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517


Neurologic Depression after Intrathecal Morphine

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Numerous investigators have administered intrathecal and epidural morphine sulfate for postoperative analgesia. While early reports indicated no side effects, others have recently indicated respiratory depression that was reversed by an intravenous administration of naloxone.1–3 In the following report we describe an instance of respiratory as well as neurologic depression after the intrathecal injection of an inadvertent large dose of morphine sulfate.

REPORT OF A CASE

A 55-year-old man scheduled for inguinal herniorrhaphy consented to participate in a study to evaluate postoperative analgesia associated with the intrathecal administration of morphine sulfate, 2 mg. The protocol was approved by the University’s Committee for the Protection of Human Subjects. The patient had a history of alcoholism and portal hypertension but hepatic and coagulation studies were normal. During the four months before surgery, the patient had abstained from alcohol.

One hour before surgery, diazepam, 10 mg, was taken orally. In the operating theater the patient was mildly sedated and could answer questions appropriately. Respiratory rate was 16 breaths/ min. He was placed in the right lateral decubitus position. A 22-gauge spinal needle was inserted into the L3–L4 interspace and a free flow of spinal fluid was obtained. Tetracaine, 11 mg, and epinephrine, 0.2 mg, mixed in an equal volume of 10 per cent dextrose solution were then injected. According to the experimental protocol, morphine sulfate, 2 mg, was to be added to the anesthetic; however, morphine sulfate, 20 mg (1.3 ml), inadvertently was added. This preparation of morphine also contained 0.5 per cent chlorobutanol (chloroform derivative) and less than 0.1 per cent sodium bisulfate. The anesthetic mixture was injected into the intrathecal space. Spinal anesthesia to the level of the sixth thoracic dermatome was obtained within a few minutes and surgery began uneventfully. After approximately one hour, the spermatic cord was manipulated and the patient became nauseated. The discomfort was relieved by the intravenous administration of benzquinamide hydrochloride, 25 mg, without affecting respiratory rate. The patient became more sedate during surgery, but continued to respond to questions appropriately.

Vital signs remained stable throughout the anesthetic course. Postoperatively, approximately four hours after the subarachnoid injection, the respiratory rate decreased within 15 minutes from 16 to 6 breaths/min. The patient appeared lethargic, but was arousable and could answer questions appropriately. With an FiO2 of 0.21, PrCO2 was 59 torr, PaO2 65 torr, and PH2 7.22. Oxygen, 2 l/min, was administered via nasal prongs and then naloxone, 0.4 mg, was given intravenously. Within one minute, the patient became more alert and his respiratory rate increased to 8 breaths/min. Fifteen minutes later, PaCO2 was 51 torr, PaO2 97 torr, and PH2 7.27. The patient had slurred speech, lethargy, downbeat nystagmus, and loss of sensation to pin prick and of motor function of the lower extremities. The latter presumably were due in part to the effects of the intrathecal tetracaine. The intravenous administration of physostigmine, 2 mg, produced no changes.

Because of persistent neurologic signs and symptoms of central depression, additional naloxone, 1.5 mg, was administered intravenously over the next two hours and then more naloxone was given by continuous intravenous infusion. The infusion rate (maximal naloxone dosage, 3 mg/hr) was adjusted to maintain an arousable mental state and a respiratory rate greater than 8 breaths/ min (PrCO2 was 42 torr). The patient’s mental state showed gradual improvement over the following 16 hours at which time the naloxone was discontinued without the recurrence of any neurologic depression. The total dose of naloxone, 30 mg, was administered over a period of 20 hours. At no time during the postoperative period did the patient complain of pain nor did he receive an analgesic. The patient was discharged from the hospital three days after surgery.

DISCUSSION

Neurologic depression after the intrathecal administration of morphine has not been observed by all investigators. Wang et al.4 reported that intrathecal

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morphine produced complete analgesia without respiratory depression in cancer patients with intractable pain. Samii et al.\textsuperscript{5} also used intrathecal morphine in doses up to 20 mg without adverse effects. However, subsequent respiratory depression after the use of intrathecal morphine in both small (1–5 mg)\textsuperscript{1,2} and large doses (15 mg)\textsuperscript{3} has been observed. With one exception,\textsuperscript{1} a more profound neurologic depression accompanied respiratory depression. Furthermore, as in our case report, a small dose of naloxone may have partially reversed respiratory depression, but a large dose of the antagonist is necessary to reverse coma, sedation, and mental depression. Even a large dose does not reverse the opiate-induced spinal analgesia.

Presumably, the analgesia of intrathecal morphine acts at the level of the spinal cord.\textsuperscript{7,8} To produce respiratory depression, morphine must reach rostral areas of the central nervous system. Because the spinal subarachnoid space acts as a reservoir for cerebral spinal fluid,\textsuperscript{3} morphine could only reach the central nervous system by the relatively slow process of convection. Accordingly, neurologic depression clinically has occurred 10–11 hours after the development of spinal analgesia.\textsuperscript{1,2} The reversal of respiratory depression, cognitive depression, and antinoception appears to require different doses of naloxone. While naloxone is generally recognized as a pure narcotic antagonist, studies by Lasagna\textsuperscript{10} and Levine et al.\textsuperscript{11} have shown that large doses of naloxone have depressive effects similar to those of morphine.

Lord et al.\textsuperscript{12} and Martin\textsuperscript{13} have suggested that there may be more than one type of opiate receptor in the nervous system. Differences in naloxone dosage required to reverse morphine effects may reflect a concentration-response relationship. That is, presumably the highest concentrations of morphine exist in the spinal cord and would require the highest concentrations of naloxone to antagonize their actions.

On the other hand, lower concentrations of morphine would be present in the respiratory centers in the brain stem and, therefore, lower concentrations of naloxone would be required to reverse respiratory depression. We agree with others that lower doses of naloxone may be required to reverse the respiratory depression of morphine than are necessary to block its other agonist actions. We do not know whether the large dose of naloxone administered to our patient had agonist action, but it had no apparent adverse effects.

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