Intrathecal morphine overdose during combined spinal–epidural block for Caesarean delivery

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We describe a 25 mg intrathecal morphine overdose during a combined spinal–epidural block for a Caesarean delivery. Naloxone infusion (5.24 mg over 24 h) was started prior to the patient becoming symptomatic and almost immediately after the overdose. Invasive therapeutics such as mechanical ventilation were avoided.

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Since it was introduced by Brownridge in 1981,1 combined spinal–epidural block has gained popularity as a standard regional technique for Caesarean delivery. Opioids associated with hyperbaric bupivacaine 0.5% 2.5 ml (12.5 mg) are commonly chosen for subarachnoid administration because they provide rapid and profound analgesia. Secondly, epidural block is used to extend spinal analgesia and to treat postoperative pain.

Occasional intrathecal morphine overdoses have been reported, but most of them were described in patients chronically exposed to these drugs and for whom tolerance is well known.2–3

However, there are few reports in the literature describing the perioperative course of an opioid intrathecal overdose.4–6 These previous cases occurred in patients undergoing orthopaedic surgery and where cerebro-spinal fluid removal, or mechanical ventilation, or both were performed. Our report details the successful treatment of intrathecal morphine 25 mg overdose that did not require such invasive managements during a combined spinal–epidural block for a Caesarean delivery.

Case report

The patient was a healthy 31-yr-old, gravida 7, para 4, at 39 weeks gestation, 156 cm and 75 kg parturient with a singleton pregnancy. She had an uncomplicated prenatal course and was scheduled for elective Caesarean delivery because of a contracted pelvis, for which she had already undergone four Caesarean sections under spinal anaesthesia.

The spinal puncture was performed by the midline approach at the L2–L3 interspace with the patient in the sitting position. The anaesthetist injected fentanyl 30 μg and 2.5 ml of what was thought to be sterile hyperbaric bupivacaine 0.5% through the spinal needle. Immediately after the injection, the solution was identified as morphine 10 mg ml⁻¹ intended to fill the reservoir of the i.v. patient-control postoperative analgesia device. The ampoules were visually checked, but the similar appearance of bupivacaine and morphine ampoules may have been responsible for the misidentification. Thus, the patient received 25 mg morphine intrathecally instead of bupivacaine. Fifteen minutes after the event, she did not report any change in temperature sensation and had no motor block. Nevertheless, the epidural block was performed (lidocaine 2% with epinephrine 1:200 000 10 ml, lidocaine 2% 10 ml) and the patient was immediately placed in supine position. Respiratory rate was 12–14 bpm while breathing 6 litres min⁻¹ 100% oxygen and she was haemodynamically stable (arterial pressure 115/62 mm Hg, heart rate 82 beat min⁻¹). An i.v. naloxone infusion at 80 μg h⁻¹ was initiated after a loading dose of 0.4 mg and vital signs were checked every 5 min.

A healthy, 3800 g boy with Apgar scores of 9 and 10 at 1 and 5 min, was delivered 90 min after the event. Following informed consent from the mother, plasma concentration of morphine was measured in the baby immediately after the
Table 1 Plasma concentrations of morphine in the mother and in the baby after intrathecal morphine 25 mg.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Plasma concentration of morphine in mother (ng litre⁻¹)</th>
<th>Plasma concentration of morphine in baby (ng litre⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T₀</td>
<td>5.0</td>
<td>5.2</td>
</tr>
<tr>
<td>T₀+4</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>T₀+8</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>T₀+12</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>T₀+16</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>T₀+20</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>T₀+24</td>
<td>2.0</td>
<td></td>
</tr>
</tbody>
</table>

Delivery (mass spectrometry, venepuncture sample) and in the mother 15 min after the injection and 4, 8, 12, 16, 20 and 24 h after the event (Table 1).

During surgery, transient hypotension responded to i.v. ephedrine 9 mg. Immediately after the end of the Caesarean section, the patient was admitted to the post-anaesthesia care unit, where arterial pressure, heart rate, respiratory rate, oxygen saturation, nausea, itching, vomiting, sedation score (0=conscious, 1=somnolent, 2=very somnolent, 3=confused, 4=comatose) and visual analogue self-rating scale (0=no pain, 10=worst pain imaginable) were checked every 15 min. There was no residual nerve block post-natally.

