Review

Unusual complications of paracetamol poisoning

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Introduction

Every physician is only too familiar with acute hepatic necrosis as the most common complication of severe paracetamol poisoning. The frequency with which paracetamol is used for self-poisoning may, however, give rise to complacency through familiarity, and the less common complications may be missed. The purpose of this review is to act as a reminder of these more unusual complications. Although there have been many reports of toxic effects on other body systems, these have often occurred in the presence of hepatic or multi-organ failure, and in such circumstances it is difficult to distinguish between cause and effect.

Cardiotoxicity

Non-specific ECG changes, mostly of the ST segment and T wave,1–8 and changes suggestive of pericarditis,6,9 have been reported in patients with paracetamol overdose without hepatic encephalopathy, but such reports are rare given the number of paracetamol-poisoned patients per year, especially in the UK. In the case reported by Will and Tomkins,1 the ECG changes may have been due to viral infection since the patient had a sore throat and atypical monocytes in the blood film.

Symptomatic or clinically apparent disturbances of cardiac function appear to be very rare after paracetamol overdose in the absence of encephalopathy.6,9–12 Most of the claims made for paracetamol cardiotoxicity have been based on post-mortem findings in patients who developed fulminant hepatic failure, and who showed histological features consistent with toxic myocarditis, such as diffuse myocardial damage with interstitial oedema or bands of necrosis and haemorrhage.10,11,13–15 It is likely that other factors contributed to toxicity, as such lesions have also been found in fulminant hepatic failure not due to paracetamol poisoning.6,16,17 Electrocardiographic abnormalities have been reported in paracetamol-induced fulminant hepatic failure as preterminal events.13,18–21 Instances of bradycardia,22 pericardial rub23 and endocarditis24 have been mentioned after paracetamol overdose. Ohtani and colleagues25 reported cardiac failure occurring 16 days after a paracetamol overdose sufficient to cause renal failure; however, it is difficult to see how paracetamol could have caused late myocardial damage in this case. Not surprisingly, ECG changes have been reported following overdose with combination preparations of dextropropoxyphene and paracetamol,26 and in one such case were clearly attributable to hypothermia.27 In 20 unselected cases of fatal paracetamol poisoning there was no evidence of myocarditis at postmortem examination.28

Two potential mechanisms for paracetamol cardiotoxicity have been postulated.29 It was suggested that paracetamol may deplete sulphhydryl groups to interfere with production of nitric oxide and lead to coronary ischaemia,8 while arrhythmias may be precipitated by metabolic complications of paracetamol poisoning such as hypoxia,6,30 hyperkalaemia,6,31 acidosis6,32 and a rise in serum free fatty acids.33,34 No systematic assessment of paracetamol cardiotoxicity per se has been reported using sensi-
ive indicators of myocardial damage in a substantial number of patients.

**Pulmonary damage**

Lung injury or changes in the pulmonary circulation in paracetamol poisoning have not been reported in the absence of fulminant hepatic failure. In 24 patients with fulminant hepatic failure due to paracetamol, eight developed severe lung injury and in two hypoxaemia contributed to death. It is not known whether the pulmonary lesion represented Adult Respiratory Distress Syndrome complicating fulminant hepatic failure, or whether it was a manifestation of direct pulmonary toxicity, but patients with lung injury had higher median encephalopathy grades, APACHE II scores and mortality. Circulatory failure requiring inotropic support occurred in all patients with lung injury, but in only 40% of those without. Pulmonary alveolar damage has been attributed to direct toxicity of paracetamol in animals.

**Haematotoxicity**

Mild thrombocytopenia is a common finding in patients with severe paracetamol poisoning, but it is rarely of significance in the absence of hepatic failure, and is usually related to the severity of liver damage. In a survey of 174 patients with paracetamol overdose, only 21 had severe liver damage (defined as a plasma AST activity >1000 IU/l) and six (29%) had minimum platelet counts <100,000/mm³. In some patients, thrombocytopenia was severe and associated with purpura and bleeding. Platelet function and structure is abnormal in patients with paracetamol-induced hepatic failure, but not in those with lesser degrees of hepatic injury.

