HEPATOTOXICITY OF MILD ANALGESICS

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- 1 Hepatotoxicity is rare when mild analgesics are used in normal therapeutic doses.
- 2 The potential of aspirin and salicylates to cause hepatotoxicity has been only recently recognized.
- 3 Salicylate hepatitis is often asymptomatic, and may only be revealed by finding elevated levels of aminotransferases.
- 4 Most cases have occurred in children or young adults with connective tissue diseases, who take high doses of salicylates for long periods.
- 5 Hepatic injury is not recognized as a complication of acute aspirin poisoning.
- 6 Following overdosage of paracetamol, a toxic intermediate metabolite causes acute hepatic necrosis which may be fatal.
- 7 Cysteamine, methionine and *N*-acetylcysteine confer protection against this severe liver damage, but the time between overdosage and treatment is critical.
- 8 The chronic therapeutic use of paracetamol should be considered a potential but very rare cause of active chronic hepatitis.
- 9 There is no clear evidence of phenacetin hepatotoxicity in man.
- 10 Phenylbutazone may cause liver injury and other analgesics can cause hypersensitivity reactions in which the liver is involved.

Introduction

HEPATOTOXICITY is very uncommon when mild analgesics are used properly in recommended doses, the only possible exception being the occurrence of hepatitis in patients with connective tissue diseases taking salicylates in high doses. However, there may be serious hepatotoxicity when some analgesics are abused or taken in overdosage.

Aspirin and salicylates

Despite their long and extensive use, aspirin and the salicylates have only recently been recognized as potentially hepatotoxic. Patients with acute rheumatic fever were first noted to have abnormal liver function tests by Nydick, Tang, Stollerman, Wroblewski & LaDue (1955), and a direct association with salicylate therapy was soon established (Manso, Taranta & Nydick, 1956). During the next 15 years there was only one further report (Okumura, Ichikawa, Aramaki & Obayashi, 1966), but in the past decade several hundred cases have been described, and the condition is being recognized with increasing frequency (see reviews by Prescott, 1975; 1977; 1978; 1979a; 1980; Schaller, 1978).

Almost all reported cases have occurred in children and young adults with connective tissue disorders such as Still's disease, rheumatoid arthritis and systemic lupus erythematosus, and females have been affected more often than males. Aspirin has been involved in the great majority of cases although there have been occasional reports of hepatitis associated with sodium and choline salicylate (for example, Rich & Johnson, 1973). About 50% of patients with juvenile rheumatoid arthritis have evidence of some degree of liver injury as shown by elevation of plasma aminotransferases during conventional high-dosage aspirin therapy (Schaller, 1978). It is assumed that young patients with connective tissue disease are particularly susceptible to the hepatotoxicity of salicylate, as similar problems have not been recognised in older patients with rheumatoid arthritis. However, adequate control studies have probably not been carried out and there are few other indications now for chronic high-dose salicylate therapy. In this context it is perhaps significant that aspirin was reported to produce moderate elevation of the plasma aspartate aminotransferase in five out of nine normal individuals (Ege & Jacobsen, 1971).

Salicylate hepatitis is usually asymptomatic, but

there may be anorexia, nausea, malaise and vague abdominal pain. During the first few weeks of treatment, liver function tests reveal mild to moderate elevation of aspartate and alanine aminotransferases, lactic dehydrogenase and to a lesser extent, alkaline phosphatase. Except in the more severely affected cases, the prothrombin time and bilirubin usually remain normal. Plasma salicylate concentrations have usually been in the excess of 200 $\mu\text{g/ml}$ and liver function tests rapidly return to normal when the drug is discontinued. The association with salicylate therapy has been confirmed repeatedly by subsequent rechallenge (Rich & Johnson, 1973; Seaman, Ishak & Plotz, 1974; Athreya, Moser, Cecil & Myers, 1975; Gitlin & Grant, 1977; Bernstein, Singsen, King & Hanson, 1977).

