Contents lists available at ScienceDirect

Current Therapeutic Research

Case report

Concurrent Quinidine and Phenobarbital in the Treatment of a Patient with 2 *KCNT1* Mutations

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ARTICLE INFO

ABSTRACT

Epilepsy of infancy with migrating focal seizures is a devastating pediatric neurologic disorder that often results in treatment-resistant seizure activity and developmental delay. The condition has been associated with mutations in the *KCNT1* gene that cause a gain of function in neuronal sodium-activated potassium channels. Quinidine has been shown to reverse this gain of function and has recently been used to reduce seizure activity in patients with these mutations. We report the case of an infant with 2 *KCNT1* mutations who experienced minor relief with quinidine and discuss the drug's important interaction with phenobarbital.

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Introduction

KCNT1 gene mutations are linked to pediatric seizure disorders.[1] Among the most devastating is epilepsy of infancy with migrating focal seizures (EIMFS), also known as migrating partial seizures of infancy. Seizures normally manifest within the first 6 months of life and often lead to severe developmental delay. Some patients are reported as having up to 200 seizures per day.[2]

The *KCNT1* gene encodes a sodium-activated potassium channel found in neurons, and mutations therein are associated with refractory seizure activity. Quinidine may reduce seizure frequency in these patients. In vitro studies suggest the drug may reverse the gain of function caused by various *KCNT1* mutations.[3] A PubMed search using the terms *quinidine* and *seizures* or *KCNT1* reveals past cases of EIMFS patients treated with quinidine. The results of these cases range from minimal or no change in seizure frequency up to and including almost complete seizure remission.[2,4–6]

Having obtained the necessary permissions from the patient's parents, as well as our institutional review board, we present the case of a patient with EIMFS and 2 mutations in the *KCNT1* gene treated with quinidine and phenobarbital. We discuss an important drug–drug interaction between the 2 drugs.

Case Report

Patient presentation

The patient is a 1-year-old girl who was the product of an uncomplicated pregnancy, labor, and delivery. She was born at 38 weeks' gestation. Her parents have no family history of seizure disorders. Immediately after birth, our patient had seizures lasting up to 6 minutes. Her seizures were manifest as head jerking, eye deviations, lip smacking, unilateral arm stiffening, and extremity tremors both focal and bilateral. Electroencephalograms revealed focal seizures alternating between right and left hemispheres (recording not included due to privacy restrictions). Daily seizure frequency varied greatly and peaked near 150 per day. Sequential attempts at seizure control with antiepileptic medications (eg, phenobarbital, levetiracetam, topiramate, oxcarbazepine, pyridoxine, clonazepam, and fosphenytoin) all failed.

Patient evaluation included an infection screen (including blood and cerebrospinal fluid cultures; toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus panel; and parvovirus B19 antibody test) and metabolic screen (including plasma amino acid studies), all of which were negative. However, a

Table 1
Timeline of quinidine treatment with and without phenobarbital.

Age, wk	Quinidine dose*, mg/kg/d	Average serum quinidine level, μg/mL	Event
4-10	40	Undetectable	Phenobarbital 9.4 mg/kg/d being given
11-12	60	Undetectable	
13-14	68	Undetectable	Quinidine removed due to QT prolongation
15-16	14	Undetectable	Quinidine restarted after sharp increase in seizure frequency
17-18	25	0.5	Phenobarbital weaned and discontinued (Weeks 17-24)
19-22	36	0.7	
23-27	47	1.1	
28-31	47	2.3	
32-36	47	1.7	
37-40	60	2.8	
41-44	60	2.3	
45-48	72	2.3	
49-50	70	3.9	

* In 4 divided doses.

comprehensive epilepsy panel, which included 87 genes (performed by GeneDx, Gaithersburg, Maryland), concluded the patient had 2 separate mutations in the *KCNT1* gene (c.1066C>T; p.Arg356Trp and c.2170_2184dup15; p.Pro724_Leu728dup). The first of these is a missense variant known to be pathogenic, and the second is a variant of uncertain significance according to the test results. Magnetic resonance imaging revealed no definite acute intracranial abnormalities other than slight asymmetry in the size of the temporal lobes with the left slightly decreased compared with the right. Repeat magnetic resonance imaging at age 8 months showed diffused volume loss consistent with that reported in patients with *KCNT1*-related seizure disorders.[5]

Treatment course

After having little success with seizure control during the first 6 weeks of life, the patient was placed on a ketogenic diet while still in intensive care. This was associated with a decrease in seizure frequency and intensity. With the parents' consent, quinidine was added to the patient's regimen, which included sugar-free phenobarbital (9.4 mg/kg/d), topiramate, and oxcarbazepine at the time. The initial dosage was 15 mg/kg/d divided every 6 hours administered via gastrostomy tube. The quinidine formulation was specially compounded using quinidine sulfate powder and a 1:1 mixture of ORA-Plus and ORA-Sweet SF (manufactured by Paddock Laboratories, LLC, Minneapolis, Minnesota) to make a 50 mg/mL suspension.[7]

Once discharged from intensive care, her quinidine dosage was gradually titrated up to 40 mg/kg/d. This dosage produced no detectable serum quinidine level, and no change in seizure frequency was evident. We hypothesized this was due to quinidine's drug–drug interaction with phenobarbital—the agent that seemed to give the patient the greatest relief at the time.

