NEONATAL INTRACTABLE SEIZURES AND VALPROIC ACID THERAPY

Seizures resistant to phenobarbital were controlled in four of six neonates by valproic acid (VPA) monotherapy and in one with polytherapy at the Moses H Cone Memorial Hospital, Greensboro, NC. The pharmacokinetics of VPA showed a prolonged half-life in neonates in contrast to the short half-life in older children and adults. A loading dose of 20 mg/kg followed by a maintenance dose of 10 mg/kg every 12 hrs was recommended until VPA clearance and serum levels are determined.

VPA-induced hyperammonemia in all six patients was reason to discontinue VPA in three. One patient with meningitis whose seizures were unresponsive to VPA died shortly after the drug was discontinued; a serum ammonia elevation to 900 umol/l after 5 days of treatment returned to normal with 24-48 hrs after discontinuing the drug. (Gal P, Weaver R et al. Valproic acid efficacy, toxicity, and pharmacokinetics in neonates with intractable seizures. Neurology March 1988;38:467-71).

COMMENT. VPA toxicity, particularly hepatotoxicity, in infants and young children may be reduced in frequency by elimination of concurrent anticonvulsants, but serum ammonia must be closely monitored even with monotherapy. Cerebral edema, increased intracranial pressure, cytotoxic changes in the brain and coma are reported with hyperammonemia exceeding 500 umol/l in neonates, and intellectual retardation and brain damage are correlated with duration of hyperammonemia and coma (Msall M et al. N Engl J Med 1984;310:1500). Animal experiments show that VPA-induced hyperammonemia is caused primarily by impairment of hepatic intramitochondrial citrullinogenesis, and the renal contribution to systemic hyperammonemia is small (Marini AM et al. Neurology March 1988;38:365).

Brown JK, at the Royal Hospital for Sick Children, Edinburgh, writing on valproate toxicity in Developmental Medicine and Child Neurology (Feb 1988;30:121), cautions that any congenital inborn error of metabolism that affects mitochondrial function or any acquired mitochondriopathy might be expected to increase the risk of serious valproate toxicity in the neonate, and VPA is not generally recommended in the newborn period. He stresses the need for detailed investigation of cases of hepatopathy, including a full screen of mitochondrial enzyme function, as well as histology for possibly Reye-type changes, before accepting a diagnosis of VPA-induced hepatotoxicity.

SEIZURES FOLLOWING DTP IMMUNIZATION

The incidence of seizures following the administration of DTP vaccine at the Group Health Cooperative of Puget Sound, Seattle, has been estimated by epidemiologists at the Harvard School of Public Health, Boston, and by the Boston Collaborative Drug Surveillance Program, Waltham, Mass. For a population of children born in GHC hospitals, 1972-83, records of hospitalizations for neurologic disease and prescriptions of common anticonvulsant drugs were reviewed to establish the probable nature of the illness, the date of its onset, and the temporal relation to DTP.

Children omitted from the study for various reasons were as follows: 1) those not hospitalized nor treated with drug therapy (e.g., uncomplicated first febrile seizures and children with infantile spasms who received only ACTH and steroids as outpatients); 2) those with seizures and a history of possible predisposition due to trauma, asphyxia, malformation, metabolic defect, premature birth, CNS infection and sepsis; 3) those without a clear date of onset for the seizures or neurologic illness; 4) 8 cases of seizures