ for between-group differences (Kruskal-Wallis test). ** $P < 0.01$ for between-group differences (Kruskal-Wallis test).

Duration of analgesia, defined by the time to first PCEA demand, and total consumption of meperidine by PCEA in 24 h are shown in table 2. Duration of analgesia was greater after 25 mg (165 min) compared with 12.5 mg (83 min; $P = 0.0005$, Mann-Whitney *U* test) but there was no difference between 25 mg and any of the larger doses. Total meperidine consumption by PCEA in the first 24 h was similar for all groups. There was no correlation between patient weight and onset or duration of analgesia in any group. Patient height was

Table 2. Time to First Patient-controlled Epidural Analgesia (PCEA) Demand and Total 24-Hour Meperidine Consumption by PCEA

	Dose of Epidural Meperidine (mg)				
	12.5	25	50	75	100
First PCEA demand (min)*	83 (44–116)	165 (127–213)	175 (117–232)	188 (127–254)	170 (122–246)
24-h meperidine consumption (mg)	260 (160–500)	200 (140–340)	240 (160–425)	300 (160–415)	220 (140–360)

Values are median and interquartile range. Duration of analgesia was greater after 25 mg versus 12.5 mg ($P = 0.0005$, Mann-Whitney U test), but there was no difference between 25 mg and any of the larger doses.

* Difference between groups, $P = 0.001$.

inversely related to duration of analgesia in the 12.5-mg group (Spearman's rank correlation coefficient (r_s) = -0.55 , $P = 0.04$) but there was no correlation in other groups. Within each group, there was no difference in pain scores between elective and nonelective cases.

Plasma concentrations of meperidine are shown in figure 2. Median concentrations were less than the minimum effective analgesic concentration of 460 ng/ml for systemic analgesia¹¹ for all doses except 100 mg.

The frequency of side effects is shown in table 3. Nausea was more frequent after the 100 mg dose compared with smaller doses ($P = 0.004$) and dizziness was more frequent after 100 mg compared with smaller doses ($P = 0.0002$). Twelve patients had one or more episodes of arterial hemoglobin oxygen saturation less than 95% but no patients had a recording less than 93%. All episodes were easily managed with supplementary oxygen administration and verbal patient

arousal without sequelae. The incidence of episodes of hemoglobin oxygen desaturation was not significantly different among groups. Arterial pressure, pulse rate, and respiratory rate did not differ between groups at any time. No patient in any group required treatment for hypotension or bradycardia and there were no instances of respiratory rate less than 10 breaths/min.

Discussion

We confirmed that a single dose of epidural meperidine produces high-quality analgesia after cesarean section. When given by a single bolus after cesarean section, a dose of 25 mg provided faster onset and longer duration of analgesia, and a greater proportion of patients that became completely pain-free, compared with 12.5 mg but no advantage was seen when the dose was increased. Patients experienced more side effects when the dose was increased as high as 100 mg. This indicates that 25 mg is the optimum dose in our population.

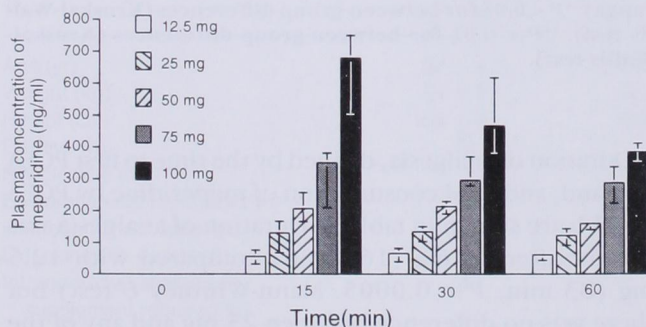


Fig. 2. Plasma concentrations of meperidine after epidural injection of five different doses of meperidine (median and interquartile range). Median concentrations were below the minimum effective analgesic concentration for systemic analgesia for all doses except 100 mg.

Table 3. Frequency of Side Effects

Meperidine Dose (mg)	Nausea*	Pruritus	Dizziness*	Sedation	SpO ₂ < 95%
12.5	0	0	2	1	1
25	0	0	2	1	1
50	0	0	2	1	3
75	1	1	4	0	4
100	4	1	9	0	3

Values are number of patients with side effects scores ≥ 3 and number of patients with one or more episodes of hemoglobin oxygen saturation < 95% in the first hour after a single bolus of epidural meperidine. More patients experienced nausea after 100 mg versus smaller doses ($P = 0.004$, chi-square test) and more patients experienced dizziness after 100 mg versus smaller doses ($P = 0.0002$, chi-square test).

