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Oxcarbazepine Use in Children and Adolescents

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Among the newer antiepileptic drugs (AEDs) released in the United States over the last decade, oxcarbazepine appears to offer some unique advantages. Although it has been on the market in the United States only since January, 2000, it has been available in other countries for more than a decade. With a relatively mild adverse effect profile, few drug interactions, and no serum concentrations to monitor, oxcarbazepine reduces or eliminates many of the concerns associated with its predecessor carbamazepine.[1,2] It is hoped that oxcarbazepine may not only improve seizure control, but also increase compliance rates in children and adolescents with partial seizures.

Mechanism of action

Oxcarbazepine is the 10-keto analog of carbamazepine. The pharmacologic activity of oxcarbazepine is due primarily to its 10-monohydroxymetabolite (MHD). The mechanisms by which oxcarbazepine and MHD act are not fully understood. They are known to block voltage-sensitive sodium channels in the central nervous system (CNS), resulting in stabilization of neural membranes, inhibition of repetitive neuronal firing, and reduced propagation of synaptic impulses. Oxcarbazepine and MHD also appear to increase calcium conductance and modulate calcium channels in the CNS.[2]

Clinical use

Oxcarbazepine is currently recommended as adjunctive treatment or monotherapy for partial seizures in adults and as adjunctive therapy for partial seizures in children from 4 to 16 years of age. There are several case series and clinical trials demonstrating the efficacy of oxcarbazepine in children and adolescents, both as an adjunct and as monotherapy.

In 1997, Guerreiro and colleagues, writing for the International Pediatric Oxcarbazepine/ Phenytoin Trial Group, reported the results of the first clinical trial of oxcarbazepine in children.[3] This multicenter, randomized, double-blind trial compared oxcarbazepine to phenytoin as monotherapy in 193 children with partial or generalized tonic-clonic seizures. Patients ranged in age from 5 to 18 years and had no prior history of maintenance AED use. Treatment consisted of a 8 week titration phase followed by a 48 week maintenance phase, with a primary endpoint of percent seizure-free patients. At the trial end, there was no difference between the groups (61% of oxcarbazepine patients were seizure-free versus 60% of the phenytoin group). The frequency of premature discontinuation due to adverse effects was significantly greater with phenytoin. In addition, both physician and patient assessments were more favorable for oxcarbazepine.

Also that year, Gaily, Granstrom, and Liukkonen published their retrospective review of children treated at the University of Helsinki between 1991 and 1994.[4] All 53 children in this review had been started on oxcarbazepine prior to the age of 7 years. The reason for starting therapy was inadequate seizure control with traditional therapies in 51 patients and carbamazepine allergy in two others; thirty of the patients received concomitant AEDs. Sixty-two percent of the children experienced at least a 50% reduction in seizure frequency. Twenty-three percent became seizure-free. The average effective dose was 47 mg/kg/day (range 21-83 mg/kg/day) for patients receiving only

oxcarbazepine and 53 mg/kg/day (range 21-86 mg/kg/day) in patients on combination therapy. Thirty-three percent of the children experienced at least one adverse effect, typically drowsiness at the start of treatment. At the time of analysis, the mean duration of therapy was 14 months. Eleven patients had been taken off therapy, 8 for lack of response, 2 for adverse effects, and 1 for apparent resolution of seizures.

Three additional studies have confirmed the efficacy of oxcarbazepine as monotherapy for simple, complex, and partial seizures evolving to secondarily generalized seizures in adults and children.[5-7] In 1999, Sachdeo and colleagues conducted the first placebo-controlled trial of oxcarbazepine in 67 previously untreated patients.[5] Patients between the ages of 10 and 69 years were randomized to receive placebo or oxcarbazepine titrated to 1,200 mg/day (600 mg twice daily). Time to first partial seizure, the primary endpoint, was significantly longer in the oxcarbazepine group. Reduction in seizure frequency (percentage decrease from baseline) was also significantly greater in the treatment group. Tolerability was considered no different.

Schachter and coworkers reported similar results in a trial of 102 adolescents and adults.[6] Patients were rapidly titrated with oxcarbazepine, using doses of 1,500 mg on day 1, then 2,400 mg/day thereafter. Length of time to a predetermined seizure threshold (4 partial seizures, 2 tonic-clonic seizures, or status epilepticus) was significantly longer with oxcarbazepine ($p = 0.0001$). Adverse effects were more common in the treatment group (75% versus 57% in controls), but most were rated as mild to moderate in severity. Only three patients in the treatment group withdrew from the study, compared to two patients in the placebo group.

