The High Incidence of Valproate Hepatotoxicity in Infants May Relate to Familial Metabolic Defects


ABSTRACT: The incidence of fatal hepatic failure associated with valproic acid (VPA) therapy is highest in children under the age of three years, particularly in those with developmental delay. The pathogenesis of VPA hepatotoxicity is unclear but may relate to the accumulation of a toxic metabolite of VPA which impairs fatty-acid oxidation. We describe two unrelated infants with developmental delay who developed hepatic failure while receiving VPA. Siblings of both children subsequently developed hepatic steatosis and intractable seizures without being exposed to VPA. This suggests that the two children who developed liver failure when receiving VPA may have had a familial metabolic disorder. Familial metabolic disorders may account partly for the higher incidence of fatal hepatotoxicity described in infants receiving VPA.

RÉSUMÉ: L'incidence élevée d'hépatotoxicité due au valproate chez les nourrissons est peut-être reliée à des anomalies métaboliques familiales. L'incidence de l'insuffisance hépatique fatale associée au traitement par l'acide valproïque (AVP) est plus élevée chez les enfants en bas de trois ans, particulièrement chez ceux qui ont un retard de développement. La pathogénèse de l'hépatotoxicité due à l'AVP n'est pas claire, mais elle peut être en relation avec l'accumulation d'un métabolite toxique de l'AVP qui entrave l'oxidation des acides gras. Nous décrivons le cas de deux nourrissons non apparentés ayant un retard de développement, qui ont développé une insuffisance hépatique sous AVP. Des membres de la fratrie des deux enfants ont ultérieurement développé une stéatose hépatique et des convulsions résistantes au traitement sans exposition à l'AVP. Ceci suggère que les deux enfants qui ont développé une insuffisance hépatique sous AVP avaient peut-être une anomalie métabolique familiale. Les anomalies métaboliques familiales peuvent être en partie responsables de l'incidence plus élevée d'hépatotoxicité fatale décrite chez les nourrissons recevant de l'AVP.

Two retrospective studies have described an incidence of fatal liver failure of between one in 500 - 800 in children less than three years of age who received valproic acid (VPA) polytherapy.\(^1\)\(^,\)\(^2\) The effect of polytherapy on VPA hepatotoxicity may relate to the known induction of cytochrome P-450 mediated metabolism by phenobarbital, phenytoin and carbamazepine. Cytochrome P-450 mediated metabolism is involved in the formation of 4-ene VPA, an unsaturated metabolite which has been implicated in the hepatotoxicity associated with VPA.\(^3\) The higher incidence of fatal VPA hepatotoxicity in infants and young children has not been explained. The pathogenesis of severe VPA hepatotoxicity is not clear but the microvesicular hepatic steatosis described in these patients is consistent with a disturbance of mitochondrial function and/or fatty-acid metabolism.\(^4\) We describe two unrelated infants receiving VPA who developed fatal hepatic failure. Both children had siblings who developed hepatic steatosis without being exposed to VPA. This suggests that an inborn error of metabolism may have been present in the two infants who developed hepatic failure when receiving VPA.

CASE REPORTS

\textbf{Patient 1}

This boy was born to non-consanguineous parents at term following an uneventful pregnancy. The delivery, birth weight and perinatal period were normal. The patient was well until nine months of age when, following a brief febrile illness, he developed acute infantile hemiplegia with hemiconvulsions. Seizure control was achieved with difficulty using phenobarbital, phenytoin, diazepam and paraldehyde. Investigations revealed the following abnormalities: aspartate aminotransferase (AST) 199 U/L, alanine aminotransferase (ALT) 60 U/L, fibrinogen 67 mg/dl (0.67 g/L), glucose 120 mg/dl (6.6 mmol/L) and...
prothrombin time 11.8 seconds. The serum ammonia, lactate, electrolytes, protein, glucose and cell count in the cerebrospinal fluid, urinary VMA studies and computed tomography (CT) of the head were normal.

