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Meperidine for Patient-controlled Analgesia after Cesarean Section

Intravenous Versus *Epidural Administration*

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Background: **Although meperidine has been used for patient-controlled analgesia both intravenously (PCIA) and epidurally (PCEA), these routes have not been compared, and many studies have suggested that there is no advantage to the epidural route for administration of lipophilic opioids.**

Methods: **A randomized, double-blind, crossover study was conducted for 24 h after cesarean section to compare the analgesic efficacy, side effects, patient satisfaction, drug use, and plasma drug concentrations with meperidine administered either as PCIA or as PCEA. Two groups, stratified for time of cesarean section during epidural anesthesia, postoperatively received either PCEA (group 1) or PCIA (group 2) with identical variables for 12 h before crossing to the other route for an additional 12 h.**

Results: **Results from 45 patients showed a similar speed of analgesic onset but, subsequently, significantly lower pain scores both at rest and with coughing in those receiving PCEA ($P = 0.0001$). Nausea and pruritus scores did not differ between the groups in the first 12 h postoperatively, but sedation scores were significantly higher with PCIA ($P = 0.0001$). Patient satisfaction scores and preference significantly favored PCEA ($P = 0.0001$), with almost 90% of participants preferring the epidural route. Meperidine use was reduced approximately 50% with PCEA ($P = 0.0001$), and plasma meperidine and normeperidine concentrations were significantly lower ($P = 0.0001$).**

Conclusions: **We conclude that after cesarean section, PCEA with meperidine produces high-quality pain relief with few side effects and has significant advantages over PCIA meperidine. With the caveat that neonatal effects in breast-feeding mothers have yet to be evaluated, it can be highly recommended in this population. (Key words: Analgesia: patient-controlled epidural; patient-controlled intravenous; post-cesarean section. Analgesics: meperidine.)**

PATIENT-CONTROLLED intravenous analgesia (PCIA) has achieved widespread popularity for postoperative pain management, whereas clinical evaluation of patient-controlled epidural analgesia (PCEA) remains limited. The latter appears attractive, however, combining the analgesic efficacy of epidural opioids with the flexibility of self-titration.

PCIA is an effective technique after cesarean section and, when compared with alternative methods, including epidural morphine, offers advantages that include fewer side effects and enhanced patient satisfaction.[1–4] PCEA also is very effective in this setting; it is preferred to intramuscular opioid[5] and has advantages over PCIA morphine.[6] Whether epidural PCEA offers significant clinical advantages over PCIA, however, remains controversial. Lipophilic opioids such as fentanyl act primarily by systemic absorption after repeated or continuous epidural administration, which thus confers little if any advantage over the intravenous route.[7] Epidural morphine has a slow onset of action and high incidence of side effects, making it unattractive for PCEA. Other opioids of low lipophilicity, for example hydromorphone, also have a dose-sparing effect epidurally compared to intravenously, but the epidural route does not improve analgesia and increases side effects.[8]

Meperidine is an opioid of intermediate lipophilicity (octanol/water partition coefficient of 39 compared to morphine's 1.4) that appears attractive for patient-controlled analgesia (PCA) *via* both routes of administration. It is effective for PCIA after cesarean section and has fewer side effects than parenteral and epidural morphine.[1,4,9] Epidurally, meperidine acts rapidly, is effective, and is preferred by obstetric patients to intramuscular meperidine or epidural bupivacaine.[10]

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PCEA meperidine has been evaluated clinically after both abdominal surgery[11] and cesarean section[5] but has not been compared with PCIA.

The aim of this randomized, double-blind, crossover study was to determine whether there is a difference in quality of analgesia, side effects, patient satisfaction, dose requirement, or plasma drug concentration when meperidine is administered as PCEA or as PCIA after cesarean section.

Materials and Methods

Fifty women, all of whom gave written, informed consent, were enrolled in this study, which had institutional Research and Ethics Committee approval. Participants were scheduled for elective cesarean section during epidural anesthesia and were instructed in the use of a PCA pump (Ivac PCA infusor, model 310, San Diego, CA) and visual analogue scales. Women requiring intraoperative opioid supplementation were to be excluded.

