# Pediatric Pharmacotherapy

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## Valproic Acid in the Treatment of Pediatric Seizures

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Previous issues of *Pediatric Pharmacotherapy* have focused on phenytoin (August 1996) and carbamazepine (November 1996). This issue continues the series on anticonvulsants with a review of valproic acid use in pediatrics. Since its introduction in the United States in 1978, valproic acid has become one of the most frequently prescribed anticonvulsants in both pediatric and adult patients. Valproic acid has been found to be effective in treating a number of seizure types and is frequently used as part of multi-drug therapy in patients with mixed seizure disorders.

Mechanism of Action

Valproic acid is a branched-chain fatty acid. Its chemical structure differs significantly from any other anticonvulsant in current use. As with other anticonvulsants, the mechanism of action of valproic acid is not fully understood. It has been theorized that valproic acid acts by increasing the concentrations of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) within the central nervous system through inhibition of GABA degradation or enhancement of GABA synthesis and release. Other research has suggested that valproic acid acts via inhibition of excitatory neurotransmitters or by action at sodium and calcium channels to reduce sustained (high frequency repetitive) neuronal firing.[1,2]

Efficacy

The efficacy of valproic acid has been established in multiple clinical trials. Comparison studies have found it to be similar to other commonly prescribed anticonvulsants, such as phenobarbital, phenytoin, and carbamazepine in the management of generalized tonic-clonic seizures, partial seizures with or without secondary generalization, and myoclonic seizures. Valproic acid has also been shown to be equivalent to ethosuximide for the treatment of absence seizures, both simple and complex. Because of its broad spectrum of anticonvulsant activity, it is frequently used in the management of children with mixed seizures types, including Lennox-Gastaut syndrome. It has also been used in the treatment of infantile spasms, but with mixed results.[1,3-6]

In addition to its use as an anticonvulsant, valproic acid is also approved for use in the treatment of bipolar disease and as prophylaxis for migraine headaches. These uses have not been well studied in children.

Pharmacokinetics

Valproic acid is available in a variety of oral dosage forms. In addition to valproic acid as a single entity, the drug may be given as a sodium salt (sodium valproate) or as a mixture of equal portions of valproic acid and sodium valproate (divalproex sodium). The divalproex mixture, which slowly disassociates and is absorbed in the intestine, was developed in an effort to avoid the gastrointestinal upset associated with the immediate release products.

Products currently available in the United States are listed in Table 1.[7] The bioavailability of these oral dosage forms approaches 95 to 100%. Due to previous reports of breakthrough seizures following a change from a brand name product to a generic product, it is recommended that patients remain on a single brand. An intravenous form of sodium valproate has recently been approved by the FDA[8] It will be marketed by Abbott Laboratories with the trade name Depacon® and is expected to be available in late spring of 1997.

Table 1. Valproic Acid Dosage Forms

| Compound | Strength[a] | Brands |
|---|---|---|
| Valproic Acid | 250 mg capsules | Depakene® or generic |

| | | |
|---|---|---|
| Sodium Valproate | 250 mg/5 ml syrup | Depakene® or generic |
| Sodium Valproate | 100 mg/ml injection | Depacon® |
| Divalproex sodium | 125 mg, 250 mg, and 500 mg delayed-release, enteric-coated tablets | Depakote® |
| Divalproex sodium | 125 mg sprinkle capsule (enteric-coated particles) | Depakote® |

[a] expressed in terms of valproic acid

The time to reach maximum serum concentrations differs among the products available. Peak concentrations occur approximately one to three hours following administration of the capsule or liquid dosage forms. Peak concentrations are delayed for up to three to five hours with the sprinkle and delayed release tablet formulations. Administration of valproic acid products with food delays the rate of absorption, but does not typically affect the extent of drug absorbed.[1,9]

Valproic acid is rapidly distributed throughout the body and is highly protein bound. As a result, significant protein loss may cause more free drug to be available, increasing clinical effect and the potential for toxicity. Although not routinely used in patient monitoring, free valproic acid serum concentrations can be measured to assess changes in protein binding.