* $P < 0.05$ for difference between groups.

EPIDURAL MEPERIDINE: DOSE-RESPONSE

Patient weight was greater in the 50-mg group compared with the 25-mg group, which may have created bias against finding a difference between the 25-mg and 50-mg doses, but the lack of difference between 25 mg and doses larger than 50 mg indicates that there is no significant benefit from doses larger than 25 mg. Little evidence exists to support a correlation between patient weight and dose requirements for epidural opioids. We found no correlation between patient weight and analgesia for any group, a similar finding to dose-response investigations of epidural morphine.¹² The inverse correlation between patient height and duration of analgesia in the 12.5-mg group suggests that height may be an important factor for smaller doses, possibly by influencing degree of spread within the epidural space, but this relationship was not confirmed with larger doses.

Duration of analgesia was 165–188 min for doses of meperidine greater than 12.5 mg and 24-h meperidine consumption by PCEA was similar for all groups. This indicates that unlike epidural morphine, epidural meperidine has a relatively short duration of action. This is in contrast to results from a previous study of cancer patients¹³ in which 100 mg epidural meperidine gave median duration of analgesia of 6 h in eight patients after surgery and 30–100 mg epidural meperidine gave median duration of analgesia of 8 h in eight patients with intractable pain. However, patients in that study were older than our patients (mean 60 yr in the postoperative group), may have been debilitated from their cancer, and received meperidine *via* a thoracic rather than a lumbar epidural catheter. A previous evaluation of epidural meperidine for postcesarean section analgesia found that 50 mg gave mean duration of analgesia of 277 min.⁶ The ready availability of further analgesia by PCEA in our study, as compared with nurse- or physician-administered boluses, may have biased our patients toward earlier requests for further analgesia. Because the duration of analgesia with epidural meperidine is relatively short, repeat dosing is necessary. Similar to other reports,^{7,8} we have found administration by PCEA to be convenient and very acceptable to patients.

We diluted each dose of epidural meperidine to a volume of 10 ml with normal saline. It has been recommended that opioids be injected into the extradural space in small volumes to minimize the risk of adverse effects.¹⁴ However, epidural fentanyl was associated with longer onset and shorter duration of analgesia when injected in diluent volumes of less than 5 ml and dilution of doses to at least 10 ml was recommended.¹⁵ Similar investigations for epidural meperidine have not

been reported and would be of interest. Epidural injection of normal saline has been found to cause segmental sensory changes,¹⁶ however, our omission of a placebo group precluded investigation of this as a possible factor contributing to analgesia in our patients.

The plasma concentrations of meperidine were less than the minimum effective analgesia concentration for all doses except 100 mg indicating that analgesia was mediated predominantly at a spinal cord level. However, plasma concentrations were greater with increasing doses and there may have been some systemic contribution to analgesia. Furthermore, meperidine has local anesthetic activity,¹⁷ which might also contribute to analgesia. Further investigation is required to determine whether the local anesthetic activity of epidural meperidine is significant at doses used clinically for analgesia.

When meperidine is used for postoperative analgesia, there is potential for systemic accumulation of its toxic metabolite normeperidine^{18,19} and there has been concern about potential transmission of normeperidine into breast milk of nursing mothers with consequent neonatal neurobehavioral changes.²⁰ However, despite these reservations, epidural meperidine has a long history of use for postcesarean section analgesia⁵ and the risk of normeperidine toxicity is likely to be small in the presence of normal renal function. A lower dose requirement with epidural administration suggests that the risk of normeperidine accumulation should be less compared with systemic administration. Nevertheless, further investigation of the potential risk to breast-fed infants of mothers receiving epidural meperidine is required, and, in the presence of renal failure, alternative analgesic drugs should be considered.

In conclusion, we performed an investigation of the dose-response relationship for epidural meperidine given for analgesia after cesarean section. Epidural meperidine provided effective analgesia but of relatively short duration. A bolus of 25 mg provided optimum analgesia with a low incidence of side effects. Plasma concentrations of meperidine were less than the systemic minimum effective analgesia concentration, which supports a spinal site of action.

