The addition of adrenaline to thoracic epidural meperidine does not improve analgesia following thoracotomy

[L'ajout d'adrénaline à la mépéridine péridurale thoracique n'améliore pas l'analgésie à la suite d'une thoracotomie]

Gregory L. Bryson MD FRCPC MSc, Calvin Thompson MD FRCPC, Sylvain Gagne MD FRCPC, Larry Byford MD FRCPC, John Penning MD FRCPC, Maan Kattan MD FRCPC

Purpose: Patient-controlled epidural analgesia (PCEA) with meperidine provides effective analgesia following thoracotomy. Accumulation of normeperidine, a meperidine metabolite with neuroexcitatory effects, has led to recommendations to limit the use of meperidine postoperatively. The purpose of this study was to determine if the addition of adrenaline to PCEA meperidine decreased meperidine consumption, reduced serum normeperidine levels, and improved analgesia following thoracotomy.

Methods: Following Research Ethics approval consenting patients were randomly assigned to PCEA with either meperidine (2 $mg \cdot mL^{-1}$) + adrenaline (2 $\mu g \cdot mL^{-1}$) or meperidine alone (2 $mg \cdot mL^{-1}$). All patients received a standardized anesthetic and similar perioperative care. Visual analogue pain scores (at rest and with activity), quality of recovery (QoR) scores, and side effects were documented six, 24, and 48 hr postoperatively. Serum levels of meperidine and normeperidine were measured at the same time points.

Results: Forty-six patients completed the study protocol. Meperidine consumption (mean ± SD) was similar in the meperidine + adrenaline and the meperidine groups (601 ± 211 mg *vs* 580 ± 211 mg over 48 hr, respectively; $P = 0.744$). Serum meperidine levels were similar at all study time points. Serum normeperidine was not detected in any sample. Pain scores, QoR scores, and adverse events were comparable in both study groups.

Conclusion: The addition of adrenaline did not influence PCEA meperidine consumption, analgesia outcomes, or QoR. Normeperidine did not accumulate in patients of either study group during the 48-hr study period. Meperidine for patient-controlled epidural analgesia, with or without adrenaline, provides effective post-thoracotomy analgesia in selected patients.

CAN J ANESTH 2007 / 54: 11 / pp 882–890

Objectif *: L'analgésie péridurale contrôlée par le patient (APCP) avec de la mépéridine offre une analgésie efficace après une thoracotomie. L'accumulation de normépéridine, un métabolite de la mépéridine aux effets neuroexcitateurs, a engendré des recommandations dans le but de limiter l'utilisation de mépéridine dans le contexte postopératoire. L'objectif de cette étude était de déterminer si l'adjonction d'adrénaline à la mépéridine APCP réduit la consommation de mépéridine, abaisse les niveaux sériques de normépéridine, et améliore l'analgésie après une thoracotomie.*

Méthode *: Avec l'assentiment du comité d'éthique de la recherche, les patients consentants ont été randomisés à une APCP avec soit de la mépéridine (2 $mg \cdot mL^{-1}$) + adrénaline (2 $\mu g \cdot mL^{-1}$), soit de la mépéridine seule (2 $mg \cdot mL^{-1}$). Tous les patients ont reçu un anesthésique standardisé et des soins périopératoires similaires. Les scores de douleur visuels analogues (au repos et à l'effort), les scores de la qualité de la récupération (QoR), et les effets secondaires ont été enregistrés à six, 24 et 48 h postopératoires. Les niveaux sériques de mépéridine et de normépéridine ont été mesurés aux mêmes temps.*

Résultats *: Quarante-six patients ont terminé le protocole d'étude. La consommation de mépéridine (moyenne ± déviation standard (SD)) était similaire dans les groupes mépéridine + adrénaline et mépéridine seule (601 ± 211 mg vs 580 ± 211 mg sur 48 h, respectivement ; $P = 0,744$). Les niveaux sériques de mépéridine étaient similaires à tous les points temporels de l'étude. Aucune normépéridine sérique n'a été détectée dans les échantillons. Les scores de douleur, les scores QoR et les événements indésirables étaient comparables dans les deux groupes à l'étude.*

From the Department of Anesthesiology, The Ottawa Hospital, Ottawa, Ontario, Canada.

Address correspondence to: Dr. Gregory L. Bryson, Department of Anesthesiology, Box 249C, The Ottawa Hospital – Civic Campus, 1053 Carling Avenue, Ottawa, Ontario K1Y 4E9, Canada. E-mail: glbryson@ohri.ca

Funding: This research was supported by the 2004 Baxter Corporation Canadian Research Award in Anesthesia, the Ontario Thoracic Society, and the Department of Anesthesiology at the University of Ottawa. Investigators were supported by the Ottawa Hospital Department of Anesthesiology.

Accepted for publication June 5, 2007.

Revision accepted August 22, 2007.

