Early Respiratory Depression Resistant to Naloxone Following Epidural Buprenorphine

JOHANNES T. A. KNAPE, M.D., Ph.D.*

Severe respiratory depression occasionally follows the epidural administration of morphine.1,2 Because of this and other side effects, other opioids have been suggested for epidural administration. The mixed opioid agonist–antagonist, buprenorphine, is associated with a 6- to 8-h duration of action and only minor side effects when given epidurally for postoperative analgesia.3,4 Although buprenorphine has been administered epidurally to several thousand patients, no late respiratory depression has been reported. Still, significant increases in PaCO₂ occur after about 3 h.4

We describe two patients who developed severe early respiratory depression following the epidural administration of buprenorphine.

REPORT OF TWO CASES

Patient 1: A 42-yr-old, 81-kg man was scheduled for elective removal of a metal hook plate from the right femur. There was no significant medical history. The patient was not taking any medications and denied the smoking of cigarettes or the consumption of alcohol. Routine physical examination did not reveal significant pathology; laboratory tests, including ECG, routine blood tests, urinalysis, and a chest roentgenogram were within normal limits. Previous general and epidural anesthesia had been uneventful.

No premedication was given. On arrival in the induction room, the arterial blood pressure was 140/90 mmHg and heart rate was 72 beats·min⁻¹. His ECG was monitored continuously, and arterial blood pressure was monitored every 2 min with an automatic oscillometric device.

Epidural analgesia was induced successfully via an epidural catheter at the L2-3 interspace with a test dose of 2 ml of 1.5% lidocaine with epinephrine (1:160,000), followed by 17 ml of the same solution. This resulted in bilateral sensory block to the T-8 dermatome level. Lactated Ringer’s solution, 1300 ml, was infused during the next 45 min and ephedrine 40 mg, was given im. A T-8 level of anesthesia resulted. Arterial blood pressures varied between 140/100 and 130/80 mmHg. A further test dose of 2 ml of 1.5% lidocaine with epinephrine (1:160,000) was administered following completion of the surgery. This test dose was given 95 min after performing the epidural block. When attempts were made to aspirate, no fluid could be produced. Five minutes later, 0.3 mg of buprenorphine in 10 ml of preservative-free saline was injected slowly. Respiratory and cardiovascular status remained stable.

Seventeen minutes after the epidural injection of buprenorphine, the patient suddenly complained of nausea. Oxygen 40% at 12 l·min⁻¹ was given via mask and dexamethasone 10 mg was given iv with relief of nausea. Although the patient remained conscious, he stated that he did not feel well and became apneic. He responded well to instructions to breathe but needed continuous encouragement. When not continuously given vigorous instructions, the patient had no urge to breathe and did not show signs of dyspnea. Blood pressure and heart rate remained stable. There was marked miosis.

Naloxone 200 µg was given iv, followed by 100 µg increments every 3 min to a total dose of 1000 µg without any effect on respiration. The administration of oxygen and continuous encouragement to breathe resulted, however, in a cooperative patient with a pink color and a respiratory rate of 8–14 breaths·min⁻¹. After 15 min of “coached” respiration, pH₁ was 7.22, PaCO₂ 66 mmHg, HCO₃⁻ 26 mEq·L⁻¹, PaO₂ 89 mmHg and repeated blood-gas analysis every 15 min showed no essential change. Ventilation was “coached” for 54 min, when spontaneous ventilation resumed. Thirty minutes later pH₁ was 7.33, PaCO₂ 54 mmHg, HCO₃⁻ 22 mEq·L⁻¹, and PaO₂ 112 mmHg. Further recovery was uneventful. There was no need for additional analgesia postoperatively.

Patient 2: Two months later, a 16-yr-old woman was scheduled for arthroscopy of the knee. She was healthy, did not smoke, and had never been anesthetized before. Routine laboratory investigations were within normal limits. An ECG and chest roentgenogram were not done.

