New Drug Review: Clobazam (Onfi®) - A "new" anticonvulsant option

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ABSTRACT

Clobazam was approved by the Food and Drug Administration (FDA) in October of 2011. This article reviews clinically significant aspects of this new drug including: the FDA-approved indications, mechanism of action, administration, drug interactions, adverse effects, clinical trial evidence, innovative properties and place in therapy.

KEYWORDS

Clobazam, Onfi, anticonvulsant

The attending neurologist on your unit has a six-year-old patient who continues to suffer from myoclonic seizures due to his Lennox-Gastaut syndrome, despite treatment with valproic acid. His mother recently heard about a newer anticonvulsant, clobazam. She wonders if it is available on the formulary and wants to know more about it.

WHAT ARE THE FDA-APPROVED INDICATIONS FOR CLOBAZAM?

Clobazam (Onfi®), approved October 2011, is indicated for the adjunctive treatment of Lennox-Gastaut syndrome (LGS) in adults and children 2 years of age and older.[1] It has shown clinical efficacy in two multi-centered controlled studies and has been granted orphan drug status. It is considered a controlled medication in class IV (C-IV), similar to the other available benzodiazepines (BZDs).

WHAT IS THE MECHANISM OF ACTION OF CLOBAZAM?

Clobazam is considered a 1, 5 benzodiazepine-derivative anticonvulsant. It displays selective binding affinity for the ω_2 site of the $GABA_a$ receptor, where it has agonistic properties and exerts its anticonvulsant effects.[2] Its decreased binding affinity to the ω_1 site of the $GABA_a$ receptor explains how clobazam is less sedating than other BZDs (i.e. diazepam, clonazepam).[3,4]

HOW IS CLOBAZAM DOSED AND HOW SHOULD IT BE ADMINISTERED?

Initial dosing for clobazam is weight based and should be administered in two divided doses in patients prescribed greater than 5 mg daily. It is recommended that patients weighing 30 kg or less should be started on 5 mg clobazam, increasing to 20 mg daily as tolerated. Patients weighing greater than 30 kg should be started on 10 mg clobazam, increasing to 40 mg daily. Dosage adjustments are needed in geriatric patients, poor metabolizers of CYP2C19, and in patients with hepatic impairment. On discontinuation, the clobazam dose should be tapered gradually by reducing the dose by 5 to 10 mg per day each week until taper is completed. Clobazam can either be given whole or crushed and mixed in applesauce.[5]

ARE THERE ANY CLINICALLY SIGNIFICANT DRUG INTERACTIONS WITH CLOBAZAM?

As clobazam is a weak inducer of CYP3A4, the effectiveness of hormonal birth control pills may be diminished when co-administered with clobazam. The manufacturer recommends additional non-hormonal contraception when clobazam is used with hormonal birth control. Additionally, alcohol ingestion increases the concentration of clobazam by ~50%; thus, patients should be counseled to avoid alcohol with use. Inhibitors of CYP2C19 may cause increased exposure to clobazam.[5]

WHAT ADVERSE EFFECTS SHOULD I DISCUSS WITH MY PATIENTS?

Typical BZD adverse effects should be expected with clobazam, but may be less problematic in some patients.[3,4] Somnolence/sedation, drooling, constipation, cough, urinary tract infection, aggression, insomnia, dysarthria, and fatigue were adverse reactions occurring in more than 5% of patients and more frequently than placebo in clinical trials.[5]

HOW DID CLOBAZAM DO IN CLINICAL TRIALS?

Though clobazam has been available in countries outside of the United States for decades, two recent double-blinded, placebo controlled trials are what garnered FDA approval. Although the trials were small, Lennox-Gastaut Syndrome affects less than two hundred thousand people and was granted an orphan drug designation by the FDA. A total of 306 patients were enrolled in the studies, with ages ranging from 2-54 years. Clobazam was adjunctive therapy, added to treatment with valproate, lamotrigine, levetiracetam, or topiramate. The primary efficacy measure was the percentage reduction in weekly drop seizures (which could include tonic, atonic, or myoclonic). Each dose of clobazam statistically significantly decreased the number of drop seizures ($p<0.01$-0.05).[6,7]

WHAT IS INNOVATIVE ABOUT THIS NEW ANTICONVULSANT?

Clobazam is the only available 1, 5 BZD. Unlike the 1, 4 BZDs, clobazam is thought to be advantageous due to a rapid onset of action, broad spectrum of activity, and long half-life. However, direct comparisons of 1, 5 versus 1, 4 BZDs are needed to support these claims in patients with LGS.[8]

WHAT PLACE DOES CLOBAZAM HAVE IN THE TREATMENT OF LENNOX-GASTAUT SYNDROME?

LGS is a debilitating form of seizure disorder and often refractory to treatment. While clobazam's mechanism of action is not unique, it may have an advantage over other BZDs in terms of its side effect profile, particularly its reduced sedating properties. Further studies are needed to evaluate clobazam's role in the treatment of other seizures types and anxiety disorders.

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