Epidural anesthesia was established to T4 with incremental doses of 0.5% plain bupivacaine with fentanyl 5 μg/ml (maximum 100 μg) *via* a lumbar catheter inserted 4 cm at the L1–L2 or L2–L3 interspace by a loss-of-resistance technique. At the first request for postoperative analgesia, patients were randomized according to a computer-derived sequence, stratified for morning or afternoon surgery, to commence PCEA for an initial 12-h period followed by PCIA for a second 12 h (group 1) or for PCIA followed by PCEA (group 2). Group 1 received a loading dose of 25 mg meperidine (50 mg/ml, antimicrobial- and antioxidant-free; David Bull Laboratories, Melbourne, Victoria, Australia) in 10 ml saline epidurally and received 10 ml saline intravenously, both injected over 3 min; group 2 received similarly formulated meperidine 25 mg intravenously and saline epidurally. The patient, research nurse, and attending nursing staff were unaware of the route of administration. After 15 min, PCA was made available, with meperidine 4 mg/ml, an incremental bolus of 5 ml (20 mg), a lockout interval of 5 min, and no concurrent infusion. A maximum of 200 mg over 2 h was available. In an attempt to maintain blinding, the PCA pump was connected to both the intravenous cannula and the epidural filter *via* a concealed three-way stopcock, and the direction of administration was altered at 12 h by an anesthesiologist not involved in the study.

Patient data included age, weight, and duration from last dose of bupivacaine to commencement in the study. Patients were awakened, if necessary, to complete 100-mm visual analogue pain scales for pain at rest and on coughing, at intervals of 15 and 30 min and 1, 2, 4, 8, 12, 16, 20, and 24 h from commencement. At the end of each 12-h period, visual analogue scales were used to assess satisfaction and the degrees of pruritus, nausea, and sedation. The extremes of these scales read, respectively, "totally dissatisfied" to "could not have been happier"; "no itch" to "worst imaginable itch"; "no feeling of sickness" to "feeling as sick as I could possibly be"; and "wide awake and alert" to "feeling as sleepy as I could possibly be." Data related to drug use and PCA demands were collected, and at the completion of the study the woman was asked her preference with regard pain relief during the two 12-h periods. Respiratory monitoring was performed according to established hospital policy, namely, nursing observation of respiratory rate and pattern and assessment of conscious state at hourly intervals during epidural opioid analgesia and for 4 h after cessation.

In addition, 20 consenting participants (11 of group 1 and 9 of group 2) had venous blood samples taken for plasma meperidine and normeperidine assays at intervals of 30 min and 4, 12, and 24 h. Samples were centrifuged and stored at −21°C before analysis by reverse-phase high-performance liquid chromatography (Waters, Millipore, Milford, MA). The coefficients of variation for meperidine at 35 and 300 μg/l were 2.8% and 1.9% (n = 5) and for normeperidine 2.6% and 1.9% (n = 5), respectively. The minimal detectable concentration both of meperidine and of normeperidine was 5 μg/l.

Data except for age were not normally distributed and thus all were described as the median and interquartile range. Wilcoxon's rank-sum test was used for estimating univariate differences between groups for most variables, with the stratum-adjusted Kruskall-Wallis chi-squared test used for analyzing differences in pain scores between the groups over time. Spearman's rank correlation was used for correlations. A P value of 0.05 was considered statistically significant.

Results

Demographics

Forty-five data sets were analyzed (group 1, n = 24; group 2, n = 21). These included relevant data from

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Table 1. Patient Group Characteristics

	Group 1	Group 2	*P* Value
n	24	21	
Age (yr)*	33 (28–36)	30 (24–35)	0.26
Weight (kg)*	75 (70–84)	71 (66–79)	0.11
Surgery			
Morning (n)	12	10	
Afternoon (n)	12	11	1.00†
Duration until analgesia requested (min)	270 (218–320)	250 (220–330)	0.96

Group 1 represents PCEA followed by PCIA, and group 2, *vice versa*. *P* values were derived from Wilcoxon's rank-sum test.