Diazepam 10 mg was given orally for premedication. Initial arterial blood pressure was 110/70 mmHg. Epidural analgesia was induced as described in the first case. A total of 16 ml of 1.5% lidocaine with epinephrine (1:160,000) was injected into the L3–4 interspace via catheter and produced a T-10 sensory blockade. Lactated Ringer’s solution 1000 ml was infused rapidly, and ephedrine 5 mg was given iv because of impending hypotension. A tourniquet was placed around the thigh 15 cm above the knee, and inflated to 500 mmHg. During the arthroscopy, which was followed by an arthrotomy, vital pulmonary and circulatory signs remained stable. At the end of the arthrotomy, the tourniquet was causing discomfort, and an additional 8 ml of 1% lidocaine with epinephrine (1:160,000) was injected via the epidural catheter (a test dose was included). Five minutes later, buprenorphine 0.3 mg in 10 ml of saline was injected slowly into the epidural space for postoperative pain relief.

Twelve minutes later, while arterial blood pressure remained stable, the patient suddenly felt nauseated and became restless. She vomited once. Oxygen 40% at 12 l·min⁻¹ was breathed by the patient via mask, and she was instructed to breathe deeply with a frequency of 8–10 breaths·min⁻¹, which she did in a cooperative manner. She felt somewhat better but became slightly drowsy. She continued to respond to verbal commands. Her pupils were pinpoint.

The administration of naloxone 800 µg iv over 8 min did not change miosis, sedation, nausea, or respiratory rate. When not instructed to breathe, she became apneic. Ten minutes after respiratory arrest with coached respiration, pH₁ was 7.27, PaCO₂ 58 mmHg, HCO₃⁻ 26 mEq·L⁻¹, and PaO₂ 112 mmHg. The patient was given "vocal, coached" ventilation for 24 min, during which period she remained remarkably calm. The tourniquet was released after 75 min of inflation.

* Resident in Anesthesiology, Research Fellow in Pharmacology. Received from the Department of Anesthesiology, Vereniging voor Ziekenverpleging, Amsterdam, and the Department of Pharmacy, Division of Pharmacotherapy, University of Amsterdam, Amsterdam. Accepted for publication October 10, 1985.

Address reprint requests to Dr. Knape: Prinsengracht 769, 1017 JZ Amsterdam, The Netherlands.

Key words: Anesthetic techniques: peridural, lumbar. Analgesics, narcotic: buprenorphine; complications: respiratory depression.
and 2 min later, the patient started to breathe by herself with a frequency of 9 to 10 breaths/min. Fifteen minutes later, $pH$ was 7.27, $PCO_2$ 47 mmHg, HCO$_3$ 21 mEq/L, and $PO_2$ 126 mmHg. Signs of late respiratory depression were not observed, and further recovery was uneventful. Pain relief lasted for 14 h. Both patients could recall the sequence of events in detail a few days later.

**DISCUSSION**

Soon after the introduction of epidural morphine for pain relief, several cases of early and late respiratory depression were reported. Early respiratory depression, which is more common with lipid-soluble opioids like meperidine and fentanyl, has been ascribed to vascular absorption of the drug. Perhaps late respiratory depression after epidural administration of morphine is related to rostral diffusion and mixing of the opioid in the cerebrospinal fluid (CSF). Because of these disadvantages, other opioids have been advocated for epidural use.

Buprenorphine, a potent, mixed-opioid agonist-antagonist, is associated with only minor side effects, and its epidural administration has been recommended for postoperative pain relief. Late respiratory depression following epidural administration of buprenorphine has not been reported. Perhaps this is due to its high lipid solubility (log octanol:water partition coefficient $= 3.96$ at $pH = 7.40$, when compared to fentanyl: 2.98) and comparatively high opioid receptor affinity. Thus, CSF buprenorphine concentrations reaching respiratory centers may be insufficient to cause late respiratory depression. Alternatively, plasma levels and, thus, supraspinal redistribution to respiratory centers may have waned before CSF levels reached the respiratory centers.

Early respiratory depression after epidural morphine is very rare and has been related to vascular uptake. Spinally administered fentanyl and morphine produce a dose-dependent suppression of resting neuronal activity and the activity in the spinal cord evoked by the application of noxious thermal stimuli in anesthetized cats. The short time course of onset of inhibition for fentanyl and the long time course of onset for morphine, among others, correspond closely with the lipid partition coefficients and the rate of drug diffusion. Epidural boluses of highly lipid-soluble opioids such as fentanyl and buprenorphine, however, may enter the CSF rapidly. Earlier studies with radionuclide have indicated that lumbar subarachnoid solutions may reach the basal cisterns within minutes. With fentanyl and buprenorphine, diffusion in the CSF toward the respiratory center seems a more likely mechanism to produce early respiratory depression because there is no clear relation between respiratory depression and plasma concentrations of the drug. The lipid-soluble opioids also penetrate the lipid tissues in the spinal cord rapidly. This may explain the early occurrence of respiratory depression, which coincided in both our patients with a period of nausea and the occurrence of miosis, and its limited duration of action, although a relation to vascular absorption, cannot be excluded. Furthermore, in two controlled studies, an early decrease in respiratory rate and a trend for $PCO_2$ to increase following epidural fentanyl and an early rise in $PCO_2$ level following epidural buprenorphine have been observed.

