Progress report

Hepatotoxicity to sodium valproate: a review

Since 1978 a number of reports have indicated a possible association between sodium valproate therapy and the occurrence of hepatitis. In this review we have analysed, with particular reference to the clinical presentation, course and coadministration of other drugs, the 42 cases with fatal hepatitis either known to the manufacturers or reported elsewhere, and the more frequent cases with milder forms of hepatitis varying in severity from a transient rise in aminotransferase activities to symptomatic cases with reversible hepatic failure. We have also considered the three reported cases with a Reye’s-like syndrome and 22 instances of hyperammonaemia which is usually found in the absence of clinical evidence of hepatic injury but can easily be confused with fulminant hepatic failure. Possible mechanisms for the hepatotoxicity in relation to recently reported experimental work and the value of liver function tests in monitoring valproate therapy are also considered.

Hepatitis-like syndrome
The incidence of abnormal serum aminotransferase activities ranges from 0-44% in 19 clinical trials with an overall incidence of 11% in the 1197 patients monitored. Only two out of 57 patients with raised aminotransferase activities in three of the series were symptomatic, with malaise, lethargy, and anorexia which rapidly resolved on reducing the dose or stopping the drug. Aminotransferase activities in non-fatal cases were usually between one and three times the upper limit of normal and not usually accompanied by rises in serum bilirubin or alkaline phosphatase, except in the most severe cases.

The clinical, biochemical, and histological findings in the 42 cases with a fatal outcome largely agree with those presented by Zimmerman and Ishak and Zafrani and Berthelot, in part because of the duplication of a proportion of the cases. The age at presentation ranged from 2½ months to 34 years with 29 of the cases (69%) aged 10 years or less. Below the age of 15 years the proportion of males was 62.5%, but above this age the proportion was lower at 30% (Table). The overall male incidence of 57% compares with figures of 57% and 35% in the publications by Zimmerman and Ishak and Zafrani and Berthelot respectively. The disproportionate vulnerability of young individuals, particularly boys, does not appear to be a reflection of prescribing habits in that age group. Indications for valproate therapy comprised focal or generalised epilepsy, except for one patient with febrile convulsions. Evidence for structural neurological defects were present in 29% of patients. There were two instances of familial involvement. In one family two sibs of 17 and 10 years
died of liver failure within three months after starting the drug. Progressive ataxia and myoclonus was associated with cerebral atrophy in the older sib, while no underlying neurological abnormality was found in the other. In another family, fatal liver failure in two brothers aged 7½ and 9 years occurred after treatment for 70 and 54 days respectively, and was associated with progressive cerebral atrophy of unknown aetiology.

In more than two thirds of the patients with a fatal outcome, prodromal symptoms are recorded comprising anorexia and vomiting, as well as loss of epilepsy control with impaired consciousness and ataxia. Delays in diagnosis were encountered in several cases because of difficulties in differentiating these features from suspected postictal loss of consciousness and toxicity from high blood levels of other anticonvulsants. In approximately one third of patients there were signs of liver damage with fever, jaundice, ascites, peripheral oedema, and easy bruising. Hepatic coma developed terminally in all of the patients and was accompanied in 30% by either hypoglycaemia, uraemia, pneumonia, or sepsicaemia.

Serum concentrations of bilirubin, alkaline phosphatase, and aspartate aminotransferase and estimations of prothrombin time were available at presentation in 29, five, 33 and 19 patients respectively. In 30 patients the rises in aspartate aminotransferase activity were greater than 100 IU/l and/or the prothrombin time was longer than 18 seconds (Fig. 1), features indicative of significant hepatocellular damage.

Reye's-like syndrome
The three patients aged 3, 8, and 14 years\textsuperscript{31} 2 9 were receiving therapy on account of chronic seizures in association with mental retardation. Symptoms of anorexia, lethargy, and vomiting were accompanied by fever (40–42°C), loss of consciousness and, within a few days, neurological features of cerebral oedema. Biochemically there was a severe metabolic acidosis, raised blood ammonia concentrations (155, 120, 208 μmol/l; normal range 11–35 μmol/l), prolonged prothrombin times, raised serum aspartate aminotransferase activities (4500, 133, and 564 IU/l respectively), but normal serum bilirubin concentrations. Death within three weeks of first symptoms occurred as a result of cerebral oedema in two and aspiration pneumonia in the third patient.

