Clinical Toxicology

Paracetamol cardiotoxicity

A. Armour and S.D. Slater

Medical Division, Victoria Infirmary, Glasgow G42 9TY, UK

Summary: A 29 year old man with a significant paracetamol overdose was found to have an abnormal electrocardiograph which, in the absence of hepatic encephalopathy, was considered due to a direct cardiotoxic effect of the drug. A functional coronary insufficiency resulting from inhibition of endothelium-derived relaxing factor secondary to depletion of sulphhydryl groups is postulated, and it is suggested that in paracetamol poisoning evidence of cardiotoxicity alone may be sufficient justification for treatment with acetylcysteine.

Introduction

The possibility that an overdose of paracetamol might be directly cardiotoxic has been the subject of few reports.^{1–6} However, the true incidence is unknown as serial electrocardiograph (ECG) monitoring is not part of routine clinical management. Moreover, anxieties have been expressed regarding unexplained deaths associated with paracetamol poisoning, some within 24 hours of ingestion.^{7,8} It cannot be ruled out that a number of these may have been cardiac in origin.

This report describes a patient with a paracetamol overdose who had unexpected ECG abnormalities for which a mechanism is proposed and specific treatment suggested.

Case report

A 29 year old man under treatment with flupenthixol decanoate for manic depression was admitted having allegedly taken 100 paracetamol tablets (50 g), 23 hours previously. Physically there were no abnormalities but his paracetamol level was 0.21 mmol/l, consistent with a serious overdose too late for treatment with acetylcysteine. Investigations showed: plasma urea concentration 4.1 mmol/l, creatinine 111 µmol/l, sodium 133 mmol/l, potassium 3.0 mmol/l, chloride 102 mmol/l, bicarbonate 26 mmol/l, aspartate aminotransferase 671 U/l, alanine aminotransferase 805 U/l, gamma-glutamyltransferase 55 U/l, alkaline phosphatase 210 U/l, bilirubin 21 µmol/l, calcium (corrected for albumin) 2.29 mmol/l and phosphate 0.58 mmol/l, and the international normalized prothrombin

time ratio (INR) was 2.0:1.0. Within 24 hours the plasma potassium concentration was normal and, apart from a transitory marginal fall then in plasma bicarbonate to 22 mmol/l, plasma urea, electrolyte and bicarbonate concentrations remained normal. The aspartate and alanine aminotransferase levels rose to 3,795 U/l and 6,080 U/l, respectively, 3 days after taking paracetamol, and thereafter improved. The maximum recorded bilirubin and INR were 38 µmol/l and 2.1:1.0, respectively. There was no hypoglycaemia.

The notable finding was an abnormal ECG taken 2 days post-ingestion (Figure 1). This showed coronary sinus rhythm, and there was 0.5–1 mm upward bowing of the ST segment in leads V2–V3 with 1–3.5 mm T wave inversion in leads V1–V5. The coronary sinus rhythm had gone by the following day but the ST/T wave changes persisted, progressively improving from day 5 of his illness, though still with borderline abnormalities at day 10 (Figure 2) when he was transferred to his psychiatric unit. Clinically, apart from initial nausea, he remained well with a normal blood pressure. Cocksackie B and echovirus titres proved negative.

Discussion

Dysrhythmias and other ECG abnormalities, especially of the ST segment or T wave, frequently occur in paracetamol poisoning in comatose encephalopathic patients,⁶ but ST/T wave changes in non-encephalopathic subjects have been reported.^{4–6} Sudden unexplained death in paracetamol overdose may occur early before acute hepatic failure is established, and even in the complete absence of histological evidence of hepatic necrosis.⁷ A direct toxic myocarditis has

Figure 1 ECG on day 3.

Figure 2 ECG on day 10.

been postulated from autopsy evidence of myocardial necrosis, present particularly in the subendocardium.^{1,5} The cause of the ECG abnormalities in encephalopathic patients is probably multifactorial and at least partly related to the severe metabolic changes. However, these cannot be implicated in patients with less hepatic upset – as in this case – or in sudden death early in the course of paracetamol poisoning.

The hepatotoxic effect of paracetamol is due to a highly reactive metabolite, N-acetyl-*p*-benzoquinoneimine, which binds to liver cell macromolecules and probably has other toxic effects. It is conjugated and deactivated by the sulphhydryl groups of hepatic reduced glutathione, whose levels become depleted in paracetamol overdose, and acetylcysteine works as a glutathione precursor and sulphhydryl group donor. Related mechanisms may account for cardiac damage.

There is evidence that the tolerance which sometimes develops to nitrates during the treatment of coronary disease is due to depletion of sulphhydryl groups, the sensitivity of the nitrate 'receptor' in vascular smooth muscle falling when its sulphhydryl groups become oxidized by prolonged exposure to nitrates.⁹ Increasing sulphhydryl availability by intravenous or oral administration of acetylcysteine has been shown to potentiate the vasodilatory response to nitroglycerine and to reverse nitrate tolerance.^{10–12} It is, therefore, suggested that a paracetamol-induced depletion of sulphhydryl groups might interfere with endo-

thelium-derived vascular relaxing factor (EDRF), the body's endogenous nitrate, and thereby lead to a functional coronary insufficiency. It is also possible that paracetamol's toxic metabolite depletes myocyte glutathione, exerts direct adverse effects on the myocardium and, as a free radical, may also be involved in the breakdown of EDRF.¹³

Acetylcysteine would, therefore, be expected to help prevent and counteract such paracetamol-mediated cardiotoxicity. In addition to donating sulphhydryl groups and acting as a glutathione precursor, it might also be of value in providing cysteine as a substrate for the formation of EDRF, since there is evidence that the latter may more closely resemble S-nitrosocysteine¹⁴ than nitric oxide.¹⁵

While general experience suggests that paracetamol cardiotoxicity has rarely been clinically significant, it may have been overlooked. We would suggest an ECG be taken on admission and in significant overdose checked daily. If ST/T wave abnormalities or a dysrhythmia are present, then treatment with a standard acetylcysteine infusion should be considered, probably irrespective of the plasma paracetamol level or time lapse from ingestion. Similar conclusions have very recently been presented for a more general beneficial effect of acetylcysteine upon the microcirculation, with evidence that it enhances survival in fulminant hepatic failure even when given later than is conventionally advised.¹⁶

References

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