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# Add-on stiripentol elevates serum valproate levels in patients with or without concomitant topiramate therapy

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ABSTRACT

*Objective:* Stiripentol (STP), valproate (VPA) and topiramate (TPM) are reported to have efficacy for Dravet syndrome. In this study, we sought to elucidate the mechanisms underlying the increased serum VPA concentrations following STP adjunctive therapy in patients with Dravet syndrome.
*Methods:* Twenty-eight patients with Dravet syndrome (age range, 1–35 years) undergoing combination therapy with VPA and STP were included in this study. We evaluated VPA and clobazam (CLB) serum concentrations before and after add-on STP. We also investigated potential factors impacting VPA metabolism during add-on STP therapy, including add-on TPM and *CYP2C9* and *CYP2C19* gene polymorphisms. The effect of STP on the metabolism of concomitantly administered CLB was also investigated.
*Results:* Add-on STP was significantly associated with the serum concentration-to-dose (CD) ratio of VPA. Two patients, who were concomitantly treated with TPM, developed severe anorexia and thrombocytopenia because of marked increases in serum VPA concentrations. Further analysis revealed that the rate of increase in the VPA CD ratio was positively correlated with TPM dose. In patients not receiving TPM, STP enhanced the rate of increase in the VPA CD ratio to a significantly greater extent in *CYP2C19* extensive metabolizers than in *CYP2C19* poor metabolizers. Add-on STP was also associated with significant increases in CLB and N-desmethyl-CLB serum concentrations.
*Conclusion:* Our findings suggest that serum VPA concentrations should be carefully monitored during STP adjunctive therapy, particularly in patients receiving concomitant TPM therapy.


## 1. Introduction

Dravet syndrome is an intractable form of epilepsy characterized by recurring, prolonged febrile and afebrile seizures in early childhood (Dravet et al., 2005). Stiripentol (STP) is an antiepileptic drug (AED) approved by the European Medicines Agency in 2008 as adjunctive therapy to valproate (VPA) and clobazam (CLB) for the treatment of Dravet syndrome. The American Academy of Neurology has recently strongly recommended STP for the treatment of Dravet syndrome, and VPA and topiramate (TPM) have also been recommended (Wilmshurst et al., 2015).

STP as adjunctive therapy to CLB and VPA for Dravet syndrome has demonstrated efficacy (De Liso et al., 2016), and is also effective for intractable seizure such as status epilepticus in adults (Strzelczyk et al., 2015). Although most side effects such as drowsiness and loss of appetite are mild to moderate in severity, 10% of cases show severe adverse events, such as somnolence, appetite loss and ataxia (Plosker, 2012; Inoue et al., 2014; Inoue et al., 2015). Given that these side effects can be caused either by STP itself or by concomitant AEDs, a dose reduction in CLB and/or VPA is recommended before any reduction in STP dose is considered (Perez et al., 1999; Chiron et al., 2000).

STP was approved in Japan in 2012 as an adjunctive therapy to VPA and CLB for Dravet syndrome. Thereafter, we observed

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marked increases in serum VPA concentrations in several patients undergoing adjunctive therapy. Significant increases in serum CLB and N-desmethyl-CLB (NDCLB) concentrations were previously demonstrated to result from the inhibition of cytochrome P450 (CYP) 2C19 and CYP3A4 (Giraud et al., 2006; Yamamoto et al., 2013; Yamamoto et al., 2014; Kouga et al., 2015). However, few studies have examined the effect of STP on serum VPA concentrations. To elucidate the mechanisms underlying the increase in serum VPA concentrations produced by add-on STP therapy, we investigated factors associated with VPA metabolism, including *CYP2C9* and *CYP2C19* gene polymorphisms. The impact of STP on the metabolism of concomitantly administered CLB was also investigated.

## 2. Methods

### 2.1. Patient selection

In this retrospective collaborative study to examine the effects of add-on STP therapy on serum VPA and CLB concentrations, a total of 33 patients with Dravet syndrome receiving STP and VPA combination therapy at Shizuoka Institute of Epilepsy and Neurological Disorders (n = 26), Ehime Prefectural Central Hospital (n = 4) and Ehime University Hospital (n = 3) between April 2015 and October 2015 were included. The following diagnostic criteria for Dravet syndrome were used: (1) onset <1 year of age in an otherwise normal infant; (2) febrile or afebrile clonic or tonic-clonic seizures, either generalized or unilateral; (3) presence of myoclonic, absence or partial seizures; (4) developmental delay becoming apparent within the second year of life, which is followed by cognitive and motor impairment; (5) usually normal electroencephalogram at onset; (6) presence of photosensitivity (Dravet et al., 2005). We also defined borderline Dravet syndrome as epilepsy with clinical characteristics similar to those of typical Dravet syndrome but lacking epileptic myoclonic seizures or exhibiting generalized tonic-clonic seizures only (Ogino et al., 1988; Hattori et al., 2008). We excluded two patients not receiving VPA and three patients without VPA serum concentration measurements before the start of add-on STP therapy. The remaining 28 patients (age, 1–35 years; 10 males [age, 10.1 ± 9.8 years (mean ± standard deviation)] and 18 females [age, 7.94 ± 10.1 years]) were included in this study. Of the final 28 patients, 18 had typical Dravet syndrome, while 10 patients were borderline.

