Phenytoin as a last-resort treatment in SCN8A encephalopathy

*Hilde M. Braakman, *Judith S. Verhoeven, †Corrie E. Erasmus, †Charlotte A. Haaxma, ‡§Marjolein H. Willemsen, and *H. Jurgen Schelhaas

Epilepsia Open, **(*):1–2, 2017
doi: 10.1002/epi4.12059

SUMMARY

SCN8A encodes Nav1.6, one of the main voltage-gated sodium channel subunits in the brain, and SCN8A mutations lead to epileptic encephalopathy. Particular mutations render the mutant channel more susceptible to inhibition by phenytoin. Yet, the potentially severe side effects of phenytoin maintenance therapy, especially cognitive impairment, are undesirable in these already cognitively impaired patients. We describe a 5-year-old patient with SCN8A encephalopathy in whom phenytoin proved successful as emergency treatment to prevent clustering of seizures and status epilepticus, thus hospital stays. The ketogenic diet, levetiracetam, zonisamide, topiramate, and phenytoin maintenance therapy resulted in adverse reactions not previously documented in SCN8A encephalopathy.

KEY WORDS: SCN8A, Phenytoin, Epileptic encephalopathy.
In a patient with the SCN8A mutation p.Val233Ile, identified by whole exome sequencing performed as described previously,6 we have observed (1) efficacy of both intravenous and oral phenytoin as an emergency treatment to prevent seizure escalation instead of maintenance therapy and (2) undocumented adverse reactions to a ketogenic diet, levetiracetam, zonisamide, and topiramate.

**Case Report**

The patient is a 5-year-old boy with hypotonia from birth, who had his first tonic-clonic seizure at the age of 4 months. The seizure frequency progressed over 1 year, to four seizures a day. The seizure semiology was always similar and there were no provocative factors such as fever. During this period, his psychomotor development stagnated. A DNA diagnostic test of the SCN1A gene revealed no mutation. Initial treatment with valproic acid and phenobarbital resulted in seizure freedom for 1 year and resumption of psychomotor development. Then, seizures recurred monthly and built up to a status epilepticus once every 2 to 3 months, requiring admission to the intensive care unit (ICU) and benzodiazepine therapy. After every status epilepticus, psychomotor skills deteriorated, including temporary loss of speech. Phenobarbital was switched to lamotrigine and clobazam, without any effect on seizure frequency. Sequential neuropsychological assessments revealed a decrease in total IQ scores from 83 (verbal IQ 88, performance IQ 83) to 63 (verbal IQ 66, performance IQ 70).

Ketogenic diet was started but had to be halted because of severe nausea and vomiting, fatigue, increased seizure frequency, and encephalopathy. All improved immediately after cessation of the diet. Seizure frequency decreased to six per year, but all led to epileptic status with ICU admittance. Benzodiazepines were no longer effective, but there was a consistently good response to intravenous phenytoin administration.

Addition of levetiracetam, zonisamide, and later topiramate to maintenance therapy resulted in rapid deterioration, with encephalopathy, ataxia, and dysarthria and recurrent status epilepticus. The encephalopathy, ataxia, and dysarthria quickly disappeared after withdrawal of all three drugs.

When a seizure occurred, administration of oral phenytoin at home or, if oral phenytoin treatment failed, intravenous administration at the emergency department, both in a dosage of 10 mg/kg, prevented clustering of seizures and status epilepticus. With oxcarbazepine, valproic acid, lamotrigine, and clobazam maintenance therapy, seizure frequency decreased to once weekly. Because of the success of phenytoin as rescue medication, it was tried as maintenance therapy. Unfortunately, this chronic use of phenytoin, even at a 2 mg/kg/day dose, resulted in severe side effects, including ataxia, dysarthria, and somnolence, and therefore had to be withdrawn.

In search of successful maintenance therapy, we have recently initiated the new sodium channel blocker lacosamide. At a 2 mg/kg/day dose, he is already more alert but still has weekly seizures for which he uses oral phenytoin (10 mg/kg) at home to prevent clustering of seizures, thus status epilepticus and hospital stays. After a seizure, he experiences 1–2 days of deterioration of his motor skills and temporary loss of speech followed by dysarthria. Currently, he walks without assistance, is able to climb, jump, and cycle with only a slight ataxia and hypotonia, and attends a school for special education.

**Discussion**

This case demonstrates a favorable response to phenytoin in status epilepticus as well as in the prevention thereof in a patient with a SCN8A mutation. The use of phenytoin and oxcarbazepine is counterintuitive in Dravet-like syndromes, because patients with classic Dravet syndrome based on SCN1A gene mutations deteriorate when treated with these drugs.7,8 Phenytoin could be an important treatment option in patients with SCN8A mutation-related epilepsy because it is primarily expected to block the increased sodium current through the mutated Nav1.6, but not to affect the function of other voltage-gated sodium channels not affected by the SCN8A mutation.9 Therefore, the diagnosis of SCN8A mutation is important for rational treatment decisions.

The potentially severe side effects of phenytoin, especially cognitive impairment, are undesirable in patients with SCN8A encephalopathy who already suffer from a delay in cognitive development. Yet, this case demonstrates that there may be merit in using phenytoin as an emergency treatment.

**Disclosure**

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

**References**