

Reversible Neonatal Cholestasis Following In Utero Exposure to Valproic Acid

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INTRODUCTION

Valproic acid (VPA) is a branched-chain carboxylic acid with broad anticonvulsant activity. Its spectrum of activity is thought to be mediated by combined molecular effects on intercellular Na⁺ currents, neuron K⁺ channels, and inhibition of gamma-aminobutyric acid (GABA) transaminase (1,2).

VPA is metabolized in the liver by cytochrome P-450 oxidase. Hepatotoxicity related to valproate therapy has been reported in certain individuals and appears to be caused by the accumulation of toxic metabolites, which may include 4-en-valproate (3). The hepatotoxicity has been ascribed to an inherited or acquired deficiency in the cytochrome P-450 enzyme-dependent beta-oxidation pathway, and is inducible by other drugs such as phenobarbital or phenytoin (4). Fatal hepatic failure can result, with a disproportionately large number of such cases observed in patients less than two years old with neurologic abnormalities, severe seizures, and multiple anti-epileptic drug therapy (3,5,6,7). However, neonatal hepatic toxicity in humans coincident with intrauterine VPA exposure has rarely been reported (8,9,10); these cases were never reversible, and confounding etiologic variables could not be excluded.

In pregnancy, VPA readily crosses the placenta and accumulates with fetal blood concentrations greater than those in the mother (11). It is a known human teratogen primarily associated with neural tube developmental defects such as spina bifida. A specific "fetal valproate syndrome," marked by fetal growth deficiency, developmental delay, and an increased incidence of craniofacial, cardiovascular, and digital abnormalities, has also been reported (1,3,12,13,14). Furthermore, a dose-dependent relationship in the occurrence of major malformations and minor anomalies has been suggested (15). Major malformations reported include persistent patent ductus arteriosus, trigonocephaly, aplasia of the first ribs, dysplasia of the sternum, meningomyelocele, aplasia of the radius, and congenital hip dislocation. Minor malformations included brachycephaly, dysmorphic facial features, long thin fingers, and inverted or accessory nipples. The teratogenic potential is thought to be mediated by a secondary zinc deficiency induced by complexing with VPA (16), as well as by inhibition of microsomal epoxide hydrolase (17), which may enhance the teratogenic

potential of concomitant anticonvulsant therapy.

Numerous animal models have been developed for the study of VPA. VPA has been shown to have equal teratogenic potential as trimethadione in mice (18). Skeletal abnormalities, delayed parturition, and postnatal growth (5) have been reported in both mice and rats receiving VPA. In addition, Paulson and Paulson (19) noted defects of the palate, eyes, heart, and limb buds in animal models. Animal models for a VPA-associated cholestasis, however, are lacking.

THE CASE

The patient is the first child of a 30 year-old, African-American female with juvenile myoclonic epilepsy. The mother's seizures had been controlled for two years prior to the pregnancy and throughout the first six months of pregnancy by 250 mg of VPA taken three times a day. Previously, she had been taking carbamazepine, diphenylhydantoin (DPH), and phenobarbital, but had stopped due to side effects, primarily disorientation. At six months gestation, the mother had experienced a seizure, at which time her serum VPA level was found to be 47 $\mu\text{g/ml}$ (normal therapeutic level = 50-120 $\mu\text{g/ml}$). Her VPA regimen was subsequently increased to 250 mg four times daily, and she had been seizure-free throughout the remainder of the pregnancy. Prenatal studies, including karyotyping, ultrasonography, and maternal testing for hepatitis B surface antigen, had been unremarkable.

At 39 weeks gestation, fetal nonstress tests had been nonreactive, and a three-minute episode of fetal bradycardia had been observed. Based on these findings, a decision had been made to induce labor. Pitocin was given intravenously and, at onset of contractions, analgesia had been provided with 50 mg of Demerol and 25 mg of Phenergan. Delivery had been normal, with vaginal vertex presentation.

At birth, the infant was noted to be small, drowsy, and jittery with a high-pitched cry. Apgar score was 8, at one and five minutes. Birth weight (2145 g), length (44.5 cm), and head circumference (28.5 cm) were all below the third percentile for gestational age. The Dubowitz score was consistent with 38 weeks gestation. Vital signs were all within normal limits, and the remaining features of physical examination of the neonate were unremarkable. However, with regard to fetal tissues, the umbilical cord was noted to be twice the average normal length and twisted. In addition, the placenta was of normal weight, but contained membranous hemosiderin deposits and multiple calcified thrombi.