The serum concentration-response relationship is not as well defined for valproic acid as it is for most other anticonvulsants. The majority of patients treated with valproic acid will achieve optimal seizure control at serum concentrations between 50 and 100 mcg/ml.[1] Patients with mixed seizure types or refractory seizures may require serum concentrations up to 150 mcg/ml before achieving the desired response.

Valproic acid undergoes extensive hepatic metabolism. The primary metabolic pathways include both glucuronidation and oxidation, resulting in the formation of at least five different metabolic products. The 2-en-valproic acid metabolite may be pharmacologically active, while the 4-en-valproic acid may be involved in the hepatotoxicity associated with this drug.

Only 1 to 3% of a dose is excreted in the urine unchanged. The usual elimination half-life of valproic acid in adults and children greater than 10 years of age is 9 to 16 hours. Younger children have a slightly shorter half-life of 7 to 13 hours, while infants have a prolonged elimination (17 to 40 hours).[1,10]

Drug Interactions

As a result of its high degree of protein binding and reliance on hepatic metabolism, valproic acid has many known interactions with other medications (Tables 2 and 3). Since valproic acid is metabolized through the hepatic cytochrome P450 enzyme system, it is affected by both inhibitors and inducers of those enzymes.

Table 2. Drugs that Affect Valproic Acid (VPA) Concentrations

| | |
|---|---|
| Chlorpromazine | ↑ VPA Concentrations |
| Cimetidine | ↑ VPA Concentrations |
| Felbamate | ↑ VPA Concentrations |
| Salicylates | ↑ VPA Concentrations |
| Carbamazepine | ↓ VPA Concentrations |
| Lamotrigine | ↓ VPA Concentrations |
| Phenytoin | ↓ VPA Concentrations |
| Rifampin | ↓ VPA Concentrations |

Table 3. Effect of Valproic Acid on Other Drugs

| | |
|---|---|
| Benzodiazepines | ↑ Sedation |
| Carbamazepine | ↑ Concentrations |
| Clonazepam | ↑ Sedation |
| Clozapine | ↑ Concentrations |
| Ethosuximide | ↑ or ↓ Concentrations |
| Lamotrigine | ↑ Concentrations |
| Phenytoin | ↑ Concentrations |
| Phenobarbital | ↑ Sedation |
| Primidone | ↑ Sedation |
| Warfarin | ↑ Anticoagulant Effect |
| Zidovudine | ↑ Concentrations |

Adverse Effects

Valproic acid is well tolerated by most patients. It lacks many of the adverse effects associated with other anticonvulsants, including their negative effects on learning ability and cognition.[11]

The most common adverse effects associated with the use of valproic acid include nausea, vomiting, and abdominal cramps (in up to 22% of patients studied), somnolence and dizziness (10 to 20%), and rash (1 to 6%). The gastrointestinal upset caused by valproic acid is

usually transient. Use of the sprinkle or delayed release products or administration with meals may lessen these effects. The CNS depressant effects of valproic acid are most pronounced during the initiation of therapy and typically respond to dosage adjustment.[1,7]

The most significant adverse effects of valproic acid are related to metabolic changes and hepatotoxicity. Metabolic disturbances such as hyperammonemia, secondary carnitine deficiency, hyperglycinemia, hyperglycinuria, propionic acidemia and propionic aciduria have all been linked to valproic acid use in children. It has been suggested that these adverse reactions reflect the "unmasking" of underlying inborn errors of metabolism and accumulation of toxic valproic acid metabolites, particularly 4-en-valproic acid.[12,13]

Severe hepatotoxicity, previously believed to be an idiosyncratic reaction, may also be linked to accumulation of 4-en-valproic acid. This rare adverse reaction should be considered as clearly separate from the dose-related, transient rise in liver function tests which occurs in up to 10% of patients.

