Oral quinine sulfate for the treatment of electrical storm and prevention of recurrent shocks in Brugada syndrome after failed cilostazol therapy

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Introduction
Brugada syndrome (BrS), an inherited ion channelopathy with an autosomal mode of inheritance, is associated with an increased risk of ventricular fibrillation (VF) and sudden death in the young. Implantable cardioverter-defibrillator (ICD) is effective in terminating VF and preventing sudden cardiac arrest in high-risk BrS patients but does not prevent recurrences of VF. An electrical storm occurs in 5% of asymptomatic BrS patients and in 45% of patients who have survived sudden cardiac arrest. Isoproterenol infusion is effective in suppressing VF episodes during electrical storms in BrS patients. Quinidine, a class IA drug, is effective in preventing recurrences of ventricular tachycardia (VT) and VF in a patient with BrS. However, quinidine is not available in most countries around the world, especially in Southeast Asia, where the disease is more prevalent. We present a case of BrS with an electrical storm while on therapy with oral cilostazol and discuss the management with oral quinine sulfate.

Case report
A 54-year-old man presented to the emergency room with 10 ICD shocks over a 1-hour period. Interrogation of the ICD revealed 10 episodes of VF terminated by appropriate shocks within 1 hour (Figure 1A and B). A single-chamber ICD had been implanted in 2013 for BrS and recurrent syncope. The first episode of an electrical storm with 18 shocks occurred 4 months after the ICD implantation and was managed successfully with intravenous isoprenaline. The patient was discharged on oral cilostazol 100 mg twice daily to prevent recurrent shocks because of nonavailability of quinidine. Before the present episode, while on cilostazol 100 mg twice daily, he had 1 electrical storm, 1 isolated episode of VF, 9 episodes of VT, and 17 episodes of supraventricular tachycardia (SVT) (Figure 2). At presentation, his clinical examination was unremarkable, and electrocardiogram (ECG) revealed type 1 Brugada pattern with marked ST elevation and QTc of 0.416 ms (Figure 3A). (QTc was calculated by Hodges’ method as the HR is > 110 beats/min). There were no precipitating factors, and serum biochemistry was normal with serum magnesium of 1.9 meq/L, potassium 4.0 meq/L, and calcium 8.8 meq/L. He received another appropriate shock 14 hours later while on isoprenaline infusion and occasional ventricular ectopic beats were noted during this period, along with partial resolution of ST elevation on the ECG (Figure 3B). Because of nonavailability of quinidine, treatment was initiated with oral quinine sulfate 300 mg thrice daily, and he was successfully weaned off isoprenaline 48 hours later. His subsequent course was uneventful, and he was discharged 7 days later on oral quinine 300 mg thrice daily along with cilostazol 100 mg twice daily, after a pulse generator replacement for premature battery depletion. There were no further episodes for 2 months, but because the patient complained of tinnitus, episodic altered hearing, and dizziness, suggestive of cinchonism, the dose of oral quinine sulfate was reduced to 150 mg thrice daily. One month later, he presented with 1 inappropriate shock for atrial fibrillation. On device interrogation, there were more than 20 nonsustained episodes of SVT, 2 episodes of monomorphic VT terminated by antitachycardia pacing, and 5 nonsustained episodes of polymorphic VT. The dose of oral quinine sulfate was increased to 300 mg thrice daily and cilostazol discontinued, as it was ineffective. A tryptophan-rich diet was advised to avoid the side effects of quinine, based on the research in malaria patients receiving quinine. The dietary modification included 2–3
portions of meat (1 portion = 60 g red meat/80 g white meat), a handful of nuts (1 handful = 1.5 oz/42.5 g, or 1/3 cup), and 3 glasses (1 glass = 200 mL) of milk per day. At 4 months follow-up, the patient is asymptomatic, with no episodes of supraventricular or ventricular arrhythmias, which abated after its withdrawal, and oral quinine sulfate was used as monotherapy.

