Pediatric Pharmacotherapy

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Phenytoin: Optimizing Therapy in Children

Pharmacology Literature Reviews

Formularly Update

It has been estimated that more than two million people in the United States have epilepsy.[1] The frequency with which anticonvulsants are prescribed makes it essential that all health care providers be familiar with basic aspects of their use. Phenytoin is one of the most frequently prescribed anticonvulsants, used as both treatment for known seizure disorders and as prophylaxis following traumatic brain injury.

Phenytoin has been available in the United States since 1938.[1] It is used for treatment of tonic-clonic seizures, both generalized and partial, psychomotor seizures, and in the management of status epilepticus.[2] Although its precise mechanism of action has not been determined, current theory suggests phenytoin acts by blocking sodium channels in neuronal tissue, resulting in a prolongation of their rate of recovery and a reduction in the frequency of sustained repetitive firing of action potentials.[3]

Several clinical trials have attempted to identify the optimal anticonvulsant regimen in adults and children with seizure disorders. From these trials, it appears that phenobarbital, phenytoin, carbamazepine, and sodium valproate have relatively equivalent efficacy.[4-6] Recently, the results of a seven-year comparative trial of monotherapy with these four anticonvulsants in children

were published.[6] Seizure recurrence rate was not significantly different among the medications tested, although the use of phenobarbital was discontinued early in the study due to prevalence of adverse drug reactions. Although phenytoin did improve seizure control in most children, it should be noted that only 39% of the children were seizure free after one year of treatment. Monotherapy, although still a goal of treatment, is not adequate for many patients.

In order to obtain the optimal results from phenytoin therapy in children, clinicians must be aware of the unique features of this drug, including its non-linear pharmacokinetics, numerous drug interactions, and potential for causing a wide variety of adverse effects.

Pharmacokinetics

Phenytoin is available in both parenteral and oral dosage forms. When administered orally, phenytoin is absorbed in the small intestine. Bioavailability varies among different dosage formulations and among products from different manufacturers. Phenytoin chewable tablets and suspension achieve peak serum concentrations one to three hours after administration in children. Extended-release capsules result in delayed peak concentrations at 10-12 hours.[7]

Phenytoin is widely distributed in the tissues, including the CNS. Volume of distribution is estimated at 0.6-0.8 L/kg in adults and slightly higher, 0.8-1.2 L/kg, in children. Phenytoin is approximately 85-95% protein bound. Measurement of free phenytoin serum concentrations should be considered in patients with altered protein status, such as those with significant renal or hepatic dysfunction. Routine measurement of free levels is not needed. Neonates tend to have a lower percentage of protein binding than older children and adults, but clinical studies have shown variable results.[7]

For most patients, maintaining serum concentrations between 10 to 20 mcg/ml provides adequate seizure control without adverse effects. It should be kept in mind, however, that individual patient response will differ. Patient variation may reflect differences in the percentage of unbound (free) phenytoin or penetration into the CNS.

Phenytoin is largely metabolized by the hepatic cytochrome P450 enzyme system; less than 5% is excreted as unchanged drug. Phenytoin exhibits non-linear (Michaelis-Menten) pharmacokinetics. The enzymes which metabolize the drug can become saturated at high serum concentrations, resulting in a capacity-limited metabolism. As a result, small increases in dose can result in large increases in serum concentrations once this saturation point is reached and phenytoin begins to accumulate.

Since it undergoes non-linear elimination, phenytoin does not have a single, true half-life. Half-life varies with serum concentration, with values as high as 500 hours reported in a child following an overdose. After maintenance therapy, phenytoin half-life is approximately 10 to 20 hours in most children.[7]

Rate of elimination appears to be correlated with age, with children under five years of age having a significantly more rapid elimination than older children and adults.[7,8] Neonates may provide the most difficult patient population for titrating phenytoin serum concentrations. Numerous studies have demonstrated the highly variable rate of elimination of phenytoin among neonatal populations, unexplained by dosage formulations or method of administration.[7,9]
Because of its non-linear elimination, routine therapeutic drug monitoring with phenytoin is complex. Many methods, graphic and computer-based, have been developed to help clinicians predict the outcome of changes in dosage on serum concentrations.[10,11] However, they have met with limited clinical success. Most clinicians rely more on gradual dose titration, based on trough serum concentrations once steady-state has been reached (after approximately five to seven days).