The initial blood glucose of the fetus was 11 mg/dl (normal = 20-65 mg/dl) (4), and continuous maintenance intravenous glucose was required over the first 5 days. By day 6, blood glucose levels normalized and intravenous glucose was discontinued. The prolonged neonatal hypoglycemia was not found to be associated with abnormal serum insulin, growth hormone, or cortisol levels.

At two days post-partum, the infant's total serum bilirubin was 5.2 mg/dl (normal < 8 mg/dL), with a direct bilirubin of 2.7 mg/dl (normal < 0.4 mg/dL). The infant was not jaundiced, stools were colorless, serum glutamic pyruvic transaminase (SGPT) levels were normal, and there was no evidence of hemolysis. The direct conjugated hyperbilirubinemia persisted beyond the first week, at which time phenobarbital treatment was initiated to augment bilirubin excretion.

Radioisotope imaging of the hepatobiliary system was used to complement blood chemistries in characterizing the hepatic process. This is the procedure of choice to evaluate patients with suspected acute cholecystitis, enterogastric reflux of bile, and neonatal biliary atresia (20). On day 8 post-partum, DISIDA™ imaging was performed using 1.1 mCi of Choletec™ (Squibb, New Brunswick, NJ), a 99m-technetium-labeled iminodiacetic acid agent of high hepatic uptake and rapid biliary excretion (21). As shown in [Figure 1](#), there was marked retention of the reagent, without excretion into the biliary tree. Abdominal ultrasonography demonstrated a normal common duct and liver without biliary distention. These findings led

to an impression of cholestasis; however, biliary atresia could not be excluded.

By age 14 days, total and direct bilirubin had decreased to 3.7 mg/dL and 3.3 mg/dL, respectively. Alkaline phosphatase was within normal limits at 230 U/L (normal < 420 U/L), SGPT was slightly raised at 57 U/L (normal < 54 U/L), and serum glutamic oxaloacetic transaminase (SGOT) was markedly elevated at 109 U/L (normal = 20-65 U/L). At 20 days post-partum, the patient was discharged on oral phenobarbital 5 mg twice daily. The stools gradually became pigmented. The pattern of hyperbilirubinemia, without significant hepatic cell injury, resolved gradually over the next two months. By five months of age, all liver functions were normal.

A second liver scan at 15 days, using 0.9 mCi of reagent, showed normal liver and gallbladder uptake at 2 hours, but no uptake in the common bile duct or gut. As shown in [Figure 2](#), a third scan performed at 43 days of age, using 0.9 mCi of reagent, demonstrated activity in the gallbladder and gut, excluding biliary atresia and supporting the diagnosis of transient neonatal cholestasis.

Additional workup for neonatal cholestasis included carnitine and alpha-1 anti-trypsin levels, urine metabolic screen, quantitative amino acids and metabolic screen, cytomegalovirus culture, HIV, and galactose-1-uridyl transferase activity, all of which were normal or negative.

DISCUSSION

This case demonstrates intrauterine growth retardation (IUGR), neonatal hypoglycemia, and cholestatic jaundice in conjunction with maternal valproic acid use. Although it has been associated with maternal VPA therapy (3), IUGR can arise from a number of predisposing factors (6), such that a causal relationship in the present case cannot be established. In the present instance, it may have been that IUGR was secondary to a long umbilical cord and the presence of thrombi in the placenta (22). Whether VPA is capable of producing such abnormalities in the umbilical cord and placenta, either directly or indirectly, is not currently known.

The principal evidence for a prolonged, reversible neonatal cholestasis included a conjugated hyperbilirubinemia accompanied by normal SGPT and elevated gamma glutamyl transferase (GGT) at 2 months of age, and the results of three sequential liver radioisotope scan studies. The elevated GGT is suggestive of a biliary obstructive process. The observation of acholic stools during the first week of life was also suggestive of cholestasis.

The pathological mechanisms for neonatal conjugated hyperbilirubinemia include mechanical obstructions, infections, metabolic dysfunctions, and toxic and autoimmune causes (6). Infectious etiologies were unlikely based upon history, maternal labwork, and the absence of significant hepatocellular injury in the patient. Furthermore, urine culture for cytomegalovirus, rectal and throat swabs for viral culture, and blood culture for bacteria were negative. Antibodies to rubella, herpes simplex, toxoplasmosis, and Epstein-Barr virus were likewise negative. Tests for galactosemia and hypothyroidism in search of a metabolic cause of the hyperbilirubinemia were negative. Lastly, family history was negative for metabolic or hepatic disease.