Conclusion *: L'ajout d'adrénaline n'a pas influencé la consommation de mépéridine APCP, l'analgésie, ou la QoR. La normépéridine ne s'est accumulée chez les patients d'aucun des deux groupes durant la période d'étude de 48 h. La mépéridine pour l'analgésie péridurale contrôlée par le patient, avec ou sans adrénaline, offre une analgésie efficace après une thoracotomie chez certains patients.*

EPIDURAL analgesia is frequently chosen for thoracotomy in an attempt to reduce the incidence of pulmonary morbidity associated with lung resection. Such complications include pneumonia, unplanned reintubation, and mechanical ventilation for > 48 hr postoperatively.[1] A meta-analysis of 65 randomized trials suggests that epidural anesthesia with local anesthetics decreases the likelihood of pulmonary infection [risk ratio (RR) 0.36; 95% confidence interval (CI) 0.21–0.65] and pulmonary complications (RR 0.58; 95% CI 0.42–0.80) following major thoraco-abdominal procedures.[2]

The use of epidural local anesthetics following thoracotomy may, however, be associated with sympathetic blockade and hypotension. The addition of bupivacaine in concentrations less than 0.25% to epidural infusions of either fentanyl[3] or meperidine[4] failed to improve analgesia when compared to those opioids alone but resulted in more frequent hypotension, vasopressor use, and oliguria.[3,4] These findings suggest that epidural opioid analgesia techniques, without local anesthesia, should be explored in an effort to improve patient analgesia without compromising hemodynamic outcomes following thoracotomy.

The physical characteristics of meperidine suggest several advantages over other opioids for epidural analgesia. Meperidine is characterized by intermediate lipid solubility,[5] weak local anesthetic action at clinically relevant concentrations,[6] and antagonism of N-methyl-D-aspartate (NMDA), an excitatory amino acid that plays a role in neuropathic pain states.[7] Patients randomly assigned to patient-controlled epidural analgesia (PCEA) meperidine had comparable analgesia as those who received fentanyl-bupivacaine and fentanyl-diamorphine mixtures, and reported fewer side effects.[8] Pursuit of meperidine-based analgesia techniques is limited by the accumulation of a neuroexcitatory metabolite, normeperidine, prompting recommendations limiting meperidine use to intervals < 48 hr and daily meperidine consumption to < 600 mg.[9] To benefit from the desirable effects of PCEA meperidine analgesia, techniques reducing meperidine consumption must be sought.

Both the consumption[10] and systemic levels of epidurally administered local anesthetics[11] and fentanyl[12] are reduced by the addition of adrenaline to the analgesic solution. To date there has been no trial evaluating the addition of adrenaline to meperidine for thoracic epidural analgesia. The primary objective of this trial was to determine if the addition of adrenaline to meperidine decreased patient-controlled epidural meperidine consumption in the 48 hr following thoracotomy. Secondary objectives were to determine if addition of adrenaline decreased serum meperidine and normeperidine levels, improved analgesia, and decreased side effects compared to meperidine alone.

Methods

Study population

This study was conducted at the General Campus of the Ottawa Hospital between September 1 2004 and June 1, 2006. Following approval of the Ottawa Hospital Research Ethics Board all patients aged 18–75 yr of ASA physical status classification I–III, scheduled to undergo thoracotomy for pneumonectomy, lobectomy, or wedge resection were screened. Patients with the following conditions were excluded: contraindications to thoracic epidural analgesia (refusal, infection, coagulopathy, etc), inability to use PCEA, hypersensitivity to study medications; chronic opioid use defined as daily consumption of greater than 20 mg of orally administered morphine or equivalent for > seven days; renal insufficiency defined as a creatinine clearance 50 $mL \cdot min^{-1}$ as calculated using the Cockroft-Gault formula;[A] planned postoperative mechanical ventilation; weight > 100 kg; prior to participation in this trial.

Study protocol

After informed written consent patients were randomly assigned to intervention and controlled groups using a computer generated random number table. Randomization was blocked in random permuted groups of four. Patients in the intervention group received epidural analgesia with the combination meperidine and adrenaline while those in the control group received meperidine alone. Allocation to

A The Cockroft Gault formula estimates the glomerular filtration rate using common clinical variables and serum chemistry. Values for the constants are gender specific – 1.23 for men and 1.04 for women. Glomerular filtration rate ($mL \cdot min^{-1}$) = [(140 – age (yr) × weight (kg) × constant] divided by serum creatinine ($\mu mol \cdot L^{-1}$).

meperidine + adrenaline or meperidine groups was performed by the Department of Pharmacy personnel using a pre-printed randomization schedule. Study personnel had no access to the randomization schedule. Pharmacists prepared the study drug in matching syringes and infusion bags identified only by patient name and study number. Patients in the meperidine + adrenaline group were supplied a 10-mL syringe containing meperidine (5 $mg \cdot mL^{-1}$) + adrenaline (2 $\mu g \cdot mL^{-1}$) in 0.9% saline and 500 mL infusion bags containing meperidine (2 $mg \cdot mL^{-1}$) + adrenaline (2 $\mu g \cdot mL^{-1}$) in 0.9% saline. Patients in the meperidine group were supplied a 10-mL syringe containing meperidine (5 $mg \cdot mL^{-1}$) in 0.9% saline and 500 mL infusion bags containing meperidine (2 $mg \cdot mL^{-1}$) in 0.9% saline. Patients, clinicians, and research personnel remained blinded to the nature of the epidural solution used throughout the study period.

