Coma, myalgia and hypoxia

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A 32-year-old man who had recently commenced oral methadone presented semiconscious, after a two-day history of myalgias, weakness and dyspnoea. On examination, he was drowsy, localising to pain, eye opening to speech and verbalising to pain. He had a respiratory rate of 10 min, a blood pressure of 135/80 mmHg and was febrile (38.1°C). There was tenderness over proximal muscle groups with marked muscle weakness of his legs and arms. Laboratory findings are presented in box 1. He was given supplemental oxygen, intravenous hydration with alkaline diuresis and antibiotics. His conscious state improved rapidly after intravenous naloxone. Over the next few days his hypoxia resolved, conscious state returned to normal, urine output and hydration remained stable. His muscle pains resolved and the muscle weakness greatly improved. He then complained of a painful, swollen right arm that was warm, tender and oedematous on examination.

Laboratory investigations
<ul style="list-style-type: none">• arterial pH 5.0• partial pressure oxygen 84 (on 10 litres/min O₂)• partial pressure carbon dioxide 4 l• blood urea nitrogen 7.0 mmol/l• serum creatinine 91 µmol/l• white blood cells 10 × 10⁹/l• serum bilirubin 18 µmol/l• urine: appearance: dark brown; haem pigment 3+, protein 1+, red cells 2/high power field• X-ray (chest, abdomen): normal• serum electrolytes, glucose, liver enzymes: normal

Box 1

Questions

- 1 What is the most likely diagnosis of his initial presentation and what diagnostic tests should be performed?
- 2 Suggest possible causes.
- 3 How do drugs predispose to muscle damage?
- 4 What are the possible explanations of his hypoxia and what tests should be performed?

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Answers

QUESTION 1

The most likely diagnosis is drug-induced nontraumatic rhabdomyolysis and coma. In this case methadone was the culprit drug. The presentation is characteristic with drowsiness, diffuse myalgias, muscle weakness and dark urine. However, the usual setting is that of an acute overdose of intravenous narcotic, not physician administered oral methadone. The diagnostic tests performed include blood and urine drug screen for narcotics and sedatives (positive), dark urine that is positive for haem pigment but with a paucity of red blood cells (3/high power field), presence of urinary myoglobin and measurement of serum creatine phosphokinase (3415 U/l), and lactic dehydrogenase (326 U/l).

QUESTION 2

Traumatic rhabdomyolysis occurs in the setting of burns, crush syndromes, prolonged convulsions and heat stroke. It is now recognised that nontraumatic rhabdomyolysis is responsible for the majority of cases, this is known to occur after drug overdose and during systemic infections.¹ Some series have implicated drugs in as many as 81% of cases of rhabdomyolysis.² Drug-induced rhabdomyolysis can be either a primary problem or secondary to seizures, hypothermia, prolonged coma or muscle compression as a result of the overdose. In our patient methadone was associated with nontraumatic, nonseptic rhabdomyolysis confirmed by elevated creatine kinase and myoglobinuria. However, unlike the other cases described, acute renal failure did not occur and rhabdomyolysis occurred after commencing oral methadone in a supervised programme. Drugs associated with primary rhabdomyolysis are listed in box 2.

QUESTION 3

The mechanism for rhabdomyolysis in response to narcotics was previously thought to be due to muscle damage from pressure necrosis due to profound sedation but this was unlikely in our patient due to the suddenness of his presentation. Other authors have observed primary rhabdomyolysis after chronic administration of methadone and hypothesised a direct myotoxic action that interferes with myocyte ATP metabolism.³ Other suggested mechanisms include inhibition of calcium metabolism by the sarcoplasmic reticulum,

Drugs causing primary rhabdomyolysis

alcohol
amphetamines
amphotericin B
antihistamines
barbiturates
benzodiazepines
cimetidine
cocaine
colchicine
cotrimoxazole
isoniazid
lithium
monoamine oxidase inhibitors
narcotics
phenothiazines
simvastatin
streptokinase
theophylline

Box 2

disruption of muscle cell membranes and altered carbohydrate metabolism.²

QUESTION 4

Possible mechanisms of hypoxia include ventilation-perfusion mismatch, shunt, diffusion impairment and hypoventilation. Investigations include arterial blood gases to confirm or exclude hypoventilation, carbon monoxide diffusing capacity, chest X-ray, V/Q scan and a pulmonary shunt study. Our patient had a normal chest X-ray and V/Q scan despite developing an axillary vein thrombosis, but a 14.9% pulmonary shunt (normal < 5 %). The existence of a significant pulmonary shunt which resolved spontaneously seems the most likely explanation, in view of the results of the shunt study. Previously narcotics have been associated with noncardiac pulmonary oedema causing hypoxia^{4,5} but not shunt. Other possibilities include micro-emboli to the pulmonary circulation from axillary vein thrombosis or narcotic-associated alveolar and interstitial pneumonitis.

Final diagnosis

Rhabdomyolysis and respiratory failure following oral methadone.

Keywords: drug-induced rhabdomyolysis, respiratory failure, methadone

- 1 Prendergast BD, George CF. Drug-induced rhabdomyolysis: mechanisms and management. *Postgrad Med J* 1993; **69**: 333–6.
- 2 Gabow PA, Kaehny WD, Kelleher SP. The spectrum of rhabdomyolysis. *Medicine* 1982; **61**: 141–52.
- 3 Koppel C. Clinical features, pathogenesis and management of drug-induced rhabdomyolysis. *Med Tox Adv Drug Exper* 1989; **4**: 108–26.

- 4 Fraser DW. Methadone overdose. Illicit use of pharmaceutically prepared parenteral narcotics. *JAMA* 1971; **217**: 1387–9.
- 5 Hojs R, Sinkovic A. Rhabdomyolysis and acute renal failure following methadone abuse. *Nephron* 1992; **62**: 362.