Thrombocytopenia is common in acute hepatic failure from any cause, and is usually attributed to disseminated intravascular coagulation, which has been repeatedly demonstrated in patients with moderate and severe paracetamol-induced hepatic necrosis. It is probably the major cause of thrombocytopenia following paracetamol overdosage, but other mechanisms may rarely be responsible, such as direct toxic effects on platelets or megakaryocytes or immunologically-mediated toxicity.

Douidar and colleagues report severe hepatotoxicity, acute renal failure and pancytopenia in a young child after repeated administration of paracetamol in excessive doses for a febrile illness.

Paracetamol can cause severe methaemoglobinaemia in cats, dogs, pigs and rats but in man it did not cause clinically significant methaemoglobinaemia even after overdosage. An earlier single report of methaemoglobinaemia after ingestion of an unknown dose of paracetamol has never been confirmed.

A patient with a genetic variant, glucose-6-phosphate dehydrogenase deficiency, who took an overdose of paracetamol and chloromethane developed severe haemolytic anaemia and renal failure. Both the normal and abnormal enzymes were modestly inhibited in vitro by very high concentrations of paracetamol (6050 mg/l) and chloromethane (2740 mg/l). However, since the dose of paracetamol said to have been taken by the patient (40 g) could only have produced a maximum plasma concentration of approximately 605 mg/l, the significance of these findings is doubtful. Subsequent regular intake of paracetamol in therapeutic doses had no effect on red-blood-cell survival in this patient.

**Oesophageal varices**

Oesophageal varices and ascites have been observed to develop rapidly following recovery from hepatic failure caused by paracetamol overdose in one patient (L.F. Prescott, unpublished data) and fatal variceal haemorrhage has been reported in such circumstances in a patient without pre-existing liver disease.

**Pancreatitis**

Although pancreatic inflammation may be seen at autopsy in patients with hepatic failure, and elevation of plasma amylase activity has been reported in a minority of patients with paracetamol poisoning, clinical evidence of pancreatitis is rare—only seven cases have been reported. One patient developed liver and renal impairment with ileus and ascites, and there was no history of alcohol abuse. In three cases, the pancreatitis was haemorrhagic. The pathophysiology of the pancreatitis is uncertain, but in some of the cases there was a prolonged delay before treatment, and dehydration may have been a factor. Paracetamol hepatotoxicity has also been associated with alcoholic pancreatitis.

**Metabolic abnormalities**

Metabolic acidosis, which may be severe, may occur early or later in association with hepatic failure. Reduced plasma bicarbonate or the degree of acidosis have long been recognized as useful early prognostic signs in paracetamol poisoning.
are probably due in part to increased production of lactate, which is not cleared by the damaged liver. Paracetamol can stimulate lactic acid production in the liver via glycolysis in animals and there was a significant correlation between admission plasma lactate and plasma paracetamol concentrations in overdose patients. The acidosis was often compensated and might therefore not be immediately obvious. In one report of patients with hepatic failure, metabolic acidosis was only present in 4/28 patients; in three it was severe and present before the onset of clinical hepatic failure. In two cases the acidosis was felt to be due to accumulation of lactic acid. Blood pyruvate, acetocacate, citrate, succinate, and fumarate were elevated in some cases, and plasma free fatty acid concentrations were increased out of proportion to the degree of ketosis.

Toxic doses of paracetamol inhibited the synthesis of glucose from lactate in isolated rat hepatocytes and decreased the availability of ATP. Inhibition of mitochondrial function (impaired and uncoupled respiration and changes in mitochondrial potential) was an early event in experimental paracetamol hepatotoxicity and prior metabolic activation of paracetamol appeared to be necessary for this effect. It was proposed that the acidosis and depression of consciousness seen in poisoned patients with very high plasma paracetamol concentrations was related directly to inhibition of mitochondrial respiration.

