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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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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

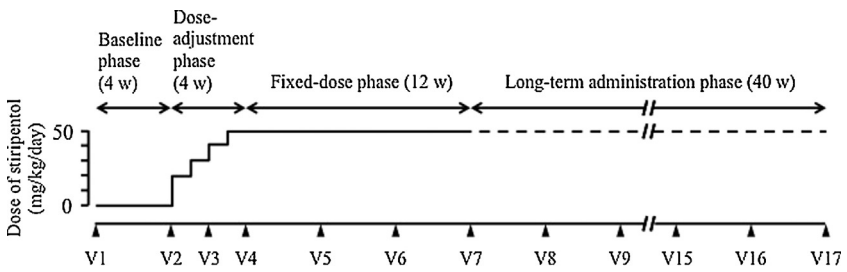

Figure 1 Study schedule. This was a multicenter, open-label study of stiripentol as add-on treatment to clobazam and valproate in Japanese patients with Dravet syndrome. The study consisted of the following phases: a 4-week baseline phase; a 4-week dose-adjustment phase; a 12-week fixed-dose phase; and a 40-week long-term administration phase. Patients received treatment from visit 2 to visit 17. In the long-term administration phase, dose of stiripentol was modified (maximum 2500 mg/day) according to each patient's response. w, Weeks; *v*, visit.

but not dose escalation was permitted only if any adverse event (AE) occurred that was considered to be related to the drug. Patients having received bromide were required to continue this drug at a fixed dosage from 8 weeks before the start of the baseline phase until the end of the fixed-dose phase. During the long-term administration phase, dose reduction but not dose escalation was permitted for safety reasons.

Procedures

Patients having $\geq$4 clonic or tonic–clonic seizures per 30 days in the baseline phase entered the subsequent dose-adjustment phase and started add-on stiripentol use. Those confirmed to benefit from add-on stiripentol at the end of the fixed-dose phase entered the long-term administration phase.

Routine laboratory tests were performed at the start and end of the baseline phase, every 2 weeks during the dose-adjustment phase, and every 4 weeks during the fixed-dose and long-term administration phases as well as at time of treatment discontinuation (if applicable). Cytochrome P450 2C19 gene (*CYP2C19*) was genotyped by PCR using DNA from blood. Blood concentrations of each antiepileptic drug administered were measured before the start of add-on stiripentol, at the end of the fixed-dose phase, and every 12 weeks, in principle, during the long-term administration phase. Patients' parents or other caregivers recorded in the seizure diary the type (defined in the 1981 International Classification of Epileptic Seizures by the International League Against Epilepsy), the day and time, and duration of each seizure.

Efficacy assessments

Patients who continued add-on stiripentol and had evaluable post-baseline seizure data were included in efficacy analyses. The number of clonic or tonic–clonic seizures in each 4-week period was calculated and converted to the number of seizures per 30 days. The primary endpoint for long-term efficacy was the responder rate at the end of the study, defined as the percentage of patients having $\geq$50% reduction in the frequency of clonic or tonic–clonic seizures during the last 4 weeks of the long-term administration phase versus the baseline phase.

Safety assessments

Patients who received at least one dose of stiripentol were included in safety analyses. All AEs (including abnormal laboratory findings) that occurred after the start of add-on stiripentol were collected in an open-ended way. The investigator assessed the severity of each AE as mild (tolerable and not interfering with daily activities), moderate (interfering with daily activities) or severe (severely disabling).

A causal relationship between each AE and stiripentol was graded as ''not related'', ''possibly related'', or ''probably related'' by the investigator. AEs considered to be potentially related to the drug (''possibly related'' and ''probably related'') were considered drug-related.

QT interval in electrocardiogram (ECG) was measured before the start of add-on stiripentol and at the end of the study. Heart rate-corrected QT interval was calculated using Fridericia's (QTcF) and Bazett's formulae (QTcB), and those values observed at the two times were compared.

Statistical analyses

Statistical analyses were conducted using SAS Version 9.1. In the calculation of a responder rate, those having been withdrawn from the study were included as non-responders. The 95% confidence interval was determined for responder rate. QTc intervals at baseline and endpoint were compared using the paired *t*-test and Wilcoxon's signed rank test. Data were considered significant if the ''*p*'' value was less than 0.05.

