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Carbamazepine: A Review of its Use in Children with Epilepsy

Carbamazepine was approved for use in adults in the United States in 1974. Its indications were expanded to include children over six years of age in 1978. In 1987, the age restriction was lifted, and carbamazepine gained approval for use in patients of all ages. Since its approval, carbamazepine use has rapidly grown. It is estimated that more than two million patients are treated with carbamazepine in this country alone. It has become one of the cornerstones of anticonvulsant therapy in the pediatric population, where it is used in partial complex, generalized tonic-clonic, mixed seizure disorders, and other partial or generalized seizures.[1,2]

The mechanism of action of carbamazepine is not fully understood. It has been postulated to act by inhibiting nerve impulse transmission through the thalamus, blunting high-frequency, repetitive neuronal firing. This inhibition is likely mediated through a delay in the recovery rate of voltage-dependent neuronal sodium channels.[3]

The efficacy of carbamazepine in children has been well established over the past decade. It appears similar to treatment with phenytoin or valproic acid monotherapy, but results are highly patient-specific.[1,4] In 1996, de Silva and colleagues[4] reported the results of a study of 167 children with partial or generalized seizures who were randomized to one of four monotherapy treatments: phenobarbital, phenytoin, carbamazepine, or valproic acid. Twenty-five percent of the children receiving carbamazepine achieved a 1-year remission, compared to 36% for phenytoin, 26% for valproic acid, and 40% for phenobarbital. The percentage of patients withdrawing from the study due to adverse effects was 4% in both the carbamazepine and valproic acid, compared to 9% in the phenytoin group. The incidence of adverse effects with phenobarbital was high enough to cause the authors to stop enrolling children into that treatment arm.

Pharmacokinetics

Carbamazepine is currently available only in oral dosage formulations in the United States. While absorption from the tablet formulations is slow (over 4 to 8 hours for regular release, 3 to 12 hours for extended-release), the chewable tablet and suspension formulation are absorbed more rapidly (in 2 to 4 hours). Absolute bioavailability cannot be assessed without the availability of an intravenous preparation for comparison, but analysis of urinary drug and metabolite concentrations has suggested nearly complete absorption of the formulations studied.

Bioavailability remains a concern with the use of generic formulations. Using the Tegretol® (Ciba-Geigy) product as a standard, generic formulations have been found to produce significantly different serum concentrations. There are now numerous case reports of both elevated and reduced serum carbamazepine concentrations associated with a change in carbamazepine product.[5] Patients and their families should be counseled to avoid changing brands of carbamazepine unless under the close supervision of a health care provider capable of monitoring for reduced efficacy or toxicity.

Carbamazepine has a large volume of distribution, estimated to be 1 to 2 L/kg, and is approximately 75 to 80% protein bound. Carbamazepine is primarily bound to albumin, and to a lesser extent, alpha-1-glycoprotein. The degree of protein binding has shown tremendous variability in the pharmacokinetic studies performed to date.[2] Protein binding may be decreased in infants, resulting in a greater proportion of free (active) drug.

Serum concentrations of carbamazepine appear to correlate well with therapeutic response. In most patients, concentrations between 4 to 12 mcg/ml result in seizure control without significant dose-related adverse effects. As with all anticonvulsants, clinicians should be aware of the highly patient-specific response to

carbamazepine and tailor therapy to the individual.[2]

Carbamazepine undergoes extensive hepatic metabolism through the cytochrome P450 enzyme system. It exhibits autoinduction, increasing the rate of its own elimination when dosing is initiated or modified. In most patients, autoinduction plateaus after three to four weeks of therapy. In adults, the elimination half-life following a single dose ranges from 11 to 30 hours. With chronic dosing, half-life declines to approximately 5 to 14 hours. Similar values have been reported in children.[1]

Carbamazepine produces a pharmacologically-active metabolite, carbamazepine-10,11-epoxide. In adults, this active metabolite is present in concentrations approximately 10% of the parent compound. Research in children has shown the metabolite to be present in concentrations up to 20% of the parent.[1,2] In addition to patient age, the dose of carbamazepine, dosing interval, formulation, and use of other anticonvulsants may affect the amount of active metabolite produced in children.[6,7] The presence of carbamazepine-10,11-epoxide should be considered in patients exhibiting signs of toxicity with serum carbamazepine concentrations within the therapeutic range.