In some cases there is more severe liver damage with aminotransferases exceeding 1,000 IU/l, and the possibility of Reye's syndrome may be suggested by associated encephalopathy (Sillanpaa, Makela & Koivikkó, 1975; Petty, Zahka & Bernstein, 1978; Ulshen, Grand, Crain & Gelfand, 1978; Knudsen, 1978). However, the degree of liver damage in these cases was hardly consistent with hepatic failure and it seems more likely that the 'encephalopathy' was due at least in part to salicylate intoxication, hypoglycaemia or hyperventilation. Liver biopsies in patients with salicylate hepatitis show periportal mononuclear cell infiltration and ballooning and vacuolation of hepatocytes with acidophilic bodies and patchy necrosis (Rich & Johnson, 1973; Seaman, Ishak & Plotz, 1974; Saltzman, Gall & Robinson, 1976). Hepatic injury is not recognized as a complication of acute aspirin poisoning.

Paracetamol

Paracetamol was shown to be hepatotoxic in cats by Eder (1964) and acute hepatic necrosis following overdosage in man was first reported two years later (Davidson & Eastham, 1966; Thomson & Prescott, 1966). With increasing use of this otherwise very safe drug, severe and sometimes fatal liver damage after overdosage has become a problem in many countries.

Hepatotoxicity is caused by the formation within the hepatocyte of a minor highly reactive alkylating metabolite which binds covalently to cell constituents causing damage and necrosis. The small amount of this metabolite formed with therapeutic doses is safely removed by rapid conjugation with reduced glutathione; but with large toxic doses glutathione is depleted, the excess metabolite being free to damage the hepatocytes. The reactive metabolite is produced by cytochrome P-450 mixed function oxidase, and the hepatotoxicity of paracetamol depends on the activity of these enzymes and the availability of glutathione (Mitchell, Jollow, Potter, Davis, Gillette & Brodie, 1973a; Jollow, Mitchell, Potter, Davis, Gillette &

Figure 1 Elevation of plasma bilirubin, alanine aminotransferase and prothrombin time ratio in a 53-yr-old man with severe liver damage following overdosage of paracetamol.

Brodie, 1973; Potter, Davis, Mitchell, Jollow, Gillette & Brodie, 1973; Mitchell, Jollow, Potter, Gillette & Brodie, 1973b).

The clinical and biochemical features of paracetamol poisoning have been reviewed (Prescott, 1975; 1977; 1978; 1979a; 1979b; 1980). There are no specific early features since consciousness is not impaired and clinical and biochemical evidence of liver injury is delayed with maximum abnormalities of liver function tests usually occurring 3–5 d after ingestion. Initial assessment therefore depends on measurement of the plasma paracetamol concentration to identify patients at risk requiring treatment with sulphhydryl compounds. Most severely poisoned patients develop nausea and vomiting within a few hours followed up with upper abdominal pain and hepatic tenderness. Mild jaundice may appear after 2–3 d and a minority of patients progress to fulminant hepatic failure after 3–6 days.

After an initial delay, there is a striking increase in plasma aspartate and alanine aminotransferases, with values sometimes exceeding 10,000 IU/l (normal range 10–40). In severely poisoned patients who recover, the plasma bilirubin may rise to 60–100 $\mu\text{mol/l}$ and the prothrombin time ratio to 2.0–3.0 (Figure 1). Regeneration is rapid and liver function

Figure 2. Massive acute centrilobular necrosis in a 54-yr-old woman who died 6 d after overdosage of paracetamol. (This figure has been published previously in *Recent Advances in Intensive Therapy*. Ed. J. McA. Ledingham, Churchill Livingstone, Edinburgh, 1977, p. 224.)

tests usually return to normal in 7–14 d with no permanent sequelae. Liver biopsies and post mortem samples show acute centrilobular hepatic necrosis (Figure 2), and follow-up biopsies in survivors usually show no residual changes or only minor abnormalities (Portmann, Talbot, Day, Davidson, Murray-Lyon & Williams, 1975; Lesna, Watson, Douglas, Hamlyn & James, 1976). However, repeated episodes of severe paracetamol-induced hepatic necrosis may progress to cirrhosis (Prescott, Oswald & Proudfoot, 1978).