Drug Interactions

Phenytoin interacts with many other medications, through several distinct mechanisms. Because it is highly protein bound, phenytoin interacts with other similarly bound drugs. Its reliance on and inhibition of the hepatic cytochrome P450 enzyme system present additional opportunities for drug interactions. The following tables list clinically significant phenytoin drug interactions.[2,12,13]

Table 1. Increased Phenytoin Effect

- allopurinol
- amiodarone
- azole antifungals
- benzodiazepines>
- chloramphenicol
- chlorpheniramine
- cimetidine
- disulfiram
- ethanol
- ibuprofen
- isoniazid
- metronidazole
- omeprazole
- phenacemide
- phenothiazines
- phenylbutazone
- salicylates
- succinimides
- sulfonamides
- sodium valproate

- ibuprofen
- tricyclic antidepressants
- trimethoprim

Table 2. Decreased Phenytoin Effect

- antacids
- antineoplastics
- barbiturates
- carbemazepine
- charcoal
- diazoxide
- enteral feedings
- ethanol
- folic acid
- influenza vaccine
- loxapine
- nitrofurantoin
- pyridoxine
- rifampin
- sucralfate
- theophylline

Table 3. Decreased Effects of Other Drugs

- acetaminophen
- amiodarone
- carbamazepine
- cardiac glycosides
- corticosteroids
- cyclosporine
- dicumarol
- disopyramide
- dopamine
- doxycycline
- estrogens
- furosemide
- haldoperidol
- levodopa
- levonorgestrel
- mebendazole
- methadone

- metyrapone
- mexiletine
- paralytics*
- oral contraceptives
- phenothiazines
- quinidine
- sulfonylureas
- theophylline
- sodium valproate

*** nondepolarizing agents such as pancuronium**

Adverse Effects

Measurement of the success of any therapeutic intervention must include not only its clinical efficacy, but also patient satisfaction with treatment. A recent survey of patients with epilepsy revealed that 49% were dissatisfied with their current regimen due to adverse drug effects.[1] In a recent comparison trial, more children receiving phenytoin withdrew from the study than those receiving carbamazepine or valproate (9% versus 4% each).[6]

The most frequently observed adverse effects associated with phenytoin involve the CNS. As serum concentrations increase above 20 mcg/ml, most patients will exhibit lateral-gaze nystagmus, impaired concentration, and ataxia. At concentrations above 40 mcg/ml, patients become stuporous or comatose. Signs of toxicity are often more subtle if serum concentrations have risen gradually.[2]

Dermatologic and cosmetic effects are common dose (concentration)-related effects of phenytoin use. Approximately 50% of patients will develop gingival hyperplasia, acne, or hirsutism with chronic therapy. Rare dose-related adverse effects include: osteomalacia, hypothyroidism, immunologic disturbances, and peripheral neuropathy. Hypersensitivity reactions are generally expressed as a rash, but can be as severe as Stevens-Johnson syndrome.

Rare idiosyncratic reactions to phenytoin include aplastic anemia and other blood dyscrasias, lupus-like reactions, and hepatotoxicity. Rapid intravenous administration (> 50 mg/min) may result in hypotension, atrial and ventricular conduction depression, ventricular fibrillation, and cardiovascular collapse. Extravasation may result in significant soft tissue injury.[2]

