ISSN: 2456-3927

NeuroPharmac Journal

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https://doi.org/10.37881/1.415

Jan-April 2019, Volume 4, Issue 1

www. neuropharmac.com

NeuroPharmac Journal

ISSN:2456-3927

Journal homepage: www.neuropharmac.com

Review Article

Stiripentol: New approved drug for the Dravet syndrome: Pharmacotherapeutics review

Aslam Pathan, PhD, MANF

Department of Pharmacology and Therapeutics, College of Medicine at Shaqra, Shaqra University, Saudi Arabia

https://doi.org/10.37881/1.415 https://orcid.org/0000-0002-6569-2306

ABSTRACT

Dravet syndrome (DS) is a severe developmental and epileptic encephalopathy characterized by the onset of prolonged febrile and afebrile seizures in infancy, and evolving to drug-resistant epilepsy with accompanying cognitive, behavioral, and motor impairment. FDA officials approved Stiripentol on 20th August 2018 for the Dravet syndrome. This review article will provide brief pharmacotherapeutics review of Stiripentol which will helpful to the neurologist and healthcare workers.

INTRODUCTION

The U.S. Food and Drug Administration in June 2018 approved use of Cannabidiol oral solution for the treatment of seizures associated with two rare and severe forms of epilepsy, Lennox-Gastaut syndrome, and Dravet syndrome, in patients two years of age and older. It is also the first FDA approval of a drug for the treatment of patients with Dravet syndrome.[1,2] Children with Dravet syndrome typically face a life dealing with developmental disability, motor impairment, and often intractable epilepsy.[3] Antiepileptic drugs (AEDs) are only partially effective, and treatments such as ketogenic diets and vagus nerve stimulation are frequently tried to improve quality of life.[4,5] Stiripentol is an allosteric modulator of the GABA-A receptor, first demonstrated as effective in animal models in the late 1970s and then tried in humans in the early 1980s.[6] As often happens, initial trials in partial epilepsy ensued, but in 2000, it was first reported by Chiron and colleagues as helpful for Dravet syndrome.[7] Stiripentol, however, also is a potent cytochrome P450 inhibitor, which decreases the metabolism, hence raising the level of drugs such as clobazam.[8,9]

Stiripentol (Diacomit)

Dosage form and Strengths:

Capsule for oral use: 250 mg or 500 mg, Powder for oral Suspension: 250 mg or 500 mg

The FDA granted approval of Stiripentol to Biocodex.

Indications and Usage:

It is indicated for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam. There are no clinical data to support the use of Stiripentol as monotherapy in Dravet syndrome.[10]

Dosage and Administration:

The recommended oral dosage of Stiripentol is 50 mg/kg/day, administered in 2 or 3 divided doses (i.e., 16.67 mg/kg three times daily or 25 mg/kg twice daily). If the exact dosage is not achievable given the available strengths, round to the nearest possible dosage, which is usually within 50 mg to 150 mg of the recommended 50 mg/kg/day. A combination of the two Stiripentol strengths can be used to achieve this dosage. The maximum recommended total dosage is 3,000 mg/day. As is advisable for most antiepileptic drugs, if Stiripentol treatment is discontinued, the drug should be withdrawn gradually to minimize the risk of increased seizure frequency and status epilepticus. Stiripentol capsules must be swallowed whole with a glass of water during a meal. Capsules should not be broken or opened.[10]

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Stiripentol Powder for Oral Suspension should be mixed in a glass of water (100 mL) and should be taken immediately after mixing during a meal. To be sure there is no medicine left in the glass, add a small amount of water (25 mL) to the drinking cup and drink all of the mixture.[10]

Missed dose:

A missed dose should be taken as soon as possible. If it is almost time for the next dose, the missed dose should not be taken. Instead, the next scheduled dose should be taken. Doses should not be doubled.[10]

Warnings and Precautions:

a. Somnolence:

Stiripentol can cause somnolence. In controlled studies in patients with Dravet syndrome, the incidence of somnolence was 67% in Stiripentol-treated patients, compared to 23% in patients on placebo. All patients in both groups were on concomitant clobazam, which is also known to cause somnolence. Co-administration of Stiripentol with clobazam results in increased levels of clobazam and its active metabolite. Other central nervous system CNS depressants, including alcohol, could potentiate the somnolence effect of Stiripentol. Prescribers should monitor patients for somnolence. If somnolence occurs during co-administration with clobazam, consider an initial reduction of clobazam by 25%. If somnolence persists, further clobazam reduction by an additional 25% should be considered, as should adjustment of the dosage of other concomitant anticonvulsant drugs with sedating properties. Prescribers should caution patients against engaging in hazardous activities requiring mental alertness, such as operating dangerous machinery or motor vehicles, until the effect of Stiripentol on mental alertness is known.[10]

b. Decreased Appetite and Decreased Weight:

Stiripentol can cause decreases in appetite and weight. In controlled studies in patients with Dravet syndrome, the incidence of decreased appetite was 46% in Stiripentol-treated patients, compared to 10% in patients on placebo. The incidence of decreased weight was 27% in Stiripentol-treated patients, compared to 6% in patients on placebo. Nausea and vomiting also occurred more frequently in Stiripentol-treated patients. Given the frequency of these adverse reactions, the growth of pediatric patients treated with Stiripentol should be carefully monitored. In some cases, decreasing the dose of concomitant valproate by 30% per week can reduce the decrease in appetite and weight.[10]

c. Neutropenia and Thrombocytopenia:

Stiripentol can cause a significant decline in neutrophil count. In controlled studies in patients with Dravet syndrome, there were 31 patients treated with Stiripentol who had both a baseline and end-of-study neutrophil count obtained. A decrease in neutrophil count from normal at baseline to less than 1500 cells/mm3 during the trial was observed in 13% of these Stiripentol treated patients, but not in any placebo-treated patients. Stiripentol can cause a significant decline in platelet count. In controlled studies in patients with Dravet syndrome, there were 31 patients treated with Stiripentol who had both a baseline and end-of-study platelet count. A decrease in platelet count from normal at baseline to less than 150,000/µL during the trial was observed in 13% of these Stiripentol-treated patients, but not in any placebo-treated patients. Hematologic testing should be obtained prior to starting treatment with Stiripentol, and then every 6 months.[10]

d. Withdrawal Symptoms:

As with most antiepileptic drugs, Stiripentol should generally be withdrawn gradually to minimize the risk of increased seizure frequency and status epilepticus. In situations where rapid withdrawal of Stiripentol is required (e.g., in the setting of a serious adverse reaction), appropriate monitoring is recommended.[10]

e. Risks in Patients with Phenylketonuria:

Phenylalanine can be harmful to patients with phenylketonuria (PKU). Stiripentol Powder for Suspension contains phenylalanine, a component of aspartame. Each 250 mg packet contains 1.40 mg

NeuroPharmac Journal
ISSN:2456-3927
Journal homepage: www.neuropharmac.com
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phenylalanine; each 500 mg packet contains 2.80 mg phenylalanine. Before prescribing Stiripentol Powder for Suspension to a patient with PKU, consider the combined daily amount of phenylalanine from all sources, including Stiripentol Powder for Suspension. Stiripentol Capsules do not contain phenylalanine.[10]

f. Suicidal Behavior and Ideation:

AEDs, including Stiripentol, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.[10]

Drug Interactions:

Clobazam:

Co-administration of Stiripentol (which inhibits CYP 3A4 and 2C19) with clobazam results in increased plasma concentrations of clobazam (a substrate of CYP3A4) and norclobazam, the active metabolite of clobazam (a substrate of CYP2C19). This may increase the risk of clobazam-related adverse reactions. Consider a reduction in dosage of clobazam if adverse reactions are experienced when co-administered with Stiripentol.[10]

Effect of Other Drugs:

Induction-based interactions leading to decreases in Stiripentol concentrations are possible when co-administered with a potent CYP1A2, CYP3A4, or CYP2C19 inducer, such as rifampin, phenytoin, phenobarbital and carbamazepine, as these enzymes all metabolize Stiripentol. Concomitant use of strong inducers with Stiripentol should be avoided, or dosage adjustments should be made.[10]

CNS Depressants and Alcohol:

Concomitant use of Stiripentol with other CNS depressants, including alcohol, may increase the risk of sedation and somnolence.[10]

Use in specific populations:

Pregnancy:

Administration of Stiripentol to pregnant animals produced evidence of developmental toxicity, including increased incidences of fetal malformations, increased embryo-fetal and pup mortality, and decreased embryo-fetal and pup growth, at maternal doses lower than the recommended clinical dose. The background risk of major birth defects and miscarriage in Dravet syndrome is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.[10]

Lactation:

There are no data on the presence of Stiripentol in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Stiripentol and any potential adverse effects on the breastfed infant from Stiripentol or from the underlying maternal condition.[10]

Pediatric Use:

Safety and effectiveness in pediatric patients below the age of 2 years have not been established.[10]

Geriatric Use:

Clinical studies of Stiripentol in Dravet syndrome did not include patients ≥65 years of age to determine whether they respond differently from younger patients. The possibility of age associated hepatic and renal function abnormalities should be considered when using Stiripentol in patients ≥65 years of age.[10]

Overdosage:

There are no data concerning overdose in humans. In mice treated with high doses of Stiripentol (600 to 1800 mg/kg i.p.), decreased motor activity and decreased respiration were observed.[10]

Clinical Pharmacology:

Mechanism of Action:

The mechanism by which Stiripentol exerts its anticonvulsant effect in humans is unknown. Possible mechanisms of action include direct effects mediated through the gamma-aminobutyric acid (GABA)A receptor and indirect effects involving inhibition of

cytochrome P450 activity with resulting increase in blood levels of clobazam and its active metabolite.

Pharmacokinetics:

The following pharmacokinetic properties of Stiripentol have been found in studies in adult healthy volunteers and adult patients. Systemic exposure of Stiripentol increases in a greater than dose proportional manner from 500 mg to 2000 mg.

Absorption:

The median time to Stiripentol peak plasma concentration is 2 to 3 hours.

Distribution:

Protein binding of Stiripentol is 99%.

Elimination:

The elimination half-life of Stiripentol ranges from 4.5 to 13 hours, increasing with doses of 500 mg, 1000 mg and 2000 mg.

Metabolism:

On the basis of in vitro studies, the main liver cytochrome P450 (CYP) isoenzymes involved in metabolism are considered to be CYP1A2, CYP2C19, and CYP3A4.

Pediatric Patients:

In a study of children (median age 7.3 years) with Dravet syndrome treated with Stiripentol, valproate, and clobazam, the apparent clearance and volume of distribution of Stiripentol were related to body weight. Elimination half-life increased from 8.5 hr (for 10 kg) to 23.5 hr (for 60 kg).[10]

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NeuroPharmac Journal

ISSN:2456-3927

Journal homepage: www.neuropharmac.com

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Cite this article: Pathan A. Stiripentol: New approved drug for the Dravet syndrome: Pharmacotherapeutics review. NeuroPharmac J. 2019; 4(1): 94-98. DOI: 10.37881/1.415