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Acute Pulmonary Edema Following Naloxone Reversal of High-dose Morphine Anesthesia

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The use of naloxone, an opiate antagonist without intrinsic agonist activity, to reverse the respiratory depression induced by large doses of narcotics administered for anesthesia has become widespread.1 2 Although this technique has the advantage of shortening or eliminating the need for postoperative mechanical ventilation, the disadvantages range from precipitation of severe pain, with accompanying excitement and activation of the sympathetic nervous system, to causation of an acute drug withdrawal syndrome. These in turn may have deleterious circulatory consequences, especially in cardiac patients. The following report illustrates dramatically the nearly disastrous result of administration of naloxone following open-heart surgery.

REPORT OF A CASE

Preoperative Summary

A previously healthy 70-year-old man had a two-month history of precordial pain and progressive congestive heart failure without evidence of myocardial infarction. Cardiac catheterization revealed 4+ mitral regurgitation and high-grade obstructions of the left anterior descending and right coronary arteries; hence, the patient was scheduled for a semi-urgent valvular repair replacement and aortocoronary bypass grafts. Weight was 71 kg, hematocrit 32 per cent, serum chemistry normal; mild restrictive and obstructive respiratory disease was present. Arterial blood gases were Pa02 73 torr, PCO2 48 torr, and pH 7.45. Electrocardiogram showed sinus rhythm, left ventricular hypertrophy, and nonspecific ST and T wave changes. Cardiomegaly with mild pulmonary edema and right pleural effusion were seen on chest x-ray. Blood pressure was 130/80 torr, pulse rate 72/min. Medications were digoxin, 0.25 mg, and furosemide, 120 mg, daily.

Operative Management

After placement of catheters and electrodes to measure continuously radial arterial pressure, central venous pressure (initial CVP = 4 torr), ECG, and urinary output, anesthesia was induced at 6:40 AM with 136 mg morphine, administered over 20 minutes and supplemented with 5 mg diazepam, and 8 mg pancuronium prior to endotracheal intubation. Ventilation through was with 100 per cent oxygen, either manually or with a constant-volume ventilator, adjusted to maintain Pa02 > 150 torr and PCO2 between 30 and 40 torr. Vital signs were stable throughout induction of anesthesia and the pre-perfusion period. Methylprednisolone (2 g) was given iv 30 min prior to cardiac bypass, instituted at 7:57 AM. Pump flows of 5 to 6 l/min at normal body temperature were maintained throughout perfusion; the heart was cooled differentially via aortic root perfusion. A flail mitral valve leaflet secondary to ruptured chordae tendineae was found, the valve was replaced with a Bjork-Shiley prosthesis, and vein grafts to the left anterior descending and the right coronary arteries were constructed. After weaning from the pump (10.04 AM), the patient's blood pressure was 75/40 torr, CVP was 14 torr, and A-V dissociation of varying degree was seen, with a ventricular rate of 65/ min. Isoproterenol infusion (4 µg/min) increased the rate to 85/min, increased blood pressure to 115/50 torr, and decreased CVP to 12 torr. These values persisted until the end of the operation even after isoproterenol was discontinued. Coronary flows were measured at 130 (RCA) and 100 (LAD) ml/min. At 11:02 AM, the patient received 2 mg diazepam, and at 11:35 AM he was transported to the surgical intensive care unit. Urinary output during operation was 1,180 ml.

