

Naloxone Therapy in Spinal Trauma: Anesthetic Effects

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Preclinical studies have attempted to establish a beneficial role for large doses of naloxone in several pathophysiologic states including shock, traumatic spine injury, and stroke.¹ Our institution is collaborating in a multicenter study of spinal cord trauma in which the neurologic outcome following a series of double-blinded pharmacologic interventions is examined. As a result of a clinical trial with this drug, we had the opportunity to anesthetize a patient receiving massive doses of naloxone as described in this case report.

REPORT OF A CASE

A 20-yr-old, previously healthy man was transferred to our institution for evaluation following a motorcycle accident. His past medical history was unremarkable and, while denying use of medication or having drug allergies, he did admit to the occasional use of alcohol and marijuana. Following admission, the patient developed progressive motor dysfunction of the lower extremities. A computerized tomography (CT) scan revealed a burst fracture at the L-1 level, and a myelogram showed blockade below T-12. An emergency decompression laminectomy with Harrington Rod stabilization was scheduled. Arterial blood pressure was 120/70 mmHg, heart rate was 70 beats/min, and respiratory rate was 16/min. Multiple abrasions were evident over the upper thorax, but the chest radiograph was normal without evidence of rib fractures or pneumothorax. Hematocrit was 44%, with a white blood cell count of 28,000 cells/mm³ with normal electrolyte end-renal function. Analysis of arterial blood gases was normal. The patient had been entered into the National Acute Spinal Cord Injury Study. This is a double-blinded study in which patients are randomized to receive either methylprednisolone, naloxone, or a placebo drug, in a multicenter attempt to investigate the impact of these drugs on spinal cord function in patients with the acute spinal injuries. Because of the double-blind nature of this study, it was impossible preoperatively to determine which of these drugs the patient had received. The drug was discontinued 30 min prior to the induction of anesthesia. As a part of this study, methotrimeprazine 20 mg had been administered to provide analgesia and sedation.

The patient arrived in the operating room sedated, though easily arousable and communicative. Preinduction monitoring included a central venous pressure and radial artery catheter. Prior to anesthesia, arterial blood pressure was 140/75 mmHg, heart rate was 95 beats/min, and the respiratory rate was 15/min. After breathing 100% oxygen for 5 min and receiving metocurine 2 mg iv, anesthesia was induced with thiopental 300 mg, followed immediately by succinylcholine

100 mg iv. Isoflurane 3% in a 50% air/oxygen mixture was initiated with controlled ventilation through a circle system. In addition, fentanyl was slowly administered iv up to 20 µg/kg, and isoflurane was then gradually decreased to 1.25%. At the surgeon's request, further neuromuscular blocking drugs were omitted. End-tidal CO₂ was 32 mmHg, pH_a was 7.40, PaCO₂ 35 mmHg, and PaO₂ 375 mmHg.

Following induction of anesthesia, the patient was turned to the prone position and surgery commenced 40 min after anesthesia was initiated. With surgical stimulation, the patient became hypertensive, with an arterial blood pressure of 160-180/110 mmHg and a heart rate of 110 beats/min. The isoflurane vaporizer concentration was increased up to 2.5-3.5 vol% with combined fresh gas flows (air/O₂ 6 l/min) to the circle system. In addition to the hemodynamic changes, the patient also began to hyperventilate spontaneously against the ventilator despite adequate ventilation as confirmed by analysis of arterial blood gases and end-tidal CO₂ monitoring. At this time the patient was noted to reach slowly for his endotracheal tube.

The vaporizer was checked and appeared to be functioning adequately, as was the circle system. Anesthetic stability was restored by four 100 mg doses of thiopental given incrementally iv along with additional doses of fentanyl up to a total of 25 µg/kg. Although transient stability was obtained with each 100 mg dose of thiopental, within 5-10 min of each dose the patient would again become hyperdynamic, hyperventilate, and again slowly reach for the endotracheal tube. When the isoflurane vaporizer setting was increased to 3.5%, the patient continued to hyperventilate, but arterial blood pressure began to decrease dramatically (below 100 mmHg systolic) with no change in heart rate. In response to progressive hypotension, the 3.5% vaporizer setting was maintained only for approximately 5-10 min before being reduced to approximately 2.7%. During this transitional period, the patient continued to hyperventilate and no spontaneous movements were noted.

Subsequently, diazepam was administered in two 5 mg iv increments, which produced relative hemodynamic stability, (blood pressure 100-120/60-70 mmHg). Spontaneous ventilation with an end-tidal CO₂ of 30-35 mmHg persisted without other patient movements. Although muscle relaxants given after Harrington Rod stabilization terminated respiratory efforts and the potential for spontaneous motor efforts, isoflurane vaporizer settings of 2-2.5% were necessary for the duration of the 7-h procedure to maintain relative hemodynamic stability.

At the end of the procedure, when isoflurane was discontinued and muscle relaxants were reversed (neostigmine 3 mg and glycopyrrolate 0.6 mg), the patient immediately began to ventilate spontaneously with a respiratory rate of 40/min, tidal volume 700 ml, and an end-tidal CO₂ at 28-30 mmHg. Arterial blood pressure was 130/80 mmHg. Morphine was administered incrementally up to 15 mg iv, and the patient was transferred to the recovery area with the trachea still intubated. He was unresponsive with a respiratory rate of 40/min, heart rate of 120 beats/min, and arterial blood pressure unchanged. Fentanyl (250 µg) administered in the recovery room had no effect on spontaneous ventilation, while arterial blood pressure increased to 155/95 mmHg. Progressive increases in blood pressure to 170/100 mmHg, hyperventilation, and tachycardia indicated inadequate analgesia; therefore, sufentanil (0.5 µg/kg) was administered. Arterial blood pressure then decreased to 125 mmHg systolic, heart rate to 95 beats/min, and respiratory rate to 15-20/min with a tidal volume of 450-500 ml. When hemodynamically stable with a fraction of inspired ox-

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ygen (F_{IO_2}) of 0.4 pH_a was 7.36, P_{aCO_2} 36 mmHg, and P_{aO_2} 102 mmHg. Extubation of the trachea occurred 90 min postoperatively, and the patient was comfortable, although somnolent. Although verbally responsive when vigorously aroused, he otherwise remained quite sedated for 12 h postoperatively, at which time he was noted to be alert and comfortable without complaint of pain. Thirty-six hours postoperatively he began to experience increasing back pain and thereafter required meperidine on a regular schedule for 3–4 days to maintain analgesia.