References

1. Cousins MJ, Mather LE: Intrathecal and epidural administration of opioids. *ANESTHESIOLOGY* 1984; 61:276–310
2. Ellis DJ, Millar WL, Reisner LS: A randomized double-blind comparison of epidural versus intravenous fentanyl infusion for analgesia after cesarean section. *ANESTHESIOLOGY* 1990; 72:981–6

3. Glass PSA, Estok P, Ginsberg B, Goldberg JS, Sladen RN: Use of patient-controlled analgesia to compare the efficacy of epidural to intravenous fentanyl administration. *Anesth Analg* 1992; 74:345-51
4. Miguel R, Barlow I, Morrell M, Scharf J, Sanusi D, Fu E: A prospective, randomized, double-blind comparison of epidural and intravenous sufentanil infusions. *ANESTHESIOLOGY* 1994; 81:346-52
5. Brownridge P, Frewin DB: A comparative study of techniques of postoperative analgesia following caesarean section and lower abdominal surgery. *Anaesth Intensive Care* 1985; 13:123-30
6. Perriss BW, Latham BV, Wilson IH: Analgesia following extradural and I.M. pethidine in post-Caesarean section patients. *Br J Anaesth* 1990; 64:355-7
7. Yarnell RW, Polis T, Reid GN, Murphy IL, Penning JP: Patient-controlled analgesia with epidural meperidine after elective cesarean section. *Reg Anesth* 1992; 17:329-33
8. Paech MJ, Moore JS, Evans SF: Meperidine for patient-controlled analgesia after caesarean section. Intravenous versus epidural administration. *ANESTHESIOLOGY* 1994; 80:1268-76
9. Chan K, Kendall MJ, Mitchard M: A quantitative gas-liquid chromatographic method for the determination of pethidine and its metabolites, norpethidine and pethidine N-oxide in human biological fluids. *J Chromatogr* 1974; 89:169-76
10. Chan K, Lau OW, Wong YC: Determination of pethidine and its major metabolites in human urine by gas chromatography. *J Chromatogr* 1991; 565:247-54
11. Austin KL, Stapleton JV, Mather LE: Relationship between blood meperidine concentrations and analgesic response: A preliminary report. *ANESTHESIOLOGY* 1980; 53:460-6
12. Martin R, Salbaing J, Blaise G, Tétrault J, Tétrault L: Epidural morphine for postoperative pain relief: A dose-response curve. *ANESTHESIOLOGY* 1982; 56:423-6
13. Glynn CJ, Mather LE, Cousins MJ, Graham JR, Wilson PR: Peridural meperidine in humans: Analgetic response, pharmacokinetics, and transmission into CSF. *ANESTHESIOLOGY* 1981; 55:520-6
14. Chrubasik S, Chrubasik J: Selection of the optimum opioid for extradural administration in the treatment of postoperative pain (editorial). *Br J Anaesth* 1995; 74:121-2
15. Birnbach DJ, Johnson MD, Arcario T, Datta S, Naulty JS, Os-theimer GW: Effect of diluent volume on analgesia produced by epidural fentanyl. *Anesth Analg* 1989; 68:808-10
16. Hore PJ, Silbert BS, Cook RJ, Beilby DSN: A double-blind assessment of segmental sensory changes with epidural fentanyl versus epidural saline in patients undergoing extracorporeal shock-wave lithotripsy. *ANESTHESIOLOGY* 1990; 72:603-6
17. Power I, Brown DT, Wildsmith JAW: The effect of fentanyl, meperidine and diamorphine on nerve conduction in vitro. *Reg Anesth* 1991; 16:204-8
18. Stone PA, Macintyre PE, Jarvis DA: Norpethidine toxicity and patient-controlled analgesia. *Br J Anaesth* 1993; 71:738-40
19. Geller RJ: Meperidine in patient-controlled analgesia: A near-fatal mishap. *Anesth Analg* 1993; 76:655-7
20. Wittels B, Scott DT, Sinatra RS: Exogenous opioids in human breast milk and acute neonatal neurobehavior: A preliminary study. *ANESTHESIOLOGY* 1990; 73:864-9