Lesson of the Week

Dihydrocodeine overdose treated with naloxone infusion

NANCY REDFERN

Naloxone is used to treat opioid overdosage as it antagonises the respiratory depression, hypotension, and diminished conscious level caused by narcotics.¹ The recommended dosage is 0.4 mg repeated twice at two or three minute intervals if required (manufacturer's data sheet), although it is likely that larger doses are often used.^{2,3} In renal and hepatic impairment narcotic effects may be prolonged^{4,5} and larger or repeated doses of naloxone may be needed. I report a case of self poisoning with dihydrocodeine in a patient with acute renal and hepatic impairment who required naloxone treatment for four days.

Case report

A 29 year old man with biochemical evidence of renal and hepatic dysfunction was admitted to hospital 13 hours after an overdose of 70 dihydrocodeine (30 mg) tablets. The history obtained from relatives did not indicate other drug ingestion and screening of the plasma for paracetamol, salicylate, and alcohol was negative. He had been assaulted several hours before taking the overdose and bruising was noted over his right buttock and thigh. On admission he was drowsy but moved in response to command, his pupils were pinpoint, the respiratory rate was 15 per minute, and the arterial blood pressure was 100/70 mm Hg. Gastric lavage was carried out but no tablets were returned. After naloxone 0.4 mg had been given intravenously his speech became coherent and he moved spontaneously. A further three doses of naloxone 0.4 mg were given intravenously over the next 25 hours. By this time, however, he was unconscious, unresponsive to pain, and had a respiratory rate of 4 per minute, a systolic blood pressure of 75 mm Hg, an arterial carbon dioxide tension (P_{aCO_2}) of 6.2 kPa (47 mm Hg), and a pH of 7.18. Naloxone 1.2 mg was given intravenously with good effect and an intravenous infusion of 0.2 mg/hour started. He had not passed urine since admission and catheterisation produced 250 ml. His serum potassium concentration was 7.4 mmol(mEq)/l, urea 20.3 mmol/l (122 mg/100 ml), creatinine 614 μ mol/l (6.94 mg/100 ml), bilirubin 11 μ mol/l (0.64 mg/100 ml), alkaline phosphatase 82 U/l, alanine transferase (serum ALT; old abbreviation SGPT) 2466 U/l, aspartate transferase (serum AST; old abbreviation SGOT) 2250 U/l, and γ -glutamyltransferase 60 U/l. After 12 hours of the naloxone infusion he was again unresponsive to pain, P_{aCO_2} was 14.3 kPa (107 mm Hg), pH 6.93, and arterial blood pressure 130/70 mm Hg. At this point, 50 hours after the overdose, artificial ventilation of the lungs was started and the naloxone infusion stopped. Peritoneal dialysis was begun as his serum potassium concentration had risen to 8.2 mmol(mEq)/l, urea to 22 mmol/l (132 mg/100 ml), and creatinine to 691 μ mol/l (7.81 mg/100 ml).

After six hours artificial ventilation was stopped and an infusion of naloxone (0.8 mg/h) begun. At this time he had a P_{aCO_2} of 5.1 kPa (38 mm Hg) and a pH of 7.3; he responded to pain but did not speak or move spontaneously. The naloxone infusion was continued at this rate for 50 hours. The P_{aCO_2} remained below 6 kPa

Gross opioid overdosage in patients with renal and hepatic failure may require treatment with large doses of naloxone over a long period

(45 mm Hg), but each time the infusion rate was decreased the P_{aCO_2} began to rise. Finally, 106 hours after the overdose he maintained a P_{aCO_2} below 6 kPa (45 mm Hg) without naloxone treatment. He remained drowsy but responsive to simple commands for the next two days. Peritoneal dialysis was carried out for a total of four days. Twenty four hours after stopping dialysis his blood biochemistry was as follows: sodium 132 mmol(mEq)/l, potassium 3.6 mmol(mEq)/l, urea 20.9 mmol/l (126 mg/100 ml), creatinine 1020 μ mol/l (11.53 mg/100 ml), bilirubin 17 μ mol/l (0.99 mg/100 ml), alkaline phosphatase 76 U/l, alanine transferase 960 U/l, aspartate transferase 498 U/l, and γ -glutamyltransferase 47 U/l. One month after admission renal and hepatic function test results had returned to normal.

Thus in the 106 hours after dihydrocodeine overdose the patient required a total of 46.6 mg of naloxone.

Comment

A 29 year old man with acutely raised serum transaminases, urea, and creatinine concentrations developed severe life threatening respiratory depression 36 hours after overdosage with dihydrocodeine 2.1 g. He was treated with artificial ventilation for six hours and naloxone for four days. In this patient, who had evidence of both renal and hepatic impairment, several aspects are worthy of comment.