Abnormalities of glucose metabolism

Hypoglycaemia occurs commonly in paracetamol-induced hepatic failure. It is mentioned here because on occasions it may be severe, difficult to correct and it indicates a poor prognosis. Hyperglycaemia has also been observed occasionally in patients with paracetamol poisoning, and disturbances of glucose metabolism were associated with glucose intolerance, impaired gluconeogenesis and an abnormal growth-hormone response to glucose.

Other metabolic abnormalities

Acute hepatic failure from any cause is associated with complex multiple metabolic abnormalities, and the picture is often complicated further by the presence of renal failure. Biochemical changes in patients with paracetamol-induced liver failure do not seem to differ from those with acute hepatic failure from other causes, and include increases in serum acid protease, aldosterone, digoxin-like immunoreactive substances, alpha-fetoprotein, carnitine and acylcarnitine esters, hepatocyte growth factor and biliprotein and hyaluronate. Other metabolic abnormalities not necessarily associated with hepatic failure include impairment of the hepatic synthesis of prealbumin, impaired galactose elimination and reduced capacity for the hepatic metabolism of other drugs. It seems likely that ‘atypical’ pyrogulamic aciduria (5-oxoprolinuria) can also be attributed to paracetamol toxicity and it may be due to relative deficiency of glycine, caused by its diversion for cysteine synthesis.

Renal failure

Before the development of effective antidotes for paracetamol poisoning, acute renal failure requiring dialysis occurred in approximately 1% of unselected patients arriving at hospital with paracetamol poisoning. Unselected patients who presented late (more than 10 h) after the overdose were more severely poisoned, and 21% developed renal failure. The incidence rose to 50–70% in patients with hepatic failure. Acute renal failure due to paracetamol poisoning in man may be prevented by the same agents which protect against hepatic toxicity. The primary pathological lesion is acute tubular necrosis, and although this often occurs in the context of hepatic failure, it can occur rarely in the absence of clinical or biochemical evidence of liver damage.

Renal biopsies and autopsy specimens showed evidence of coagulative necrosis of the proximal tubule cells, tubular dilation, collections of cellular debris within damaged tubules, rupture of tubular membranes, interstitial oedema and infiltration with lymphocytes and plasma cells. There have also been reports of interstitial nephritis and distal tubular damage.

There are two clinical forms of nephrotoxicity following paracetamol overdose. In the first, oliguric renal failure develops within 24–48 h, and is accompanied by proteinuria, microscopic haematuria and lumbar pain. It usually occurs in the context of hepatotoxicity, and it varies in severity from oliguria lasting only a few hours to the rapid onset of anuria requiring prolonged haemodialysis. The other is associated with hepatic failure, and the onset is delayed. In such circumstances there is often multiple organ failure, and endotoxaemia and disseminated intravascular coagulation have been proposed as aetiological factors. Panos and colleagues showed that plasma renin activity, atrial natriuretic factor and aldosterone concentrations were elevated according to the severity of renal failure. The increase in plasma renin was associated with marked renal vasoconstriction and reduced renal prostaglandin excretion. Hypophosphataemia occurs in paracetamol poisoning.
poisoning,\textsuperscript{103,118} and the mechanism appears to be increased renal loss of phosphate.\textsuperscript{119,120} Paracetamol interferes with the excretion of a water load\textsuperscript{121} and it has been used for the treatment of diabetes insipidus.\textsuperscript{122} Abnormal fluid retention with haemodilution and water intoxication has been observed in patients with paracetamol poisoning given excessive volumes of intravenous fluids (L.F. Prescott, unpublished data).\textsuperscript{123} Hyponatraemia is common in patients with acute hepatic failure, and while this may be due in part to haemodilution, there is also a shift of sodium into the intracellular compartment.\textsuperscript{124}

