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Management of Accidental Spinal Administration of Extended-release Epidural Morphine

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WE describe a case of accidental spinal injection of extended-release epidural morphine (EREM) intended for epidural administration. Intraoperative and postoperative management were tailored to minimize the potential for postoperative respiratory depression. The patient was successfully treated without postoperative artificial ventilation, despite known delivery of 7.5 mg EREM to her subarachnoid space.

Case Report

A 45-yr-old woman presented for exploratory laparotomy and resection of an ovarian remnant. She had a history of hypothyroidism, insomnia, and recent abdominal pain for which she took levothyroxine sodium, zolpidem tartrate, and oxycodone–acetaminophen before surgery. Her planned anesthetic was general endotracheal anesthesia, after administration of 7.5 mg lumbar EREM (DepoDur®; Pacira Pharmaceuticals, San Diego, CA) and 20 μg subarachnoid fentanyl *via* a combined spinal–epidural technique, as per routine at our institution using lower than recommended doses of EREM as part of a combined spinal epidural technique.[1] Combined spinal–epidural was performed using a custom combined spinal–epidural tray (Smith's Medical, Keene, NH) without event, except that the resident physician accidentally exchanged the opaque 3-ml plastic syringe containing EREM for the 5-ml clear syringe designed for spinal drug administration (fig. 1). After confirming free flow of cerebrospinal fluid (CSF) and injecting the EREM into the CSF, the resident immediately removed both needle and syringe without aspirating again. The 20 μg fentanyl intended for spinal administration was not given. A plan for intraoperative and postoperative management was developed and discussed with all anesthesia providers and the patient's surgeons. The spinal injection was made 1 h before surgery, during which time the patient was conversant and did not experience respiratory depression (fig. 2). General anesthesia was induced and maintained using no opioid, one half minimum alveolar concentration isoflurane, and 60% nitrous oxide. Dexmedetomidine was started when increases in heart rate and blood pressure were noted with incision and was maintained at 0.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$ until extubation. Bispectral Index monitoring was maintained with a value less than 50. The patient was uneventfully extubated, in the operating room, 6 h after the spinal injection. In the postanesthesia care unit, a naloxone infusion was begun prophylactically at 40 μg/h, a dose that we often use for mild opioid side effects. Over the next 2 h, this dose was titrated without reversal of analgesia and with improvement in somnolence to 140 μg/h. Seven hours after spinal injection, the patient was discharged to the intermediate care unit on supplemental oxygen. She was somnolent but easily arousable, with a respiratory rate of 10 breaths/min and stable vital signs. Overnight, her vital signs remained stable, and no changes in naloxone infusion were required (fig. 3). The patient first reported pain 22 h after spinal injection, and the naloxone infusion was stopped. Twenty-five hours after spinal injection, intravenous morphine patient-controlled anesthesia was started, and she used 20 mg by the morning of postoperative day 2, roughly 48 h after the EREM dose. On postoperative day 1, she was also begun on 1.5 mg scopolamine diaminodiphenylsulfone every 72 h and ondansetron for nausea, which persisted until postoperative day 4. By postoperative day 2, a diagnosis of post–dural puncture headache was given consideration because the patient's persistent nausea was associated with a nonpostural headache. However, she elected to have conservative management with intravenous fluids and butalbital–acetaminophen–caffeine rather than an epidural blood patch. She was discharged on postoperative day 5 with a good understanding that a medical error had been made in her care that required heightened vigilance and extra precautions by her healthcare workers.

Discussion

This is the first published account of intrathecal administration of EREM. With no published pharmacokinetic data on the administration of intrathecal EREM, many have hypothesized that this error could lead to "profound and long-lasting respiratory depression necessitating temporary artificial ventilation, hemodynamic support, and continuous administration of opioid antagonists,"[2] as might also be expected in unintentional intrathecal doses of standard morphine. However, the vehicle for morphine in EREM consists of a liposomal compound known as DepoFoam® (Pacira Pharmaceuticals), which is also used in the administration of intrathecal chemotherapeutic agents to allow for the extended release of this agent in the CSF.[3,4] For EREM, none of more than 900 patients in five randomized controlled studies of efficacy were described to experience known spinal administration of EREM,[5–9] and there are no descriptions or published data in the literature to guide the treatment of a patient who receives intrathecal EREM.