Postoperative Course

In the surgical intensive care unit, initial blood pressure was 100/50 torr (mean 65 torr), CVP was 14 cm H2O, and ECG showed complete A-V dissociation with variable ventricular rate. The patient was still unconscious, his skin was warm and pink, peripheral pulses were excellent, and the chest was clear except for a few coarse rales and rhonchi. Blood gases were Pa02 72 torr, PCO2 40 torr, and pH 7.36 during mechanical ventilation with an Fi02 of 0.5 (later increased to 0.6). Hematocrit was 31 per cent, and electrolytes were normal. Intravenous fluids were given at a rate of 50 ml/hour; urinary output averaged 225 ml/hour for the first six hours. Infusion of isoproterenol was started again (at the same rate); this increased ventricular rate to between 80 and 110/ min and blood pressure to 110/60 torr (mean 75). For the next three hours the patient remained generally unresponsive to painful and verbal stimuli; pupils were moderately enlarged, reactive, and equal. Blood pressure varied between 85 and 110 torr systolic, CVP rose slowly to 16 cm H2O, and cardiac rhythm varied among normal sinus rhythm, 2:1 block, and

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complete A-V dissociation. \( P_a \) was 95 torr, \( P_{co2} \) 39 torr, and \( pH \) 7.32. Concern was felt about the patient’s persistent unresponsiveness in view of his age and the longer than usual pump run (127 minutes). The possibility of air embolism was also considered. Because it was felt that a more wakeful state might increase the blood pressure and possibly improve A-V conduction, it was decided to reverse the residual narcotic depression by a narcotic antagonist. Accordingly, at 3:45 pm, naloxone, 0.4 mg, was injected iv over a period of 1/4 minutes. The effect can only be described as dramatic; within one minute the patient—who had been lying quietly, unresponsive, with good peripheral perfusion, clear lungs, and his respiration easily controlled by the ventilator—became exceedingly agitated and disoriented, attempted to sit up, fought the ventilator, and altogether presented a picture of considerable distress. His blood pressure rose rapidly to 170/100 torr. CVP to more than 18 cm H2O; cardiac rhythm did indeed convert to sinus tachycardia. Frothy red-tinged fluid began to pour from the endotracheal tube, faster than it could be suctioned away. The patient’s color became poor; rales and wheezes were heard over both lung fields. Ventilation was assisted manually with 100 per cent oxygen and positive end-expiratory pressure, with intermittent tracheal suctioning. Approximately 2 liters of fluid were obtained in all. Morphine (single doses of 5 mg, iv) was given in order to attenuate the effects of the antagonist. Over a period of 20 minutes a total dose of 30 mg morphine was necessary before the patient quieted and pulmonary edema subsided, at which point it was again possible to ventilate him adequately with the respirator. He became drowsy once more, but continued to respond to verbal commands and painful stimuli. Blood-gas values of samples obtained during the acute phase of this episode (manual ventilation) were \( P_a \) 92 torr, \( P_{co2} \) 40 torr, and \( pH \) 7.38. By 5:15 pm, \( P_a \) had increased to 176 torr during controlled ventilation by machine with 100 per cent oxygen and 5 cm H2O PEEP. Chest x-ray was no different from that obtained three hours earlier, blood pressure was 110 torr systolic, CVP fell gradually to 12 cm H2O, and cardiac rhythm alternated between a sinus mechanism and varying degrees of block. Isoproterenol infusion was continued at the same rate until the following morning.

The patient’s condition continued to improve. The episodes of A-V block diminished in frequency, disappearing entirely within the next two days. He was weaned from the ventilator on the second postoperative day, and discharged in good condition on the twelfth postoperative day. He remains well, without observable neurologic deficit and without evidence of congestive failure. He has no recall of the operation or of the episode of pulmonary edema.

**Discussion**

The first question raised by this case is that of how to determine the proper dose of naloxone in the clinical situation. Theoretically, the proper dose is based upon the agonist: antagonist ratio. For morphine: naloxone this ratio has been determined in *vitro* and *in vivo* under equilibrium conditions. For clinical purposes the equilibrium dose ratio can be no more than a starting point. Equilibrium conditions are almost never present. The time intervals between injection of morphine and injection of naloxone are variable, and the rate of elimination of morphine is not known. No rapid method for determination of the blood level of narcotics is in use. The sensitivity of the patient to the depressant effect of morphine differs among patients, and changes in the same patient with time and conditions. The situation is further complicated by the presence of other drugs, which may act additively (or antagonistically) with morphine. Hence, even a clinical assessment of the magnitude of the morphine effect is unlikely to be of decisive value. These difficulties are reflected in the attempts of several investigators to establish empirically a "correct" schedule of doses of naloxone in the presence of morphine and other narcotics, but in healthy volunteers and in patients.