Drug Interactions

Carbamazepine is involved in a number of drug interactions. The mechanisms for these reactions include alterations in absorption, protein binding, and metabolism. This latter effect results in the most clinically significant interactions, as a result of carbamazepine's metabolism through and stimulation of the cyctochrome P450 enzyme system, specifically the CYP3A4 subgroup.[8]

The following tables list clinically significant interactions with carbamazepine.[2,8,9] Pediatric health care providers should be particularly attune to the interaction between carbamazepine and the macrolide antibiotics. This reaction has resulted in severe cardiotoxicity. In addition to single-agent antibiotics, combination products such as erythromycin-sulfisoxazole (Pediazole®) are contraindicated in patients receiving carbamazepine.

Table 1. Drugs that Increase Carbamazepine Concentrations

Cimetidine	Ketoconazole
Clarithromycin	Loratadine
Danazol	Niacinamide
Diltiazem	Nicatinamide
Erythromycin	Propoxyphene
Fluoxetine	Terfenadine
Fluvoxamine	Valproic Acid
Isoniazid	Verapamil
Itraconazole	

Table 2. Drugs that Decrease Carbamazepine Concentrations

Charcoal	Phenytoin
Cisplatin	Primidone
Doxorubicin	Rifampin
Felbamate	Theophylline
Phenobarbital	Tricyclic Antidepress.

Table 3. Drugs Affected by Carbamazepine

Drug	Effect
Acetaminophen	Increased metabolic rate (↑ risk of toxicity)
Alprazolam	Decreased concentrations
Clonazepam	Decreased concentrations
Clozapine	Decreased concentrations
Cyclosporine	Decreased concentrations
Doxycycline	Decreased concentrations
Ethosuximide	Decreased concentrations
Felbamate	Decreased concentrations
Haloperidol	Decreased concentrations
Lithium	Increased CNS toxicity
Methsuximide	Decreased concentrations
Oral Contraceptives[a]	Decreased efficacy
Pancuronium[b]	Decreased efficacy
Phenytoin	Unpredictable changes
Primidone	Increased concentrations
Theophylline	Unpredictable changes
Tricyclic Antidepressants	Decreased concentrations
Valproic Acid	Decreased concentrations
Vasopressin[c]	Potentiation of effect
Warfarin	Decreased concentrations

[a] patients should be counseled to utilize an alternative birth control method

[b] also seen with other nondepolarizing neuromuscular blocking agents

[c] also seen with desmopressin, lypressin

Adverse Effects

The most common adverse effects associated with carbamazepine use are gastrointestinal and neurologic effects, consisting of nausea, vomiting, drowsiness, dizziness, ataxia, and vertigo. These reactions typically occur upon initiation of therapy or with dosage increases. Most patients respond to a reduction in dose. Gradual changes in dosage often avoids these effects. In some patients, these reactions can be prevented by giving smaller doses on a more frequent interval, avoiding high peak serum carbamazepine concentrations.

Carbamazepine-associated blood dyscrasias range from mild to severe. Mild effects, such as transient leukopenia and thrombocytopenia, occur in up to 10% of patients. Severe carbamazepine-induced agranulocytosis and aplastic anemia have an estimated incidence of 1 in 600,000 patients. Hypersensitivity reactions can range from a mild rash seen in 5% of patients to Stevens-Johnson syndrome. Other adverse reactions include elevated liver function tests, jaundice and hepatitis, pancreatitis, and renal dysfunction. These reactions are not dose-related and may occur at any time during therapy. Although routine monitoring of blood counts and liver function tests are often recommended, the predicative capacity of these tests has not been established.[9]

Following a carbamazepine overdose, signs and symptoms of toxicity in children include dystonic reactions, tremor, ataxia, nystagmus, seizures, impaired consciousness, arrhythmias, alterations in blood pressure, hyponatremia, and respiratory depression. After gastric decontamination, treatment consists of supportive measures.[1,10]

Dosing Recommendations

In most pediatric patients, carbamazepine is initiated at a dosage of 5 to 10 mg/kg/day and increased every 5 to 7 days as necessary. Most children will respond to dosages of 20 to 30 mg/kg/day, divided into two to three doses per day. A maximum daily dosage of 1,000 mg is suggested for children less than 16 years, although therapy should be guided by serum concentration monitoring and patient response. In older children and adults, therapy is typically started with 200 mg given twice daily and titrated to a usual maintenance dosage of 800 to 1,200 mg per day. The dosing interval, from twice to four times daily, is determined by the dosage formulation used.[11]

Carbamazepine is available in 200 mg regular-release tablets, 100, 200, and 400 mg extended-release tablets, 100 mg chewable tablets, and a 100 mg/5 ml suspension.[9] Patients switching from the regular-release to the extended-release product should receive the same **total** daily amount (in mg), divided into two doses. Patients/families should be instructed to shake the suspension well before measuring the dose. Carbamazepine may be given with food to avoid stomach upset. Administration with enteral feedings may delay absorption.