Mehrotra and colleagues reported the use of intravenous quinine in the acute management of arrhythmic storm in a 10-year-old child because of nonavailability of quinidine. Quinidine is manufactured in India but is not available for local use. Nonavailability of quinidine in Southeast Asian countries, where the disease is highly prevalent, makes it difficult to manage patients with an electrical storm and recurrent shocks and puts the patient’s life at risk. Frequent electrical storms, nonavailability of quinidine, and difficulty in procuring the drug prompted us to consider oral quinine sulfate as an alternative. Quinine and its levorotatory diastereomer quinidine have similar pharmacologic activities in many aspects. In experimental arrhythmias, both quinidine and quinine suppress VF thresholds, reverse aconitine-induced atrial fibrillation, decrease ouabain-induced abnormal ventricular beats, and increase atrial refractory periods and His-Purkinje conduction. In humans, quinine is effective in suppressing both spontaneous and inducible ventricular arrhythmias without the proarrhythmic potential of QT prolongation, torsades de pointes, or heart block. The mean dose of oral quinine sulfate necessary for antiarrhythmic response in adults is 927 mg/day, which is much less than that required for antimalarial activity. Quinidine prolongs QTc, but quinine has no effect on the QT interval. The absence of QT prolongation and lower incidence of torsades de pointes with quinine is due to its stereoselective effect, resulting in 14 times less potency in blocking the hERG channel, the potassium
channel essential for myocardial repolarization. Unlike quinidine, quinine has the advantage of being readily available in most countries, and hence, further studies are needed to assess the effectiveness of oral quinine sulfate in the treatment of ventricular arrhythmias in BrS patients. Quinine remains the most commonly used antimalarial therapy despite toxicity concerns, especially in children. A link between quinine toxicity and glucose-6-phosphate dehydrogenase deficiency is known but accounts for only a fraction of adverse response. The cognitive side effects contribute to a significant fraction of adverse reactions to quinine, attributed to tryptophan transport inhibition and tryptophan starvation. Tryptophan, an essential amino acid not produced by the body, is a direct precursor for the synthesis of the key neurotransmitter 5-hydroxytryptamine (serotonin). Tryptophan is also a precursor for quinine biosynthesis, and these 2 molecules have marked structural similarity. Quinine binds competitively and reversibly at the tryptophan binding sites in place of tryptophan owing to their similar structures. The symptoms of tryptophan deficiency in humans are neurocognitive and are akin to those seen in cinchonism. The cognitive effects of tryptophan depletion, such as tinnitus, overlap with common quinine side effects. Confirming the hypothesis of

Figure 1  Details of implantable cardioverter-defibrillator (ICD) interrogation at the time of presentation. A: The log of therapies delivered by the ICD reveals that from 16.06 to 17.07 hours the patient has 10 shocks delivered for ventricular fibrillation (VF). B: Intracardiac electrogram of 1 of the above episodes from the device shows a ventricular ectopic beat falling on the T wave, initiating a polymorphic ventricular tachycardia (VT) degenerating into VF correctly identified by the device. The patient received an appropriate therapy with a 35-joule shock terminating the VF (not in the picture).
low tryptophan levels causing neurocognitive side effects, in malaria patients on quinine therapy side effects are more common in patients with low serum levels of tryptophan, and increasing the dietary intake of tryptophan ameliorates these side effects.

In our BrS patient, oral cilostazol as monotherapy was ineffective in preventing electrical storms and episodes of ventricular arrhythmias. Similar to our experience, failure of oral cilostazol as monotherapy in preventing electrical storm has been reported. Spontaneous AF is seen in 10%–53% of BrS cases and is associated with higher incidence of syncopal episodes and documented VF. In the present case, monotherapy with quinine also resulted in suppression of supraventricular arrhythmias, and further studies are needed to validate this finding.

In conclusion, oral quinine sulfate is effective in the treatment of electrical storm and prevention of recurrent ICD shocks in BrS patients. High tryptophan diet is helpful in the management of common side effects of quinine, such as cinchonism. In countries where quinidine is not available, oral quinine sulfate should be considered as an alternative to prevent recurrent ICD shocks and electrical storms.
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