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Pulmonary Edema Following Naloxone Administration in a Patient Without Heart Disease

ROSS H. TAFF, M.D.*

Naloxone, an opiate antagonist with little or no intrinsic agonist activity, often is used to reverse the effects of narcotics. There have been several reports of adverse effects following naloxone administration. These include hypertension,[1] pulmonary edema,[2] ventricular arrythmias,[3] and cardiac arrest.[4] With the exception of one patient who received 0.1 mg iv of naloxone, the usual single dose mentioned in these reports varied between 0.2–0.4 mg iv.

To minimize any adverse reactions, I commonly administer naloxone in incremental doses of 0.04–0.08 mg iv over several minutes. In one healthy man, this practice lead to pulmonary edema.

REPORT OF A CASE

A 26-year-old, 85-kg male was scheduled for an operative arthroscopy on an outpatient basis. There was no significant medical history. The patient was not taking any medications and was allergic to tetanus toxoid. Laboratory tests, which included chest roentgenogram, CBC, and urinalysis, were all within normal limits. An EKG was not done. The patient's only prior anesthetic was for a tonsillectomy as a child. An iv was started in the operating room. Monitoring included an EKG, a blood pressure cuff, a precordial stethoscope, a neuromuscular blockade monitor, and an oxygen analyzer. The patient was not premedicated. A combination of thiopental 775 mg, fentanyl 300 mcg, pancuronium 1.5 mg, metocurine 6 mg iv, and 70% nitrous oxide was used for the anesthetic. The surgery lasted 77 min. The last 50 mcg of fentanyl was given iv 20 min before the surgery was finished. The total anesthesia time was 110 min. Ventilation was controlled with a tidal volume of 0.85 l at a rate of 8 breaths·min^{-1}. Blood pressure varied between 90/60 and 120/80 mmHg during surgery. Muscle relaxants were reversed with a combination of edrophonium 30 mg and atropine 0.8 mg iv. Nitrous oxide was discontinued, and the trachea was extubated after 100% oxygen had been given for several minutes.

The patient was quite sleepy with small pupils and slow, shallow respirations. The neuromuscular blockade monitor showed a sustained response to a tetanic stimulus with no fade. Incremental doses of naloxone 0.04–0.08 mg iv were given over 5–10 min. The total dose used was 0.3 mg. The patient became more awake, and respirations increased in rate and depth. He then was transferred to the recovery room. A total of 1,100 ml of lactated Ringer's solution was given iv.

In the recovery room, the initial blood pressure was 140/90 mmHg,

* Clinical Instructor in Anesthesia, Harvard Medical School, Staff Anesthesiologist, Mount Auburn Hospital, Cambridge, Massachusetts 02238.

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Address reprint requests to Dr. Taff: Department of Anesthesiology, Mount Auburn Hospital, 330 Mt. Auburn Street, Cambridge, Massachusetts 02238.

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heart rate 100 beats·min^{-1} and respiratory rate 26 breaths·min^{-1}. Within a few minutes he started coughing up pink frothy sputum. He was cyanotic, pale, cold, and clammy. One hundred per cent oxygen via a mask was given, and the patient was placed in a sitting position. EKG monitoring showed a sinus rhythm at 100 beats·min^{-1}. The patient continued to cough up pink sputum for approximately 20 min. His respiratory rate varied between 20–28 breaths·min^{-1}. Blood pressure and heart rate were stable. He, surprisingly, denied any problems with his breathing and only complained of a deep chest pain while coughing. With 100% oxygen via a mask, Pa_{O_2} was 110 mmHg (table 1). A chest roentgenogram was within normal limits. The patient improved over the next few hours without any treatment except inhalation of oxygen (table 1).

Investigations to determine the cause of the pulmonary edema included EKG, cardiology consultation, echocardiogram, lung scan, and cardiac enzymes. All results were within normal limits. The following day the patient's only complaint was some minor deep chest discomfort, and he was discharged to return home.

TABLE 1. Analysis of Arterial Blood Gases after Naloxone Administration

Time (min)	F_{IO_2}	Pa_{O_2} (mmHg)	Pa_{CO_2} (mmHg)	*p*Ha	Base Excess (mEq·l^{-1})
30	100	110	60	7.21	25
310	60	93	46	7.38	28
760	60	196	44	7.37	25

DISCUSSION

Adverse reactions secondary to naloxone have been reported previously.[1–3] They were all, however, in patients with preexisting heart disease until the report by Andree[4] of cardiac arrest in two healthy women. We described a case of pulmonary edema following naloxone in a patient without preexisting heart disease.

When our patient began having respiratory difficulty, several causes were considered, including aspiration pneumonia, fat and pulmonary emboli, valvular heart disease, myocardial infarction, and naloxone administration. There was no evidence of aspiration, because the sputum clearly was pink in color. Chest roentgenogram was negative for infiltrates, and the clinical course was not consistent with aspiration pneumonia. The operative procedure did not involve any long bones, so a diagnosis of fat emboli was discarded. Pulmonary emboli and cardiac causes were excluded by normal lung scan, EKG, cardiac enzymes, and echocardiogram. Cardiology consultation confirmed the diagnosis of pulmonary edema but could not provide a cause. Because the patient was a healthy young man, and the anesthetic was totally uneventful until the administration of naloxone, no conclusion could be made other than pulmonary edema secondary to naloxone. The normal chest roentgenogram was unexpected, but the clinical picture and arterial blood gas values were all consistent with acute pulmonary edema and its resolution.

Because the diagnosis of pulmonary edema was made by arterial blood gases and clinical examination, venous pressures were not measured. The patient already was improving, vital signs were stable, and therapy would not have been altered by knowing the central venous pressures.

The reasons given for adverse reactions following naloxone are reversal of analgesia and release of catecholamines by a central mechanism. Reversal of analgesia was probably not the mechanism, because the patient never complained of pain and did not require narcotics in the postoperative period.

Sympathetic release usually is manifested by hypertension and tachycardia. It is interesting that this patient's blood pressures in the recovery room for the first half hour ranged from 120/90–140/100 mmHg, with a heart rate of 100 beats/min.$^{-1}$ However, he appeared to be very vasoconstricted. He was cold, clammy, pale, sweating, and it was very difficult to draw an arterial sample of blood despite easily palpable pulses. Support for this mechanism comes from Patshke,[5] who anesthetized dogs with halothane and nitrous oxide and gave morphine followed by naloxone. Hypertension was seen immediately following naloxone, even though the dogs still were anesthetized. Freye[6] also suggested that naloxone competes with narcotic reception sites in the central nervous system and causes a pressor response. This remains to be proven. The reaction does not appear to be allergic in nature, because the usual signs of anaphylactic reaction, hives, rash, bronchospasm, and hypotension are not present in any of the reports.

In summary, a case of pulmonary edema after naloxone administration in a healthy young patient is presented. This case is significant because the recommendations for smaller incremental doses given over a longer time period were followed. It reinforces the concept that the administration of naloxone is not without danger, even in the healthy patient.

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