Severe hypotension from epidural meperidine in a high-risk patient after thoracotomy

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A sixty-eight-year-old female developed severe hypotension immediately after the administration of epidural meperidine for post-thoracotomy pain. Two preceding injections of epidural opiates had been uneventful. The cardiovascular collapse was difficult to reverse and may have contributed to the patient's subsequent death. Cardiovascular complications have not been reported frequently as a possible side effect of epidural opiate analgesia.

The administration of narcotics via the epidural route is increasingly used to relieve postoperative pain. It has been suggested that epidural anaesthesia and analgesia lead to a lower postoperative morbidity¹ in high-risk patients.

A case is described in which epidural administration of 50 mg meperidine diluted in 10 ml normal saline solution was followed shortly by unexpected and prolonged hypotension which was resistant to standard resuscitative measures. This may have contributed to the patient's eventual death.

Case report

A 68-year-old 52 kg asymptomatic female was admitted for elective right upper lobectomy for squamous cell cancer. The diagnosis had been established on the basis of a chest x-ray done for investigation of upper respiratory infection and subsequent transthoracic needle aspiration one month before the current admission. She had a past history of hypertension and mild congestive heart failure

and she was a heavy smoker with a 100 pack-year cigarette habit. There was no history of cerebral vascular disease. Preadmission medication consisted of: theophylline 300 mg PO BID, diltazem 60 mg PO QID, digoxin 0.125 mg PO QD, and ampicillin 500 mg PO TID. The physical examination revealed bilateral carotid, abdominal and bilateral femoral bruits. Carotid artery doppler study revealed almost total right carotid artery stenosis. The electrocardiogram revealed nonspecific ST-T changes. A chest x-ray showed a right upper lobe mass and mild cardiomegaly. Pulmonary function tests showed FEV₁ 1.85 L, FVC 2.08 L with FEV₁/FVC ratio 0.89. Arterial blood gas analyses while breathing room air were pH 7.44, PCO₂ 33 mmHg, PO₂ 66 mmHg, HCO₃ 23 mmol · L⁻¹. Renal profile revealed an elevated creatinine 249 mmol · L⁻¹ and a normal BUN of 7.1 mmol · L⁻¹. The patient was seen by the cardiology, vascular surgery and nephrology services. It was felt that the patient had chronic stable renal insufficiency. There was no indication for further investigation or treatment preoperatively.

The patient was given premedication with promethazine 25 mg and glycopyrrolate 0.2 mg IM. On arrival in the operating room intravenous and arterial lines were placed. The patient was preoxygenated and anaesthesia was induced with 100 mg thiopentone and 200 µg fentanyl followed by tracheo-bronchial intubation with a left 37 Fr double-lumen tube after 80 mg succinylcholine. Anaesthesia was maintained with isoflurane, oxygen and pancuronium. Immediately after induction of anaesthesia a pulmonary artery catheter was placed via the right internal jugular vein. The initial haemodynamic measurements were heart rate 80 bpm, blood pressure 150/80 mmHg, central venous pressure 11 mmHg, pulmonary artery pressure 32/17 mmHg, pulmonary capillary wedge pressure 14 mmHg. Blood gas analyses during two lung ventilation were pH 7.40, PaCO₂ 33 mmHg, PaO₂ 539 mmHg, HCO₃ 23 mmol · L⁻¹. The patient was haemodynamically stable during the two and a half hour operation. Total blood loss was 400 ml. The patient received 4 L of Ringer's lactate (RL) IV intraoperatively. The final

Key words

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intraoperative haematocrit was 32 per cent and urine output was 600 ml. After the surgical procedure was completed an epidural catheter was placed at the T₁₀-T₁₁ space directed cephalad following a negative pressure aspiration test for CSF and blood. No drugs were injected via the catheter at this time. The patient was transported to the surgical intensive care unit (SICU), awake, breathing spontaneously and haemodynamically stable.

In the SICU the initial assessment showed a systolic blood pressure 140 mmHg, pulse 86 bpm, CO 4.2 L · min⁻¹, CI 2.6 L · min⁻¹, SVR 1810 dynes · sec · cm⁻⁵, CVP 6 mmHg, PCWP 7 mmHg. Her postoperative course was initially marked by poor urine output which was presumed to be prerenal in origin. It was felt that the fluid losses had possibly been underestimated. The patient received IV volume challenges totalling 1500 ml crystalloid and the PCWP increased from 7 mmHg to 14 mmHg. Despite fluid, dopamine 3 µg · kg⁻¹ · min⁻¹, and repeated doses of furosemide: (40 mg + 80 mg + 500 mg) in the first eight hours postoperatively, she remained oliguric with an urine output of 15–20 ml · hr⁻¹. The patient was haemodynamically stable during this period with a systolic blood pressure between 120 and 150 mmHg. A pulse oximeter was used to monitor O₂ saturation which remained > 95 per cent throughout this period.