* Values are median and interquartile range for patient age, weight, and duration from end of surgery to request for analgesia.

† Fisher's exact test.

one participant who withdrew 16 h after the study began because of dissatisfaction with the analgesia obtained with PCIA. The five exclusions included two cases in which the epidural catheter dislodged prematurely and two study protocol violations due to technical problems with the PCA pump. The fifth was a patient who withdrew after only 2 h because of her dissatisfaction with analgesia from PCIA. Patient characteristics did not differ significantly between the two groups (table 1).

Analgesia

Those initially having PCEA had significantly lower pain scores at rest from 2 to 12 h and with coughing from 1 to 12 h. This continued after the crossover, with those having PCEA in the second 12 h having significantly lower scores at each time interval until 24 h (figs. 1 and 2). The association between group and pain score was highly significant for both 12-h periods ($P = 0.0001$, Kruskall-Wallis test). Analyzing each route of PCA separately, there was no difference in pain scores between the periods 4–12 h and 16–24 h. This demonstrated that neither an order nor a carryover effect was operating.

Side Effects and Satisfaction

Side effect scores are listed in table 2. There was no difference between groups in the incidence or severity of nausea over time or in the incidence of pruritus in the first 12 h (84% with PCEA *vs.* 64% with PCIA). The severity of pruritus was similar in the first 12 h, although thereafter it was significantly greater in those having PCEA ($P = 0.009$, Wilcoxon's test). There was no difference between the first and second 12-h periods for PCEA, but those having PCIA second had significantly lower pruritus scores than those having it first ($P = 0.05$, Wilcoxon's test). No patient requested treatment for pruritus. Sedation was significantly greater with PCIA ($P = 0.0001$ Kruskall-Wallis test). There was no difference in sedation between the first and second periods for either route of PCA. No patient was observed to have a respiratory rate of less than 10 breaths/min or excessive sedation.

Satisfaction scores were highly significantly greater for PCEA compared with PCIA over time ($P = 0.0001$, Kruskall-Wallis test). Almost 90% of participants preferred PCEA (table 2). There was no difference in satisfaction with PCEA for the two 12-h periods; however, those having PCIA second, after PCEA, reported greater

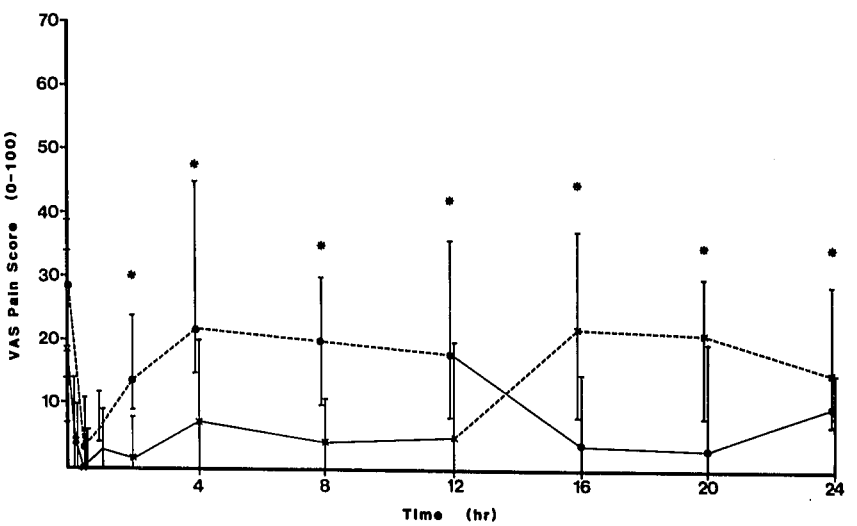

Fig. 1. Visual analogue pain scores (median and interquartile range) at rest on a 0–100 scale during the 24 h from commencement of patient-controlled analgesia. Crosses = group 1; circles = group 2; solid line = period of PCEA; dashed line = period of PCIA. *$P < 0.05$, Wilcoxon's rank-sum test.