Following a written request, the National Spinal Cord Study confirmed that the patient had received a 5.4 mg/kg bolus of naloxone followed by a maintenance infusion of 4.26 mg · kg⁻¹ · h⁻¹ until the time of surgery. A total of 3,575 mg of naloxone had been administered to the patient preoperatively.

DISCUSSION

This patient presented several atypical responses to anesthesia. Although the induction and maintenance of anesthesia during positioning was uneventful, subsequent surgical stimulation resulted in the unstable anesthetic course as outlined in the case report. The spontaneous hyperventilation during the intraoperative and postoperative period was unusual and unexplainable by central nervous system or cardiopulmonary pathology. The administration of both morphine and fentanyl postoperatively was not associated with the expected changes in ventilation or circulation, while sufentanil produced a rapid reduction in respiratory rate and hemodynamic stability.

Several recent publications in both anesthetic and neuroscience literature suggest possible explanations for some of the observed responses. Following the discovery of specific opioid receptors and endogenous opioid peptides, mechanisms of general anesthesia based on interactions with these systems were proposed. The strongest experimental evidence of such an interaction has been demonstrated for nitrous oxide analgesia. Reversal of nitrous oxide analgesia with naloxone has been demonstrated in mice,² rats,³ and humans.^{4,5} Prolonged exposure to nitrous oxide decreases opiate receptor density⁶ in the brain, and tolerance to nitrous oxide analgesia has been demonstrated.² Other studies have failed to support these observations.^{7–9} This controversy is not an issue in this patient's management because nitrous oxide was not part of the anesthetic.

Although of greater relevance, there are fewer studies of inhaled anesthetics with naloxone. Finck *et al.*¹⁰ demonstrated electroencephalographic evidence that naloxone decreases the depth of general anesthesia in the rat and proposed that inhaled anesthetics act in part through the release of endogenous opioid factors. Of particular interest, Arndt and Freye¹¹ have demonstrated that naloxone can reverse the cardiovascular effect of halothane in the dog. However, subsequent studies using both MAC^{12–14} and the righting reflexes¹⁵ as anesthetic endpoints stand as evidence that inhaled anesthetics are not

naloxone reversible. Studies of intravenous nonopioid anesthetics with naloxone suggest that ketamine and propofol may interact with opioid receptors.^{16,17}

Many endogenous opioid peptides are thought to interact with delta receptors, while naloxone's greatest opioid antagonist actions are exerted preferentially, although not exclusively, at the mu receptor subtype.^{18,19} Therefore, studies attempting to elucidate an interaction between anesthetics and opioid peptide using naloxone may be conceptually flawed.²⁰ For in addition to its major action as a mu opioid antagonist, naloxone possesses non-specific analeptic properties.²¹ There is evidence suggesting that naloxone's analeptic activity may result from interactions with both central acetylcholine and gamma aminobutyric acid (GABA) neurotransmitter systems.²² Thus, while our patient's response certainly suggests a considerable analeptic property for naloxone, the non-specificity of the agent, particularly with the large doses administered in this protocol, would seem to preclude a statement regarding opioid mechanisms of general anesthesia.

Regardless of the mechanism, the patient presented in this case report demonstrated an attenuated response to isoflurane's anesthetic properties, despite adequate mechanical ventilation with a potent respiratory depressant. Drummond and Brown recently reported that naloxone does not influence spontaneous respiration during isoflurane anesthesia. However, the 2 mg dose of naloxone used in their study was considerably less than the dose administered to our patient.²³ Although our patient's infusion of naloxone was discontinued just prior to induction of anesthesia, recent pharmacokinetic studies^{24,25} suggest that sufficient serum levels of naloxone following a massive dose could remain to exert a prolonged clinical effect, as suggested here.

While malfunction of the isoflurane vaporizer could explain the noted responses, the same vaporizer was found to perform normally during subsequent cases the same day. In addition, vaporizer calibration was checked with an infrared analyzer and found to be accurate at the fresh gas flow rates used in this case. Thus, impaired delivery of anesthetic is not a likely cause of the observed responses.

Methotrimeprazine (Levoprome®) was administered preoperatively to our patient. This phenothiazine-like drug is used as a centrally acting sedative/analgesic in the National Acute Spinal Cord Injury protocol. It is interesting to note that this agent normally potentiates the sedative action of other central depressants such as anesthetics but did not alter the effects of morphine 5 mg on pain threshold or the ventilatory response to carbon dioxide in volunteers.²⁶ Such an interaction did not seem to occur in this patient. Perhaps this agent is in part responsible for the long postoperative analgesia (36 h) and sedation.

In conclusion, this patient represented a rare opportunity to observe the response in humans to a general anesthetic following massive doses of naloxone. Should naloxone become a promising therapeutic intervention for spinal injury, then the problems of choice of anesthetic agent and interpretation of responses to these agents may be anticipated, as suggested by this report.

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