Acute liver injury

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During metabolism in the liver the concentration of a drug or its metabolic products may be locally increased. This provides a theoretical basis for the large and ever-increasing number of reports of acute liver damage following drug therapy. If a drug or its metabolic product is a cellular poison we may expect a direct hepatotoxic reaction with a constant relationship to the level of drug in the serum and consequently with a relationship to the dose, ie, predictable liver injury (Scheuer, 1973).

Predictable Acute Liver Injury

Thanks to careful testing of new drugs before release by the manufacturers few drugs in use today cause predictable acute liver injury in normal dosage. Chloroform is a well known example of an obsolescent drug which predictably results in fatty change and, in more severe cases, acute necrosis of the liver. Amongst currently used drugs there have been instances of hepatic necrosis following antibiotics used in cancer chemotherapy (Ream, Perlia, Wolter, and Taylor, 1968; Moertel, Reitemeier, and Hahn, 1968), but the most significant example of predictable acute hepatic failure following normal therapeutic dosage of a drug is the acute fatty liver which occasionally complicates tetracycline therapy during pregnancy or in patients with impaired glomerular filtration. The reaction is predictable to the extent that it is dependent on the serum concentration of tetracycline (Whalley, Martin, Adams, and Combes, 1970). Deepening jaundice and hepatic precoma and coma are fortunately rare events with this drug, being limited to those patients in whom impaired renal excretion can lead to abnormally high serum tetracycline levels.

Paracetamol, the widely used analgesic, predictably produces acute liver injury when taken in suicidal overdose. After an initial two to three days' period of irritability, which may be mistaken for hysteria, jaundice and other signs of acute liver failure appear. By the fourth day the liver becomes

tender and histologically shows a uniformly distributed centrilobular coagulative necrosis (fig 1). In the early stages there is also vacuolation of adjacent surviving hepatocytes. Out of 200 patients admitted to the Liver Unit at King's College Hospital with signs of liver damage following an overdose of between 10 and 100 g of paracetamol, 29 died in fulminant hepatic failure (Portmann, Talbot, Day, Davidson, Murray-Lyon, and Williams, 1975).

Fig 1 Coagulative necrosis of centrilobular liver parenchyma seven days after paracetamol overdose. Surviving hepatocytes contain fine vacuoles (needle biopsy, HE $\times$ 450).

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Predictable acute liver poisoning by a drug, although dose-related, may be potentiated by such factors as stress, pregnancy, malnutrition, alcohol and other drugs. The liver injury appears after a short, constant latent period. Such toxic effects are reproducible in animals. These criteria, however, do not apply to the majority of instances of drug-induced acute liver damage, the manifestations of which are unpredictable.

Unpredictable Acute Liver Injury

Unpredictable drug reactions are, by definition, inconstant, occurring in only a small proportion of individuals exposed to the drug in question. Signs of liver damage appear after a variable latent period of up to three weeks. The severity of damage is variable, but may be great and is unrelated to dosage. The nature of the acute liver injury associated with a particular drug may vary from one patient to another, but in an individual patient unpredictable acute liver injury falls into one of three broad categories, namely, cholestatic hepatitis, acute hepatitis and severe hepatic necrosis.

CHOLESTATIC HEPATITIS

In these cases jaundice dominates the clinical picture with conjugated hyperbilirubinaemia and raised serum transaminase levels. Histologically in the liver there is bile retention, predominantly centrizonal, in hepatocytes as well as in canaliculi. Single cell necrosis is seen in the parenchyma with acidophil bodies, but this is not a prominent feature. Portal tracts are infiltrated by lymphocytes and sometimes by eosinophils. A variant of this, following therapy with the long-acting sulphonamide combination, co-

Fig 2 Intracellular bile pigment in a patient with cholestatic hepatitis following treatment with co-trimoxazole (Septrin). Single necrotic hepatocytes (acidophil bodies) and mitotic figures are randomly scattered in the parenchyma (needle biopsy, HE $\times$ 450).