Results

Subjects

Of 27 patients screened, 24 (15 males and 9 females; aged 1–24 years) started stiripentol. At enrollment, the 24 patients had a median weight of 20 kg (range, 10–55 kg) and were on clobazam at a mean (standard deviation [SD]) dose of 0.36 (0.16) mg/kg/day and on valproate at 26.9 (9.37) mg/kg/day. Fourteen of them were also receiving bromide at 861 (394) mg/day. Among the 24 patients, mental retardation was present in 23, photosensitivity in 11. The mean age at onset of epilepsy was 5.8 (range, 2–14) months.

SCN1A mutations were found in 16 of 17 patients whose DNAs were available for the gene analysis (Inoue et al., 2014).

All 24 patients that started add-on stiripentol completed the fixed-dose phase, and 3 of them (Patients 5, 12 and 23) terminated the study due to poor response without entering the long-term administration phase. The remaining 21 patients (14 males and 7 females; aged 1—24 years) entered the long-term administration phase and 19 of them completed the study. The reasons for study discontinuation in the two patients (Patients 2 and 4) were withdrawal of consent and use of prohibited drug (midazolam injection) for the treatment of status epilepticus, respectively.

Efficacy

All 24 patients that completed the fixed-dose phase were included in efficacy analyses. Table 1 shows individual data on the frequency of clonic or tonic—clonic seizures, responder rate, and the mean duration of clonic or tonic—clonic seizures over time in the long-term administration phase. The responder rate was 67% at the end of the fixed-dose phase and 54% at the end of the long-term administration phase, indicating that the effect of stiripentol was durable for up to 56 weeks. Two patients (Patients 9 and 19) were free from clonic and tonic—clonic seizures throughout the period of treatment with stiripentol. One of them (Patient 19) also became free from all types of seizures.

For the 19 patients who completed the study, the mean (SD) duration of clonic or tonic—clonic seizures was 1.9 (1.5) min at the start of the dose-adjustment phase (baseline), 0.8 (0.6) min at the end of the fixed-dose phase, and 2.6 (6.7) min at the end of the study ($p = 0.6194$ versus baseline, paired t-test). The apparently longer duration of seizures after long-term administration of stiripentol probably reflected an outlier observed in Patient 1 (30 min). The mean (SD) duration of seizures as calculated by excluding this outlier was 1.1 (0.7) min at the end of the study ($p = 0.0489$ versus baseline, paired t-test).

Safety

All 24 patients that started stiripentol were included in safety analyses. The median duration of treatment with the drug was 393 (range, 127—400) days.

After the start of add-on stiripentol, a total of 322 AEs occurred in all 24 patients, and 142 of them reported in 22 patients were considered drug-related. Table 2 lists drug-related AEs reported in ≥2 patients analyzed by severity. In addition to the severe AEs listed in Table 2, malnutrition, pneumonia, and bronchitis, each reported in 1 patient, were graded as severe.

The most frequent drug-related AEs were somnolence (19/24 [79%]), loss of appetite (16/24 [67%]), ataxia (14/24 [58%]), and elevated gamma-glutamyltransferase (GGT) (9/24 [38%]). For somnolence, the median time to onset after the start of add-on stiripentol was 14.5 (range, 1—314) days. Eighteen patients experienced this event during the first 4 weeks of stiripentol use, i.e., in the dose-adjustment phase. As of the end of the study, the event lasted for a median duration of 122.5 (range, 15—378) days, and was still ongoing in 2 patients. For decreased appetite, the median time to onset after the start of add-on stiripentol was 82.0 (range, 7—302) days, with 10 patients developing the event in the dose-adjustment phase. As of the end of the study, the event lasted for a median duration of 75.0 (range, 11—372) days and was still ongoing in 4 patients. For ataxia, the median time to onset after the start of add-on stiripentol was 15.0 (range, 2—302) days, with 12 patients developing the event in the dose-adjustment phase. As of the end of the study, the event lasted for a median duration of 134.0 (range, 5—372) days and was still ongoing in 2 patients. For elevated GGT, the median time to onset after the start of add-on stiripentol was 57.0 (range, 43—362) days. As of the end of the study, the event lasted for a median duration of 339.0 (range, 34—344) days and was still ongoing in 7 patients.

