Narcotic Analgesics in Anuric Patients

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Three cases are presented to illustrate the prolonged effects of narcotic analgesics in patients with absent renal function.

REPORT OF THREE CASES

Case 1. A 66-year-old Caucasian woman, weighing 62 kg, had chronic renal failure. She was on the hemodialysis program. Cervical laminectomy was performed for quadriplegia, using nitrous oxide and halothane. Five and a half hours after operation (2.25 hours from the time zero in figure 1) the patient received a subcutaneous injection of morphine sulfate, 4 mg. This was repeated 8 hours later. The following day she became hypotensive and had irregular respirations. Hemodialysis was started, and persistent hypotension (systolic pressure 55-20 mm Hg) necessitated an infusion of isoproterenol. The patient had periods of apnea, was semiresponsive, and had small pupils. Arterial blood-gas values during breathing of oxygen by face mask were: Paco₂, 129 mm Hg; PaO₂, 57 mm Hg; pH 7.24; base excess -3. Morphine overdose was diagnosed, and naloxone (Narcan), 0.4 mg, was given iv. Within a minute, blood pressure rose to 140/70 mm Hg, the patient became lucid, her pupils dilated, and her respiratory rate increased. The isoproterenol was discontinued without a fall in blood pressure. Arterial blood-gas values an

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DIALYSIS

NALOXONE
(0.2 mg IV)

MORPHINE
(4 mg SC)

SYSTEMIC BLOOD PRESSURE
(mm Hg)

RESP RATE
(minutes)

HOURS

Fig. 1. Changes in systemic blood pressures and respiratory rate in Case 1. Time zero is 3½ hours after the end of the surgical procedure.

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hour later were: $P_{a}O_{2}$ 52 mm Hg; $P_{a}CO_{2}$ 36 mm Hg; pH 7.35; base excess -3. Approximately two hours later a second iv injection of naloxone was given because the blood pressure, respiratory rate and level of consciousness had decreased. All three variables responded again, and also to two subsequent injections of naloxone. The final injection of naloxone was 32 hours after the last dose of morphine sulfate. The patient was never jaundiced, and two days after the episode, total bilirubin was 0.6 mg/100 ml, LDH 350 IU/l, SGOT 55 IU/l.

**Case 2.** A 62-year-old Caucasian man who had a history of chronic cough and two myocardial infarctions had elective resection of an abdominal aortic aneurysm at another hospital. General anesthesia with nitrous oxide, Innovar, and pancuronium was used. Following the operation, the patient remained oliguric, and blood urea nitrogen and creatinine increased (fig. 2). In 3 1/2 postoperative days, he received a total dose of 62 mg morphine sulfate by im injection, and on the sixth day, meperidine, 35 mg. Prior to the administration of meperidine, he was noted to have small pupils and Cheyne-Stokes respirations. He became progressively more obtunded and was transferred to this hospital for hemodialysis.

Arterial blood-gas values during breathing of oxygen were: $P_{a}O_{2}$ 63 mm Hg; $P_{a}CO_{2}$ 60 mm Hg; pH 7.23. The patient’s breathing was irregular, with an unusual pattern unlike a rhythmic Cheyne-Stokes pattern. His pupils were small and he was semireponsive. Naloxone, 0.4 mg, was given iv, and within a minute the patient became responsive, the pupils dilated, and the respiratory rate increased and became regular. Arterial blood-gas values 15 minutes later were: $P_{a}O_{2}$ 64 mm Hg; $P_{a}CO_{2}$ 40 mm Hg; pH 7.35. During the subsequent 48 hours, the patient required four more doses of naloxone, 0.4 mg, for slow respirations with periods of apnea. The last dose of naloxone was approximately 4 days after the last dose of morphine, and 3 1/2 days after the single dose of meperidine. On the day of admission to this hospital, total bilirubin was 1.1 mg/100 ml, SGOT 240 units; the patient was never jaundiced.

**Case 3.** A 73-year-old Caucasian man was admitted with sudden onset of renal failure of uncertain etiology. A diagnosis of vasculitis was considered.
During admission for investigation, a perforated duodenal ulcer was plicated. Twelve days later, the ulcer had to be oversewn because of hemorrhage. General anesthesia with nitrous oxide, droperidol, and d-tubocurarine was used. In the 2½ days following this last operation, he received a total dose of 100 mg morphine by subcutaneous injection (fig. 3). In the subsequent 5 days he received diazepam (Valium), 80 mg. im. During this postoperative period he remained on mechanical ventilation because of difficulty in weaning, associated with retention of carbon dioxide and decreased consciousness. His pupils were small, respiratory rate about 12/min and irregular. Nine days after operation (5.25 days after discontinuing morphine) he was given naloxone, 0.4 mg. He immediately became more responsive, and his respiratory rate increased and became regular. Arterial blood-gas values 40 minutes after naloxone were: Pao₂ 73 mm Hg; Paco₂ 48 mm Hg; pH 7.45; base excess +8. An hour prior to naloxone the values had been: Pao₂ 75 mm Hg; Paco₂ 56 mm Hg; pH 7.40; base excess +9. The patient received five subsequent injections of naloxone, 0.4 mg, over the next 34 hours. The final dose of naloxone was 6½ days after the last dose of morphine. During the postoperative period, the patient had received hemodialysis on five occasions, using a Kolff tub with Travenol ultra-flow tubing, with Diasol as the dialysate.

DISCUSSION

The narcotic antagonist naloxone hydrochloride usually causes no significant respiratory or cardiovascular change in subjects who have not received prior narcotics. The cases reported here suggest that any significant response at the time of injection of naloxone resulted from antagonism of an existing effect of narcotics or their breakdown products in the body. It is significant that naloxone reversed both hypercapnia (Cases 1, 2, 3) and hypotension (Case 1), suggesting that the narcotic or its breakdown products had both respiratory and cardiovascular effects.

The marked clinical effect of the narcotic in these patients was prolonged, naloxone producing a response as long as 6 days (Case 3) after narcotic administration. This may have been associated with the presence of renal failure, since prolonged central nervous system effects have been associated with narcotic administration in this type of patient. Even in subjects with normal renal function, detectable levels (0.001–0.004 µgm/l) of morphine are found as long as 48 hours after iv injection.

The prolonged effect seen in these patients was the result of systemic levels of either morphine or its breakdown products. Thus it is possible that the narcotic or its breakdown products accumulated in the body because of abnormal renal function. It was significant that the response to naloxone was seen even in the presence of hemodialysis (Case 3).

The prolonged effect may also reflect continued metabolism, release of the drug as well as its metabolites from tissues, or enterohepatic recirculation.

In the patients whose cases are presented there was no evidence of hepatic disease, suggesting that alteration of hepatic biotransformation was probably not the cause of the prolonged action.

The cases of three patients with postoperative renal failure are presented to draw attention to the marked, prolonged cardiovascular and respiratory effects that may follow administration of morphine. Naloxone reversed both actions, as long as 6½ days after injection of the narcotic analgesic.

REFERENCES