Hyperammonaemia
There are 22 reported instances of symptomatic hyperammonaemia in the absence of overt liver disease.\textsuperscript{32-38} Seventeen were children aged 9 months to 14 years, and five were adults aged 20 to 51 years. The development of impaired consciousness (confusion, stupor, coma) and ataxia was usually

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Fig. 1  Serum concentrations of aspartate aminotransferase and bilirubin and prothrombin time estimations in 33, 29 and 19 of the fatal hepatitis cases respectively in whom data were available.

preceded by gastrointestinal symptoms of nausea, vomiting, anorexia, and diarrhoea. Weight loss of up to 22 kg occurred in association with anorexia lasting one to two months. In a few patients lethargy developed acutely within one to 48 hours of starting valproate therapy. Blood ammonia concentrations ranged from 58 to 668 μmol/l and were associated with mild rises in serum aspartate aminotransferase activities (up to 127 IU/l) in seven, but with no other liver function abnormality in the remainder. Within one to three days of stopping the drug all patients became asymptomatic and all biochemical abnormalities returned to normal. Severe hyperammonaemia in children with congenital disorders of the urea cycle can also be precipitated by sodium valproate therapy. One child, aged 11 months, with ornithine carbamyl transferase deficiency, developed hyperammonaemia after six weeks treatment and subsequently died despite the drug being stopped.41 Hyperammonaemia may also occur in asymptomatic patients receiving valproate and may not be accompanied by changes in EEG, clinical signs or changes in blood chemistry. Difficulties have arisen in the diagnosis of the cause of disordered levels of consciousness in the absence of liver damage, as loss of seizure control and psychotic changes may occur with toxic concentrations of valproate, whereas at therapeutic concentrations it may increase the blood levels of phenobarbitone resulting in drowsiness, lethargy, and ataxia.

Histological abnormalities
Microvesicular fat was a predominant feature in 10 out of 26 patients with a
fatal illness and in both patients with a non-fatal illness in whom liver histology was available.\textsuperscript{48} In four patients it was the only abnormality, but in the other eight it was associated with prominent centrilobular necrosis. In the remaining 16, centrilobular necrosis without fatty deposition was the predominant feature. In the three patients with a Reye's-like syndrome there was marked microvesicular fatty change associated in two with similar changes in the proximal tubular cells of the kidney. In the one case where electron microscopy was carried out there were numerous abnormal mitochondria with distortion of cristal and residual bodies.

**Dosage and concomitant use of other drugs**

Data on dosage were available in 22 of the 42 patients with fatal hepatotoxicity. In nine of them more than the recommended maximum dose of 30 mg/kg/day was given (Fig. 2). Although the duration of therapy before the onset of the hepatic illness ranged from one week to two years, it was between one and two months in one third of the 36 patients in whom data were available and longer than five months in only two of them (Fig. 3).

Thirty six patients had received other drugs concurrently, mostly anticonvulsants and known potent inducers of microsomal drug metabolising enzymes, including phenobarbitone, phenytoin, carbamazepine and primidone. Twelve patients had been treated with one inducing drug, 12 with two and eight with three or more inducing drugs. One patient had received halothane anaesthesia and another therapeutic doses of paracetamol. Other drugs used concurrently had no recognised inducing or hepatotoxic effects, namely clonazepam, diazepam, nitrazepam, and paraldehyde. In 16 patients one of these drugs was used,
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Fig. 3  Duration of therapy before onset of hepatic illness in 36 of the fatal hepatitis cases in whom data were available.

in two patients two were used and in five patients three or more were used. The delay in onset of the first clinical features of hepatitis was shortened by increasing the number of drugs combined with sodium valproate and was significantly decreased when the combination was with two or more drugs not considered as enzyme inducing agents (Fig. 4).

The difficulties in attributing liver damage to the use of valproate used in

Fig. 4  Relationship between duration of therapy before onset of fatal hepatitis and number of inducing and non-inducing drugs co-administered.

*p<0.05, compared with group of patients not receiving any non-inducing drugs (Student's t test).
combination with other drugs is exemplified by the following case of a 68 year old woman who presented with serum aminotransferase concentrations two to three times the upper limit of normal nine months after starting valproate (600 mg/day). Concomitant therapy with benoxaprofen (600 mg nocte), methyldopa, frusemide, fluphenazine, and nortriptyline was not changed. Four months later she was admitted to hospital with anorexia, nausea, and vomiting. Jaundice and hepatomegaly were found on examination. Serum concentrations of aspartate aminotransferase were 17 times above the upper limit of normal and the prothrombin time was 20 seconds (control 12 seconds). Autoimmune or viral markers were absent. Death occurred seven weeks later from progressive hepatic and renal failure. Histological examination of a needle biopsy of the liver five days before death and also at necropsy showed characteristic appearances of microvesicular fatty infiltration together with eosinophilic degeneration, severe cholestasis and a moderate mixed cell infiltrate throughout the lobule. There was reticulin condensation with early perisinusoidal fibrosis around the hepatic venules.

