NEW DRUGS

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Stiripentol

Approved indication: Dravet syndrome

Diacomit (Emerge Health)
250 mg and 500 mg capsules
250 mg and 500 mg powder for oral suspension

Dravet syndrome is a severe myoclonic epilepsy in infancy. It usually emerges in the first year of life. The seizures are difficult to control and the infants develop intellectual disability. Stiripentol has been approved as an adjunctive treatment for infants with generalised tonic-clonic and clonic seizures which are not controlled by valproate and a benzodiazepine.

Stiripentol is an aromatic alcohol which is unrelated to the structure of other antiepileptic drugs. It increases activity in the GABAergic system, but it also interacts with anticonvulsant drugs. Stiripentol inhibits cytochrome P450 (CYP) 1A2, 2C8, 2C9, 2C19, 2D6 and 3A4. It therefore increases the plasma concentrations of antiepileptic drugs including carbamazepine, clobazam, phenytoin and valproate. There are many other potential pharmacokinetic interactions, including with benzodiazepines.

Stiripentol is well absorbed, but there is extensive first-pass metabolism. While they are not the main method of metabolism, CYP1A2, 2C19 and 3A4 are involved. The clearance of stiripentol decreases after several doses probably because it inhibits its own metabolism. A steady state is established after 2–5 days. Most of the metabolites are excreted in the urine. The elimination half-life is 4.5–13 hours.

As Dravet syndrome is rare, the trials of stiripentol have involved small numbers of patients. The two main trials of efficacy involved a total of 64 patients. In these double-blind trials stiripentol was added to optimised treatment with clobazam and valproate. The recommended daily dose was 50 mg/kg. An infant was considered to have responded to treatment if there was at least a 50% decrease in the frequency of seizures.[1,2]

One of these trials was in France. It randomised 21 children (average age 9.4 years) to stiripentol and 20 to placebo. In the first two months of the trial 15 (71%) in the stiripentol group responded compared with one (5%) in the placebo group. Nine of the children taking stiripentol became seizure free.[1]

The other trial was in Italy and involved 23 children with an average age of 9.1 years. After two months, eight children responded to stiripentol (66.7%). Only one (9.1%) in the placebo group responded. Three of the children taking stiripentol became free of seizures.[2]

During the trials there were more adverse events in the children taking stiripentol, compared to placebo. More frequent effects included drowsiness, agitation, irritability, hypotonia, nausea and vomiting. There was also loss of appetite and weight loss. Elevation of gamma-glutamyltransferase has been reported so liver function should be checked every six months, as should a full blood count because of the risk of neutropenia.

While it is difficult to know if the effect is due to its interaction with clobazam and valproate, stiripentol reduced seizures more than a placebo did. When starting stiripentol it should be given two or three times a day with the dose being gradually increased. The doses of clobazam and valproate may need to be reduced if adverse effects emerge. Long-term efficacy and safety data are limited. For example, does the weight loss, which was seen in 24% of the children taking stiripentol, have a long-term effect on growth?

T manufacturer provided useful information

REFERENCES

1. Chiron C, Marchand MC, Tran A, Rey E, d'Athis P, Vincent J, et al; STICLO study group. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. Lancet 2000;356:1638-42. https://doi.org/10.1016/S0140-6736(00)03157-3
2. Guerrini R, Tonnelier S, d'Athis P, Rey E, Vincent J, Pons G, et al; STICLO Italian study group.. Stiripentol in severe myoclonic epilepsy in infancy (SMEI): a placebo-controlled Italian trial. Poster session 496. Epilepsia 2002;43 Suppl 8:155. https://doi.org/10.1111/j.1528-1167.2002.tb06320.x

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, and the European Medicines Agency and the Therapeutic Goods Administration.