New Developments

Although carbamazepine has developed a prominent role in the treatment of seizures in childhood, it is associated with significant adverse effects and numerous drug interactions. In order to overcome these disadvantages, researchers have modified the structure of the original compound. Oxcarbazepine, a derivative of carbamazepine, is expected to be available soon in the United States.[12] This compound does not rely on oxidative metabolism. As a result, oxcarbazepine appears to have fewer adverse effects and drug interactions than carbamazepine. In the future, it is hoped that products like oxcarbazepine and a parenteral formulation of carbamazepine will be available, expanding the utility of this valuable anticonvulsant for children.

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Pharmacology Literature Review

Cisapride Drug Interactions

Cisapride has become a common therapy in children with gastric motility disorders.

Unfortunately, this drug is associated with a significant number of drug interactions. Of greatest concern are those interactions leading to increased cisapride concentrations and resulting in prolongation of the QT_c interval and cardiac arrhythmias. The authors of this brief review discuss the spectrum of interactions and their clinical significance. Bedford TA, Rowbotham DJ. Cisapride: Drug interactions of clinical significance. **Drugs 1996;15:167-75.**

Evaluating Causality of Adverse Effects

As most clinicians are aware, it is common for medications in Phase I and II clinical trials to be linked with numerous mild side effects, such as headache and nausea, in normal volunteers. In an effort to establish the background incidence of these "side effects," the authors of this study surveyed 130 healthy adult volunteers prior to receiving any test medication. Only 11% of the volunteers tested were free of medical symptoms. The most commonly reported symptoms which might have been mistakenly linked to medication use in a clinical trial were fatigue (65% of patients), headache (25%), and nasal congestion (30%). Meyer FP, Troger U, Rohl F. Adverse nondrug reactions: An update. **Clin Pharmacol Ther 1996;60:347-52.**

New Developments in Anticonvulsants

Several new areas of anticonvulsant research are presented in this brief review. The authors discuss newer anticonvulsants and new dosage formulations of older drugs, as well as changing practice patterns regarding the implementation and duration of therapy. They also address the proposed benefits of "rational" polytherapy versus monotherapy. Sabers A, Gram L. Drug treatment of epilepsy in the 1990s: Achievements and new developments. **Drugs 1996;52:483-93.**

Placebo Response

The authors of this review present an interesting look at the effect of placebo response in clinical trials of medications as well as in clinical practice. The results from actual studies are used as examples to aid in the discussion of the mechanisms and factors influencing placebo effects. Weiner M, Weiner GJ. The kinetics and dynamics of responses to placebo. **Clin Pharmacol Ther 1996;60:247-54.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 10/25/96:

1. Fexofenadine (Allegra®) was added to the formulary. This second-generation H_1-blocker is a derivative of terfenadine (Seldane®), without the parent compound's potential for serious drug interactions. The recommended dosage in adults and children over 12 years of age is 60 mg given twice daily. It has not been studied in younger children.

2. Usage guidelines have been approved for fosphenytoin (Cerebyx®). This water-soluble prodrug of phenytoin is associated with fewer adverse effects than parenteral phenytoin. Fosphenytoin may be used in the ICU setting for medical emergencies where immediate seizure control is required and for the control of seizures in patients with hypotension. In other settings, fosphenytoin is restricted to the control of seizures in patients without IV access, in the emergent control of seizures for patients in areas without cardiac monitoring, for initiating therapy (loading) patients in those areas, and for maintenance therapy in patients with a history of severe local adverse reactions to phenytoin.

3. Insulin lispro (Humalog®) was added to the formulary. This agent is a rapid-acting insulin analog designed to more closely match the action of endogenous insulin than other currently available products.

4. Adverse drug reactions (ADRs) occurring during the previous quarter were reviewed. For more information about the system, contact the Drug Information Center at 924-8034.

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