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Acute Pulmonary Edema in Healthy Teenagers Following Conservative Doses of Intravenous Naloxone

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Pulmonary edema has occurred following naloxone administration in patients with congestive heart failure¹ and during cardiopulmonary resuscitation.² In those reports, as in others in whom hypertension,³ supraventricular and ventricular arrhythmias,^{2,3} and ruptured cerebral aneurysm⁴ followed naloxone administration, the dose employed was 400 mcg iv. Subsequently, smaller doses have been recommended.^{4,5} We present two young males in whom the administration of 100 mcg of naloxone iv was associated with the acute onset of pulmonary edema.

REPORT OF TWO CASES

Patient 1. A 17-year-old, 197-cm, 85-kg male patient was scheduled for arthroscopy of the left knee. His blood pressure was 128/80 mmHg and heart rate 52 bpm, with no apparent physical abnormalities and no history of drug abuse. He had fractured his left patella 5 years earlier. Preoperative studies revealed a 13.8 g/100 ml hemoglobin, a normal urinalysis, and a normal chest roentgenogram.

Premedication consisted of hydroxyzine, 100 mg po, and glycopyrrolate, 0.2 mg im. Ninety minutes later, droperidol, 2.5 mg, and fentanyl, 50 mcg, were given iv during 3 min of 100% oxygen administration. Tracheal intubation followed the iv administration of thiopental, 350 mg, and succinylcholine, 120 mg. Anesthesia was maintained with additional fentanyl, 450 mcg iv, isoflurane, 0.5 to 1.0%, and nitrous oxide 65% in oxygen. The arthroscopy lasted 70 min, during which time the blood pressure remained between 110/40 and 120/60 mmHg, and the heart rate ranged from 50 to 70 bpm. Dextrose 5% and lactated Ringer's solution, 1.0 l, was infused iv during the procedure.

At the conclusion of the operative procedure, spontaneous ventilation had not returned, the pupils were pinpoint, and there was no evidence of residual neuromuscular blockade. After receiving naloxone,

100 mcg iv, the patient awakened promptly, and the trachea was extubated. Immediately he began to expectorate copious quantities of pink frothy sputum. Approximately 30 min after the administration of naloxone, while he was breathing oxygen, 6 l/min by nasal cannula, pH_a was 7.26, Pa_{CO_2} 55 mmHg, and Pa_{O_2} 76 mmHg; he was breathing deeply at a rate of 20 \cdot min⁻¹, heart rate was 120 bpm, and arterial blood pressure was 150/80 mmHg. A portable anteroposterior supine chest roentgenogram demonstrated pulmonary edema. Brisk diuresis followed the iv administration of furosemide, 20 mg. Forty minutes later, with an FI_{O_2} of 0.4 via a face tent, pH_a was 7.33, Pa_{CO_2} 53 mmHg, and Pa_{O_2} 86 mmHg. A chest roentgenogram obtained 5 h after admission to the recovery room showed clearing of the pulmonary edema. His respiratory status improved rapidly, and he was discharged from the hospital on the following day, after a cardiologist had evaluated him and found no abnormalities. The patient underwent uneventful arthrotomy 2 months later but did not receive naloxone.

Patient 2. A 16-year-old, 175-cm, 82-kg male patient was admitted with acute appendicitis. Physical examination showed a well-developed adolescent with an arterial blood pressure of 130/80 mmHg, heart rate 80 bpm, and oral temperature 37.3°C. Medical history proved unremarkable; there was no history of drug abuse. Hemoglobin was 14.7 g/100 ml, and urinalysis was normal, but a chest roentgenogram was not obtained.