Dihydrocodeine is excreted in the kidney either unchanged or as a glucuronide derivative.⁶ Little, however, is known about its pharmacokinetics. The ingestion of a single large dose of dihydrocodeine 13 hours earlier would have been expected to cause severe narcosis at the time of admission. The slow onset of respiratory depression after admission suggests either continued absorption of the drug from the gastrointestinal tract into the blood stream or the accumulation of an active metabolite of dihydrocodeine. Although dihydrocodeine, in common with other opioids, will delay drug absorption by delaying gastric emptying,⁷ gastric lavage in this patient did not indicate tablets in the stomach. Thus delayed absorption of dihydrocodeine is not likely to have been the mechanism of delayed onset of respiratory depression in this patient. The accumulation of active metabolites has been suggested as a possible cause of persistent narcosis despite decreasing drug concentrations in a recent case of dihydrocodeine narcosis in renal failure.⁸

Unfortunately, it was not possible to determine the cause of the acute hepatic and renal impairment which was present on admission. An overdose of paracetamol two to three days before the dihydrocodeine overdose would cause renal impairment, but a raised bilirubin concentration and greater γ -glutamyltransferase activity would also be expected. Alternatively, the increased transaminase activity may have been

Western Infirmary, Glasgow G11 6NT

NANCY REDFERN, MB, BS, BSC, registrar in anaesthetics

Correspondence to: Hope Hospital, Salford M6 8HD.

due to muscle necrosis resulting from the assault. The activity was, however, much higher than would be expected from the observed damage, and assault does not explain the renal impairment.

Naloxone is a short acting specific opiate receptor antagonist with a plasma half life of only 68 minutes.⁹ The greater the amount of narcotic ingested the larger the amount of antagonist needed to inhibit competitively its effect. This patient had ingested a large dose of narcotic, the effects of which were apparently prolonged by renal and hepatic impairment. Although the initial 0.4 mg of naloxone was effective the dose interval was too long and the patient had severe respiratory depression 25 hours after admission. The subsequent infusion rate of 0.2 mg/h was also insufficient to maintain adequate respiration and the patient was again comatose 37 hours after admission. When the infusion rate was increased to 0.8 mg/h respiration was adequate.

Clearly, the difficulty with this patient was maintaining therapeutically effective naloxone concentrations. The manufacturer suggests that repeated administration of naloxone may be necessary but gives no indication of the dosage and frequency of administration. To maintain therapeutically effective concentrations of a short acting drug, such as naloxone, when antagonising the effects of a large dose of much longer acting agonist requires either frequent bolus doses or an infusion of adequate concentration. Thus it is important to remember when treating gross opioid overdosage in patients with renal and

hepatic failure that large doses of naloxone may be required over a long period.

I thank Dr J G Mone, for permission to publish a case admitted under his care, and Dr W S Nimmo for his helpful criticism of the report.

References

- ¹ Evans LEJ, Roscoe P, Swainson CP, Prescott LF. Treatment of drug overdosage with naloxone, a specific narcotic antagonist. *Lancet* 1973; i:452-5.
- ² Proudfoot AT. *Diagnosis and management of acute poisoning*. 1st ed. Oxford: Blackwell Scientific Publications, 1982.
- ³ Vale JA, Meredith TJ. *Poisoning: diagnosis and treatment*. 1st ed. London: Update Publications Ltd, 1982.
- ⁴ Bennett WM. Drug prescribing in renal failure. *Drugs* 1979;17:111-23.
- ⁵ Wright R, Alberti KGMM, Karran S, Millward-Sadler GH, eds. *Liver and biliary disease*. 1st ed. London: W B Saunders, 1979.
- ⁶ Bowman WC, Rand MJ. *Textbook of pharmacology*. 2nd ed. Oxford: Blackwell Scientific Publications, 1980.
- ⁷ Nimmo WS, Heading RC, Wilson J, Tothill P, Prescott LF. Inhibition of gastric emptying and drug absorption by narcotic analgesics. *Br J Clin Pharmacol* 1975;2:509-13.
- ⁸ Barnes JN, Goodwin FJ. Dihydrocodeine narcosis in renal failure. *Br Med J* 1983;286:438-9.
- ⁹ Berkowitz BA. The relationship of pharmacokinetics to pharmacological activity: morphine, methadone and naloxone. *Clin Pharmacokinet* 1976;1:219-30.

(Accepted 29 March 1983)

Communicable Diseases

Rubella surveillance

Prepared by the Public Health Laboratory Service Communicable Disease Surveillance Centre

The last major epidemic of rubella was in 1978 and 1979, when most areas of Britain experienced an outbreak in one or other of those years. This was followed by three years (1980-2) of small outbreaks.

Reports of rubella to the Royal College of General Practitioners and to the Communicable Disease Surveillance Centre, and from local notification systems in Bristol, Newcastle, Leeds, and Manchester suggest that the rubella outbreak

this year is larger than those of 1980-2 but not as large as in 1978-9 (figure). For the four week period ending 31 May 1983, the average weekly rate of reports of clinical rubella to the Royal College of General Practitioners was 16.9 per 100 000 compared with 22.6 in the four week period ending 6 June 1978, 17.8 in the four week period ending 5 June 1979, and 7.5, 5.9, and 8.5 respectively for 1980-2. Laboratory reports to the Communicable Disease Surveillance Centre so far number 1115 this year (weeks 1-22) compared with 1315 for the equivalent period in 1978 and 1342 in 1979 and with 322, 234, and 673 respectively for 1980-2. Data from four of the cities (table) where rubella is notifiable show the usual patchy distribution, with Bristol and Newcastle recording fairly large outbreaks.

Surveillance of rubella between 1978 and 1983.

Notifications of rubella in four cities

	Notifications weeks 01-22					
	1978	1979	1980	1981	1982	1983
Bristol	586	318	314	63	90	1178
Manchester	963	188	160	57	34	212
Leeds	685	2398	440	230	183	456
Newcastle	113	567	157	88	51	857

Outbreaks of rubella usually peak in June, so that numbers may start to decline in the next few weeks.