Myoclonic seizures were observed after three weeks and the child received VPA (35 mg/kg/day) for three days. The serum AST activity was 230 U/L when measured on the day after starting VPA. Myoclonus and hypoglycemia but failed to demonstrate the underlying mechanism. A 4 hour period of death, again revealed only marked steatosis and necrosis of the liver.

At nine months of age the child developed an illness characterized by vomiting and lethargy. Ten hours after the onset of vomiting she was found dead in her crib. Autopsy revealed diffuse steatosis of the liver and an acute duodenal ulcer.

An older sister of Patient 1 was born following a normal pregnancy; the delivery, birth weight and perinatal period were normal. This child was well until four months of age, when she failed to thrive following the introduction of cereals. No investigations were performed. At nine months of age the child developed an illness characterized by vomiting and lethargy. Ten hours after the onset of vomiting she was found dead in her crib. Autopsy revealed diffuse steatosis of the liver and a small, perforated duodenal ulcer.

Patient 2
This boy, the first child of non-consanguineous parents, was born following a normal pregnancy and delivery. The birth weight and perinatal period were normal. At three months of age brief episodes of head shaking and arm stiffening were observed, which were not investigated and which resolved spontaneously by five months. The child’s gross motor development was slow and he could not sit without support at nine months of age. At ten months of age the child presented in status epilepticus following a mild respiratory illness. He was treated with phenobarbital, phenytoin, diazepam, thiopental and lignocaine. The serum activities of AST and ALT were elevated at 72 U/L and 55 U/L respectively. Computed tomography of the head was normal. Electroencephalography (EEG) showed severe generalized dysfunction with periodic lateralizing epileptiform discharges (PLEDS). Myoclonic seizures developed which were refractory to nitrazepam. Forty-eight hours after receiving VPA the patient was noted to be jaundiced and drowsy. All the anti-epileptic drugs, valproic acid, phenytoin, phenobarbital and nitrazepam, were discontinued. The patient developed rapidly progressive liver failure and died two months later. Findings at autopsy were atrophy of the cerebral cortex and hepatic steatosis with minimal fibrosis, consistent with a diagnosis of progressive neuronal degeneration of childhood with liver disease.

The following investigations gave normal or negative results: CBC, BUN, creatinine, serum potassium, plasma amino acids, alpha-1 antitrypsin, immunoglobulin electrophoresis, sweat test, plasma phytanic acid, stearic acid, oleic acid, linoleic acid, alpha-3 globulin, ceruloplasmin, thyroid function studies, immunoglobulin electrophoresis, sweat test (x2), alpha-1 antitrypsin, hepatitis B surface antigen and viral antibody studies (for hepatitis A, cytomegalovirus, Ebstein-Barr, herpes simplex, rubella and measles).

### Table 1: Alanine Tolerance Test

<table>
<thead>
<tr>
<th>TIME (min)</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dl)</td>
<td>81</td>
<td>81</td>
<td>67</td>
<td>63</td>
<td>56</td>
</tr>
<tr>
<td>Alanine (micromol.)</td>
<td>262</td>
<td>3266</td>
<td>3449</td>
<td>—</td>
<td>3603</td>
</tr>
<tr>
<td>Lactate (mmol.)</td>
<td>1.1</td>
<td>—</td>
<td>1.8</td>
<td>2.5</td>
<td>2.8</td>
</tr>
</tbody>
</table>

### Discussion
The incidence of fatal VPA hepatotoxicity in children under the age of three years on multiple antiepileptic drugs was one in 500 and one in 800 in two retrospective studies. Many of these children had unexplained severe neurological abnormalities prior to receiving VPA. Fourteen of the 16 children under three years of age had experienced a recent episode of status epilepticus. Hepatic failure usually occurred within six months.
of the start of VPA therapy, was not related to dose or serum VPA concentration and progressed despite drug withdrawal. Histological findings in most patients revealed microvesicular hepatic steatosis usually accompanied by necrosis.1,5

