amination of the patient. Valproic acid therapy should be discontinued immediately in the presence of suspected or apparent substantial hepatic dysfunction. In some patients, hepatic dysfunction has progressed despite discontinuance of the drug. Since elevations in hepatic enzyme concentrations may be dose related, the benefit of improved seizure control which may accompany higher doses of the drug must be weighed against the potential risks. Valproic acid should be used with caution in patients with a history of hepatic disease. Children and patients receiving multiple anticonvulsants or those with congenital metabolic disorders, severe seizure disorders accompanied by mental retardation, or organic brain disease may be at particular risk of hepatotoxicity. Because children younger than 2 years of age, especially those with the previously listed conditions, have a considerably increased risk of developing fatal hepatotoxicity compared with older patient groups, valproic acid should be used in these patients only with extreme caution and as a single agent; the benefits of seizure control must be weighed against the potential risks. Above 2 years of age, the frequency of fatal hepatotoxicity decreases considerably in progressively older patient groups. Valproic acid should *not* be used in patients with hepatic disease or substantial hepatic dysfunction.

Because the use of valproic acid has been associated with life-threatening pancreatitis in children and adults (see Cautions: Pancreatitis), patients and guardians should be instructed that if symptoms of pancreatitis (e.g., abdominal pain, nausea, vomiting, anorexia) develop, prompt medical evaluation is needed. If pancreatitis is diagnosed, valproic acid usually should be discontinued and alternative therapy for the underlying medical condition should be initiated as clinically indicated.

Because the use of valproic acid has been associated with hyperammonemic encephalopathy, patients should be advised that if symptoms of this disorder (e.g., lethargy, vomiting, changes in mental status) develop, they should notify their clinician promptly. (See Cautions: Endocrine and Metabolic Effects.) If such symptoms are present, plasma ammonia concentrations should be determined, and, if these concentrations are increased, valproic acid therapy should be discontinued. Appropriate treatment of hyperammonemia should be initiated and the patient should be evaluated for an underlying genetic abnormality, urea cycle disorder. Asymptomatic elevation of ammonia concentrations is more common than hyperammonemic encephalopathy. In patients with asymptomatic elevations, plasma ammonia concentrations should be closely monitored and, if elevations persist, discontinuance of valproic acid therapy should be considered. Prior to the initiation of valproic acid therapy, an evaluation for urea cycle disorders should be considered in patients with a history of unexplained encephalopathy or coma, encephalopathy associated with a protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine concentrations; patients with cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low BUN concentration, or protein avoidance; patients with a family history of urea cycle disorders or unexplained infant deaths (particularly males); and patients with other signs or symptoms of urea cycle disorders.

Anticonvulsant drugs (including valproic acid) should not be discontinued abruptly in patients receiving the drugs to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life.

Since valproic acid may cause thrombocytopenia and inhibit platelet aggregation, platelet counts, bleeding time, and coagulation studies should be determined before and periodically during therapy with the drug and before surgery is performed in patients receiving the drug. In one study of the drug as monotherapy for seizures, 27% of patients receiving approximately 50 mg/kg per day of valproic acid had at least one platelet count of 75,000/mm^3/L or less; the probability of thrombocytopenia appeared to increase significantly at total serum valproate concentrations of 110 mcg/mL or greater (females) or 135 mcg/mL (males). Some clinicians have recommended thromboelastography as a more reliable method to assess the effects of valproic acid on coagulation. If clinical evidence of hemorrhage, bruising, or a disorder of hemostasis coagulation occurs during valproic acid therapy, dosage should be reduced or the drug withdrawn pending further evaluation.

Valproic acid is contraindicated in patients with known hypersensitivity to the drug. Valproic acid also is contraindicated in patients with known urea cycle disorders. (See Cautions: Endocrine and Metabolic Effects.)

■ **Pediatric Precautions** Experience with valproic acid therapy in the management of seizures indicates that children younger than 2 years of age are at an increased risk of developing fatal hepatotoxicity. (See Cautions: Precautions and Contraindications.) The drug should be used with extreme caution and as single-agent therapy in such children, and the benefits of valproic acid therapy weighed against the risks. The incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups (i.e., older than 2 years of age).

Younger children, especially those receiving enzyme-inducing drugs, will require larger maintenance doses to attain targeted total and unbound valproic acid concentrations for the management of seizures. The variability in free fraction limits the clinical usefulness of monitoring total serum valproic acid concentrations alone. Interpretation of valproic acid concentration in children should include consideration of factors that affect hepatic metabolism and protein binding.

The safety and efficacy of valproic acid for acute manic episodes in patients younger than 18 years of age and for migraine prophylaxis in patients younger than 16 years of age have not been established. In addition, safety and efficacy of divalproex sodium extended-release tablets in pediatric patients have not been established and use of this preparation in this age group is not recommended.