Assuming that the morphine in EREM could behave as immediate release in CSF, management of a patient without artificial ventilation after spinal administration of 7.5 mg morphine may seem novel. However, such management after 6–25 mg spinally administered morphine has been previously described in the literature. Therapy in these patients consisted of observation without intubation, CSF aspiration, and naloxone infusion.[10–13] We did not know how the EREM dose we administered would behave in comparison with these similar doses of standard morphine. We chose to institute increased monitoring during the postoperative period along with a naloxone infusion, titrated to a low dose without reversal of

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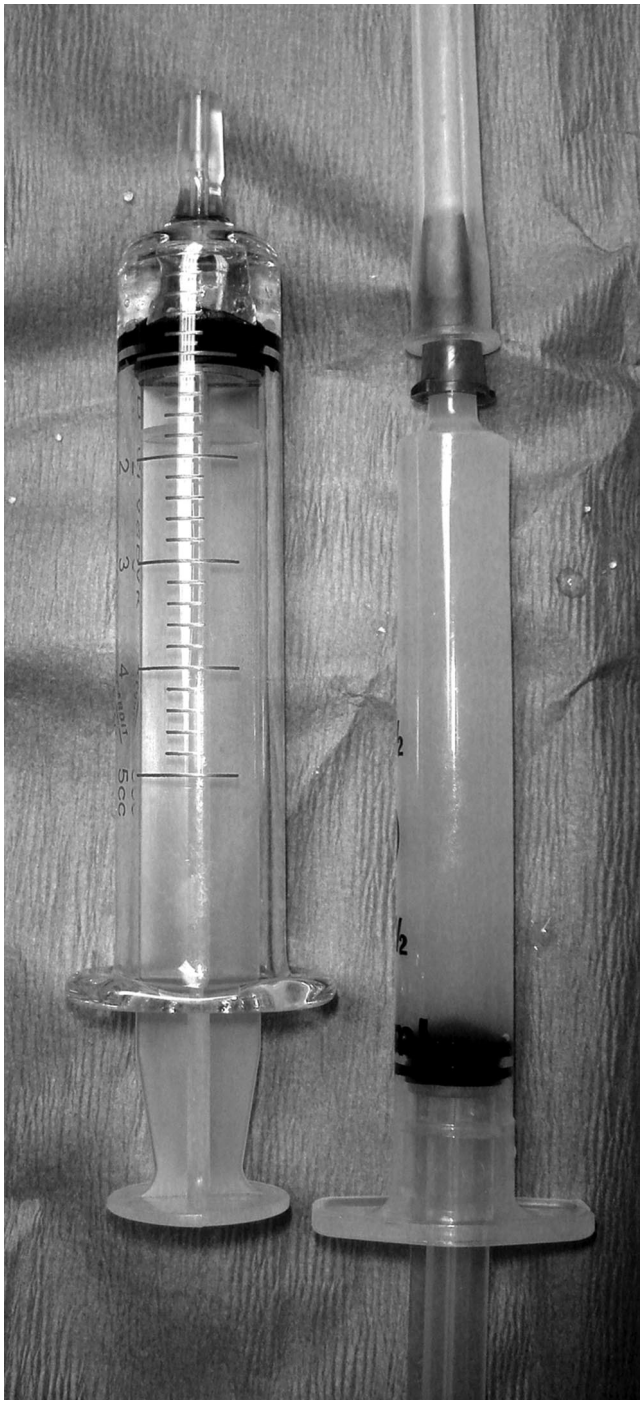

Fig. 1. Photograph of combined spinal–epidural components showing the clear glass 5-ml syringe (*left*) and the opaque extended-release epidural morphine syringe (*right*).

analgesia. Although pharmacokinetic data after intrathecal EREM was of interest to us, we did not draw serial serum levels of morphine because it was not clinically warranted.