Three hours after the injection of morphine, and because of a respiratory rate of 8 bpm and somnolence (sedation score 2), naloxone i.v. infusion was increased to 200 µg h⁻¹. This resulted, 20 min later, in an increased respiratory rate (10–12 bpm) and decreased sedation. At the same time, it was realized that the morphine ampoule was not sterile, and prophylactic antibiotic treatment was initiated using meticillin 1 g/8 h and ciprofloxacin 200 mg/12 h initially i.v., then orally after 48 h. It was stopped on day 7.

Six hours after the end of the Caesarean section, the patient was admitted to the intensive care unit where arterial pressure, heart rate, respiratory rate, oxygen saturation, nausea, itching, vomiting, sedation score and visual analogue self-rating scale were checked every hour. During the following 24 h the patient’s respiratory rate was normal (lower respiratory rate 8 bpm), she was haemodynamically stable (lower arterial pressure 100/65 mm Hg, higher arterial pressure 141/72 mm Hg) and did not vomit. Sedation score was never greater than 2. She complained of mild pruritus and nausea that responded to i.v. meperidine. Urinary catheter was removed on day 1. The patient never reported a visual analogue score of more than six. Pain was controlled easily with proacetaminophen 2 g/6 h. Naloxone infusion was discontinued 24 h after its introduction (arterial pressure 120/80 mm Hg, heart rate 75 beat min⁻¹, respiratory rate 15 bpm, oxygen saturation 98% while breathing room air). She received a total of 5.24 mg naloxone i.v. over the 24 h acute phase.

The patient spent 24 h in the intensive care unit and was discharged to home on day 8. Three months after the event, no signs of meningitis or fever were reported.

Discussion

Accidental massive overdoses of opioids have been reported in various settings, including dysfunction of a patient-controlled analgesia device, and during epidural or intrathecal anaesthesia. In our patient, the event was because of an accidental intrathecal morphine injection because of misidentification of drug ampoules. The similar appearance of hyperbaric bupivacaine 0.5% and morphine 10 mg ml⁻¹ ampoules may have been responsible for this event. However, the anaesthetist should have checked the drugs, which were prepared by a nurse before injection.

Depending on route of administration, excessive doses of opioids may result in a variety of adverse outcomes, including hypothermia, myoclonic seizures, pulmonary oedema, respiratory depression, coma and death.

Intrathecal morphine overdoses in patients who were not chronically exposed to this drug have been reported with morphine doses ranging from 5 to 15 mg. These previous reports discussed the management of patients who received less opioid than our patient. Kaiser and Bainton have described success in treating a 5 mg intrathecal injection of morphine after 4 h by the removal of 50 ml of cerebro-spinal fluid from the lumbar area and its replacement with saline. Pomonis and colleagues reported four cases of intrathecal morphine overdoses (15 mg), that occurred in patients undergoing orthopaedic operations under spinal anaesthesia and who necessitated mechanical ventilation despite naloxone infusion (the authors did not report the dose of naloxone). A third report, described an 8 mg intrathecal morphine overdose that did not require mechanical ventilation, probably because of naloxone infusion (9.6 mg over 24 h). The common finding among these three reports is the late recognition of the intrathecal morphine overdoses (1.5–4 h after the event). In our report, naloxone infusion was begun prior to the patient becoming symptomatic and nearly immediately after the morphine injection (15 min). That may explain the success of this non-invasive treatment. Nevertheless, this should be accomplished with small incremental doses to avoid the severe hypertension, dysrhythmias, and pulmonary oedema that are presumably a result of the rapid increases in sympathetic tone that may accompany the sudden return of pain when opioid effects are antagonized too rapidly.

However, in massive intrathecal morphine overdoses (≥250 mg) it is important to consider more invasive treatments. Groudine and colleagues, describing a 250 mg intrathecal morphine overdose in a patient chronically exposed to this drug, suggest that attempts to remove as much drug as possible from the cerebro-spinal fluid by aspiration and, if necessary, irrigation should be started immediately. This may avoid direct neurotoxicity of morphine that seems to be responsible for myoclonus unresponsive to i.v. naloxone.
Myoclonus has been experimentally induced in rats\textsuperscript{12} and was reported during massive intrathecal morphine overdoses despite naloxone treatment.\textsuperscript{3} It is interesting to observe that myoclonus did not occur in our patient despite intrathecal morphine 25 mg.

Sixteen hours after the event, plasma concentrations of morphine were no longer detectable (Table 1). However, ventilatory response does not seem to be correlated with plasma concentrations of morphine after intrathecal injection.\textsuperscript{13}

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