Phenytoin, like most other anticonvulsants, is a known teratogen. Fetal hydantoin syndrome has been recognized since 1976 in infants born to women receiving chronic phenytoin therapy. Features include craniofacial abnormalities, such as a broad nasal bridge, microcephaly, or cleft lip and palate, as well as limb defects ranging from hypoplastic nails to malformed phalanges and dislocated hips. The estimated risk of defects is 10% in offspring of women receiving phenytoin.[14] It has been suggested that the mechanism of

teratogenicity may be linked to accumulation of oxidative metabolites of phenytoin associated with a genetic impairment of epoxide hydrolase.[14,15]
For many families, the most concerning adverse effect of phenytoin is its effect on learning and behavior. Although study methodology and testing limitations make interpretation of the data difficult, phenytoin use has been associated with a reduction in cognitive function. The long-term impact of this effect is not known. In relation to other anticonvulsants, phenytoin appears to be associated with a greater impact than either carbamazepine or sodium valproate, but has less effect than phenobarbital.[16] The American Academy of Pediatrics has recently published guidelines for minimizing the impact of anticonvulsants on cognition, highlighting the need for frequent reevaluation of the patient's progress in school.[17]

Dosing Recommendations

Phenytoin is available as an injectable preparation, chewable tablets, capsules, and a suspension formulation which provide prompt drug release, and capsules which provide an extended release of drug, allowing once or twice daily dosing. Dose conversion is necessary when switching dosage forms. The injection and capsules are phenytoin sodium (containing 92% phenytoin by weight). The suspension and tablets are phenytoin base (100% phenytoin).
Most clinicians are familiar with the Dilantin® brand manufactured by Parke-Davis.[2] Generic formulations of phenytoin are also available; however, past problems with bioequivalence should alert clinicians to monitor patients carefully when switching brands.
Phenytoin therapy is often initiated with the use of a loading dose to achieve target serum concentrations more rapidly. The need for loading and the choice of route (IV versus PO) should be based on the severity and frequency of seizures. If a loading dose is desired, 15-20 mg/kg may be given as a single dose or in two (IV) or three (PO) divided doses .
Maintenance dosage requirements vary with patient age. As described previously, rate of elimination is more rapid in younger children, resulting in the need for larger dosages. In a study of 135 children with epilepsy, Bauer and Blouin[18] found a proportional inverse relationship between age and optimal dose. Patients between the ages of 0.5 to 3 years required an average 9.5 mg/kg/day, while children 4-6 years required 7.5 mg/kg/day, children 7-9 years of age required 7.0 mg/kg/day, and children 10-16 years of age required only 6 mg/kg/day. Recently O'Mara and colleagues[19] documented similar dosing needs in children following acute head injury.
It is essential that the need for compliance be stressed with the patient and his or her family. Lack of adherence to phenytoin therapy is common; studies estimate the rate of noncompliance to be between 15 to 60%.[20] Adolescents are more likely than adults to be noncompliant. Most cite the unwanted cosmetic

side effects associated with phenytoin as the primary reason for discontinuing or reducing their medication intake.

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Pharmacology Literature Review

Drug-induced Methemoglobinemia

Although rare, this adverse effect can result in significant morbidity and mortality. The authors of this review provide a thorough background into the mechanism and clinical manifestations of methemoglobinemia as well as a discussion of medications known to be associated with its development and methods for treatment. Of interest to pediatrics health care providers, the potential for toxicity with local anesthetics, including EMLA® cream, is briefly discussed. Coleman MD, Coleman MA. Drug-induced methaemoglobinaemia: Treatment issues. **Drug Safety 1996;14:394-405**.

Scabies Treatments

This article provides a concise review of options for eliminating scabies. The author weighs the usefulness of preparations by comparing demonstrated efficacy rates and tolerability. Topical permethrin and oral ivermectin (not available in the U.S.) were selected as the best choices due to their high rates of efficacy and limited toxicity. Elgart ML. A risk-benefit assessment of agents used in the treatment of scabies. **Drug Safety 1996;14:386-93.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 7/26/96:

1. Ibutilide (Corvert®) was added to the formulary, restricted to use in the following areas: intensive care units, electrophysiology lab, the Chest Pain Center, and other special procedures areas with appropriate monitoring equipment. This Vaughan

Williams class III antiarrhythmic is indicated for the conversion of atrial fibrillation or flutter. Ibutilide has not been studied in the pediatric population.

2. The class review of the ophthalmic products was completed. A number of new products were added. For further information, contact the Drug Information Center at 924-8034.

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