Seizure (2008) 17, 92–97

ELSEVIER

SEIZURE

www.elsevier.com/locate/yseiz

CASE REPORT

Acute hepatic injury in four children with Dravet syndrome: Valproic acid, topiramate or acetaminophen?

Joost Nicolai [a,*], Boudewijn Gunning [c], Piet L. Leroy [b], Berten Ceulemans [d], Johan S.H. Vles [a]

[a] Department of Neurology, University Hospital Maastricht, Maastricht, The Netherlands
[b] Department of Paediatrics, University Hospital Maastricht, Maastricht, The Netherlands
[c] Department of Neurology, Epilepsy Centre Kempenhaeghe, Heeze, The Netherlands
[d] Epilepsy Centre for Children and Youth, Pulderbos, Belgium

Received 27 February 2007; received in revised form 19 June 2007; accepted 10 July 2007

KEYWORDS
Dravet syndrome;
Acetaminophen;
Stiripentol;
Topiramate;
Valproate;
Liver toxicity

Summary We describe four children with Dravet syndrome treated with the combination of valproic acid (VPA) and topiramate (TPM) who developed transient liver toxicity. The time-interval between fever, administration of acetaminophen, epileptic status and liver enzyme disturbances in our four cases suggests that accumulation of toxic acetaminophen-metabolites is possibly responsible for liver toxicity. If acetaminophen and its metabolites cause those liver problems in children treated with the combination of VPA and TPM, the advice to use acetaminophen for treating fever in children using this combination, should be changed. Only future clinical observations and research can solve this clinical dilemma.

Introduction

Dravet syndrome (severe myoclonic epilepsy in infancy) is characterized by febrile and afebrile, generalised and partial seizures that start in the first year of life. Later, myoclonic seizures, atypical absences and developmental delay occur. Seizures are often therapy-resistant to antiepileptic drugs. Antiepileptic treatment with valproic acid (VPA), clobazam and stiripentol or the combination of VPA and topiramate (TPM) is often advised.

Acute hepatic injury is a possible complication of many drugs. Acute VPA-induced liver toxicity is fatal in the majority of patients.[1] Especially in very young children the risk is high; the risk of fatal liver failure in children under 2 years of age receiving VPA as polytherapy is 1:600. In children between 3 and 10 years using VPA polytherapy the risk is 1:8.300.[2] The relation between TPM and hepatotoxicity has been

Abbreviations: ALAT, alanine aminotransferase; APTT, activated partial thromboplastin time; ASAT, aspartate aminotransferase; CBZ, carbamazepine; INR, International normalised ratio; IV, intravenous; PT, prothrombin time; TPM, topiramate; VPA, valproic acid (valproate)

* Corresponding author at: Department of Neurology, University Hospital Maastricht, PO Box 5800, 6202 AZ Maastricht, The Netherlands. Tel.: +31 43 3875058; fax: +31 43 3877055.
E-mail address: jnic@sneu.azm.nl (J. Nicolai).

1059-1311/$ – see front matter
doi:10.1016/j.seizure.2007.07.003

suggested before in two case-reports.[3,4] However, in both publications the adult patients used multiple antiepileptic drugs including TPM. No reports on hepatotoxicity in children or adults receiving TPM monotherapy have been published till now. There is evidence that ingestion of acetaminophen in therapeutic dosages can cause an evident rise in alanine aminotransferase (ALAT) in 31—44% of healthy, adult volunteers.[5]

We describe four children with Dravet syndrome who developed a serious rise of liver enzymes. All were treated with the combination of VPA, TPM and acetaminophen.

Case report

Case No. 1, a 5-month-old boy from non-related parents visited our outpatient clinic because of generalised tonic—clonic seizures and partial seizures with rhythmic twitches of the tongue and facial musculature. EEG registration showed multifocal spikes and for this reason carbamazepine (CBZ) was started. Metabolic screening revealed no aminoaciduria, no organic aciduria and normal serum total, free, and acyl-carnitine concentrations. Cerebrospinal fluid analysis and MRI scan showed no abnormalities. Because of the fact that his seizure frequency worsened and myoclonic seizures were noted, CBZ was withdrawn and VPA was initiated at the age of 8 months. Several episodes of epileptic status occurred, triggered by febrile episodes.

He was admitted to Kempenhaeghe epilepsy centre for further analysis and treatment. At the age of 12 months, TPM was added to his medication and gradually increased, because of ongoing seizures. The diagnosis of Dravet syndrome was confirmed when a c.2684T > G (p.Leu895Arg) mutation was found in exon 15 of the SCN1A gene.

At the age of 15-month, he suffered from an epileptic status triggered by influenza B infection. The day before, he was given acetaminophen 240 mg q.i.d. (73 mg/kg/day) by his parents in order to suppress his fever. A rise in liver enzymes was noted, and L-carnitine 100 mg/kg/day was started on the day of admission. His antiepileptic medication was continued in dosages equal to those before admission and acetaminophen was stopped. ASAT (2229 U/l) and ALAT (2022 U/l) levels peaked at day 1. Coagulation times were increased (APTT 20.9 s; INR 2.1). Screening for Hepatitis virus A, B and C, Epstein-Barr virus and Cytomegalovirus was negative. A spontaneous decrease of transaminases and coagulation parameters to almost normal values was noticed in the week after admission. On discharge, L-carnitine was added to his regular medication. Three months later, he was admitted again to the paediatric intensive care unit because of an epileptic status triggered by fever (39.5 °C) of unknown origin. Also this time, his parents had given him acetaminophen. The rise of liver enzymes and coagulation disturbance was even more severe now (ASAT 7326 U/l; ALAT 5203 U/l; APTT 24.4 s; PT 32 s; INR 2.6). VPA concentration was 45 mg/L (normal range 40—100 mg/L). Transaminases gradually normalised despite the continuation of VPA, TPM, and L-carnitine. Also this time, screening for viral hepatitis was negative.

The medical histories of Case No. 1 and the other three children are summarised in Table 1. Antiepileptic drug concentrations were only measured in case 1 (second episode), 3 and 4. All parents used acetaminophen according to the manufacturers instructions. The dose used at home was not documented at admission in the other children. It is important to note that case Nos. 1 and 3 developed a rise in liver enzymes while receiving adequate L-carnitine prophylaxis (advised dose: 100 mg/kg/day[6,7]). In case No. 2, carnitine concentration was measured on the day of admission. At that moment she showed a serious rise in transaminases. Total, free, and acyl-carnitine concentrations in plasma were normal. In case Nos. 3 and 4 the rise of transaminases was less impressive, however a significant elevation of ammonia was noted. Because of the serious rise in ammonia, a partial ornithine transcarbamylase deficiency was ruled out in both children.

Discussion

In Dravet syndrome (severe myoclonic epilepsy in infancy), seizures are often therapy-resistant. In a randomized add-on study, the addition of stiripentol to VPA and clobazam has been shown effective in Dravet syndrome.[8] The efficacy of TPM in Dravet syndrome has been proven in an open label study[9] and in a retrospective analysis, adding TPM to the combination of VPA, clobazam, and stiripentol seemed helpful.[10] In recent literature discussing the treatment of Dravet syndrome, the combination of VPA and TPM is advised, together with strict acute seizure treatment and prevention of hyperthermia.[11]

The molecular basis of Dravet syndrome is a mutation of the SCN1A gene expressing a sodium channel alpha subunit. This sodium channel is only expressed in neuronal tissue, so a relation between liver failure and the SCN1A gene mutation does not seem obvious.

VPA-induced hepatic failure has been related to carnitine deficiency. Chronic use of VPA leads to a