Although we do not have data to support whether the vehicle for EREM diminished or increased the likelihood of artificial ventilation, this case suggests that accidental administration of EREM may be successfully managed without the negative sequelae that have been previously

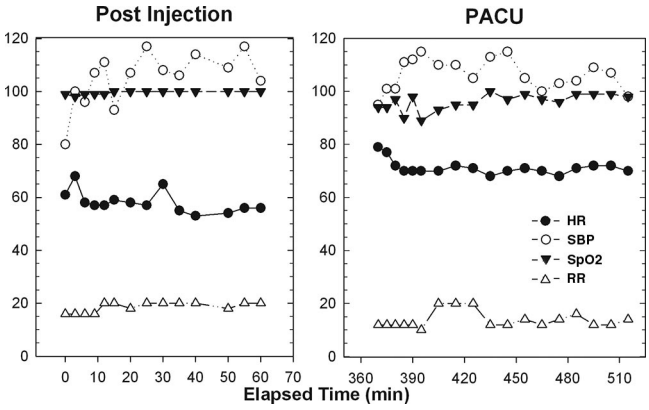

Fig. 2. Graphs of vital signs immediately after injection and in the postanesthesia care unit (PACU). HR = heart rate; RR = respiratory rate; SBP = systolic blood pressure; Spo_2 = pulse oximetry.

hypothesized.[2] In fact, we were surprised that the spinally administered EREM in this patient seemed to behave similarly to epidurally administered EREM. However, of note, our patient did seem to experience more somnolence initially, less analgesia subsequently, and a great deal more nausea than typically encountered with epidurally administered EREM.[5–9] This may be explained by the unknown pharmacokinetics of EREM in the spinal space. However, partial dose administration may also help to explain this patient's favorable outcome. Although a dose much higher than is typical for spinal administration of morphine was most likely given, it remains possible that the entire

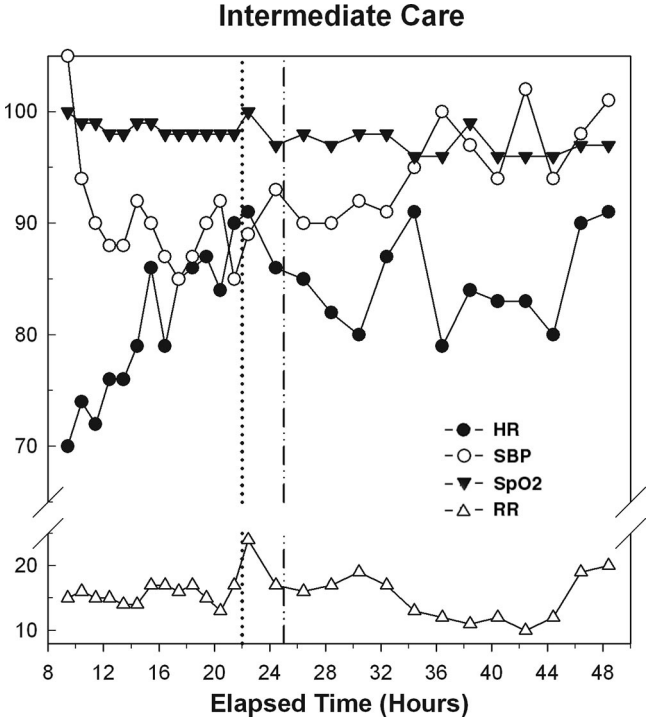

Fig. 3. Graph of vital signs through 48 h in intermediate care. The *dotted line* represents the point at which naloxone was discontinued and the *dashed line* represents the point at which an intravenous patient-controlled analgesic infusion was started. HR = heart rate; RR = respiratory rate; SBP = systolic blood pressure; Spo_2 = pulse oximetry.