Following placement of an 18G intravenous catheter an epidural catheter was placed between the fifth and tenth thoracic vertebrae using a 17G Tuohy needle. All patients were monitored with electrocardiography, pulse oximetry, and end-tidal gas analysis. An arterial cannula for continuous arterial pressure monitoring was inserted in all patients. All epidurals were placed in the sitting position and the catheters advanced 5 cm into the epidural space. Analgesia and sedation for epidural insertion was provided with midazolam 20 $\mu g \cdot kg^{-1}$ *iv* followed by fentanyl 50 µg *iv* boluses titrated to patient comfort. Intravenous or subarachnoid placement of the epidural catheter was ruled out with two 3-mL test doses of 2% lidocaine plain given at five-minute intervals. Ten minutes following the second test dose, evidence of a three-dermatomal sensory block was sought using loss of sensation to pin prick. Patients without sensory block were given a third 3 mL dose of 2% lidocaine. Those failing to demonstrate dermatomal sensory anesthesia had their epidural catheters replaced and the test dose procedure repeated. Patients still without sensory anesthesia were withdrawn from the study.

Patients in both groups received 0.1 $mL \cdot kg^{-1}$ weight from the blinded study syringe (equivalent to meperidine 0.5 $mg \cdot kg^{-1}$ ± adrenaline 0.2 $\mu g \cdot kg^{-1}$) before induction of anesthesia. Immediately thereafter a PCEA pump that contained the blinded study infusion mixture was programmed to deliver a continuous infusion of 5 $mL \cdot hr^{-1}$ (equivalent to meperidine 10 $mg \cdot hr^{-1}$ ± adrenaline 10 $\mu g \cdot hr^{-1}$). Upon arrival to recovery room patients were allowed to self-administer 5 mL boluses every 15 min and the continuous infusion was decreased to 2.5 $mL \cdot hr^{-1}$ (equivalent to meperidine 5 mg ± adrenaline 5 $\mu g \cdot hr^{-1}$).

Management of anesthesia

Induction and maintenance of anesthesia was at the discretion of the attending anesthesiologist with the following restrictions: a) following test dose, no epidural local anesthesia was administered; b) fentanyl at induction of anesthesia, including that given for placement of the epidural, was limited to 3 $\mu g \cdot kg^{-1}$; c) inadequate anesthesia was treated by increasing concentrations of the volatile agent to a maximum of 1.3 minimum alveolar concentration (MAC), at which point fentanyl in 50 µg boluses to a maximum of 100 $\mu g \cdot hr^{-1}$ was administered; d) co-analgesics such as clonidine, ketamine, or intravenous lidocaine were prohibited. Anti-emetic prophylaxis was not administered. Ketorolac 30 mg *iv* was given if surgical hemostasis was adequate. Naproxen 250 mg *po* tid (or 500 mg *pr* bid if unable to take *po* medications) was started on the evening of surgery. Acetaminophen 650 mg *po* or *pr* was given every four hours when the patient was awake.

Patients with inadequate analgesia were assessed and treated in a standardized fashion. Epidural placement of the catheter was confirmed by demonstrating a sensory block with 2% lidocaine plain and patient teaching regarding PCEA was reinforced. Those patients with visual analogue pain scores > 3 at rest or 5 with activity (on a 0–10 scale) had their PCEA boluses and infusion rates increased by 50%. Patients with excessive sedation had their continuous infusions discontinued and boluses decreased by 50%. Patients with significant respiratory depression were given naloxone in 40 µg boluses until respiratory rate was > 10 min^{-1}. Patients who experienced pruritus received diphenhydramine 25–50 mg *iv* every four hours as required. Patients who experienced nausea received prochloperazine 5–10 mg *iv* or ondansetron 2–4 mg *iv* every four hours as required.

Outcome assessment

Consumption of PCEA meperidine was recorded from the epidural infusion pump on arrival to the postanesthesia care unit (PACU) and six, 24 and 48 hr postoperatively. Visual analogue pain scores (VAPS) were recorded at rest and with activity using a 10 cm scale anchored at, "no pain" and "worst pain imaginable." Blood pressure and fluids infused were recorded on arrival in the PACU, six, 24, and 48 hr postoperatively. Recovery was assessed using a quality of recovery (QoR) score[13] at six, 24, and 48 hr postoperatively,and a 10-cm visual analogue score anchored at "poor recovery" and "excellent recovery." The incidences and timing of nausea, vomiting, and pruritus were sought through review of patient records

and by direct questioning on daily patient interviews. Serious adverse events such as respiratory depression, pneumonia, respiratory failure, myocardial infarction and death were noted and described. Hospital length of stay was recorded.

Venous blood for analysis of serum meperidine and normeperidine levels was drawn six, 24, and 48 hr postoperatively. Samples were sent to the Clinical Biochemistry Laboratory at St. Michael's Hospital, Toronto, Ontario for analysis. Tandem gas chromatography – mass spectrometry assays for meperidine and normeperidine were performed according to methods described by Ishii *et al.*[14] The lower limit of detection defined in this publication was 0.5 $ng \cdot mL^{-1}$. There is excellent correlation of this assay with known concentrations of meperidine (r = 0.986). The dynamic range for the assays quoted by St. Michael's laboratory was from 5–1000 $ng \cdot mL^{-1}$ (0.005–1.0 $mg \cdot L^{-1}$) for both meperidine and normeperidine analyses.