The patient received epidural narcotics for postoperative pain. The initial dose was 25 µg sufentanil in 10 ml of normal saline, administered on request two hours after the trachea was extubated. The assessment of analgesic effect was based on the patient's subjective report and was considered good because she was free of pain. The analgesic effect lasted four hours. The second analgesic administration consisted of 50 mg preservative-free meperidine in 10 ml of normal saline solution which gave good analgesia for another three and a half hours. Both epidural administrations had been uneventful.

Five minutes after the third analgesic administration of 50 mg meperidine in 10 ml of normal saline solution the systolic blood pressure decreased from 150 mmHg to 40 mmHg. The rapid development of hypotension was followed by progressive respiratory depression. Initially, the patient was drowsy but remained responsive to verbal stimuli. Over the next 10 min she became unable to maintain her airway in the absence of jaw support and her lungs were ventilated with 100 per cent oxygen and the trachea was intubated. Aspiration of the epidural catheter was negative for blood or cerebral spinal fluid (CSF). A double-check of the medication revealed that the appropriate ampoule of meperidine had been administered.

The decrease in BP was associated with sinus tachycardia of 160 bpm with multiple PVC's and 3 mm ST segment depression. The hypotension did not respond to divided doses of naloxone (0.8 mg total dose), ephedrine

(100 mg total dose) or to 1 L RL during the initial 5 min. One ampoule (44 meq) of sodium bicarbonate was administered followed by repeated boluses of 100 µg phenylephrine and a dopamine infusion at a rate of 10 µg · kg⁻¹ · min⁻¹. Another 1.5 L RL solution was administered over the next ten minutes and another ampoule of bicarbonate.

During the hypotensive crisis no blood loss was identified. A nasogastric tube was inserted and 100 ml of clear gastric fluid was drained. Both chest tubes functioned well and a chest x-ray ruled out pneumothorax. After half an hour of resuscitative measures the systolic blood pressure reached 50 mmHg and heart rate 138 bpm with occasional ventricular ectopic beats. Haematocrit measured at the end of the first half hour was 22 per cent and two units of packed red cells were administered over the next half hour. After the first hour of resuscitative measures systolic BP was 106 mmHg and HR was 140 bpm. The pupils were fully dilated but responsive to light. After two hours the BP reached 140 mmHg and the patient was drowsy but easily arousable. The trachea was still intubated. The patient was breathing spontaneously through a T-piece on 40 per cent oxygen and tolerating the tube well. Her lungs were clear to auscultation. Initial ST-T changes consistent with inferior wall ischaemia had resolved when an ECG was done after two hours. She was extubated after six hours. No neurological deficit was recorded. During the first 24 hours after the operation the patient received 9 L of crystalloid fluid plus two units of blood. The haematocrit was 33 per cent and the total output of urine in first 24 hr was 1.0 L. After the hypotensive crisis had resolved the patient was haemodynamically stable. Further PCWP was kept in the range of 10–14 mmHg. The time course of the circulatory failure, haemodynamic variables and blood gases measurements during resuscitation are displayed in the Table.

The second day after surgery, the patient remained afebrile. There were no significant elevations of white blood cell count or serum creatine kinase MB isoenzyme or serum digoxin level. Blood, sputum and urine bacterial cultures were negative. The serum creatinine increased to 419 mmol · L⁻¹ and BUN to 40 mmol · L⁻¹. The plan was to ultra filtrate the patient.

The third day arterial blood gas measurements deteriorated overnight and the chest x-ray showed interstitial and alveolar oedema. The patient developed respiratory distress and died in acute pulmonary oedema unresponsive to resuscitative measures. Permission for autopsy was refused.

Discussion

The first striking characteristic of this case was the unexpected, acute, severe hypotension, temporally rela-

TABLE Time course of circulatory failure after second injection of epidural meperidine

Variable	Pre-injection	Post-injection 30 minutes	Post-injection one hour	Post-injection two hours
SBP (mmHg)	140	50	106	140
CVP (mmHg)	10	2	11	13
PCWP (mmHg)	14	6	14	15
CO ($l \cdot min^{-1}$)	3.9	5.7	4.2	4.3
CI ($l \cdot min^{-1} \cdot m^{-2}$)	2.4	3.7	2.6	2.7
SVR ($dyne \cdot s \cdot cm^{-5}$)	1683	771	1361	1870
HR ($beats \cdot min^{-1}$)	98	144	142	139
FiO ₂	0.21	1.0	1.0	0.40
PO ₂ (mmHg)	70	112	175	200
PCO ₂ (mmHg)	42	39	29	26
SaO ₂ (%)	98	97	100	100
HCO ₃ (mmol l^{-1})	22	15	18	23
pH	7.32	7.21	7.47	7.52

SBP = systolic blood pressure, SaO₂ = arterial oxygen saturation.