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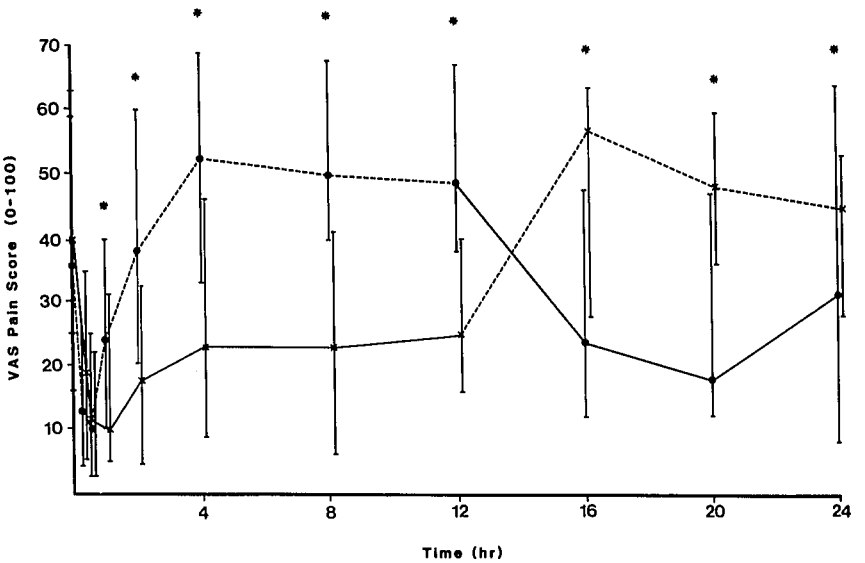

Fig. 2. Visual analogue pain scores (median and interquartile range) with coughing on a 0–100 scale during the 24 h from commencement of patient-controlled analgesia. Crosses = group 1; circles = group 2; solid line = period of PCEA; dashed line = period of PCIA. *$P < 0.05$, Wilcoxon's rank-sum test.

dissatisfaction than those having it first ($P = 0.09$, Wilcoxon's test).

Patient-controlled Analgesia and Plasma Drug Concentrations

The two routes of PCA differed significantly over time with respect to number of demands made ($P = 0.0001$, Kruskall-Wallis test), which were about double for those having PCIA (table 3). There was no difference between the two periods for PCEA, but those having PCIA second made significantly fewer demands than those having it first ($P = 0.03$, Wilcoxon's test). The ratio of demands received to made differed significantly only during the second 12 h, when those having PCEA after PCIA were more likely to make a successful demand ($P = 0.05$, Wilcoxon's test; table 3). There was no significant difference for either route over time, although there was a trend to a higher ratio for those having PCEA in the second 12 h ($P = 0.12$, Wilcoxon's test).

Table 2. Side Effects and Patient Satisfaction

	Group 1	Group 2	*P*
n	24	21	
Nausea score			
0–12 h	0 (0–2)	0 (0–19)	0.24
12–24 h	0 (0–5)	0 (0–2)	0.88
Pruritus score			
0–12 h	12 (6–27)	10 (0–20)	0.28
12–24 h	0 (0–9)	17 (0–52)	0.01
Sedation score			
0–12 h	49 (21–60)	72 (60–76)	0.01
12–24 h	68 (53–83)	41 (15–65)	0.02
Satisfaction score			
0–12 h	90 (70–100)	61 (33–81)	0.005
12–24 h	35 (26–65)	90 (73–100)	0.0001
Preference for PCEA (n)	21	18	1.00*

Values are median and interquartile range for nausea, pruritus, sedation, and satisfaction scores on a 0–100 scale and number expressing preference for epidural patient-controlled analgesia. Group 1 represents PCEA (0–12 h) followed by PCIA (12–24 h), and group 2, *vice versa*. *P* values were derived from Wilcoxon's rank sum test.