Statistical analysis

Analysis of the primary outcome, meperidine consumption at 48 hr, employed an unpaired Student's *t* test. Analyses of secondary outcomes such as serum meperidine, serum normeperidine, VAPS, arterial blood pressure, heart rate, fluid intake and sedation scores were assessed using repeated measures analysis of variance. Meperidine consumption, meperidine serum concentration and pain scores were correlated using a Pearson's correlation coefficient. The QoR scores were compared using the Wilcoxon rank sum test. The frequency of nausea, vomiting, pruritus, respiratory depression, or other adverse events were compared using a Chi-square statistic. Statistical significance was assumed probabilities of < 0.05 for all analyses.

Sample size was based on a retrospective review of 22 patients undergoing thoracotomy at the Ottawa Hospital that demonstrated a mean meperidine consumption of 406 ± 184 mg of meperidine in the first 24 hr. A trial enrolling 20 patients per group would have an 80% power to detect a 30% reduction in meperidine consumption assuming a two-tailed alpha error of 0.05. Sample size was increased to 25 per group to account for withdrawals and variance in meperidine consumption between 24 and 48 hr postoperatively.

Results

A total of 195 patients undergoing thoracotomy for lung resection were screened for participation in this trial. Twenty-five patients were randomly assigned to each of the meperidine + adrenaline and meperidine groups. Three patients in the meperidine + adrenaline group and one in the meperidine group were withdrawn following randomization. The progress of the trial and reasons for withdrawal are documented in Figure 1 in keeping with the Consolidated Standards for Reporting Trials (CONSORT) Guidelines. Baseline characteristics of the remaining patients (22 meperidine + adrenaline and 24 meperidine) along with selected intraoperative data are described in Table I.

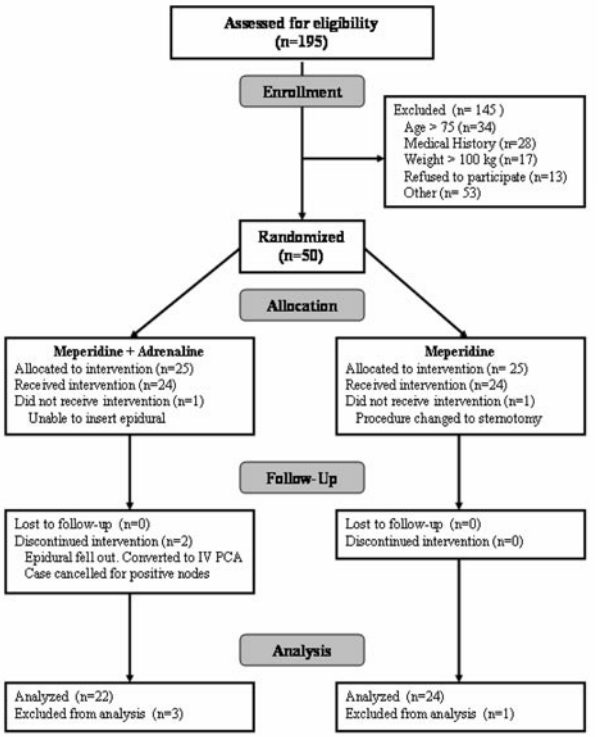

FIGURE 1 CONSORT recruitment flowchart.

On arrival in the PACU median Ramsey sedation scores were 3 in both groups. Sedation prohibited two patients in the meperidine + adrenaline group and five in the meperidine group from completing pain assessment on arrival to the PACU. Among the remaining patients (20 meperidine + adrenaline and 19 meperidine) mean VAPS at rest were 2.6 ± 2.5 and 3.3 ±2.7, in the meperidine + adrenaline and meperidine groups respectively ($P = 0.396$). Visual analogue pain scores with activity were also similar (3.7 ± 2.3 *vs* 4.3 ± 3.1, $P = 0.502$).

Cumulative meperidine consumption throughout the 48-hr study interval is represented graphically in Figure 2. Total 48-hr meperidine consumption ranged from 188 to 1098 mg among study participants and

TABLE I Baseline and intraoperative characteristics

	Meperidine + adrenaline (n = 22)	*Meperidine (n = 24)*
Age (yr)	63.4 ± 8.1	60.0 ± 8.7
Height (cm)	164.5 ± 8.6	168.0 ± 9.6
Weight (kg)	70.5 ± 14.4	75.8 ± 13.8
Systolic blood pressure (mmHg)	134.2 ± 18.2	133.0 ± 18.1
Diastolic blood pressure (mmHg)	79.3 ± 8.7	79.8 ± 9.0
Serum creatinine ($mmol \cdot L^{-1}$)	76.2 ± 14.3	81.8 ± 19.7
Estimated creatinine clearance ($mL \cdot min^{-1}$)	80.7 ± 23.3	88.3 ± 24.9
Type of surgery		
Wedge resection	3 (14)	4 (17)
Lobectomy	17 (77)	16 (67)
Pneumonectomy	2 (9)	2 (8)
Other	0 (0)	2(8)
Epidural interspace		
T4-5	1 (4)	0 (0)
T5-6	5 (23)	9 (37)
T6-7	13 (59)	11 (46)
T7-8	3 (14)	4 (17)
Duration of anesthesia (min)	200 ± 48	192 ± 78
Total intraoperative fentanyl (μg)	245 ± 60	253 ± 79
Total intraoperative fluids (mL)	1334 ± 513	1275 ± 502

Nominal data described as number (%). Continuous data described as mean ± standard deviation.