These histological features are different from those described in reactions to the other drugs she was receiving including chronic active hepatitis with methyldopa, the canalicular reaction associated with tricyclic antidepressants or the predominantly cholestatic lesion seen with benoxaprofen.

Experimental studies and mechanisms of hepatotoxicity
Experimental studies by us (J M Tredger and H M Smith, unpublished observations) have shown that the administration to mice of large single intraperitoneal doses of sodium valproate (400–1000 mg/kg) can produce a dose dependent microvesicular hepatic steatosis. These observations parallel those obtained in rats by Lewis et al. The same investigators showed that phenobarbitone could augment the fatty infiltration induced by valproic acid given acutely and our findings suggest that this is also true after chronic administration of sodium valproate. In mice and rats the acute administration of sodium valproate alone or after pretreatment with the microsomal enzyme inducing agents phenobarbitone, β-naphthoflavone, pregnenolone 16 α-carbonitrile, Arochlor 1254 and clofibrate produced no significant liver necrosis and no increase in serum aspartate aminotransferase activity. Such findings suggest that metabolites of valproate whose production in rodents is augmented by common enzyme inducing agents are not acutely hepatotoxic. This does not, however, preclude the involvement in susceptible human individuals of particular metabolites whose sustained production may lead to liver damage and may be augmented by coprescribed drugs, including those not established as inducing agents.

In man the relatively frequent occurrence of minor reactions, their reversibility on stopping or reducing the dose of valproate together with the occasional, though rare, severe cases suggests a mixed direct hepatotoxicity/idiiosyncratic reaction. Similar considerations apply to the hepatotoxicity of other drugs, such as isoniazid. The lack of rash and eosinophilia distinguishes valproate hepatotoxicity from other drug reactions such as that associated with paraminosalicylic acid, where generalised hypersensitivity is thought to be the mechanism. The
occurrence of microvesicular fatty infiltration has not been described in immunologically mediated hepatotoxic reactions and is more likely to result from direct interference with mitochondrial function and fatty acid oxidation by valproate or one of its metabolites. The most likely of these is 2-propyl-4-pentenoic acid because structural analogues of this metabolite are known to have hepatotoxic effects similar to valproate. For example, 4-pentenoic acid produces a Reye’s-like syndrome in rats\textsuperscript{58} and methylene-cyclopropylacetate, a metabolite of hypoglycin, gives rise to microvesicular hepatic steatosis in Jamaican vomiting sickness.\textsuperscript{57, 58} A different metabolite, however, may be responsible for the development of hepatic necrosis as steatosis and necrosis appear to occur independently of each other after valproate ingestion. It is also possible that the necrosis is sometimes related to other drugs (or their metabolites) administered concurrently with sodium valproate.

With respect to the hyperammonaemia, Coulter and Allen have postulated a role for the valproate metabolite, propionic acid, concentrations of which were increased in four children who experienced severe vomiting, lethargy or coma while on the drug.\textsuperscript{32} The observed rise in blood ammonia concentrations in one of these children was attributed to inhibition of the urea cycle enzyme, carbamyl phosphate synthetase I by propionate. These proposals, however, are not consistent with observations that propionate did not inhibit urea cycle enzymes in vitro whereas valproate did\textsuperscript{59} and that increases in blood ammonia concentrations have been noted without concomitant rises in the concentrations of propionic acid.\textsuperscript{35}

Use of liver function tests in monitoring valproate therapy
Measurement of serum aminotransferase will be of most value during the first three months of therapy when the frequency of hepatotoxic reactions is greatest. Such monitoring should be mandatory in the apparently predisposed patients with mental retardation, structural brain damage or metabolic disorders. Particular care should attend multiple drug therapy because this appears to accelerate the onset of valproate hepatotoxicity. Testing at monthly intervals would be a reasonable frequency and in those patients in whom abnormalities of serum aminotransferases develop, the dose of valproate should be lowered until the values return to normal. Failure of normalisation or a continued rise in aminotransferases is an indication for withdrawal of the drug and careful observation of the patient for early symptoms of hepatitis such a lethargy, lassitude, anorexia, nausea, and vomiting. Despite these precautions, it is likely that a small number of severe reactions related to individual idiosyncracy will not be prevented from developing abruptly without preceding rises in serum aminotransferase concentrations.

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