* Fisher's exact test.

Table 3. Details of Patient-controlled Analgesia and Drug Use

	Group 1	Group 2	*P*
n	23	21	
Demand ratio			
0–12 h	0.86 (0.75–0.97)	0.87 (0.75–0.94)	0.95
12–24 h	0.88 (0.74–0.93)	0.93 (0.86–1.0)	0.05
Demand rate/h			
0–12 h	1.0 (0.8–1.3)	2.3 (2.0–2.9)	0.0001
12–24 h	1.9 (1.3–2.1)	1.1 (0.75–1.3)	0.005
Meperidine dose (mg)			
0–12 h	181 (155–241)	426 (380–480)	0.0001
12–24 h	365 (269–418)	200 (160–244)	0.0002

Values are median and interquartile range for the ratio of successful demands to total demands, demand rate, and meperidine use. Group 1 represents PCEA (0–12 h) followed by PCIA (12–24 h), and group 2, *vice versa*. *P* values were derived from Wilcoxon's rank sum test.

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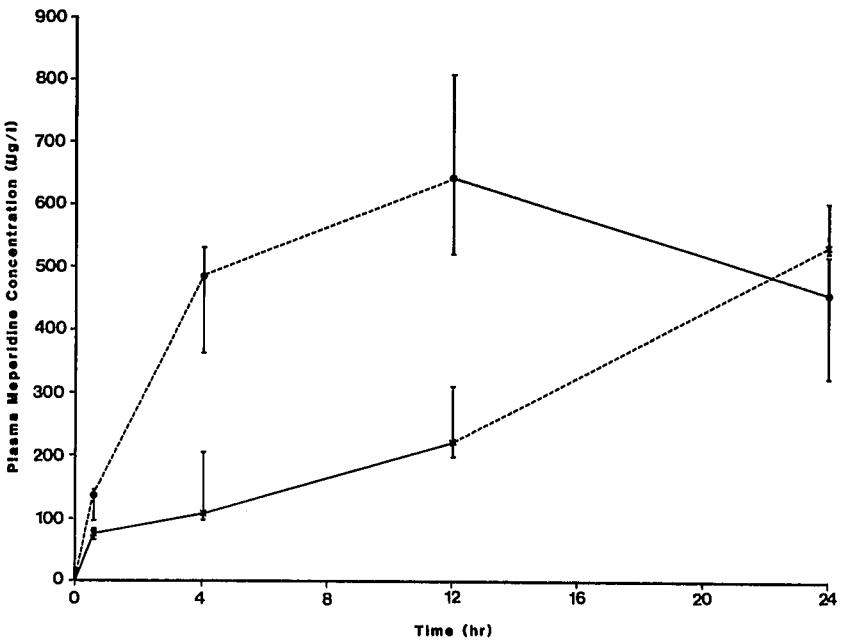

Fig. 3. Plasma meperidine concentrations (median and interquartile range) in micrograms per liter during the 24 h from commencement of patient-controlled analgesia. Crosses = group 1 (n = 11); circles = group 2 (n = 9); solid line = period of PCEA; dashed line = period of PCIA. The groups were significantly different over time (P = 0.002, Kruskall-Wallis test).

PCEA resulted in a meperidine dose requirement that was highly significantly reduced compared to that with PCIA (table 3). There was no difference in use over time with PCEA, but those having PCIA second used significantly less meperidine than those having it first (P = 0.005, Wilcoxon's test).

Plasma drug concentrations are shown in figures 3 and 4. Plasma meperidine concentration was significantly lower over time in those having PCEA (P = 0.002), as was plasma normeperidine during the first 12 h (P = 0.002), although this difference reduced to a trend during the second period (P = 0.1, Kruskall-Wallis tests). There was no correlation between plasma meperidine concentration at 12 and 24 h and pain scores at those times within each group.