Two studies have evaluated oxcarbazepine as adjunctive therapy in children. Glauser and colleagues, for the Oxcarbazepine Pediatric Study Group, studied 267 children (3 to 17 years of age) refractory to standard AEDs.[8] Patients were randomized to receive either placebo or oxcarbazepine. Children in the treatment group experienced a significantly greater reduction in seizure frequency. Forty-one percent of the oxcarbazepine patients had at least a 50% decrease in seizure frequency, compared to 22% of the controls. Oxcarbazepine doses ranged from 6 to 51 mg/kg/day, with a median of 31.4 mg/kg/day. Adverse effects were common in both groups, occurring in 91% of the treatment group versus 82% of controls. The majority of these reactions were mild in severity and did not result in withdrawal from the study.

Bares and colleagues found similar results in a trial comparing oxcarbazepine to placebo as adjunctive therapy in 694 adolescents and adults.[9] In this 28 week dose-ranging trial, oxcarbazepine was found to reduce seizure frequency by 26% at doses of 600 mg/day, 40% at 1,200 mg/day, and 50% at 2,400 mg/day. These values were compared to an 8% reduction in patients receiving placebo. The frequency of adverse effects was also found to be dose-dependent, with 84% of patients receiving a dose of 600 mg/day experiencing an adverse effect compared to 98% of patients given 2,400 mg/day. The authors suggest that a slow titration to the lowest effective dose is preferable for minimizing adverse effects.

Pharmacokinetics

Oxcarbazepine is well absorbed after oral administration and is rapidly metabolized to MHD. In adults, average time to maximum serum concentrations is 4.5 hours. Bioavailability is not affected by the presence of food. MHD is approximately 40% protein bound, predominately to albumin. The average volume of distribution of MHD in adults is 49 L.

The elimination half-life of the parent compound is approximately 2 hours in adults, while the MHD metabolite has an average half-life of 9 hours, allowing for twice daily dosing. Unlike carbamazepine, oxcarbazepine does not undergo autoinduction. MHD is further metabolized in the liver by conjugation with glucuronic acid. Approximately 4% of the dose is oxidized to an inactive 10,11-dihydroxy metabolite. MHD and these other metabolites are then excreted by the kidneys. Patients with severe renal impairment (ie, creatinine clearance < 30 ml/min) have been shown to have prolonged elimination of MHD and require dosage adjustment.[2]

The pharmacokinetics of oxcarbazepine have also been studied in children. In a study of 31 patients between the ages of 2 and 13 years, those less than 6 years of age had an oxcarbazepine area under the curve 30 to 40% lower than older children, indicating a more rapid elimination in younger patients. Older children had an elimination pattern similar to adults.[10]

Drug interactions

One of the advantages of oxcarbazepine is its relative lack of influence on concomitant therapies, including other AEDs. When given in combination, oxcarbazepine has minimal effect on the serum concentrations of these agents, but

may be altered by their ability to induce hepatic enzymes (Table 1).[2] As with any drug interaction, individual response may vary. Serum concentrations of other AEDs should be closely monitored when oxcarbazepine is added.

Table 1. Oxcarbazepine interactions with AEDs

Other AED	Effect on other AED	Effect on oxcarbazepine or MHD
carbamazepine	none	40% decrease
phenobarbital	14% increase	25% decrease
phenytoin	none*	30% decrease
valproic acid	none	18% decrease

* at doses > 1,200 mg/day, oxcarbazepine has been shown to increase phenytoin concentrations up to 40%

While it has little effect on other AEDs, oxcarbazepine can have a significant effect on the elimination of other drugs, through its ability to inhibit CYP2C19 and induce CYP3A4/5. One of the most important interactions is between oxcarbazepine and oral contraceptives. Oxcarbazepine may reduce serum concentrations of ethinyl estradiol and levonorgestrel by as much as 30 to 50%, rendering them less protective. Female patients should be advised to use an additional or alternative form of contraception.[2]

Oxcarbazepine may also interact with dihydropyridine calcium antagonists through its effects on CYP3A4/5. It has been shown to reduce concentrations of felodipine as much as 28% after repeated dosing. Verpamil has been shown to produce a 20% reduction in MHD concentrations, although the clinical significance of this interaction is not established.[2]

Adverse effects

Oxcarbazepine is generally well tolerated. The most commonly reported adverse effects in clinical trials and post-marketing surveillance studies of adults have been dizziness and difficulties with coordination (22-28%), headache (13-31%), diplopia or blurred vision (4-17%), fatigue (13%), nausea, vomiting, or abdominal pain (4-33%), ataxia and gait disturbances (5-13%), constipation (4-5%), and tremor (4-6%). In the pediatric trial by Glauser, results were similar.[8] The most frequently reported adverse effects were nausea, vomiting, and abdominal pain (9-36%), headache or somnolence (32-35%), dizziness (29%), diplopia or vision abnormalities (14-17%), ataxia (14%), nystagmus (10%), and abnormal gait (10%).