Drug	Reference
Chlorpromazine	Cheongvee, Hurst, and Smith (1967)
Trifluoperazine (Stelazine)	Kohn and Myerson (1961)
Chlordiazepoxide	Lo, Eastwood, and Eidelman (1967)
Tolbutamide	Gregory, Zaki, Sarcosi, and Carey (1967)
Chlorpropamide	Reichel, Goldberg, Ellenberg, and Schaffner (1960)
Dapsone	Millikan and Harrell (1970)
Erythromycin estolate	Fischer and Hoak (1964)
Mercaptopurine	Shorey, Schenker, Suki, and Combes (1968)
Azathioprine	Sparberg, Simon, and Del Greco (1969)
Amitriptyline	Morgan (1969)
Phenobarbital	Pagliari, Campesi, and Aguglia (1969)
Oxypheisatin	Pearson, Grainger, Scheuer, and MacIntyre (1971)
Methyldopa	Toghill, Smith, Benton, Brown, and Matthews (1974)
Chloramphenicol	Gjone and Orning (1966)
Sulphamethoxazole	Perez, Schaffner, and Popper (1972)
Diazepam	Perez, Schaffner, and Popper (1972)

Table I Drugs associated with cholestatic hepatitis and representative documentary sources

trimoxazole (trimethoprim + sulphamethoxazole, Septrin) is shown in figure 2. The more commonly used drugs with which this type of cholestatic hepatitis reaction has been described are listed in table I.

ACUTE HEPATITIS

Here the clinical picture is similar to viral hepatitis with fever, malaise and nausea, with or without jaundice. The serum transaminases are raised. Histology of the liver, exemplified in a patient with an adverse reaction to methyldopa, shows 'spotty' necrosis with acidophil bodies in the parenchyma, swelling of Kupffer cells and infiltration of portal tracts by a variable mixture of lymphocytes, plasma cells and eosinophils (fig 3). Table II lists the more widely used drugs with which this viral-hepatitis-like reaction has been documented.

Fig 3 Acute hepatitic reaction to methyldopa. Acidophil bodies, clumps of lymphocytes and swollen Kupffer cells mark foci of 'spotty' parenchymal necrosis. The slightly expanded portal tract contains lymphocytes and plasma cells (needle biopsy, HE $\times 450$).

Drug	Reference
Methyldopa	Toghill, Smith, Benton, Brown, and Matthews (1974)
Rifampicin and isoniazid	Lal, Singhal, Burley, and Crossley (1972)
Rifampicin	Scheuer, Summerfield, Lal and Sherlock (1974)
Isoniazid	Maddrey and Biotnott (1973)
Phenindione	Mohamed (1965)
Sulphamethoxazole (Septrin)	Dujovne, Chan, and Zimmerman (1967)
PAS	Fulkerson, Husen, Lieberman, and Stein (1969)
Ethionamide	Conn, Binder, and Orr (1964)
Ethacrynic acid	Datey, Deshmukh, Dalvi, and Purandere (1967)
Diphenylhydantoin	Pezzimenti and Hahn (1970)
Carbamazepine	Ramsay (1967)
Phenylbutazone	Ecker (1965)
Indomethacin	Ferich, Bannister, and Grech (1967)
Clindamycin	Elmore, Rissing, Rink, and Brooks (1974)
Colchicine	Borurchow (1966)
Papaverine	Ronnov-Jessen and Tzernlund (1969)

Table II Drugs associated with acute hepatitic reaction mimicking viral hepatitis with representative documentary sources

SEVERE HEPATIC NECROSIS

Here, after a variable latent period of up to three weeks, the patient becomes restless and may develop the picture of fulminant hepatic failure, rapidly passing into hepatic coma. Jaundice often appears later, together with evidence of blood coagulopathy with widespread bruising and haemorrhage. Liver histology shows sharply circumscribed confluent parenchymal necrosis, approximately related to the central parts of the lobules. The surrounding hepatocytes are often vacuolated and contain fat. In the more severe and fatal cases there is submassive or massive hepatic necrosis. Such a histological picture, in a case of fulminant hepatic failure following halothane anaesthesia, is illustrated in figure 4. The drugs with which this type of severe reaction has been described are listed in table III.