Discussion

In this study, PCA variables and the maximum available meperidine dose were identical in both groups; double-blinding was attempted (although not achieved in every case, because some patients were aware of a

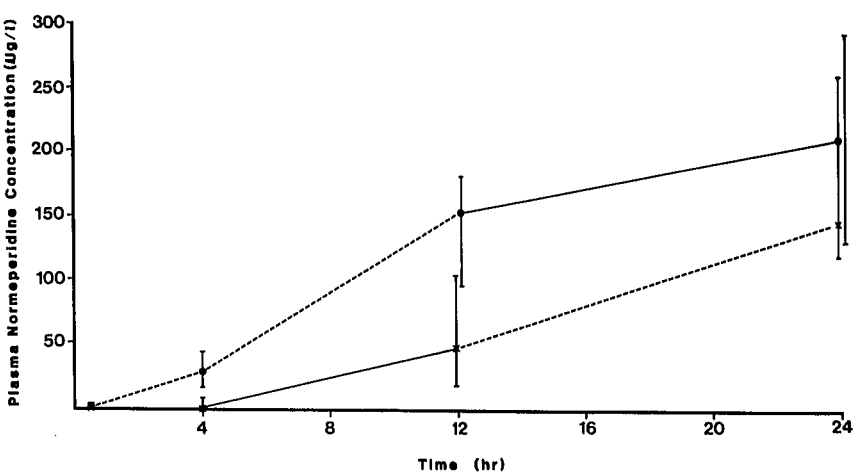

Fig. 4. Plasma normeperidine concentrations (median and interquartile range) in micrograms per liter during the 24 h from commencement of patient-controlled analgesia. Crosses = group 1 (n = 11); circles = group 2 (n = 9); straight line = period of PCEA; dashed line = period of PCIA. The groups were significantly different over 0–12 h (P = 0.002, Kruskall-Wallis test).

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cool sensation with epidural administration and others experienced a local skin response to intravenous administration); and participating patients acted as their own control. In studies of crossover design, between-subject variation is eliminated, but order and carryover effects should be considered. No order effect with regard to pain relief was found in this study. To test for a carryover effect, pain scores at 4 h after PCA *via* one route were compared between patients for whom this was the first treatment route and those for whom it followed the other treatment. No carryover effect was operating. The likelihood that pain intensity changed over the short postoperative period studied seems low, because pain scores remained the same during both 12-h periods in the presence of a similar requirement for meperidine when using PCEA and the pain scores were not showing a downward trend at 24 h postoperatively.

PCEA with meperidine was shown to provide significant advantages over PCIA with meperidine as a postoperative analgesic technique after cesarean section. The quality of pain relief was superior; the degree of sedation and consumption of opioid were reduced significantly; and both satisfaction and patient preference significantly favored PCEA.

Analgesia

Both PCIA and PCEA have been reported to be effective and appropriate methods of postoperative pain management after cesarean section. PCIA is more effective than intramuscular opioid regimens[2–4] and is a suitable alternative to epidural morphine.[1–4] Although the analgesia achieved is of lesser quality than that achieved with intraspinal morphine, bothersome side effects are fewer, and thus patient acceptability may be similar or enhanced.[3,4] PCIA with meperidine results in good analgesia at rest, less sedation than morphine or oxymorphone, and high patient satisfaction.[4,9] PCEA with sufentanil provides more effective early pain relief during movement and less sedation than PCIA with morphine,[6] and a recent nonblinded study showed that PCEA meperidine provided superior analgesia to intramuscular meperidine, allowing women to ambulate and care for their infants earlier.[5]

Many comparisons of the epidural and intravenous route have failed to demonstrate better pain relief after epidural administration of highly lipophilic opioids, including administration by PCA techniques.[7,12,13,§] In those studies, measured plasma opioid concentrations were similar, indicating that rapid vascular uptake and systemic absorption predominantly account for analgesic efficacy. Hydromorphone, which shares morphine's low lipophilicity, confers advantages epidurally with respect to a lower opioid requirement, reduced subjective drowsiness, and more rapid postoperative recovery, but at the expense of increased pruritus.[8] The latter study and others in which drug use was reduced with PCEA[14] have been limited, however, by lack of a double-blind design and the use of PCA variables that differed between groups.

