Hepatic necrosis with doxapram hydrochloride

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Summary: We report the first case of acute hepatic necrosis, which we believe to have been caused by the administration of the respiratory stimulant, doxapram hydrochloride (Dopram).

Introduction

The respiratory stimulant doxapram hydrochloride has a useful place in the treatment of ventilatory failure in patients suffering from chronic lung disease with impaired respiratory drive. The drug is usually well tolerated with few serious adverse effects. However, we report a case of hepatic necrosis which we believe was caused by the administration of doxapram.

Case report

A 68 year old man with bronchiectasis was admitted with a 1 week history of green sputum and general malaise. The patient had suffered respiratory problems from childhood and usually produced half a cupful of clear sputum daily. Enquiry revealed no recent foreign travel, no contact with jaundiced individuals, no history of ankle oedema, and infrequent consumption of alcohol. Inhaled salbutamol was the only medication prescribed before his admission.

On examination he was alert, non-icteric, but pyrexial (37.5°C), centrally cyanosed, clubbed and making little respiratory effort. There were no stigmata of chronic liver disease. Examination of the cardiovascular system was normal, except for a 3 cm elevation of the jugular venous pressure. Auscultation of the chest revealed basal crackles, worse on the right, and a bilateral expiratory wheeze. Palpation of the abdomen was normal.

Arterial puncture (breathing air) revealed a partial pressure of oxygen (P_{O_2}) of 4.46 kPa (normal range 10–13 kPa), partial pressure of carbon dioxide (PCO_2) was 7.71 kPa (normal 4.7–6.0 kPa). The haemoglobin concentration was 16.1 g/l, and the white blood count $18.4 \times 10^9/l$ (90% neutrophils, 7% lymphocytes).

Serum sodium and potassium were normal, the urea was elevated at 12 mmol/l. The chest radiograph showed changes consistent with bronchiectasis with patchy shadows in the right lower zone, suggestive of infection. *Haemophilus influenzae* was later cultured from the sputum.

A diagnosis of respiratory failure due to an infective exacerbation of bronchiectasis was made. The patient was treated with physiotherapy, 24% oxygen (via a face mask), nebulized salbutamol 5 mg (then repeated 8 hourly), oral co-trimoxazole 960 mg (repeated 12 hourly), intravenous hydrocortisone 100 mg (repeated 8 hourly), oral frusemide 40 mg (repeated daily), and oral amiloride 5 mg (repeated daily). However, he became mildly confused and repeat arterial puncture showed that the PCO_2 had risen to 9.87 kPa. The blood pressure was 160/90 mm Hg. A doxapram infusion was commenced at 2 mg/min, the PCO_2 then fell to 7.18 kPa (PO_2 was 5.9 kPa), and the patient improved. The infusion was discontinued after 24 h. Nebulized salbutamol was changed to the inhaled form after 3 d, the intravenous hydrocortisone was changed to oral prednisolone (30 mg/24 h), diuretics were continued for a fortnight and the co-trimoxazole was stopped after a week.

Twenty-four hours later the patient was afebrile and his general condition improved considerably. However, a biochemical screen taken 16 h after admission, showed that the alanine aminotransferase (ALT) was grossly elevated at 5064 IU/l (normal 2–53 IU/l), the bilirubin mildly raised at 30 mmol/l (normal 3–17 mmol/l), the gamma glutamyl transferase (gamma GT) was 78 IU/l (normal 0–50), and the alkaline phosphatase (alk phos) 222 IU/l (normal 260–500 mmol/l), the serum creatinine was 220 mmol/l (normal 60–120 mmol/l), the serum proteins were normal, and serum urate greater than 1000 mmol/l (normal 260–500 mmol/l). At no stage were there symptoms or signs of hepatic insufficiency.

Figure 1 shows that the liver function tests returned

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Figure 1 Improvement of liver function tests with time. (■) Alanine aminotransferase (IU/l); (▲) γ glutamyl transferase (IU/l); (●) bilirubin (μ mol/l); (D) doxapram.

to normal over 3 weeks and after 3 d the serum urate and renal function had returned to normal. There was no haematological or biochemical evidence of disseminated intravascular coagulation.

The liver was biopsied 8 d after admission and the histology showed preservation of the lobular architecture with features of recent confluent centrilobular necrosis with reticulin collapse. Pigmented macrophages in the necrotic zones contained lipofuscin but Perls' stain for haemosiderin was negative. There was no fatty change of adjacent hepatocytes and the adjacent sinusoids were not significantly dilated. The features were consistent with the effect of a toxic agent.

The patient's auto-immune profile was negative, paired serological titres for hepatitis A and B viruses, Q fever, leptospirosis, toxoplasma, and atypical pneumonia were normal. Three blood cultures were sterile.

Ten months after his admission the patient has remained well with normal liver function tests.

Discussion

Hepatic necrosis was suspected by the gross serum elevation of alanine aminotransferase compared with the more modest rises of gamma glutamyl transferase,

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alkaline phosphatase, and bilirubin, and this was confirmed histologically. Alanine aminotransferase is cytosol-bound (Zakin & Boyer, 1982) and is released in very large amounts immediately the hepatocyte is damaged by toxic substances (Schmidt *et al.*, 1975).

Similar centrilobular liver necrosis can occur in severe right ventricular failure (RVF) (Sherlock, 1951). However, with the passive venous congestion which accompanies RVF typically, centrilobular congestion, dilatation of sinusoids, haemosiderin within macrophages and fatty changes to adjacent parenchyma are seen. None of these features were present in the biopsy from our patient. Moreover, the patient maintained a normal blood pressure throughout his illness and was not in severe RVF.

The mechanism of doxapram-induced hepatitis is uncertain. An infusion of doxapram is known to cause reversible fatty change in rats' liver (Branham & Woolles, 1966) with large amounts of doxapram and its metabolites present in both liver and bile. Severe hepatic fatty change (with elevation of the serum transaminase concentrations, but without necrosis) has also been reported in an infant after doxapram administration (Hunt *et al.*, 1979).

Doxapram is oxidized to its principle metabolite (AHR 5955) by the liver and an enterohepatic pathway has been suggested with the bile an important excretory route (Robson & Prescott, 1978). It is unknown whether this metabolite has any pharmacological activity (Martindale, 28th Ed, 1982). The effect of hypoxia on the metabolism of doxapram is unclear although its excretion appears to be similar in both healthy volunteers and in patients with respiratory failure (Robson & Prescott, 1978).

Co-trimoxazole is known rarely to cause hepatic necrosis (Ransoff & Jacobs, 1981) but this and other medications were continued during the phase of biochemical recovery. The very high urate (out of proportion to the degree of renal impairment) may be explained by a combination of liver cell death and hypoxia, leading to organic acidaemia. Organic acids (including lactate) compete for excretion with uric acid in the renal tubule causing retention of urate.

Doxapram was prescribed for 24 h only and the hepatic function quickly returned to normal after the infusion was stopped. In the absence of an obvious infective aetiology we conclude that the hepatic necrosis was caused by the administration of doxapram.

This case has been reported to the Committee on Safety of Medicines and the manufacturers.

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