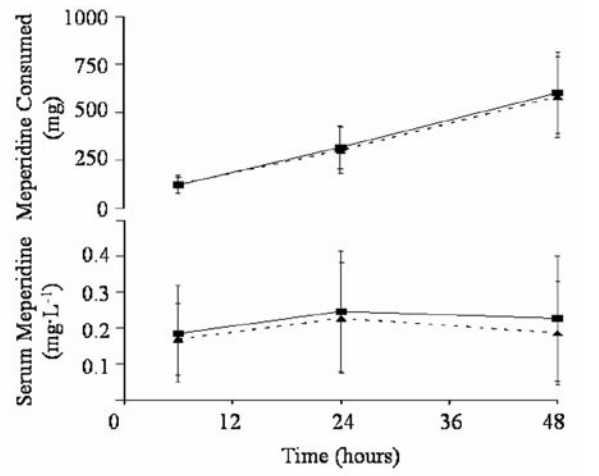

FIGURE 2 Cumulative meperidine consumption and serum meperidine levels
■ Meperidine + adrenaline
▲ Meperidine

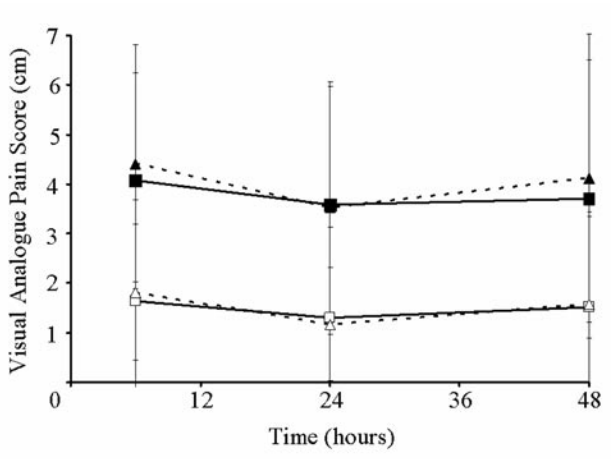

FIGURE 3 Visual analogue pain scores at rest and with activity
■ Visual analogue pain score with activity (meperidine + adrenaline)
▲ Visual analogue pain score with activity (meperidine)
□ Visual analogue pain score at rest (meperidine + adrenaline)
Δ Visual analogue pain score at rest (meperidine)

was similar in the meperidine + adrenaline (601 ± 211 mg) and meperidine (580 ± 211 mg) groups (P = 0.744). The addition of adrenaline had no effect on the serum levels of meperidine assessed over the study period (Figure 2). Serum meperidine levels ranged from 0.02 to 0.82 $mg \cdot L^{-1}$ among study participants and were not correlated to duration of treatment (P = 0.076). Allocation to study group did not influence 48-hr serum meperidine levels (0.23 ± 0.17 *vs* 0.19 ± 0.14 $mg \cdot L^{-1}$ in meperidine + adrenaline and meperidine groups respectively; P = 0.400). Normeperidine was undetectable in the serum of any study participant at all time points. Patients reported satisfactory and consistent analgesia across the 48-hr study interval (Figure 3) despite the wide range of consumption and serum levels of meperidine noted in the study. There was no correlation between VAPS with activity at 48 hr with either cumulative meperidine consumption (r = 0.210, P = 0.159) or serum meperidine levels (r = -0.060; P = 0.700) at the time of assessment.

After the 48-hr study interval patients resumed usual postoperative care. Significant cardiovascular and respiratory events were noted. There were three postoperative deaths (one meperidine + adrenaline, two meperidine) from pneumonia six to 162 days following surgery. An additional patient from each group had an unanticipated transfer to the intensive care unit to treat hypotension. One patient from the meperidine + adrenaline group was returned to the operating room for evacuation of a hemothorax. Confusion or hallucinations were reported by three

TABLE II Adverse events

	Meperidine + adrenaline (n = 22)	*Meperidine (n = 24)*	*P value*
Nausea	13 (59)	14 (58)	0.96
Vomiting	4 (18)	5 (21)	0.82
Anti-emetic administered	13 (59)	15 (63)	0.81
Pruritus	9 (41)	4 (17)	0.07
Respiratory depression (RR < 8)	1 (5)	1 (4)	0.95
Hypotension (SBP < 90 mmHg)	8 (36)	8 (33)	0.83

All adverse events are expressed as number (%) experiencing the complication at anytime over the first 48 hr after surgery. There were no significant differences between the groups (Chi-square). SBP = systolic blood pressure; RR = respiratory rate.