In retrospective reviews of reported cases, children under the age of two years appear to be at greatest risk for fatal hepatotoxicity, particularly those receiving multiple anticonvulsants, those with congenital metabolic disorders, and those with mental retardation or organic brain disease.[13] Hepatotoxic effects typically occur during the first six months of therapy, but can occur at any time. Although recommended by many sources, the utility of routine monitoring of hepatic function in these patients is questionable.

Families of young children receiving valproic acid should be aware of the need to seek immediate medical attention when signs or symptoms of jaundice, vomiting and anorexia, lethargy, increased seizures, edema, or abnormal bleeding are noted.[12,13] Prophylactic carnitine supplementation has been recommended as a means of correcting possible underlying metabolic dysfunction, but this therapy remains controversial.[14,15]

Other adverse effects reported with valproic acid use in children include transient alopecia, weight loss or gain, tremor, changes in personality (aggression, irritability, hyperactivity), and, rarely, amenorrhea and acute pancreatitis. Dose-related thrombocytopenia and abnormal platelet function appear to be the result of valproic acid-induced inhibition of platelet aggregation and fibrinogen depletion.[7,12,16]

In addition to these adverse effects, all female patients of child-bearing age taking valproic acid should be counseled about the increased risk of neural tube defects in the exposed fetus. This risk may be lessened by the administration of folic acid prior to and early in the course of pregnancy.[7]

Overdosage

Initial signs and symptoms of valproic acid overdosage or elevated serum concentrations include nystagmus, headache, ataxia, tremor, and hallucinations or changes in vision. Patients may progress to heart block or coma. Treatment of valproic acid overdosage consists of supportive therapy in symptomatic patients. Naloxone may be beneficial in reversing the CNS depression, although results have been mixed.[1,7,12]

A recent publication by Murakami and colleagues[15] suggests that carnitine supplementation may alter metabolism of the toxic dose, reducing the production of 4-en-valproic acid and alleviating the coma associated with hepatic dysfunction.

Dosing Recommendations

It is suggested that valproic acid be initiated at dosages of 15 to 20 mg/kg/day in children and titrated at weekly intervals by 5 to 10 mg/kg/day until seizures are controlled or adverse effects become intolerable.[1,7] Most pediatric patients respond to dosages of 20 to 40 mg/kg/day. The maximum recommended dosage is 60 mg/kg/day; however, some children with refractory seizures may require higher dosages to achieve the desired degree of seizure control.

Valproic acid continues to gain acceptance as a first-line anticonvulsant therapy due to its efficacy in a wide variety of seizure types. It is particularly useful in patients with mixed seizure types. In addition, its availability in many different oral dosage forms allows easy titration of dosages. As with the other anticonvulsants, patients receiving valproic acid must be closely monitored for adverse effects and drug interactions.

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## Pharmacology Literature Review

Pharmacokinetics of Sedatives in Neonates

The authors provide an extensive review of the pharmacokinetic trials performed to date with sedatives in neonates. Benzodiazepines, primarily midazolam, and opioids are reviewed in depth. Studies involving chloral hydrate and propofol are also discussed. For many of the agents, the authors provide data from adult trials for comparison. Jacqz-Aigrain E, Burtin P. Clinical pharmacokinetics of sedatives in neonates. **Clin Pharmacokinet 1996;31:423-43.**

## Formulary Update

The Pharmacy and Therapeutics Committee met on 2/28/97. There were no additions or deletions to the formulary.

1. Simvastatin was added to the formulary. This agent is another HMG-CoA reductase inhibitor used in the treatment of hyperlipidemia.



*If you have any comments or would like to be on our mailing list, please contact Marcia Buck by mail at Box 274-11, University of Virginia Medical Center, Charlottesville, VA 22908 or by phone (804) 982-0921, fax (804) 982-1682, or e-mail to mlb3u@virginia.edu.*