Epidural meperidine has been a popular opioid for post–cesarean section analgesia in some countries for almost a decade,[10,15] and the first clinical trial of postoperative PCEA used meperidine.[11] The current study confirmed the rapid onset of effect of epidural meperidine: pain scores were similar at 15 min after either an epidural or intravenous bolus. Rapid analgesic action is probably due both to rapid systemic absorption and to transfer and uptake into dorsal horn opiate receptors, because peak plasma and cerebrospinal fluid concentrations are achieved in 10–30 min.[16,17] A study of design similar to the current one, using fentanyl,[7] reported pain scores that were significantly lower after intravenous administration.

High-quality analgesia is of particular importance in the early postdelivery period, when mothers wish to care for their infant and ambulate freely. This is the first blinded study using an opioid other than morphine to report superior analgesia (both at rest and on movement) with epidural compared to intravenous administration. An explanation may be the intraspinal potency and pharmacokinetics of meperidine, or alternatively, the local anesthetic properties meperidine shares with other opioids of the synthetic phenylpiperidine series.[18,19] Clinically subarachnoid meperidine has been used for spinal anesthesia, and epidural meperidine in high doses (to 3.8 mg/kg) has been reported to produce surgically adequate sensory and motor block.[20] However, after usual analgesic doses of up to 50 mg, clinically apparent hypotension, sensory, or motor effects have not been reported in obstetric patients. Nevertheless, systematic evaluation of potential dermatomal sensory, motor, and sympathetic change was not performed in this study and would be of interest.

§ Hongnat JM, Beelenfant F, Levy R, Alfonsi P, Chauvin M: Epidural *versus* intravenous alfentanil by PCA in postoperative patients (abstract). ANESTHESIOLOGY: A754, 1991.

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Side Effects and Satisfaction

In this study, groups were similar with respect to the incidence and severity of nausea, which occurred in only 25% of patients and was usually very mild. Pruritus is a frequent and often irritating side effect of most intraspinal opioids; however, this study supported clinical experience that after epidural meperidine it is mild and of minimal clinical significance.[5,10,15] Although a pruritic effect from intraoperative fentanyl may have had a confounding influence, systemic meperidine also may cause pruritus, and this study confirmed that the incidence is similar to that with epidural meperidine.[1,5] Sedation scores were significantly lower in those having PCEA. Although there was a trend for patients having afternoon surgery to have higher scores, the time of operation had no effect on sedation scores for either route of PCA analyzed separately. In addition to the quality of pain relief, patient satisfaction after cesarean section may be affected by the severity of opioid-induced side effects,[2,3] with a negative correlation, for example, existing between increasing sedation and degree of satisfaction.[9] Both better pain relief and less sedation may have contributed to the marked preference of participants for the epidural route, irrespective of the order of administration.

No clinically detectable respiratory depression was noted in either group. Cerebrospinal fluid drug concentrations rapidly peak and decay such that the potential for respiratory depression is low.[21] Although early respiratory depression may occur, it has been reported in the obstetric population only after inadvertent subarachnoid administration[22] or excessive clinical dosage.[5,23] There have been no documented cases of delayed respiratory depression[24] and—the above-mentioned accidental subarachnoid administration aside—no case of clinically significant depression after an estimated 150,000 post–cesarean section epidural boluses (of 50 mg).‖ Nevertheless, clinical vigilance must be maintained at all times, and detailed investigations of the respiratory and ventilatory effects of epidural meperidine, reports of which are lacking, would be of interest.