The safety of valproate sodium injection has not been studied in pediatric patients younger than 2 years of age. If a decision is made to use the injection in this age group, the manufacturer states that it should be used with extreme caution and only as monotherapy, and the potential benefits should be weighed against the possible risks. No unusual adverse effects were observed in clinical trials employing IV valproate sodium for the management of seizure disorders in 24 pediatric patients 2–17 years of age.

■ **Geriatric Precautions** The safety and efficacy of valproic acid in geriatric patients (older than 65 years of age) for the treatment of manic episodes associated with bipolar disorder or prevention of migraine headaches have not been established.

In a case review of almost 600 patients treated with valproic acid for manic episodes, approximately 12% of patients were older than 65 years of age. A higher percentage of these patients reported accidental injury, infection, pain, somnolence, or tremor during valproic acid therapy compared with younger patients. Discontinuance of valproic acid therapy occasionally was associated with somnolence or tremor. The manufacturer states that it is unclear whether these events indicate additional risks of drug therapy or whether they result from preexisting medical conditions or concomitant medication use in these geriatric patients.

Results of a double-blind, multicenter study of geriatric patients (mean age: 83 years) with dementia who were receiving valproic acid (125 mg daily, titrated to a target daily dosage of 20 mg/kg) indicate that the incidence of somnolence was higher in patients receiving valproic acid than in those receiving placebo and discontinuance of therapy because of somnolence was higher in those receiving valproic acid than in those receiving placebo. In about 50% of patients with somnolence, a reduced nutritional intake and weight loss also were observed. The incidence of dehydration also appeared to be higher in geriatric patients receiving valproic acid than in those receiving placebo. In the patients who experienced the mentioned adverse effects, a trend for lower baseline albumin concentration, lower valproic acid clearance, and higher BUN was observed. Therefore, it is recommended that initial dosage of valproic acid be reduced and subsequent dosages be increased more slowly in geriatric patients. In addition, the manufacturer recommends regular monitoring of fluid and nutritional intake, dehydration, somnolence, and other adverse effects in these individuals. Dosage reduction or discontinuance of valproic acid should be considered in geriatric patients with decreased food or fluid intake and in those with excessive somnolence.

■ **Mutagenicity and Carcinogenicity** Studies of valproic acid that used bacterial and mammalian test systems have shown no evidence to date of a mutagenic potential for the drug.

In rats and mice receiving valproic acid dosages of 80 and 170 mg/kg daily for 2 years, an increased incidence of subcutaneous fibrosarcomas occurred in male rats at the higher dosage level and a dose-related trend for an increased incidence of benign pulmonary adenomas was observed in male mice. The importance of these findings to humans is not known.

■ **Pregnancy, Fertility, and Lactation** Safe use of valproic acid during pregnancy has not been established. Adverse fetal effects have been observed in reproduction studies in rats and mice. Valproic acid can cause teratogenic effects in humans, such as neural tube defects (e.g., spina bifida). Several reports suggest an association between use of valproic acid in pregnant, epileptic women and an increased incidence of birth defects (particularly neural tube defects) in children born to these women; such malformations may be associated with high plasma concentrations during the first trimester. Some experts state that prophylactic use of folic acid may prevent or decrease the incidence of neural tube defects. Valproic acid should be used in pregnant women with seizure disorders or women with seizure disorders who might become pregnant only if the drug is clearly shown to be essential in the management of their seizures. Women should be apprised of the potential hazard to the fetus; this is especially important when valproic acid therapy is being contemplated or used for the management of a spontaneously reversible condition not ordinarily associated with permanent injury or risk of death (e.g., prophylaxis of migraine headache). Tests to detect neural tube and other defects using current accepted procedures should be considered a part of routine prenatal care in childbearing women receiving valproic acid for the management of seizure disorders.

Other congenital anomalies (e.g., craniofacial defects, cardiovascular malformations, anomalies involving various body systems) compatible and incompatible with life also have been reported in children of women treated with valproic acid during pregnancy; sufficient data to determine the incidence of these anomalies are not available. The higher incidence of congenital anomalies in the children of women with seizure disorders treated with anticonvulsant drugs during pregnancy cannot be regarded as a direct effect of such therapy. There are intrinsic methodologic problems in obtaining adequate drug teratogenicity data in humans. Genetic factors and/or the epileptic disorder also may contribute to the development of congenital anomalies.

Patients receiving valproic acid may develop clotting abnormalities. A pregnant patient taking multiple anticonvulsant agents, including valproic acid, developed hypofibrinogenemia; the patient then gave birth to an infant with afibrogenemia, who subsequently died of hemorrhage. If valproic acid is to be used during pregnancy, clotting parameters should be monitored closely. He-