Other drug-related AEs still ongoing as of the study end were weight loss in 3 patients and tremor in 2 patients. The duration of drug-related AEs was not definitely related to subjects' demographic factors such as age and gender.

Drug-related AEs required dose reduction for stiripentol ($n = 9$) and/or either concomitant antiepileptic drug in 19 patients. Somnolence ($n = 5$) and loss of appetite ($n = 5$) were the main reasons for stiripentol dose reduction, with 2 patients having both reasons. At the end of the study, 19 patients were treated with stiripentol at a median dose of 48.7 (range, 29.9—65.3) mg/kg/day (1 at ≤30 mg/kg/day, 3 at 31—40 mg/kg/day, 13 at 41—60 mg/kg/day, and 2 at >60 mg/kg/day). No definitive dose-dependent or concentration-dependent relationship could be found for drug-related AEs, many of which occurred in the dose-adjustment phase.

The effect of stiripentol on QTc interval was evaluated in 19 patients who had ECGs before and after the start of add-on stiripentol. The mean (SD) QTcF interval was 352.15 (24.13) ms at baseline and 360.65 (31.45) ms at the endpoint ($p = 0.1819$). The mean (SD) QTcB intervals at the respective times were 376.91 (28.74) ms and 382.92 (23.68) ms ($p = 0.3525$). No patients had a QTcF or QTcB interval exceeding 450 ms.

Ten severe drug-related AEs were reported in 2 patients (Patients 11 and 14). Patient 11 developed severe somnolence in the dose-adjustment phase, but received escalating doses of stiripentol (20—50 mg/kg/day) as scheduled. The somnolence resolved after a stiripentol dose reduction to 42 mg/kg/day but reappeared at the mild intensity when the stiripentol dose reincreased to 46 mg/kg/day. The event then recovered spontaneously and no such events recurred despite an increase of stiripentol dose to 53 mg/kg/day. Thus, appropriate stiripentol dose reduction could manage the severe somnolence, while maintaining a ≥50% reduction in the frequency of seizures. In this *CYP2C19* extensive metabolizer, the blood concentration of norclobazam, the main metabolite of clobazam, increased almost twice after the start of add-on stiripentol (from 0.5 μg/mL in the baseline phase to 1.0 μg/mL at the end of the fixed-dose phase), suggesting that the severe somnolence might possibly be related to norclobazam. A causal relationship between stiripentol and the AE could not be ruled out either because of their temporal association, although the blood stiripentol concentration was not higher in this patient (7.2 μg/mL at the end of the fixed-dose phase) than in the other patients (mean 9.0 μg/mL with SD 4.5, $n = 21$). Patient 14 developed

Table 1 Data of the study patients.