TABLE III Assessment of recovery

Quality of recovery score (0-18 scale); [median (range)]	*Meperidine + adrenaline (n = 22)*	*Meperidine (n = 24)*	*P value*
6 hr	13 (7 – 14)	13 (10 – 15)	0.625
24 hr	13 (9 – 14)	13 (9 – 14)	0.620
48 hr	13 (8 – 18)	14 (7 – 18)	0.093
Visual analogue recovery score (0-10 scale); (mean ± SD)			
6 hr	7.7 ± 1.7	7.6 ± 2.4	0.980
24 hr	8.2 ± 1.8	7.8 ± 1.8	0.465
48 hr	8.0 ± 1.8	8.2 ± 2.2	0.735

patients in the meperidine group. Median length of stay was five days [interquartile range (IQR) = 3] for the meperidine + adrenaline group and six days (IQR = 4) for the meperidine group. Side effects common to opioid analgesia were noted in a number of study participants (Table II) and were not influenced by the addition of adrenaline. A trend suggesting an increased incidence of pruritus in the meperidine + adrenaline group (41%) when compared to the meperidine group (17%) did not reach statistical significance ($P = 0.07$). Approximately one third of patients experienced hypotension, defined as a systolic blood pressure of less than 90 mmHg. Despite the frequency of adverse events patients in this study reported good quality of recovery during the first 48 hr following surgery (Table III).

Discussion

Epidural analgesia reduces pulmonary complications in the postoperative period[2] but the ideal analgesic solution for a given surgical procedure remains to be determined. The results of this study demonstrate that effective post-thoracotomy analgesia may be obtained with PCEA meperidine, with or without adrenaline. The addition of adrenaline did not influence PCEA meperidine consumption, analgesia outcomes, or quality of recovery. Normeperidine accumulation was not noted in patients of either study group during the 48-hr study period.

Epidural adrenaline is believed to promote prolonged and enhanced activity of both local anesthetics[15] and opioids[12] by increasing the mass of drug at the spinal cord and roots. Adrenaline may have analgesic properties of its own, acting through α_2-adrenergic receptors in the spinal cord, and has been shown independently to produce segmental hypoalgesia in healthy volunteers.[16] The minimally effective concentration of adrenaline for continuous epidural infusion is approximately 1.5–2 $\mu g \cdot mL^{-1}$ with higher concentrations raising theoretical concerns of spinal cord ischemia.[17] The effect of the addition of adrenaline seems more pronounced on pain with activity compared with pain at rest.[18] Why then, did the addition of adrenaline to PCEA meperidine result in neither a reduction in drug consumption nor an improvement in recovery characteristics in our study? Three possible explanations may be offered.

First, we observed significant inter-individual variability in meperidine consumption with 48-hr consumption ranging between 219 and 1143 mg. The addition of adrenaline to continuous infusion techniques using local anesthetic-opioid mixtures led to reductions in drug consumption of approximately 25%.[10,17,18] It is possible that a 25% reduction in drug consumption from adrenaline was overshadowed by the observed five-fold variability in patient opioid requirements. A second consideration may be that satisfactory analgesia was obtained from the continuous epidural infusions used in both groups thereby limiting adrenaline's "treatment effect." In theory, patient-controlled techniques should permit titration to the lowest effective dose of drug that provides adequate analgesia; however, mean VAPS at rest were < 2 in both groups at all time points, minimizing the opportunity for titration. However, mean 48-hr meperidine consumption in both study groups was approximately 600 mg, 360 mg more than the maximum 240 mg of meperidine available to patients by continuous infusion over the same time period. If adrenaline were to have a clinically significant treatment effect it should be demonstrable in those 72 patient-requested 5 mg boluses. Lastly, it may be possible that the pharmacokinetics of meperidine, particularly its lipid solubility, precluded a clinically relevant adrenaline effect. A highly lipid soluble opioid may be subject to rapid

uptake and distribution away from the epidural space minimizing the beneficial effects of adrenaline. The interaction between epidurally administered opioids and adrenaline is complex but there is a consistent negative correlation between lipid solubility and duration of drug residence in the epidural space.[19] The octanol water partition coefficient[20] of meperidine (39) is intermediate between those of morphine (1.4) and alfentanil (145), drugs whose epidural residence was prolonged by adrenaline.[19] Meperidine's relatively weak lipid solubility suggests that a pharmacokinetic effect did not confound our results. Aside from inter-individual variability it would therefore appear that the absence of an adrenaline treatment effect on PCEA meperidine consumption is a justifiable conclusion from our results. While these results failed to demonstrate a role of adrenaline, they may support a role for PCEA meperidine in postoperative analgesia.