Given the results of these series of investigations, and in the context of maternal VPA use, a toxic cause for the hyperbilirubinemia was hypothesized. Although a primary mechanical obstruction can not be ruled out, mechanical obstruction secondary to VPA exposure must be considered. The transient biliary obstruction reported in the present case may represent one possible outcome from a spectrum of VPA-induced injuries. These injuries may be totally reversible, or show progression to more serious states such as atrophy and necrosis.

Single reports have associated maternal VPA with neonatal hyperbilirubinemia, failure-to-thrive, and fatal liver failure accompanied by cholestasis (8,9,10). Bantz (8) described a child with growth deficiency, multiple

congenital malformations, and hyperbilirubinemia; however, extensive workup including liver function tests and imaging studies was not reported, complicating etiological determination of the hyperbilirubinemia. Legius et al. (10) described two siblings who died from liver failure: a boy with cholestasis accompanied by liver atrophy and necrosis, and a girl with IUGR, direct hyperbilirubinemia, hypoglycemia, dysmorphic features, cardiomyopathy, hypocalcemia, and seizures. Felding and Rane (9) reported an infant with liver dysfunction, failure-to-thrive, and a transient cholestatic form of hyperbilirubinemia. Ultrasonography revealed normal liver and bile ducts. However, the case was confounded by the maternal use of both VPA and diphenylhydantoin.

This case adds to the presently limited understanding of the role of maternal VPA in a reversible pattern of neonatal complications, and unlike the case reported by Felding and Rane, was free from the confounding influence of other anti-convulsant medications. Carbohydrate metabolism normalized by day six, conjugated hyperbilirubinemia resolved after two months, and postnatal growth accelerated to the fiftieth percentile by six months.

When compared to the general population, children of epileptic mothers are at increased risk for congenital malformations. Although disposition genetics and the underlying seizure disorder itself may serve as contributing factors (2), animal and biochemical studies seem to indicate that drug therapy itself is the primary factor (3).

The drugs of choice (i.e., most effective, least toxic) for patients with generalized tonic-clonic, simple partial, and complex partial seizures are phenytoin, carbamazepine, and valproic acid (23). Teratogenic data is most extensive with respect to phenytoin, which, like VPA, is designated a pregnancy category D risk factor drug (3). Carbamazepine, as a pregnancy category C risk factor drug (2), may also produce malformations.

With the known and newly reported possible risks associated with anticonvulsant medication, the benefits of therapy must be weighed very carefully. Current management of epileptic women of child-bearing potential involves the administration of antiepileptic drugs only if the medication is clearly shown to be essential to seizure management (2). Drugs administered to prevent major seizures should not be discontinued due to the strong possibility of precipitating status epilepticus, with attendant hypoxia and risk of fatality to the mother and unborn child. If the nature, frequency, and severity of the seizures do not pose a serious threat to the patient, discontinuation of the drug before and during the pregnancy may be considered. However, this determination is made difficult by the current lack of knowledge regarding whether even minor seizures may pose some hazard to the developing embryo or fetus.

In summary, this is the first report of reversible neonatal cholestasis associated with maternal single-agent anticonvulsant therapy with VPA. Although a causal relationship cannot be definitively established, the role of VPA, given its known hepatotoxicity and the considerable evidence against other etiologies, is highly suggestive, and warrants further investigation.

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BIOGRAPHY

Douglas Chang graduated from Yale University (New Haven, CT, USA) in 1988 with a B.S. in Engineering Sciences, Mechanical. He studied lumbar spine biomechanics during a one-year fellowship at the Wilhem Schulthess Klinik (Zurich, Switzerland) in the Departments of Neurology and Rheumatology. In 1992, the author completed an M.S. in Mechanical Engineering at the University of Washington (Seattle, WA, USA), where he studied cervical spine trauma. He is currently in his fifth year of the MD/PhD program at the University of California, San Diego (La Jolla, CA, USA), studying knee injuries in the Cartilage Tissue Engineering lab at the Department of Bioengineering. His clinical interests are in Pediatric Orthopaedics and Rehabilitation.

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