The patient was later admitted for serial blood sampling following a 75-mg dose of quinidine. We calculated quinidine's half-life in our patient to be approximately 2 hours. Higher and/or more-frequent doses of quinidine would be needed to reach sustained levels in the usual target range (2–5 μg/mL for cardiac arrhythmias), or phenobarbital likely would have to be abandoned altogether to allow quinidine a chance to exert its effect, if any.[4]

The patient was admitted several times during the next few weeks for cardiac telemetry while quinidine was increased up to 68 mg/kg/d. At 68 mg/kg/d, QT prolongation precluded further dosage increases (QT interval approached 530 msec; normal range = 440–450 msec). Due to the potential for cardiac arrhythmias, the decision was made to discontinue quinidine altogether. However, following a sharp increase in seizure frequency (every 2

minutes), it was restarted within 2 days at a very low dosage of 14 mg/kg/d.

Four months into the patient's treatment course, the decision was made to slowly decrease and stop phenobarbital altogether and relegate it to an occasional rescue medication due to its unfavorable interaction with quinidine and depressive effects on the patient's central nervous system. Phenobarbital was slowly decreased every 2 to 3 weeks over an 8-week period (Weeks 17-24; see the Table 1) in decrements of 0.8 to 3.2 mg/kg/d (exact phenobarbital concentrations over time would have been included but were not available). Thereafter, the patient's quinidine levels became detectable and even rose to within the normal target range as the dose of quinidine was slowly increased once again (Table 1). Electrocardiograms were performed weekly, and the QT interval remained in the normal range. The patient's seizure frequency during this time interval was very erratic and inconsistent showing no definitive correlation between quinidine dose or serum level and seizure control. Despite increasing doses and blood levels of quinidine over time, the longest period of seizure freedom for this patient has been about 3.5 days.

The patient continues a regimen that includes quinidine (70 mg/kg/d), topiramate, clobazam, and levetiracetam on an outpatient basis. Lorazepam, phenobarbital, and fosphenytoin are only used as rescue medications when needed. Because her serum quinidine levels are still on the low end of the target range, we plan to increase the dose of quinidine further in hopes a higher average serum drug level will contribute to greater seizure control.

Discussion

We report the case of a patient with EIMFS and 2 mutations in the *KCNT1* gene treated with quinidine and phenobarbital among other antiepileptic drugs. Although 1 variant is of uncertain significance, the fact that this patient carries 2 mutations in the *KCNT1* gene contributes to the uniqueness of her case. The early presentation of symptoms also sets her case apart from others in the literature and suggests her condition may be somewhat more severe. Her treatment with concomitant quinidine and phenobarbital presented a challenge, as well, and illustrates the influence drug–drug interactions can have in therapy.

Phenobarbital is a well-known inducer of cytochrome P450 enzymes and can greatly increase the metabolic clearance of other drugs, such as quinidine, that are substrates for those enzymes.[8] Its enzyme-inducing effects were evident as the patient's quinidine therapy was initiated. Serum quinidine levels were never detectable when both drugs were being used on a chronic basis (Table 1). It was also difficult to quantify quinidine's effect on the

patient's seizure frequency, except when it was briefly withdrawn altogether. Only then did it become clear quinidine was, in fact, helping to decrease the patient's seizure frequency to some degree.

The ideal dosing interval for quinidine in this patient was difficult to determine. Pharmacokinetic studies suggest quinidine be dosed every half-life to avoid large fluctuations in serum concentration.[9] They indicate quinidine's half-life in pediatric patients averages 3.97 (0.46) hours with even shorter half-lives in patients younger than age 12 years (2–3 hours). Drug disposition studies show using quinidine concomitantly with antiepileptic drugs, such as phenobarbital and phenytoin, can decrease the drug's half-life by 50%. Based on evidence in the literature, quinidine's half-life in this patient was predicted to be approximately 2 hours. This prediction was supported by the pharmacokinetic estimates obtained from the patient-specific data gathered via serial blood sampling. Although a 2-hour dosing interval likely would have been ideal for this patient, a 6-hour dosing interval was chosen for the practical purpose of easing caregiver burden.

A final point worth mentioning is that of the conditions under which QTc prolongation occurred in this patient. This problem was encountered when both phenobarbital and quinidine (68 mg/kg/d) were on board but with no detectable serum quinidine level. Yet, when the quinidine regimen was again increased (72 mg/kg/d) without concurrent phenobarbital such that a normal serum quinidine level was detectable, QTc prolongation was not an issue. We found this to be quite perplexing as one would expect to see more QTc prolongation with detectable quinidine levels as opposed to undetectable levels. This reinforced the need to continue monitoring the patient's QTc interval very closely over time as long as quinidine was being used.

Conclusions

Although complete seizure freedom was not attained for this patient, her case demonstrates quinidine contributed to decreased seizure frequency to some extent. As other researchers have suggested, more study will be needed in this arena to better determine the ideal dosing regimen for quinidine if it continues to be used in treating these patients. Our case demonstrates the important influence drug–drug interactions can have on therapeutic outcomes and suggests concomitant use of enzyme-inducing drugs, such as phenobarbital, is best avoided if quinidine therapy is chosen for the treatment of *KCNT1*-positive epilepsy.

Author Contributions

CP: Wrote significant portions of the manuscript and revised and edited the manuscript.

JE: Conceived of the study idea and revised and edited the manuscript.

PC: Was involved in treatment planning and revised and edited the manuscript.

EO: Was involved in treatment planning, wrote significant portions of the patient presentation, and revised and edited the manuscript.

DD: Was involved in treatment planning and revised and edited the manuscript.

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