### 2.2. Study design

We evaluated changes in VPA and CLB serum concentrations and performed the following routine laboratory examinations: white blood cell, red blood cell and platelet counts; hemoglobin, fibrinogen, amylase and ammonia level analyses; and liver function tests. VPA and CLB serum concentrations were measured at almost the same time following the ingestion of AEDs in all patients, both before (3.2 ± 1.6 h) and after (3.2 ± 1.8 h) the administration of add-on STP. We analyzed data collected during the stable period in 16 patients who did not demonstrate any side effects (99 ± 40 days after initiation of add-on STP therapy) and during the episodes of adverse reactions in 12 patients (53 ± 39 days). The concentration-to-dose (CD) ratios of VPA and CLB were calculated by dividing serum concentration (μg/ml for VPA, ng/ml for CLB) by dose, adjusted for body weight (mg/kg). We also analyzed the influence of concomitant AEDs, especially TPM, on serum VPA concentrations. Because serum concentrations of STP and other AEDs, excluding VPA and CLB, were not available for all patients, doses (not the serum concentrations) of these AEDs were used for analysis in this study.

*CYP2C9* and *CYP2C19* genotypes were determined by polymerase chain reaction (PCR) using DNA extracted from peripheral blood cells of all participating patients. PCR products for *CYP2C9*2, CYP2C9*3, CYP2C19*2* and *CYP2C19*3* were measured by the PCR-based invader method or real-time PCR. Results were confirmed by nucleotide sequence analysis.

This study was approved by the ethics committee of each institution. Written informed consent was obtained from the parents or legal guardians of patients included in this study.

### 2.3. Statistical analysis

Data were analyzed using IBM SPSS® version 20 (Chicago, IL, USA) using paired and non-paired *t*-tests, the *U* test for small numbers of patients, and correlation analysis. Results were expressed as means ±standard deviation (SD), or medians and range. The statistical significance level was set at $<0.05$.

## 3. Results

### 3.1. VPA, CLB and NDCLB serum concentrations

Of the 28 subjects receiving AEDs, 19 were additionally treated with CLB. Other concomitant AEDs included TPM and potassium bromide in eight and five patients, respectively, as well as zonisamide, phenobarbital, lamotrigine, levetiracetam, clonazepam and clorazepate, in one patient each. Twelve patients had side effects, such as drowsiness and loss of appetite, and recovered following the reduction of antiepileptic drugs by 117 ± 143 days after initial appearance of the side effects (Table 1).

The serum VPA CD ratio was significantly increased following add-on STP therapy (4.0 ± 1.3 vs. 4.6 ± 1.7 (μg/ml)/(mg/kg); $p = 0.006$; Fig. 1A). VPA concentrations were increased in two-thirds of the patients, and were above 140 μg/ml in six patients. Two patients developed severe anorexia and thrombocytopenia (54 days after add-on STP in case A, and 28 days after add-on STP in case B; Fig. 2) because of marked elevations in VPA serum levels, without elevation of serum ammonia level, after the start of add-on STP therapy. These patients did not exhibit impaired consciousness as a symptom of encephalopathy. Interestingly, both patients were treated with TPM as well. Furthermore, the rate of increase in the VPA CD ratio was negatively correlated with the rate of change in platelet count (Fig. 1B; $p = 0.029$, $r = -0.421$). There was no significant relationship between serum VPA concentration and ammonia level. There were no significant changes in other blood or biochemical parameters evaluated in this study. No significant relationships were found between the VPA CD ratio and STP dose or between the VPA CD ratio and VPA dose.

Serum CLB concentrations, expressed as CD ratio, were significantly increased following add-on STP therapy (368.8 ± 218.2 vs. 623.0 ± 272.0 (ng/ml)/(mg/kg); $p = 0.003$; Fig. 1C). Furthermore, serum NDCLB concentrations, expressed as CD ratio, were also significantly increased following add-on STP therapy (1,610.7 ± 1,292.4 vs. 6,614.4 ± 4,543.3 (ng/ml)/(mg/kg); $p = 0.001$; Fig. 1D).

### 3.2. The role of CYP polymorphisms

We next examined *CYP2C9* and *CYP2C19* polymorphisms for their associations with serum drug concentrations. For *CYP2C9*, 93% of the patients were extensive metabolizers (*1/*1), and 7% were intermediate metabolizers (*1/*3). There was no significant difference in the rate of increase in VPA CD ratio between *CYP2C9* extensive and *CYP2C9* intermediate metabolizers (Fig. 3A). For *CYP2C19*, 85% of the patients were extensive metabolizers (*1/*1, *1/*2, *1/*3), and 15% were poor metabolizers (*2/*2, *2/*3, *3/*3).