Patient No.	Gender	Age (yr)	Number of tonic or tonic–clonic seizures (per 30 days)										
			Baseline phase	V6-7	Long-term administration phase								
					V7–8	V8–9	V9–10	V10–11	V11–12	V12–13	V13–14	V14–15	V15–16	V16–17
1	M	1	11.1	3.1	0	0	0	6.2	2.0	0	0	0	0	1.0
2	M	1	5.3	3.2	2.3	–	–	–	–	–	–	–	–	–
3*	F	2	7.2	3.4	5.1	3.4	7.0	4.2	5.3	4.0	3.6	4.4	5.4	1.0
4*	F	2	10.0	8.5	7.5	8.7	9.6	7.5	18.2	30.0	–	–	–	–
5*	F	2	5.3	4.2	–	–	–	–	–	–	–	–	–	–
6*	M	3	4.6	1.9	1.9	1.8	0	0	0	1.0	0	0	1.0	1.4
7	F	4	33.2	4.4	0	0	0	6.4	2.3	6.6	4.8	4.2	5.7	6.0
8*	M	4	15.9	4.2	16.8	11.6	10.3	17.1	9.6	5.0	0	0	6.4	1.4
9*	M	4	4.8	0	0	0	0	0	0	0	0	0	0	0
10*	M	4	10.9	5.4	5.5	10.3	4.8	6.4	4.2	2.6	7.7	5.1	9.3	3.1
11	F	5	15.5	6.0	9.3	6.1	6.5	8.8	3.3	5.0	7.7	7.5	13.3	6.8
12*	M	5	9.5	8.0	–	–	–	–	–	–	–	–	–	–
13*	M	5	5.1	1.2	0.9	2.1	2.0	2.2	5.3	2.9	1.5	1.7	5.7	6.2
14*	M	5	14.2	0	7.1	7.7	3.2	25.7	12.8	5.1	1.4	0	1.2	3.2
15	F	8	10.2	6.5	6.8	7.5	16.0	17.1	4.2	12.8	12.8	3.2	1.1	5.0
16	M	8	13.7	5.7	8.5	6.4	1.8	10.0	5.3	5.3	8.5	6.4	10.7	6.4
17	F	10	157.9	54.8	37.7	44.5	82.8	25.7	60.0	82.7	55.3	82.8	79.2	121.0
18*	M	10	7.5	6.0	28.5	6.8	7.5	10.0	2.1	3.2	7.5	6.0	4.2	6.4
19	M	12	16.0	0	0	0	0	0	0	0	0	0	0	0
20*	M	18	5.2	4.2	6.4	5.8	7.2	4.2	7.5	7.5	4.2	3.8	3.6	4.2
21*	M	21	12.0	3.2	4.2	5.3	1.4	1.0	3.2	5.3	4.2	4.2	8.5	7.5
22	M	23	18.4	3.1	3.3	1.0	14.0	13.8	9.6	5.3	11.7	11.7	17.1	6.0
23*	F	23	6.3	6.3	–	–	–	–	–	–	–	–	–	–
24	F	24	7.2	0	2.2	2.0	1.1	3.2	11.7	5.3	1.0	2.1	6.0	6.0
Responder, *n* (%)			–	16 (67)	12 (50)	13 (54)	12 (50)	8 (33)	12 (50)	13 (54)	13 (54)	14 (58)	8 (33)	13 (54)
Tonic or tonic–clonic seizure duration (min)														
Mean (SD)			1.9 (1.5)	0.8 (0.6)	1.4 (2.1)	1.3 (2.6)	1.2 (2.2)	1.6 (2.7)	1.8 (2.5)	1.2 (1.3)	0.7 (0.6)	0.8 (0.8)	1.9 (3.9)	2.6 (6.7)
[Range]			[0.2–5.2]	[0–2.7]	[0–10.0]	[0–12.3]	[0–10.3]	[0–12.5]	[0–10.0]	[0–5.4]	[0–1.9]	[0–3.0]	[0–17.6]	[0–30.0]

Patients are identified by the same numbers as used in Table 1 in Inoue et al. (2014).

* Patients who also received a bromide.

§ Responders, defined as patients having ≥50% reduction in the frequency of seizures as compared to baseline.

Table 2 Drug-related adverse events.