Until the discovery of the mechanisms of paracetamol hepatotoxicity by Mitchell and his colleagues, there was no effective treatment for paracetamol poisoning. We first reported the successful use of cysteamine (Prescott, Newton, Swainson, Wright, Forrest & Matthew, 1974), and there have been numerous subsequent reports confirming protection against severe liver damage by cysteamine, methionine and *N*-acetylcysteine (Prescott, Park, Sutherland, Smith & Proudfoot, 1976; Crome, Vale, Volans, Widdop & Goulding, 1976; Rumack & Peterson, 1978; Prescott, Illingworth, Crichtley, Stewart, Adam & Proudfoot, 1979; and others). Early treatment is essential, as the critical time interval between overdosage and treatment for complete protection against severe liver

damage is 8 hours. After this time the incidence and severity of liver damage increases progressively and there is no protection after 15 hours (Prescott *et al.*, 1979). The mechanisms of protection by these agents are unknown. They may act as precursors or alternative substrates for glutathione, or as inhibitors of the oxidative metabolism of paracetamol.

Only about 25% of patients with paracetamol poisoning develop liver damage, and without treatment the overall mortality from hepatic failure is 1–3%. *N*-acetylcysteine therapy is indicated in patients with plasma paracetamol above a treatment line joining plots of 200 µg/ml at 4 h and 30 µg/ml at 15 hours. Without treatment, about 60% of such patients will develop severe liver damage (Prescott *et al.*, 1979).

There have been a few reports of liver damage in patients allegedly taking paracetamol for therapeutic purposes (Barker, de Carle & Anuras, 1977; Johnson & Tolman, 1977; Rosenberg, Meyer, Manning & Neelon, 1977; Ware, Upchurch, Eigenbrodt & Norman, 1978; Bonkowsky, Mudge & McMurtry, 1978). In some patients, the doses were clearly excessive, whereas in others the quoted plasma paracetamol concentrations (37 µg/ml at 24 h and 15 µg/ml at 40 h after the last dose) (Barker *et al.*,

Figure 3 Plasma bilirubin (Δ), alanine aminotransferase ($\circ$), urea ($\bullet$) and phenylbutazone concentrations ($\square$) in a 17-yr-old girl following overdosage of phenylbutazone.

1977) can only be interpreted as indicating gross overdosage. In addition, in one report the patients were suffering from infectious mononucleosis, a condition in which hepatitis is not uncommon. Nevertheless, the chronic use of paracetamol, like aspirin, should be considered a potential cause of active chronic hepatitis although this must be very uncommon.

Phenacetin

Phenacetin produces acute hepatic necrosis in animals largely through its conversion to paracetamol but it is considerably less active than the latter drug in this respect (Mitchell, Potter, Hinson, Snodgrass, Timbrell & Gillette, 1975). There is no clear evidence for the hepatotoxicity of phenacetin in man.

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Phenylbutazone and other analgesics

Most anti-inflammatory analgesics can occasionally cause acute generalized 'hypersensitivity' reactions in which the liver may be involved. Phenylbutazone, however, can cause acute liver injury without involvement of other systems with therapeutic doses and following overdosage (Juul, 1965; Muscat-Baron & Freeman, 1966; Catterall, 1968; Färber & Liel, 1968; and others). An example of acute liver injury following overdosage of phenylbutazone in a 17-yr-old girl is shown in Figure 3. The initial plasma concentration of phenylbutazone was 670 $\mu\text{g/ml}$ and liver damage was delayed with peak elevation of the plasma bilirubin and alanine aminotransferase on days 6 and 7, respectively. As judged by the plasma half-life of only 21 h, phenylbutazone metabolism was very rapid in this patient despite the presence of liver damage.

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