Meperidine Consumption and Plasma Drug Concentrations

PCEA with meperidine has been reported to have a dose-sparing effect of 30–50% compared to PCIA with meperidine, based on historical controls and observational data.[11,#] This study has confirmed that after lower abdominal surgery, opioid dose requirements are reduced by as much as half compared with PCIA. The pattern and rate of consumption of both intravenous and epidural meperidine were consistent with those previously reported.4,5,9,11,25,26 Patients using PCIA second made fewer demands and used less meperidine than those having it first, presumably because a shorter initial loading phase to achieve an analgesic plasma concentration was required in the presence of an established plasma meperidine concentration. As mentioned, an alternative explanation of less pain in the second 12 h after cesarean section seems unlikely. In the evaluation of PCEA by Yarnell and colleagues,[5] the greater dose of meperidine used by patients after cesarean section, despite a smaller incremental dose and longer lockout interval, probably reflects their larger loading dose and the use of a concurrent infusion.

In this study, despite an approximately doubled frequency of demands with PCIA, both routes were associated with a similar ratio of successful demands to total demands (near unity), suggesting that the variables chosen were satisfactory for optimum efficacy. The influence of choice of PCA variables on total opioid consumption and respiratory parameters requires further research.

Although plasma analgesic concentrations after systemic opioid administration vary widely, the mean minimum effective analgesic concentration for severe postoperative pain is about 450 μg/l, and a concentration of 700 μg/l provides relief of severe pain in 95% of cases.[26,27] Plasma drug concentrations were sampled from half of the participants in this study, with similar numbers from each group; a power calculation based on the observed differences at 4 and 12 h indicated 95% power to reject a type II error. Plasma meperidine concentration with PCIA was similar to that previously reported[26] and was greater than the mean minimum effective analgesic concentration at 12 h after surgery in all but one patient. As previously described,[11] median concentrations with PCEA until 12 h after surgery were usually subanalgesic, remaining lower than the mean minimum effective analgesic concentration in 80% of patients. There was no correlation between plasma meperidine concentration and pain score for either

‖ Brownridge P: Personal communication, and our departmental obstetric database of epidural administrations.

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group. Glass and colleagues[7] suggest that this lack of correlation probably reflects the continuously changing relationship between plasma drug concentration and effect during PCIA, and that for PCEA, systemic absorption is of little significance in terms of pain relief. Plasma meperidine concentration did increase with time during PCEA, indicating the likelihood of a systemic contribution to analgesia with continuing postoperative PCEA. Nevertheless, taken in conjunction with the clinical findings, these data provide convincing evidence that the mechanism of analgesic action of epidural meperidine is principally spinal.

Normeperidine

Although from a maternal perspective, meperidine appears an ideal opioid for post–cesarean section PCEA, its use during breast-feeding in the early puerperium has been questioned. Maternal normeperidine toxicity is unlikely in this population in the presence of normal renal function but has been reported in postoperative patients having PCIA.[28–30] Median plasma drug concentrations in women from both groups were less than those associated with central nervous system toxicity,[29,31] but concentrations associated with continued postoperative meperidine administration after 24 h warrant further investigation. After repeated doses, meperidine is present in breast milk, and maternal normeperidine concentration remains persistently increased.[32] Because their neonatal elimination half-lives are markedly prolonged,[32] regular nursing may lead to progressive drug accumulation and may prolong adverse neonatal opioid effects, in addition to posing the risk of neonatal normeperidine toxicity. Wittels and colleagues[25] have demonstrated greater neonatal neurobehavioral depression with PCIA with meperidine than with PCIA with morphine on the 3rd day of life. Although the clinical significance of these effects is arguable, the significantly lower maternal plasma meperidine and normeperidine concentrations associated with PCEA suggest an additional potential advantage of this approach. The neonatal behavior of breast-fed infants of women receiving meperidine by PCEA warrants investigation.

PCEA with meperidine has significant advantages over PCIA with meperidine after cesarean section, in terms of quality of pain relief, side effects, dose requirements, and maternal satisfaction. Further studies are warranted to determine if other benefits ensue with respect to postoperative recovery, including postoperative oxygenation, maternal–infant interaction, and neonatal behavior during breast-feeding, and to compare the two routes of PCA in other surgical populations.

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