Hypersensitivity reactions with oxcarbazepine are rare, occurring less frequently than with carbamazepine. There is a potential for cross-sensitivity between the two drugs. Approximately 25 to 30% of patients who have had hypersensitivity reactions to carbamazepine will also experience hypersensitivity with oxcarbazepine.[2]

Hyponatremia is another rare adverse effect associated with oxcarbazepine use. In clinical trials, approximately 2.5% of patients experienced a serum sodium less than 125 mmol/L within 3 months of starting therapy. Borusiak and colleagues reported 9 cases of hyponatremia and 4 cases of hypochloremia in 48 children treated with oxcarbazepine at their institution over a 4 year period.[11] The authors found no relationship between the development of hyponatremia and dose or serum MHD concentrations. In most patients, hyponatremia is transient and levels return to normal with conservative management, such as fluid restriction or dose reduction. In some cases, discontinuation of oxcarbazepine has been necessary.

Both oxcarbazepine and MHD are known to be teratogenic.[2] All female patients of child-bearing age should be counseled regarding the risks of this therapy. As mentioned previously, these patients should also be warned of the decreased effectiveness of standard oral contraceptives with oxcarbazepine use.

Dosing recommendations

In adults, oxcarbazepine is typically started at a dose of 300 mg twice daily. The dose may be increased at three day intervals in patients not receiving other anticonvulsants. In patients given oxcarbazepine as an adjunctive therapy, dose titration should proceed more slowly, with changes made at weekly intervals. In patients converting to monotherapy with oxcarbazepine, the other anticonvulsants should be tapered off slowly, over 3 to 6 weeks, while the oxcarbazepine dose is titrated upwards. The usual maintenance dose for oxcarbazepine in adults is 600 to 2,400 mg/day. Although some patients in clinical trials required up to 2,400 mg/day to achieve adequate seizure control, many were unable to tolerate the adverse CNS effects at this dose.[2,9]

In children, oxcarbazepine should be initiated at a dose of 8 to 10 mg/kg/day, divided into two doses. As in adults, dosage titration should be done slowly, over a 2 week period. The median maintenance dose in children, based on the Glauser study,[8] was 31 mg/kg/day (range 6 to 51 mg/kg/day). The manufacturer also provides the

following target daily maintenance doses for pediatric patients: 900 mg/day for children 20 to 29 kg, 1,200 mg/day in patients 29.1 to 39 kg, and 1,800 mg/day in patients > 39 kg, although many patients appear to respond at lower doses. Additional dose-ranging studies are needed in younger children to evaluate the impact of more rapid oxcarbazepine clearance in this group.

Oxcarbazepine dosing should be initiated at half the usual dose in patients with severe renal dysfunction and increased slowly until optimal response is achieved. No dosing adjustments are required for hepatic dysfunction.[2]

Availability

Oxcarbazepine is marketed as Trileptal® by Novartis. It is available in 150, 300, and 600 mg scored tablets and a 60 mg/ml fruit-flavored suspension. The suspension comes in a 250 ml bottle. A 10 ml oral dosing syringe and a press-in adapter for the syringe are provided by the manufacturer with each bottle. Both tablets and suspension should be stored at room temperature. The suspension must be used within 7 weeks of first opening the container.[2]

Summary

Oxcarbazepine offers a number of advantages compared to older AEDs. It is generally well tolerated, has few drug interactions, and does not require serum concentration monitoring. As monotherapy or as an addition to other AEDs, oxcarbazepine has been shown to reduce seizure frequency in children and adults. While more research is needed on its potential as single agent therapy in children, oxcarbazepine appears to have a definite place in the management of partial seizures in childhood.

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Pharmacology Literature Review

Cognitive and behavior effects of topiramate

This article focuses on an important aspect of managing patients on topiramate, its adverse effect on learning and behavior. The authors review the literature published to date on these effects, provide tools for patient evaluation, and make recommendations for further study. This is a very useful article for clinicians caring for patients on topiramate. Nagel BJ, Brewer VR, Phelps SJ. Cognitive and behavioral side effects associated with topiramate. **J Pediatr Pharmacol Ther 2001;6:258-70.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 10/26/01:

1. Galantamine (Reminyl®) was added to the Formulary for the treatment of mild to moderate dementia of Alzheimer's type. Rivastigmine was deleted.
2. A combination product containing abacavir, lamivudine, and zidovudine (Trizivir®) was added for patients with HIV infection.
3. Nesiritide (Natrecor®), recombinant human B-type natriuretic peptide, was added for patients with acutely decompensated CHF.
4. Bivalirudin (Angiomax®), a synthetic thrombin inhibitor modeled after hirudin, was added for use in patients undergoing percutaneous transluminal coronary angioplasty.
5. Zanamivir (Relenza®), a neuraminidase inhibitor for the treatment of influenza, was removed from the Formulary due to lack of use.
6. Temozolomide (Temodar®) and the hepatitis A/hepatitis B combination vaccine (Twinrix®) were rejected.

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