In our patients, the early respiratory depression following epidural buprenorphine could not be reversed by naloxone iv, 1000 and 800 µg, respectively. Because respiratory depression related to buprenorphine can only be attenuated partially by naloxone, we preferred not to take the risk of the adverse effects (such as hypertension, cardiac hyperventilation, and pulmonary edema of high doses of naloxone following the reversal of opioids). Recently, there was a description of a patient who developed a severe respiratory depression following the administration of epidural hydromorphone, a moderately lipid-soluble opioid, and a small dose of droperidol. One might argue that in our first patient, the administration of domperidone, a primarily peripherally acting dopamine-receptor antagonist with a plasma elimination half-life of 7.5 hr, may have contributed to the respiratory depression. Droperidol in large doses, however, is devoid of significant respiratory depressant effects, although depression may occur in some individuals. Although the respiratory effects of domperidone have not been investigated in humans in a double-blind manner, the drug does increase resting minute ventilation in animal experiments, probably by an effect on the carotid body. The values of $pH$ and $PCO_2$ in both patients are compatible with the occurrence of uncompensated (acute) respiratory acidosis due to acute hyperventilation, although there is an apparent discrepancy between these values in both patients. These blood-gas measurements were made in a routine laboratory so the possibility exists of some error in the measurements due to either a fault in the machine itself or the handling of the samples prior to analysis.

Thus, the early respiratory depression that coincided with nausea and miosis in our patients probably was determined by an effect of the opioid itself. In our second patient, the deflation of the tourniquet leading to a release of lactic acid into the circulation probably contributed to an increase in respiratory drive due to an increase in CO$_2$ content of the blood once lactic acid has been metabolized. These cases demonstrate that early respiratory depression in patients given epidural buprenorphine can be resistant to naloxone, but do not necessarily demand endotracheal intubation and artificial ventilation. The importance of continuous respiratory monitoring when using highly lipid-soluble opioids in the epidural space is emphasized.
The author expresses gratitude to James G. Bovill, M.D., F.F.A.R.C.S.I., Professor of Anesthesiology, University of Leiden, for his help in the preparation of the manuscript.

REFERENCES

Anesthesiology
64:384–387, 1986

Importance of the Level of Paralysis Recovery for a Rapid Antagonism of Atracurium
Neuromuscular Blockade with Moderate Doses of Edrophonium

D. Hennart, M.D.,* A. d’Hollander, M.D., Ph.D.,† C. Plasman, M.D.,‡ M. de Jonckheere, M.D.‡

Edrophonium, 500 µg · kg⁻¹ or more, effectively antagonizes paralysis induced by long-acting muscle relaxants such as d-tubocurarine and pancuronium.¹⁻⁴ Because of the high rate of spontaneous recovery from paralysis produced by atracurium in normal⁵,⁶ patients and those patients with various pathologic conditions,⁷,⁸ atracurium neuromuscular blockade should be reversed rapidly by edrophonium. Nevertheless, as shown recently by Rupp and coworkers,⁹ the prerreversal level of neuromuscular blockade influences markedly the speed of the antagonism induced by edrophonium even for the new muscle relaxants of intermediate duration of action.

The goal of this study was to antagonize atracurium-induced paralysis with 500 µg · kg⁻¹ of edrophonium from three predetermined levels of twitch height recovery (i.e., zero, 10, and 25%) in order to select the prerreversal twitch height level at which a 2-Hz train-of-four (TOF) ratio of 75% can be obtained within 15 min. The value of 75% of TOF is widely used as the adequate criterion to indicate that at least the power for respiratory muscles is returned near the preanesthetic state.¹⁰,¹¹

Patients and Methods

Thirty adult patients (ASA Class 1 or II) undergoing elective surgery were studied after informed consent was obtained. The study was approved by our Ethical Com-