According to these studies and according to reference texts, the dose given to the present patient was not unreasonable. In retrospect (see above), it seems obvious that there is no single dose or combination of doses that can be expected to be optimal in every patient and every situation. This has been, indeed, the conclusion reached by Heisterkamp and Cohen. They recommend an initial dose of 0.1 or 0.2 mg naloxone, to be followed by additional doses of the same magnitude as required. This recommendation has been accepted by the manufacturer in the 1976 edition of the PDR. However, it may be that even an initial dose of 0.1 mg is too high in some cases. One of the two patients reported by Michaelis and co-workers in whom ventricular fibrillation developed immediately during or after injection of naloxone received only 0.1 mg of the antagonist.

It is also of interest to inquire into the hemodynamic mechanisms of the nearly disastrous response to naloxone in our patient. A case reported by Tanaka resembles the present case closely. In his patient, hypertension with pressures as high as 340/150 torr and paroxysmal atrial tachycardia developed, beginning during the slow injection of 0.4 mg naloxone and reaching its peak in 10 minutes. The underlying reactions in this and in our case were probably similar, and probably represented a massive sympathetic response to the pain and awakening elicited by the narcotic antagonist, resulting in hypertension and tachycardia. One patient’s heart was able to support the pressure load, the other’s was not. The present patient’s history shows clearly that his heart was only marginally competent prior to operation. It may be considered surprising that this heart could generate an arterial pressure of 170/100 torr. However, it is not surprising that left ventricular failure and pulmonary edema soon followed. A probable additional factor in this patient was the presence of a relatively large fluid volume in the systemic vascular bed, which had been given intentionally during the state of obvious vasodilatation after morphine administration in the desire to utilize the patient’s Starling mechanism to increase cardiac output (CVP at the end of the operation was 12 torr).
It is well known that a strong sympathetic stimulus will shift blood volume from the systemic or high-pressure to the pulmonary or low-pressure vascular bed. Thus, this patient may be thought of as having experienced a sudden increase in pulmonary blood volume far larger than could have been produced by any external transfusion. Both of these factors together—by no means a rare combination in situations of this type—account fully for the observed fulminating pulmonary edema.

In conclusion, we report an unusual reaction to the injection of 0.4 mg naloxone in a patient who had received 136 mg morphine 11 hours earlier. The reaction was a precipitous widespread activation of the sympathetic nervous system, which induced pulmonary edema in accordance with the history of the patient and his hemodynamic status at the time of the naloxone injection.

REFERENCES


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Plastic Particulate Contaminants in the Medicine Cups of Disposable Non-spinal Regional Anesthesia Sets

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The past several years have seen the increased use of disposable regional anesthesia sets. The actual advantage of these sets over reusable goods has not been well documented. The disposable trays are convenient to use, and most anesthesiologists feel confident in the sterility and general cleanliness of the contained material. It is supposed that the cost of such equipment is less than that of the reusable variety. Previous reports have documented some problems with disposable equipment. We have identified another possible hazard in disposable epidural and nerve block trays—that of particulate contaminants in the medicine cups of the trays.

METHODS

The trays examined were selected at random from the stock supplied us at our institution. Abbott Epidural, Abbott Nerve Block, Pharmaseal Epidural, and Travenol Epidural sets were included in the series. The trays were opened as they would be in clinical practice, except that surgical gloves were not worn, to insure no particles of powder from the gloves fell into the tray. In each tray, the cup designed to hold the local anesthetic was removed, and its outside carefully wiped with a damp sponge and inspected to