**Muscle damage**

On the basis of increased plasma creatine phosphokinase activity, it has been proposed that paracetamol in overdose might cause muscle damage.\textsuperscript{7,21,125–129} Many of these patients were alcoholics or had also taken other drugs. Muscle necrosis was found in histological sections from all of 26 patients with fatal overdosage with paracetamol.\textsuperscript{130}

**Effects on the outcome of pregnancy**

Despite the widespread use of paracetamol in pregnancy, information on the effects of an overdose in pregnancy is remarkably sparse. A follow-up study of 48 women who had been exposed to paracetamol overdose during pregnancy failed to detect any teratogenic potential.\textsuperscript{131} Similar negative results were obtained in other follow-up studies of paracetamol poisoning during pregnancy.\textsuperscript{132,133} Other authors have reported overdoses of paracetamol in the second and third trimesters of pregnancy, with subsequent delivery of normal babies irrespective of the occurrence of liver damage in the mother.\textsuperscript{134–141}

Fetal death occurred at 27–28 weeks, and there was maternal liver damage and disseminated intravascular coagulation with recovery after a paracetamol overdose.\textsuperscript{136} Microscopic sections of the foetal liver showed total lysis of hepatocytes and Kupffer cells, but this probably reflected post-mortem autolysis rather than paracetamol hepatotoxicity. An infant of 29 weeks gestation was delivered without significant liver damage after her mother took an overdose of aspirin and paracetamol. The mother had a plasma paracetamol concentration of 160 mg/l at 16 h after ingestion and developed severe liver damage. The cord blood paracetamol concentration was 75 mg/l, and the half-life of paracetamol in the infant was considerably prolonged (26 h) despite exchange transfusions.\textsuperscript{143}

Acute-on-chronic exposure to aspirin, paracetamol, codeine and carisoprodol in a 35-week pregnant woman was associated with transient mild liver damage in the mother, and prolongation of the prothrombin time with normal liver function tests in the neonate.\textsuperscript{144} This probably resulted from a combination of factors, including prematurity, hypoxia and salicylate intoxication.

Paracetamol crosses the placenta readily\textsuperscript{145,146} and although it is metabolized similarly by human foetal and adult liver microsomes \textit{in vitro} and in isolated hepatocytes from foetal liver, the rate is much slower than in adult liver preparations.\textsuperscript{147} There is no contraindication to the use of N-acetylcysteine in pregnancy, and as with paracetamol poisoning generally, a good maternal prognosis depended on early treatment with N-acetylcysteine.\textsuperscript{133} However, the antidote did not cross the placenta in sheep, and its ability to prevent liver toxicity in the human foetus is uncertain.\textsuperscript{148} At present, there is no well-documented case of liver damage in the foetus or neonate following maternal overdosage with paracetamol. Unnecessary and useless treatment such as exchange transfusion or Caesarean section should not therefore be used.

**Conclusions**

Hepatic and renal damage are well-recognized complications of severe paracetamol poisoning, but overt toxicity affecting other organs is very rare in the absence of fulminant hepatic failure. In many of the reports of extra-hepatic toxicity, other factors such as chronic alcoholism and simultaneous overdosage with other drugs may have contributed to the organ damage rather than paracetamol or its metabolites. This is particularly the case with ‘cardiotoxicity’. It seems remarkable that no systematic assessment of paracetamol cardiotoxicity or skeletal muscle damage has been made to date.

Although thrombocytopenia occurs in paracetamol poisoning, it is of no clinical significance in terms of bleeding, unless accompanied by fulminant hepatic failure. Gastrointestinal bleeding has occurred after paracetamol overdosage in the absence of fulminant hepatic failure, but the incidence is too low to justify routine endoscopic evaluation for bleeding in every paracetamol-poisoned patient.

However, there are a number of unusual complications that are potentially serious and merit monitoring or investigation. Although pancreatitis is rare, it is a serious complication, and estimation of serum amylase should be undertaken in all patients who present late or in whom dehydration is suspected. This should ensure early recognition and appropriate therapy. We should be alert to the presence of severe metabolic acidosis in patients with very high plasma paracetamol concentrations or depression of con-
References