The postoperative use of meperidine has come under increased scrutiny following a number of case reports of seizures[21–23] related to the accumulation of a toxic meperidine metabolite. Meperidine is metabolized through n-demethylation to normeperidine a compound possessing both analgesic and neurotoxic properties. Normeperidine is eliminated more slowly than its parent compound (elimination half-life 15 *vs* three to six hours) and is further delayed in patients with renal insufficiency (35 hr).[21] Systemic normeperidine levels noted in patients reported with seizures ranged from 0.375–3.2 $\mu g \cdot mL^{-1}$.[21–23] Concern over meperidine-related neurotoxicity led the Agency for Health Care Policy Research to state "meperidine should be reserved for very brief courses in otherwise healthy patients who have demonstrated an unusual reaction…during treatment with other opioids."[B] Similarly the National Pharmaceutical Council in cooperation with the Joint Commission on Accreditation of Healthcare Organizations suggested limiting the use of meperidine to less than 48 hr or less than 600 mg in 24 hr.[9]

The results of the present study suggest that adequate post-thoracotomy analgesia may be obtained using PCEA meperidine with doses well below the recommended limits. Previous research comparing intravenous and epidural meperidine use 48 hr after thoracotomy identified serum normeperidine levels approximately 0.2 $\mu g \cdot mL^{-1}$following consumption of approximately 1000 mg of meperidine.[24] Symptoms of neuroexcitation including "shakiness and/or tremors" occurred only in those patients with levels > 0.3 $\mu g \cdot mL^{-1}$.[24] We were unable to demonstrate any measurable serum normeperidine levels in either study group raising the possibility of measurement error. We were, however, reassured by the clinical chemist who commented that the assay was appropriate and that "if any (normeperidine) was present it was at a level 50-fold below the dynamic range of the assay which was from 0.005 to 1.0 $\mu g \cdot mL^{-1}$." The exclusion of patients with renal dysfunction defined by a creatinine clearance of < 50 $mL \cdot min^{-1}$and the lower 48-hr consumption of meperidine may account for our findings. Higher normeperidine levels are expected in patients with impaired renal function and a greater potential for drug accumulation. No patient in our study had symptoms of tremors or seizures suggesting that clinically relevant concentrations of normeperidine were not achieved.

Expected reductions in opioid-related side effects were not associated with the addition of adrenaline to meperidine PCEA. Over half of the subjects reported nausea while a third were noted to be hypotensive regardless of the treatment group. Pruritus appeared more common in the meperidine + adrenaline group, though not reaching statistical significance, a finding also noted in previous research.[25] Given the relative frequency of side effects it is somewhat surprising that patients rated the quality of their postoperative recovery favourably.

There is no universally accepted measure of quality of life or patient satisfaction validated for perioperative use. The nine-item QoR score was developed to address the relative contributions of physical and psychosocial well being in patients recovering from surgery. The QoR was developed and validated in patients undergoing a variety of surgical procedures[13] and since been shown to correlate with patient satisfaction.[26] The QoR scores reported in the present study (Table III) are consistent with those reported among inpatient surgical procedures and in patients of ASA physical status III or greater.[26] The divergence between side effects and satisfaction may, in part, be explained by research demonstrating that patient satisfaction is more influenced by factors such as information, involvement in decision making, continuity of care, and privacy rather than pain and discomfort.[27,28] Within the limitations of the assessment tools available it appears that PCEA meperidine, with or without adrenaline, provides reliable, effective analgesia that is well accepted by patients.

The addition of adrenaline to PCEA meperidine does not influence analgesia, side effects, or QoR. For

B *Agency for Health Care Policy and Research.* Acute Pain Management (Clinical Guide). AHCPR Publication No.92-0032 . 1992: 1–2.

patients with preserved renal function, PCEA meperidine provides effective postoperative analgesia with neither neuroexcitatory side effects nor accumulation of normeperidine. Patient-controlled epidural analgesia meperidine, with or without adrenaline, may be considered for post-thoracotomy analgesia when the sensory or motor blockade associated with epidural local anesthesia is unacceptable.

Acknowledgements

We would like to thank the Division of Thoracic Surgery for their cooperation, Ms. Denise Wozny for her statistical guidance, and Ms. Sharon Finlay for her exceptional work in recruitment and data collection.

References

1 *Harpole DH Jr, DeCamp MM Jr, Daley J, et al.* Prognostic models of thirty-day mortality and morbidity after major pulmonary resection. J Thorac Cardiovasc Surg 1999; 117: 969–79.

2 *Ballantyne JC, Carr DB, deFerranti S, et al.* The comparative effects of postoperative analgesic therapies on pulmonary outcome: cumulative meta-analyses of randomized, controlled trials. Anesth Analg 1998; 86: 598–612.

3 *Badner NH, Komar WE.* Bupivacaine 0.1% does not improve post-operative epidural fentanyl analgesia after abdominal or thoracic surgery. Can J Anaesth 1992; 39: 330–6.

4 *Etches RC, Gammer TL, Cornish R.* Patient-controlled epidural analgesia after thoracotomy: a comparison of meperidine with and without bupivacaine. Anesth Analg 1996; 83: 81–6.

5 *Ngan Kee WD.* Epidural pethidine: pharmacology and clinical experience. Anaesth Intensive Care 1998; 26: 247–55.

6 *Jaffe RA, Rowe MA.* A comparison of the local anesthetic effects of meperidine, fentanyl, and sufentanil on dorsal root axons. Anesth Analg 1996; 83: 776–81.