7.5 mg EREM was not administered spinally because we did not attempt to aspirate CSF after administration of the drug.

Our current system for safe EREM administration has safeguards that failed us and this patient. We use custom-assembled combined spinal–epidural kits with uniform assignment of syringes of different type and size filled with solutions with visibly different opacity (fig. 1). Because of this sentinel event, we are introducing additional safeguards to include withdrawal of EREM from the vial only after the spinal needle has been removed from the patient, and verbal confirmation of the drug and dose being given by two providers at the time the EREM is administered.

In conclusion, our practice of using a dose of EREM lower than recommended,[14] the patient's previous use of opioid and possible opioid tolerance, and her good health may have contributed to this outcome. In any case, this single example of intrathecal EREM is not presented to imply that this practice is safe: The pharmacokinetics of EREM in the spinal space have not been published, and this route of administration has not been adequately studied. Rather, we believe this case does imply that preservation of an acceptable patient recovery is possible with appropriate and thoughtful management of known accidental spinal administration of EREM.

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In Reply:—We read with great interest the case report by Dr. Gerancher and Dr. Nagle[1] about the effects of accidental spinal administration of extended release epidural morphine (DepoDur®; Pacira Pharmaceuticals, San Diego, CA). In their report, the authors note that no published pharmacokinetics data are available for this drug after intrathecal administration.

Pacira Pharmaceuticals, Inc., performed a study of the effects of DepoDur® on intrathecal administration to dogs during the drug's development, which we would like to report. Adult male beagle dogs (n = 3, each group) were prepared with chronic intrathecal and epidural catheters. Animals received 30 mg DepoDur® in 3 ml by both routes, 7 days apart, in random order. Seven days after the last of the intrathecal and epidural dosing intervals, animals received an intravenous dose of morphine sulfate, 30 mg in 3 ml. All morphine treatments resulted in mild behavioral depression in arousal, muscle tone, and coordination; no animal required intervention. The rank order of time to onset was shortest for intravenous morphine sulfate, followed by intrathecal DepoDur® and then epidural DepoDur®. Duration was less than 10 h after intravenous administration and 48–72 h after intrathecal and epidural administration. Administration of morphine by all routes evoked mild bradycardia of similar onset and magnitude. Duration was shortest after intravenous administration; duration was similar after intrathecal and epidural administration. A mild decrease in blood pressure was observed after intravenous administration, whereas intrathecal and epidural administration were without effect. Respiratory rates were moderately diminished after all routes of administration. The duration of effect was similar after all routes. Body temperature was not affected after intravenous or epidural administration, whereas a modest decline was observed after intrathecal administration that resolved by 24 h.

Free morphine concentration after intravenous dosing declined to below detection limit by 24 h. In contrast, free morphine was detected for several days after intrathecal or epidural administration. The pharmacokinetic parameters for free morphine in the circulation were similar after intrathecal and epidural administration: Tmax was 6.3 ± 2.0 compared with 4.0 ± 1.0 h, Cmax was 39 ± 18 compared with 78 ± 6 ng/ml, $t_{½}$ was 9.7 ± 3.2 compared with 10.3 ± 3.3 h, and $AUC_{0-\infty}$ was 727 ± 84 compared with 1,002 ± 150 $ng \cdot h \cdot ml^{-1}$. In conclusion, after administration of DepoDur® intrathecally or epidurally to dogs, morphine release from the liposomal vehicle, as measured by serum pharmacokinetics of free morphine, was similar. No direct cerebrospinal fluid pharmacokinetics data have been collected after intrathecal administration of DepoDur®. In general, epidural and intrathecal DepoDur® resulted in prolonged and similar behavioral and physiologic effects. Pacira Pharmaceuticals never recommends intrathecal administration of DepoDur®, and the risk of respiratory depression from intrathecal injection is unknown.

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