In the case of halothane a causal relationship between its use in anaesthesia and subsequent severe hepatic necrosis has been difficult to establish, despite numerous retrospective investigations, and has been the subject of much controversy (Sharpestone, Medley, and Williams, 1971; Simpson, Strunin, and Walton, 1971). The incidence of jaundice after multiple exposures to halothane was estimated by Mushin, Rosen, and Jones (1971) to be between 1 in 6000 and 1 in 22 000 anaesthetics. Of 31 patients with liver necrosis following halothane exposure admitted to King's College Hospital over four years up to 1974, there were 16 deaths. This corresponds closely to the 51% mortality recorded by Inman and Mushin (1974) using data from the Committee on Safety of Medicines. McPeck and Gilbert (1974) rightly pointed out that similar reactions occur after other anaesthetic agents with unknown incidence, possibly as frequently as with halothane, and that retrospective surveys based on voluntary reporting of cases are inevitably biased. Nevertheless, in the 15 cases of post-halothane liver necrosis from the King's College Hospital series from which histology is available, similar features to those illustrated in fig 4 are seen in all, to a lesser or greater degree, and there can be little doubt that this kind of reaction,

Drug	Reference
Halothane	Peters, Edmondson, Reynolds, Meister, and Curphey (1969)
Monoamine oxidase inhibitors	Holdsworth, Atkinson, and Goldie (1961)
Imipramine	Powell, Koch-Weser, and Williams (1968)
Pyrazinamide	Brincourt and Teyssier (1968)
Cyclophosphamide	Aubrey (1970)

Table III Drugs associated with severe hepatic necrosis/fulminant hepatic failure with representative documentary sources

Fig 4 Submassive hepatic necrosis seven days after the fourth halothane anaesthetic within nine months. The centrlobular necrosis is less well circumscribed than in paracetamol overdose (see fig 1). Periportal hepatocytes, at the top of the field, are swollen and vacuolated. The lymphocytic infiltrate is not specific and could be secondary to liver cell destruction. (Postmortem needle sample, HE $\times$ 450).

although rare, does occur. What is in doubt is its incidence relative to that of similar reactions with other anaesthetics. Until a prospective survey has established these statistics there is no evidence to suggest that halothane is a comparatively hazardous anaesthetic agent (*British Medical Journal*, 1974).

Difficulties in Attributing Acute Liver Injury to a Particular Drug

Unpredictable injury is not usually reproducible in animals. The liver injury following exposure to halothane illustrates the difficulty of closing the gap between suspicion and proof in implicating an unpredictable drug reaction as the cause of liver injury;

the number of individuals exposed to the drug is almost always unknown and as these reactions are infrequent it is difficult to estimate their incidence. In many cases, such as with rifampicin, it is usual for the patient to have had a multiplicity of drugs, and not only may it be difficult to decide which drug is responsible, but interactions of combinations of drugs on the liver can give surprising and paradoxical results (Berthelot, 1973). It should also be remembered that patients receiving drugs are no less likely than others to develop viral hepatitis. This is particularly so in the case of drug addicts.

Criteria for Acceptance of Drug Toxicity as the Cause of Acute Liver Injury

1 Viral hepatitis and vascular disturbances, eg, hypotensive shock, should as far as possible be excluded.

2 As soon as a drug is suspected of causing liver damage it should be withheld from the patient; most signs and symptoms of acute liver injury will then subside provided that the patient is not in fulminant hepatic failure. The ultimate test of drug hepatotoxicity is that the condition recurs on challenge with the drug (Perez, Schaffner, and Popper, 1972) but this is in many cases too hazardous to test.

3 Finally, any instance of unexplained acute liver disease requires documentation of all drug therapy given up to three weeks previously. If data from sufficient numbers of patients are collected a pattern of frequency of association with particular drugs may be built up. Then is the time to investigate the mechanisms involved.

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