	Dose-adjustment phase ($n = 24$)	Fixed-dose phase ($n = 24$)	Long-term administration phase ($n = 21$)	Overall ($n = 24$)			
				Total	*Mild*	*Moderate*	*Severe*
Any drug-related AE, *n* (%)	20 (83.3)	18 (75.0)	14 (66.7)	22 (91.7)	*9 (37.5)*	*11 (45.8)*	*2 (8.3)*
Drug-related AEs occurred in at least 2 patients in overall, *n* (%)							
Somnolence	18 (75.0)	2 (8.3)	3 (14.3)	19 (79.2)	*10 (41.7)*	*7 (29.2)*	*2 (8.3)*
Loss of appetite	10 (41.7)	5 (20.8)	8 (38.1)	16 (66.7)	*7 (29.2)*	*8 (33.3)*	*1 (4.2)*
Ataxia	12 (50.0)	1 (4.2)	2 (9.5)	14 (58.3)	*6 (25.0)*	*7 (29.2)*	*1 (4.2)*
Elevated GGT	0 (0)	8 (33.3)	1 (4.8)	9 (37.5)	*7 (29.2)*	*2 (8.3)*	*0 (0)*
Tremor	2 (8.3)	4 (16.7)	0 (0)	6 (25.0)	*6 (25.0)*	*0 (0)*	*0 (0)*
Elevated AST	2 (8.3)	1 (4.2)	1 (4.8)	4 (16.7)	*4 (16.7)*	*0 (0)*	*0 (0)*
Weight loss	0 (0)	2 (8.3)	2 (9.5)	3 (12.5)	*1 (4.2)*	*2 (8.3)*	*0 (0)*
Decreased WBC count	1 (4.2)	1 (4.2)	1 (4.8)	3 (12.5)	*3 (12.5)*	*0 (0)*	*0 (0)*
Dry skin	0 (0)	3 (12.5)	0 (0)	3 (12.5)	*3 (12.5)*	*0 (0)*	*0 (0)*
Decreased neutrophil count	1 (4.2)	2 (8.3)	2 (9.5)	2 (8.3)	*2 (8.3)*	*0 (0)*	*0 (0)*
Decreased platelet count	1 (4.2)	1 (4.2)	2 (9.5)	2 (8.3)	*2 (8.3)*	*0 (0)*	*0 (0)*
Constipation	1 (4.2)	1 (4.2)	1 (4.8)	2 (8.3)	*2 (8.3)*	*0 (0)*	*0 (0)*
Agitation	2 (8.3)	0 (0)	0 (0)	2 (8.3)	*2 (8.3)*	*0 (0)*	*0 (0)*
Initial insomnia	2 (8.3)	0 (0)	0 (0)	2 (8.3)	*2 (8.3)*	*0 (0)*	*0 (0)*
Hypotonia	1 (4.2)	0 (0)	1 (4.8)	2 (8.3)	*1 (4.2)*	*1 (4.2)*	*0 (0)*
Diarrhea	1 (4.2)	1 (4.2)	0 (0)	2 (8.3)	*2 (8.3)*	*0 (0)*	*0 (0)*
Elevated blood ALP	0 (0)	1 (4.2)	1 (4.8)	2 (8.3)	*2 (8.3)*	*0 (0)*	*0 (0)*

Data are numbers and percentages (in parentheses) of patients. AE, adverse event; ALP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; WBC, white blood cell.

severe somnolence, severe decreased appetite, and severe ataxia in the dose-adjustment phase, but received escalating doses of stiripentol (20—50 mg/kg/day) as scheduled because of its dramatic effect on his seizures. The AEs persisted despite dose reduction for clobazam, while the decreased appetite and ataxia resolved after a stiripentol dose reduction to 43 mg/kg/day. However, in response to a gradual stiripentol dose increase to 58 mg/kg/day, severe decreased appetite and ataxia recurred. Severe malnutrition also occurred thereafter despite a gradual dose reduction to 55 mg/kg/day and did not respond to supportive care and a further dose reduction to 49 mg/kg/day. Bronchitis and pneumonia followed and necessitated hospital care. The stiripentol dose was further reduced to 45 mg/kg/day, after which the pneumonia, bronchitis, and malnutrition resolved. As of the end of the study, the severe somnolence, ataxia and decreased appetite were still ongoing. In this *CYP2C19* poor metabolizer, the blood concentration of stiripentol was 20.2 μg/mL at the end of the fixed-dose phase. Considering the higher blood concentration of stiripentol in this patient than in the other patients, the drug probably caused the malnutrition, which made the patient more susceptible to infections. In this patient, stiripentol, at 50 mg/kg/day, was definitively effective in controlling seizures during the fixed-dose phase, yet toxic; it was very difficult to adjust its dose to non-toxic, maximally effective levels.

Discussion

In this multicenter open-label study, we evaluated the long-term safety and efficacy of stiripentol (50 mg/kg/day) in 24 Japanese patients with Dravet syndrome inadequately controlled by clobazam and valproate with or without bromide. Of 24 patients that started stiripentol add-on therapy, 19 completed the study. We found that long-term add-on stiripentol use to clobazam and valproate exerted a durable effect in controlling seizures lasting for up to 52 weeks. Although drug-related AEs (somnolence and loss of appetite) were common, they were usually mild or moderate. Two patients had severe AEs but were able to remain on the study.