Premedication consisted of glycopyrrolate, 0.2 mg, hydroxyzine, 50 mg, and meperidine, 50 mg im. Twenty minutes later he received thiopental, 500 mg iv, followed by succinylcholine 140 mg iv, and the trachea was intubated during cricoid pressure. Anesthesia was maintained with fentanyl 450 mcg iv, isoflurane 0.5%, and 60% nitrous oxide in oxygen. The surgical procedure lasted 1 h, during which he received lactated Ringer's solution 250 ml iv. Following surgery, naloxone 100 mcg iv, was administered because the patient failed to breathe spontaneously and had pinpoint pupils. He immediately awakened, the trachea was extubated, and he was transported to the recovery room. On his arrival there, his arterial blood pressure was 130/60 mmHg, heart rate 140 bpm, respiratory rate 24 breaths \cdot min⁻¹, and he appeared to be in mild respiratory distress. Ten minutes later, he remained lethargic and subsequently received additional naloxone 100 mcg iv and 300 mcg im. Tachycardia and tachypnea persisted, and diffuse rales were noted upon auscultation of the chest. One hour after his admission to the recovery room with an FI_{O_2} of 0.2, his Pa_{O_2} was 32 mmHg, Pa_{CO_2} 49 mmHg, and pH_a 7.31. Oxygen was administered. A chest roentgenogram demonstrated diffuse pulmonary edema. Furosemide 80 mg iv produced prompt diuresis and rapidly improved his clinical condition, arterial blood gas values, and chest roentgenographic findings. Cardiologic evaluation the following day revealed no evidence of cardiac abnormalities. He left the hospital 4 days postoperatively without sequelae.

DISCUSSION

Pulmonary edema may result from a variety of causes, but the differential diagnosis can be divided conveniently into cardiac and noncardiac categories. Cardiac causes

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include cardiomyopathy, valvular heart disease, and congenital heart disease. Noncardiac pulmonary edema, or adult respiratory distress syndrome (ARDS), accompanies a wide variety of life-threatening insults. Neither of these two patients had evidence of structural cardiac disease or of a primary disease process known to predispose to ARDS. The second patient had an unruptured, acutely inflamed appendix removed at operation; it may have been a source of systemic sepsis.

Previous reports of severe complications following naloxone administration have emphasized the risk in patients with preexisting cardiac disease^{1,3} or hypertension,⁴ and the risk of naloxone given iv in 400-mcg doses.¹⁻⁴ Consequently, smaller doses have been recommended.^{4,5} Our first patient received 100 mcg (1.2 mcg/kg) iv. The second received two 100-mcg doses (each 1.2 mcg/kg) iv, plus an additional 300 mcg (3.7 mcg/kg) im. Respiratory distress was evident after the first iv dose.

The moderate increases in heart rate and blood pressure, presumably secondary to catecholamine release, that were seen in our two patients should not produce acute left ventricular failure in otherwise healthy teenagers. However, certain parallels may exist between the problem in these two patients and neurogenic pulmonary edema (NPE), a type of ARDS that may occur in the absence of underlying cardiac or pulmonary disease. NPE may develop quickly after profound stimulation of the central nervous system.⁶ It appears to result from an outpouring of adrenal catecholamines,⁷ which leads to pulmonary venoconstriction,⁸ pulmonary hypertension,⁹ and, perhaps, an increase in pulmonary vascular permeability.¹⁰ Systemic arterial hypertension is not necessary for the development of NPE.¹¹ NPE occurs most frequently after damage to periaqueductal areas of brain tissue, which are rich in endogenous opioids.¹² Postoperatively, CSF endorphin levels are lower than control.¹³ Naloxone will inhibit further the endogenous pain suppression pathway and may permit unopposed noradrenergic transmission from medullary centers that may precipitate NPE.

Pulmonary edema with hypoxemia possibly could explain the fatal ventricular dysrhythmias seen by Andree² in two young adults who received naloxone. In support of that hypothesis, Andree's second patient developed "copious quantities of frothy pink fluid" during resuscitation. Many episodes of acute pulmonary edema may not be diagnosed in young adults because of a low index of suspicion. Unless a routine postoperative chest roent-

genogram demonstrates pulmonary edema, otherwise healthy patients might recover without obvious clinical symptoms or signs of respiratory embarrassment. Certainly, we diagnosed pulmonary edema in our second patient less rapidly than in our first patient, in whom vigorous expectoration of pink, frothy fluid provided gross evidence.

In summary, we present two cases in which young, previously healthy adolescents developed acute pulmonary edema shortly after receiving small doses of naloxone for antagonism of residual narcotic drugs. These cases emphasize the need for cautious administration of naloxone and for careful observation of patients who receive naloxone to reverse narcotic effects, even if they have no history of hypertension or cardiovascular disease.

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