ted to the epidural injection of 50 mg meperidine in 10 ml of normal saline solution. The decision to change from epidural sufentanil to epidural meperidine was due to the lack of familiarity of the ICU staff with epidural sufentanil. Meperidine is the epidural opioid used most frequently in our intensive care unit due to its extremely low incidence of delayed respiratory depression.² The hypotension could have been caused by one of several mechanisms:

First, the cause could have been systemic absorption of meperidine from the epidural space. Normally after injection into the epidural space, meperidine is rapidly absorbed both systemically and into the CSF. The concentrations in blood and CSF are directly proportional to the dose injected³ (in this case $1 \text{ mg} \cdot \text{kg}^{-1}$). The blood concentration after administration of 50–100 mg meperidine in the epidural space can reach analgesic levels of $0.2\text{--}0.7 \mu\text{g} \cdot \text{ml}^{-1}$ within 20 min, although there is high individual variability.^{3,4} The fraction of the dose crossing the dura has been calculated to be 3.7 per cent for meperidine.⁵ The rest of the epidural meperidine is taken up systemically via the epidural venous plexus or via non-neuronal tissue.

The second possibility might be inadvertent intravascular injection of meperidine into epidural vessels. Even after one or two normal injections, the migration of the catheter into an epidural vessel may not be recognized by an aspiration test. Ravindran *et al.*⁶ reported an adverse reaction due to inadvertent intravascular injection following three normal epidural injections of 10 ml of 0.75 per cent bupivacaine solution, but this has not been reported with epidural administration of narcotics. Meperidine has negative inotropic and positive chronotropic effects on the heart. If IV injection is accompanied by histamine release this would contribute to meperidine induced hypotension.⁷

The third possible cause of meperidine-induced hypotension is extensive spinal or epidural anaesthetic blockade. Inadvertent subarachnoid or subdural injection can follow migration of the catheter.^{8,9} Meperidine has some local anaesthetic effect and has been used as a spinal anaesthetic agent.¹⁰ However, with epidural narcotics there has been no proven sympathetic blockade. Glynn *et al.* found no evidence of sympathetic blockade with epidural meperidine by using plethysmography to demonstrate an unchanged skin blood flow.³

Recent pharmacokinetic data regarding epidural meperidine show the persistence of meperidine in CSF between 12 and 24 hr,⁵ which could be due to a slow release of lipophilic drug from subarachnoid nervous tissue. This could cause a cumulative effect with repeated doses. The CSF concentration of meperidine at the time of request for additional analgesia varies greatly.¹¹

Another striking feature of this case was that the hypotension was unresponsive to naloxone and standard resuscitative measures. Torda *et al.*¹² reported one severely ill patient who had undergone repair of a thoracic aortic aneurysm and who developed hypotension which appeared to be related to epidural morphine administration and which responded to naloxone. Robinson *et al.*¹³ reported hypotension following epidural administration of meperidine in patients after narcotic anaesthesia with fentanyl had been given during cardiac surgery. This was easily corrected by infusion of crystalloids without pharmacological support. All other reports emphasize the circulatory stability with epidural opioids.

There were many other factors which may have contributed to the cardiovascular collapse in this patient. We feel the collapse was related to the epidural meperidine because of the temporal relationship and because most other likely causes were excluded.

The patient was normovolaemic, as documented by the haemodynamic variables prior to the final epidural meperidine injection. There were no clinical or laboratory findings to support a diagnosis of anaphylaxis, sepsis or toxins. It is unclear why the hypotension was relatively resistant to vasopressors but epinephrine might have been a more appropriate choice in this situation.¹⁴ The lack of response to naloxone suggests that the hypotension was not mediated by the usual opioid agonist-receptor interaction.

In conclusion, the anaesthetists' challenge in prevention of postoperative pain is made more difficult in the presence of a sick patient with limited physiological reserves. Even when two injections of opioids through the epidural catheter have been uneventful, this does not guarantee that the next administration will be uneventful. Epidural meperidine may have cardiovascular side-effects which can be life-threatening especially in critically ill patients. The high-risk patient for general anaesthesia may also be a high-risk patient for postoperative epidural meperidine analgesia. A continuous epidural infusion may decrease some of the risks and side-effects associated with bolus injections. The advantage of epidural analgesia has to be balanced against the associated morbidity of the technique in each patient.

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Résumé

Une patiente de soixante huit ans a développé une hypotension sévère immédiatement après l'administration de mepéridine par voie épidurale pour le traitement de sa douleur post thoracotomie. Les deux injections précédentes d'opiacés par voie épidurale furent sans complications. Le collapse cardiovasculaire qui s'en suivit a été difficile à traiter et peut avoir contribué au décès de la patiente. Les complications cardiovasculaires ne sont pas fréquemment décrites comme effets secondaires possibles de la thérapie aux opiacés par voie épidurale.