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Long-term safety and efficacy of stiripentol for the treatment of Dravet syndrome: A multicenter, open-label study in Japan

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Dravet syndrome;
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Stiripentol;
Long-term administration;
Tolerability;
Efficacy

Summary
Background: We have previously shown the benefits of short-term add-on stiripentol therapy for Dravet syndrome inadequately controlled by clobazam and valproate in Japanese patients. We report here the outcomes of long-term stiripentol use.
Methods: Patients with Dravet syndrome having ≥4 clonic/tonic—clonic seizures per 30 days while on clobazam and valproate (with or without bromide) received add-on stiripentol for 16 weeks. Those benefiting from stiripentol (50 mg/kg/day; up to 2500 mg/day) continued the therapy for additional up to 40 weeks. Responders were defined as those whose clonic/tonic—clonic seizures became ≤50% frequent as compared to baseline.
Results: Of 24 patients starting stiripentol, 21 received the drug for >16 weeks and 19 completed the study. At the endpoint, the responder rate was 54%, with 2 patients remaining clonic/tonic—clonic seizure-free. Twenty-two patients experienced stiripentol-related adverse events, with two having severe ones. They included somnolence (79%), loss of appetite (67%), ataxia (58%), and elevated gamma-glutamyltransferase (38%). No adverse events led to study discontinuation, but 19 patients required dose reduction for stiripentol and/or either antiepileptic drug combined. Stiripentol dose reduction was done in 9 patients, mostly due to somnolence or loss of appetite.
Conclusions: During adjunctive stiripentol use with clobazam and valproate, careful monitoring for adverse events such as somnolence and loss of appetite is recommended, and dose

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reduction may become needed for any of the antiepileptics. Despite the need for safety precautions, the durable responses to stiripentol for up to 56 weeks suggest that the drug is effective as an adjunct to clobazam and valproate for the treatment of Dravet syndrome.

Introduction

Dravet syndrome (severe myoclonic epilepsy in infancy [SMEI]) is a rare intractable epilepsy with onset during the first year after birth whose incidence is estimated at approximately one per 40,000 children in the US (Hurst, 1990), one per 30,000 to 20,000 infants in France (Yakoub et al., 1992), and one per 28,600 individuals in the UK (Brunklaus et al., 2012). In Japan, Oka et al. (2006) reported its prevalence in Okayama Prefecture as 9 per 250,997 (one per 28,000) children aged less than 13 years.

Seizures of Dravet syndrome are considerably resistant to conventional antiepileptic drugs, with standard therapy having yet to be established. Several investigators have reported some response to bromide (Ernst et al., 1988; Oguni et al., 1994), topiramate (Coppola et al., 2002; Kröll-Seger et al., 2006; Nieto-Barrera et al., 2000), and levetiracetam (Striano et al., 2007).

Stiripentol, as an adjunct to clobazam and sodium valproate (valproate), was reported to significantly reduce the frequency of seizures as compared to placebo in patients with Dravet syndrome in two double-blind, placebo-controlled studies, one conducted in France and the other in Italy (Chiron et al., 2000; Kassaï et al., 2008). Based on these findings, stiripentol has been approved for use in Europe as an adjunct to clobazam and valproate for the treatment of Dravet syndrome since 2007.

In a previous open-label study, we found that stiripentol, administered in conjunction with conventional antiepileptic drugs, was effective for the management of Dravet syndrome in Japanese patients (Inoue et al., 2009). We subsequently designed another multicenter open-label study to evaluate the safety and efficacy of add-on stiripentol for Dravet syndrome inadequately controlled by clobazam and valproate with or without bromide (STP-1 study) and have observed that the drug administered at a fixed dose for 12 weeks is effective and tolerated well (Inoue et al., 2014). We report here the results of the long-term administration phase of the study.

Subjects and methods

Study design

The multicenter, open-label STP-1 study consisted of 4-week baseline, 4-week dose-adjustment, 12-week fixed-dose, and 40-week long-term administration phases (Fig. 1). This study was conducted in compliance with the Declaration of Helsinki and the Good Clinical Practice. The study protocol, including genetic sample collection, was reviewed and approved by the ethical committee of each participating institution. Prior to enrollment, all patients and/or their parents gave written informed consent to the study. This study was registered at the Japan Pharmaceutical Information Center as JapicCTI-101116.

Subjects

The eligibility criteria for the STP-1 study were described previously (Inoue et al., 2014). Briefly, male and female patients aged 1—30 years and weighing ≥5 kg who had been diagnosed as having Dravet syndrome and were receiving clobazam and valproate (with or without bromide) as the only antiepileptic drugs when giving informed consent were considered for enrollment. The diagnostic criteria for Dravet syndrome included: (1) onset within a year after birth in an otherwise normal infant; (2) febrile or afebrile clonic or tonic—clonic seizures, either generalized or unilateral; (3) myoclonic, absence and partial seizures may follow; (4) developmental delay becomes apparent within the second year of life and is followed by cognitive and motor impairment. Other ancillary information for the diagnosis of Dravet syndrome included; (5) electroencephalogram (EEG) is usually normal at the onset; and (6) photosensitivity may be present (more than 40% of patients). The diagnosis of each patient was validated by an independent committee of specialists. Patients were to start adjunctive stiripentol use if they had ≥4 clonic or tonic—clonic seizures per 30 days while on clobazam and valproate (with or without bromide) in the 4-week baseline phase.

Treatment

Dosage of stiripentol

In the baseline phase, all patients continued to receive only clobazam and valproate (with or without bromide). In the dose-adjustment phase, add-on stiripentol was started at 20 mg/kg/day (or 1000 mg/day for patients weighing ≥50 kg), which was then escalated at weekly intervals with 10 mg/kg/day (500 mg/day for those weighing ≥50 kg) increments to 50 mg/kg/day (2500 mg/day for those weighing ≥50 kg). The drug was administered at this fixed dose for 12 weeks. In the subsequent phase, dose modification according to each patient's response was allowed within the upper limit of 2500 mg/day.

Concomitant antiepileptic drugs

Throughout the study period, all patients were to continue to receive clobazam and valproate and were prohibited from taking any other antiepileptic drugs. Continued use of bromide that had been instituted before enrollment and as-needed use of intrarectal or parenteral diazepam for the rescue purpose were permitted exceptionally.

No dosage modifications were allowed from 4 weeks before the start of the baseline phase until the end of the phase. During the subsequent phases, dose reduction