Both of our patients had many of the characteristic features described in young children developing progressive liver failure after being exposed to VPA. Both were under the age of three years, had developmental delay, had recently been in status epilepticus and were receiving other antiepileptic drugs at the onset of the liver failure. In addition, autopsies in both demonstrated hepatic steatosis and necrosis. In view of the clinical course and autopsy findings, the cause of death in each patient was attributed initially to VPA induced hepatic failure. Although increased serum hepatic enzyme activity was observed in both patients prior to receiving VPA, this increase was mild and was attributed to the effects of status epilepticus6 or other antiepileptic drugs.7,8

Autopsies on the two siblings of patient 1 demonstrated hepatic steatosis. The older sibling was found dead in bed following a brief illness characterized by vomiting and lethargy. Patients with inherited disorders of fatty acid oxidation, including medium chain fatty acid CoA dehydrogenase complex deficiency in brain, decreased pyruvate dehydrogenase activity in liver and muscle, a defect in citric acid cycle activity in liver and fibroblasts.27 Thus, patients with PNDC have inborn errors of metabolism which may be exacerbated by treatment with VPA.

Hepatic steatosis was observed in two siblings of patient 1 and also in the sibling of patient 2 although they had not been exposed to VPA. In addition, the clinical presentations in the younger siblings of patient 1 and the sibling of patient 2 were similar to those of patients 1 and 2. This suggests that both of our patients may have had an underlying metabolic disorder. Inborn errors of metabolism present usually during the neonatal period or infancy. Thus, it is possible that the increased incidence of fatal VPA hepatotoxicity in children under three years of age may relate, at least in part, to the manifestation of familial metabolic defects in this age group. This is supported by the most recent review of valproic acid hepatic fatalities in the United States.2 Thus, siblings of three previously reported cases of fatal hepatotoxicity1 developed hepatic failure without ever being exposed to VPA.2 Similarly, although VPA was associated with fatal hepatotoxicity in siblings in two unrelated families, autopsy findings in these children were consistent with PNDC.5

The development of hepatic failure in some children with inborn errors of metabolism who were also receiving VPA may be more than coincidental. Glutathione peroxidase deficiency has been described in a child with PNDC.28 Glutathione has a major role in preventing toxic liver injury both by inhibiting covalent binding of macromolecules and also by protecting against oxidative stress.29 Thus, conditions associated with depletion of glutathione may predispose patients to VPA hepatotoxicity. Children with urea cycle disorders may also be predisposed to VPA toxicity. Fatal hepatotoxicity was associated with VPA therapy in a 3 year old girl whose two siblings had also died in early childhood.30 All three children had persistent vomiting and convulsions and alanine loading tests in the surviving family members suggested that the children probably had ornithine carbamyl transferase (OCT) deficiency.30 Markedly decreased OCT activity has also been demonstrated in a child of 3 years who died of liver failure after receiving VPA.31 Similarly, hyperammonemia was precipitated by VPA therapy in a patient with argininosuccinic aciduria.32 The toxic effect of VPA in children with urea cycle disorders may relate to inhibition of...
carbamyl phosphate synthesis by VPA, possibly due to the formation of CoA esters of VPA resulting in a decrease of available free CoA.\textsuperscript{33,34}

This report describes two unrelated families with probable inborn errors of metabolism where a child died of liver failure following the use of VPA. Inborn errors of metabolism probably contribute to the particularly high incidence of liver failure described in infants and young children receiving VPA polytherapy. Certain metabolic disorders may be exacerbated by VPA. We suggest that infants at high risk should be screened carefully for familial hepatic disease prior to treatment with VPA.

\textbf{ACKNOWLEDGEMENTS}

The authors gratefully acknowledge the assistance of Dr. S.I. Goodman (Denver, Colorado) for measurement of the long, medium and short chain acyl CoA dehydrogenases and Ms. Jenny Toone for measurement of PEP carboxykinase.

\textbf{REFERENCES}