Twenty-two out of the 24 patients treated with stiripentol developed drug-related AEs, including somnolence (79%), loss of appetite (67%), ataxia (58%), and elevated GGT (38%). Most of these frequent drug-related AEs occurred in the early phase of stiripentol use and lasted long. The drug-related AEs reported in the long-term administration phase were similar in nature, severity and frequency to those reported in the earlier phases, suggesting that no new AEs were associated with long-term stiripentol use. No drug-related AEs led to study discontinuation, while some required dose reduction for stiripentol and/or either concomitant antiepileptic drug. Stiripentol is a potent CYP inhibitor (Giraud et al., 2006; Tran et al., 1997) and is likely to have pharmacokinetic interactions with other antiepileptic drugs combined. Therefore, if any drug-related AE occurs during concomitant use of stiripentol with any other antiepileptic drug, dose reduction should be considered for stiripentol and/or the antiepileptic drug combined. Notably, stiripentol often increases the blood concentration of clobazam and its main metabolite, norclobazam. Therefore, therapeutic dose monitoring for clobazam may be beneficial at the start of stiripentol use and at the onset of any AE. Some patients, like Patient 14 in our series, can respond to stiripentol only when its blood concentrations are higher than usual. In an effort to optimize the dose for the drug in such patients, the acceptable balance between its effectiveness and toxicity should be taken into account.

Our previous study of adjunctive stiripentol use involved 25 Japanese patients with Dravet syndrome refractory to conventional antiepileptic drugs (Inoue et al., 2009). Six of them (24%) were withdrawn from the study, including one due to loss of appetite. Overall, the most frequently reported AEs were loss of appetite, drowsiness, hyperactivity/irritability, and ataxia. Thanh et al. (2002) evaluated long-term safety and efficacy of add-on stiripentol administered to 46 French patients with Dravet syndrome refractory to clobazam and valproate for a median duration of 2.9 years (range, 2 months to 5.5 years). The most frequent drug-related AEs reported in that study were loss of appetite and weight loss as well as ataxia, sleep disorder and hypotonia.

Wirrell et al. (2013) retrospectively reviewed the clinical charts of 82 US patients who had been treated with stiripentol for Dravet syndrome for a mean duration of 28.5 months (SD, 20.3 months). They found that the most frequent drug-related AEs after the start of stiripentol therapy were sedation/somnolence and decreased appetite. Six patients discontinued stiripentol use, including four due to any drug-related AE. The French (Thanh et al., 2002) and US studies (Wirrell et al., 2013) reported remarkably similar safety profiles of long-term add-on stiripentol therapy to that observed in our present study, although these studies had several methodological differences, including a longer follow-up and non-requirement for combined use of clobazam and valproate (the latter in the US study [Wirrell et al., 2013] only). In the EU, 227 patients treated with stiripentol (152 Dravet and 75 non-Dravet patients) since 2007 were prospectively followed up in a postmarketing clinical experience investigation (DIAVEY postmarketing survey). After a mean exposure of 22 months, drug-related AEs reported in ≥4% patients were elevated GGT (17%), elevated AST (14%), loss of appetite (13%), somnolence (9%), fatigue (8%), aggressiveness and irritability (9%), neutropenia (7%), ataxia (5%) and elevated ALT (4%). Of 152 patients with Dravet syndrome, 111 (73%) completed the survey (DIAVEY postmarketing survey in Transparency Commission).

In the present study, the responder rate at the end of the long-term administration phase was 54% as compared to 67% at the end of the fixed-dose phase, indicating a durable effect of add-on stiripentol lasting for 52 weeks. Two patients remained seizure-free throughout the long period of treatment. In our previous study, we observed a similar responder rate (48% [11/23]) after treatment with stiripentol for a mean duration of 6.1 (range, 3—14) months (Inoue et al., 2009). The French study also showed a similar responder rate (50% [23/46]), though defined somewhat differently, and demonstrated a dose-dependent relationship at doses up to 50 mg/kg/day (Thanh et al., 2002). In the present study, 19 (79%) out of 24 patients completed the 56-week stiripentol use. DIAVEY postmarketing survey found a similar percentage (73%) of patients continuing stiripentol therapy during the long-term follow-up.

Thus, long-term add-on stiripentol to clobazam and valproate was safe and effective for the management of Dravet syndrome in Japanese patients. This finding renders further support to the evidence of its benefits observed in Japanese and non-Japanese patients.

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