7 *Ebert B, Andersen S, Krogsgaard-Larsen P.* Ketobemidone, methadone and pethidine are non-competitive N-methyl-D-aspartate (NMDA) antagonists in the rat cortex and spinal cord. Neurosci Lett 1995; 187: 165–8.

8 *Smith AJ, Haynes TK, Roberts DE, Harmer M.* A comparison of opioid solutions for patient-controlled epidural analgesia. Anaesthesia 1996; 51: 1013–7.

9 *National Pharmaceutical Council, Joint Commission on Accreditation of Healthcare Organizations.* Pain: current understanding of assessment, management, and treatments, 2001. Available from URL; http://www.npcnow.org/resources/PDFs/PainExecSummary.pdf.

10 *Niemi G, Breivik H.* Adrenaline markedly improves thoracic epidural analgesia produced by a low-dose infusion of bupivacaine, fentanyl and adrenaline after major surgery. A randomised, double-blind, cross-over study with and without adrenaline. Acta Anaesthesiol Scand 1998; 42: 897–909.

11 *Burm AG, van Kleef JW, Gladines MP, Olthof G, Spierdijk J.* Epidural anesthesia with lidocaine and bupivacaine: effects of epinephrine on the plasma concentration profiles. Anesth Analg 1986; 65: 1281–4.

12 *Baron CM, Kowalski SE, Greengrass R, Horan TA, Unruh HW, Baron CL.* Epinephrine decreases postoperative requirements for continuous thoracic epidural fentanyl infusions. Anesth Analg 1996; 82: 760–5.

13 *Myles PS, Hunt JO, Nightingale CE, et al.* Development and psychometric testing of a quality of recovery score after general anesthesia and surgery in adults. Anesth Analg 1999; 88: 83–90.

14 *Ishii A, Tanaka M, Kurihara R, et al.* Sensitive determination of pethidine in body fluids by gas chromatography-tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci 2003; 792: 117–21.

15 *Neal JM.* Effects of epinephrine in local anesthetics on the central and peripheral nervous systems: neurotoxicity and neural blood flow. Reg Anesth Pain Med 2003; 28: 124–34.

16 *Curatolo M, Petersen-Felix S, Arendt-Nielsen L, Zbinden AM.* Epidural epinephrine and clonidine: segmental analgesia and effects on different pain modalities. Anesthesiology 1997; 87: 785–94.

17 *Niemi G, Breivik H.* The minimally effective concentration of adrenaline in a low-concentration thoracic epidural analgesic infusion of bupivacaine, fentanyl and adrenaline after major surgery. A randomized, double-blind, dose-finding study. Acta Anaesthesiol Scand 2003; 47: 439–50.

18 *Niemi G, Breivik H.* Epinephrine markedly improves thoracic epidural analgesia produced by a small-dose infusion of ropivacaine, fentanyl, and epinephrine after major thoracic or abdominal surgery: a randomized, double-blinded crossover study with and without epinephrine. Anesth Analg 2002; 94: 1598–605.

19 *Bernards CM, Shen DD, Sterling ES, et al.* Epidural, cerebrospinal fluid, and plasma pharmacokinetics of epidural opioids (part 2): effect of epinephrine. Anesthesiology 2003; 99: 466–75.

20 *Fukuda K.* Intravenous opioid anesthetics. *In*: Miller DR (Ed.). Miller's Anesthesia 6th ed. Philadelphia: Churchill Livingstone; 2005.

21 *Stone PA, Macintyre PE, Jarvis DA.* Norpethidine toxicity and patient controlled analgesia. Br J Anaesth 1993; 71: 738–40.

22 *Kussman BD, Sethna NF.* Pethidine-associated seizure in a healthy adolescent receiving pethidine for postope-

rative pain control. Paediatr Anaesth 1998; 8: 349–52.
23 *Mauro VF, Bonfiglio MF, Spunt AL.* Meperidine-induced seizure in a patient without renal dysfunction or sickle cell anemia. Clin Pharm 1986; 5: 837–9.
24 *Slinger P, Shennib H, Wilson S.* Postthoracotomy pulmonary function: a comparison of epidural versus intravenous meperidine infusions. J Cardiothorac Vasc Anesth 1995; 9: 128–34.
25 *Ngan Kee WD, Khaw KS, Ma ML.* The effect of the addition of adrenaline to pethidine for patient-controlled epidural analgesia after caesarean section. Anaesthesia 1998; 53: 1012–6.
26 *Myles PS, Reeves MD, Anderson H, Weeks AM.* Measurement of quality of recovery in 5672 patients after anaesthesia and surgery. Anaesth Intensive Care 2000; 28: 276–80.
27 *Auquier P, Pernoud N, Bruder N, et al.* Development and validation of a perioperative satisfaction questionnaire. Anesthesiology 2005; 102: 1116–23.
28 *Heidegger T, Husemann Y, Nuebling M, et al.* Patient satisfaction with anaesthesia care: development of a psychometric questionnaire and benchmarking among six hospitals in Switzerland and Austria. Br J Anaesth 2002; 89: 863–72.

Maligne Lake, Jasper National Park - *Alberta*