OXCARBAZEPINE (TRILEPTAL®)

Oxcarbazepine (Trileptal®), a 10-keto analogue of carbamazepine, is an antiepileptic drug indicated for the treatment of partial seizures with or without secondary generalization. The FDA granted licensing approval in the United States for oxcarbazepine on January 14, 2000. Oxcarbazepine is indicated for use as monotherapy or as an adjunct to combination therapy for partial seizures in adults and as an adjunctive therapy in children, ages 4-16.

Clinical Pharmacology

Oxcarbazepine is structurally similar to carbamazepine and has an identical anticonvulsant profile but is better tolerated. Oxcarbazepine does not have an epoxide metabolite, like carbamazepine. The epoxide metabolite is thought to be the source of considerable neurotoxicity in overdoses with carbamazepine. The parent compound, oxcarbazepine, and its metabolite 10-monohydroxy (MHD) are active. The exact mechanism of action of both compounds is unknown. In vitro studies indicate that they possibly block voltage-sensitive sodium channels, and thereby stabilize hyperexcitable neuronal membranes and inhibit repetitive firing and impulse propagation. There is also evidence that potassium conductance and high-voltage calcium channels may both be affected by oxcarbazepine.

Pharmacokinetics

Oxcarbazepine is available as a 150, 300, and 600mg scored tablet, that can be crushed. Oxcarbazepine is readily absorbed from the gastrointestinal tract. Food does not appear to alter the rate or extent of absorption; bioavailability is >90%. When oxcarbazepine is absorbed, it is immediately reduced to its main active metabolite, MHD. MHD is 40% plasma protein-bound and has an apparent volume of distribution of 49 liters. Peak serum levels of MHD are reached in 4 to 6 hours with an elimination half-life of 8 to 10 hours. Less than 1% of the parent compound is renally excreted. MHD is metabolized in the liver further by secondary glucuronidation to inactive conjugated products. Clearance in children older than 8 years approaches that of adults. MHD easily crosses the blood brain barrier and placental transfer is thought to be great.

Blood oxcarbazepine concentrations of 8-20 mg/L (20-200 umol/L) are in the therapeutic range, although they are not necessarily available for use in the management of patients either therapeutically or after an overdose.

Dosage and Administration

Oxcarbazepines indicated for use as monotherapy or as adjunctive therapy with other antiepileptic drugs (AEDs).

Monotherapy:

A starting dose of 600mg/day given in two divided doses is recommended for adults. It is suggested that the dose be increased, if clinically indicated, by 300 mg/day every third day or 600 mg/day at weekly intervals. A final dose of 1200-2400mg/day has been shown to be effective as monotherapy in adults not previously treated with AEDs. A dose of 2400 mg/day has been shown to be effective in patients who convert to monotherapy from other AEDs. In one study, 88% of the patients switched to oxcarbazepine from carbamazepine experienced improvement in their seizure control.

Adjunctive Therapy:

In adjunctive therapy in children, oxcarbazepine should be initiated at a dose of 8-10 mg/kg not exceed 600 mg/day divided into twice daily doses of 4-5 mg/kg/dose. Dosing in pediatrics is based on weight. Patients with a weight of 20-29 kg, 30-39 kg or greater than 39 kg, should be titrated as clinically indicated to a target dose of 900 mg/day, 1200 mg/day or 1800 mg/day respectively over two weeks (target dose of 15-30 mg/kg/day) over a two week schedule. In children less than 2 years of age, oxcarbazepine has not been studied.

In patients with renal impairment who have a creatine clearance less than 30ml/min, the initial starting dose of Trileptal® should be reduced by one-half. In patients with mild to moderate hepatic impairment, dose adjustments are not recommended. Oxcarbazepine is classified by the FDA as a Category C drug of unknown risk when used by pregnant women.

Oxcarbazepine and its MHD metabolite are both excreted in breast milk with a milk-to-plasma concentration of 0.5. Thus a decision must be made by lactating women who are on the drug either to stop taking the drug while nursing or to stop nursing.

Drug Interactions

Oxcarbazepine can increase blood phenytoin concentrations by up to 40% and phenobarbital levels by 14%. Patients on oxcarbazepine should use caution when consuming alcohol, as its sedative and neurologic effects may be magnified. It is not known to affect carbamazepine or valproic acid levels. Oxcarbazepine is readily converted to an
active metabolite MHD; this reaction is not dependent on the CYP-450 enzyme system. Although oxcarbazepine does directly inhibit CYP-450 isoenzyme CYP2C19 and induce CYP3A4/5, clinical symptoms related to the metabolism of other drugs have not been observed. Caution should be used with concurrent drugs which are metabolized by these pathways due to induction and inhibition of CYP-450 isoenzymes. For example, oxcarbazepine may decrease the effectiveness of contraceptives. Oxcarbazepine does not induce or inhibit its own metabolism. 3

Clinical Toxicology

Oxcarbazepine has a lower incidence of side-effects than carbamazepine and, causing less hepatic auto-induction, is not known to provoke hepatotoxicity. The most common adverse reactions associated with oxcarbazepine use were: dizziness, somnolence, headache, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, abdominal pain, tremor, dyspnea and abnormal gait. 4.5.9 There is a 25-30% incidence of cross-reactivity in patients who have developed an allergic rash to carbamazepine. A less common adverse effect found in 2.4% of patients was hyponatremia (Na<125mmol/L) and hypochloremia. 1.6

Symptoms seen after an acute oxcarbazepine poisoning include neurotoxicity with lethargy, slurred speech, sedation, and coma. Since experience with acute poisoning is limited, the full range of its toxicity is unknown. Likewise its toxic effects of sedation may be exaggerated by the concomitant overdose with other psychotropic drugs or alcohol.

Over Dose Management

The international product information published in 1996 by the manufacturer states that patients who take an overdose should be treated symptomatically.

The removal of the drug by gastric lavage and/or activated charcoal is recommended. 1,2 Ipecac is contraindicated in oxcarbazepine overdose, since the sedating effects of the drug may pose a risk of vomiting-related aspiration. The efficacy of multiple doses of charcoal is unclear. Overdosed patients should be closely monitored with frequent vital signs and frequent checks of their neurologic and respiratory status. Hospital admission is advisable depending on the circumstances and dose. There is little data available on the efficacy of hemodialysis or hemoperfusion in the treatment of the poisoned patient.

Conclusion

Oxcarbazepine is being used in about 54 countries including the United States. 8 Case report and clinical trials illustrate the ability for oxcarbazepine to cause hyponatremia. 9 Most patients were asymptomatic and only required monitoring of sodium levels. The manufacturer does offer a warning stating the serum sodium level should be monitored for patients during maintenance treatment with oxcarbazepine, particularly if patients are receiving other medications known to decrease serum sodium levels or if symptoms of hyponatremia develop. 1 Case reports of large ingestions up to 24 grams have been reported and all patients survived with only symptomatic treatment. 1 Oxcarbazepine does appear to be a reasonable choice for the treatment of partial seizures with or without secondary generalization.

Robert A. Lee
Pharm. D. Candidate
Massachusetts College of Pharmacy and Health Sciences
Boston, MA

5. Sachdeo R: Safety and Efficacy of 1200 mg/day of oxcarbazepine monotherapy Vs. placebo in untreated patients with recent-onset partial seizures. The American Academy of Neurology 1999 annual meeting.