Quinidine, A Life-Saving Medication for Brugada Syndrome, Is Inaccessible in Many Countries

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Objectives
The aim of this study was to determine the availability of quinidine throughout the world.

Background
Quinidine is the only oral medication that is effective for preventing life-threatening ventricular arrhythmias due to Brugada syndrome and idiopathic ventricular fibrillation. However, because of its low price and restricted indication, this medication is not marketed in many countries.

Methods
We conducted a survey of the availability of quinidine by contacting professional medical societies and arrhythmia specialists worldwide. Physicians were e-mailed questionnaires requesting information concerning the quinidine preparation available at their hospital. We also requested information concerning cases of adverse arrhythmic events resulting from unavailability of quinidine.

Results
A total of 273 physicians from 131 countries provided information regarding the availability of quinidine. Quinidine was readily available in 19 countries (14%), not accessible in 99 countries (76%), and available only through specific regulatory processes that require 4 to 90 days for completion in 13 countries (10%). We were able to gather information concerning 22 patients who had serious arrhythmias probably related (10 cases) or possibility related (12 cases) to the absence of quinidine, including 2 fatalities possibly attributable to the unavailability of quinidine.

Conclusions
The lack of accessibility of quinidine is a serious medical hazard at the global level. (J Am Coll Cardiol 2013;61:2383–7) © 2013 by the American College of Cardiology Foundation

E-mail received on June 8, 2012 (no editing was done):

Hi, I hope this finds you well!
I am sorry to trouble you, but I have no one else to ask! I have a patient who had an out-of-hospital cardiac arrest a couple of years ago, and had a defibrillator implanted. He returned last week with multiple shocks for VF, and a suspicious ECG for Brugada syndrome. He did not respond to beta-blocker therapy and I wanted to start quinidine for him – I recall having a few patients at Sunnybrook as a resident who were taking quinidine, and we ordered it without a problem. I tried to get quinidine for this patient via SAP with Health Canada, and it was declined – they stated they did not provide it for NEW patients, only patients already on the therapy. How are you managing your Brugada patients with multiple shocks or recurrent arrhythmias? This seems completely ridiculous!

With kind regards,
Signed by a Cardiology Fellow in Canada (personal communication, 2012)

Limited patient access to curative or life-prolonging medications is a major problem worldwide. It is well acknowledged that this problem commonly results from the inability...
of healthcare resources to meet the high costs of patented drugs or even that of generic substitutes (e.g., antiretroviral medications in Africa or heart failure therapy for the uninsured in the United States) (1,2). Less well recognized is the opposite situation, in which the unavailability or inaccessibility of a life-saving medication is governed by its low price and restricted indication for a low-prevalence disease, rendering unfavorable pharmaceutical market forces from the perspective of the industry. The latter setting is exemplified by the case of quinidine (3–5).

Quinidine is the only oral medication that has consistently shown efficacy in preventing arrhythmias and terminating arrhythmic storms due to recurrent ventricular fibrillation (VF) in patients with Brugada syndrome (6–14), idiopathic VF (15–20), and early repolarization syndrome (21–23). Without appropriate drug therapy, such events can prove lethal even in patients with an implantable cardioverter-defibrillator (ICD), who may receive numerous ICD shocks per day, eventually leading to cardiogenic shock. Quinidine is also the only antiarrhythmic drug that normalizes the QT interval in patients with the congenital short QT syndrome (24,25). However, ever since the unexpected cessation of quinidine production by its main manufacturer (26), prescribing this valuable medication has become increasingly difficult in many countries. In fact, on several occasions during recent years, the first author had to mail emergency supplies of quinidine overseas to physicians treating patients in urgent need of this medication because of arrhythmic storms. In view of this emerging problem, we conducted a worldwide survey designed to estimate the magnitude of the shortage of quinidine and its clinical implications.

Methods

We conducted a survey of the availability of quinidine by contacting professional societies of cardiology, national working groups on arrhythmia and electrophysiology, arrhythmia specialists, and cardiologists worldwide through e-mail. We also took advantage of dedicated e-mail networks (Foro Iberoamericano de Arritmias en Internet, with >700 subscribers) and a Chinese forum. Additional e-mail addresses were obtained via a literature search for articles published on Brugada syndrome, idiopathic VF, and early repolarization syndromes. All recipients were e-mailed a questionnaire requesting information concerning the quinidine preparation available at their hospital (including commercial name and manufacturer). We also requested information pertaining to the actual time required for quinidine to be supplied for use as well as the regulatory processes involved. In addition, we specifically requested information about the number of patients at each center treated with quinidine for Brugada syndrome, idiopathic VF, or early repolarization syndromes. Corroborating evidence was sought from at least one other physician or pharmacist and all searchable public and regulatory bodies to validate physician reports. Finally, we requested information concerning cases of serious adverse arrhythmic events (defined as recurrent life-threatening ventricular arrhythmias or ICD shocks) resulting from unavailability of quinidine. All contacted physicians were also requested to forward the study questionnaire to contacts of their own. Therefore, although the number of responders is known, the number of physicians who declined to respond is not. The entire e-mail survey was conducted from June to September 2012.

Arrhythmic events were defined as related to unavailability of quinidine when the following criteria were met: 1) occurrence of arrhythmias known to respond to quinidine (i.e., polymorphic ventricular tachycardia or VF) in an appropriate clinical setting (i.e., a definite diagnosis of Brugada syndrome or idiopathic VF with or without early repolarization); 2) inability to administer quinidine at the time of its prescription; and 3) further ventricular tachyarrhythmias requiring defibrillation occurring from the time of quinidine prescription to the time of its actual administration. Events associated with unavailability of quinidine were further classified as “probably resulting” from the absence of the medication in cases in which resolution of arrhythmia was ultimately achieved by administration of quinidine. All cases in which quinidine was never administered were classified as “possibly resulting” from unavailability of quinidine. The definitions in the preceding text take into account that the efficacy of quinidine for these specific arrhythmic syndromes is well established (6,18–20, 22,27,28).

Results

We received information concerning the availability of quinidine in 131 countries (Fig. 1). Missing data are almost exclusively from African countries. There was discordant information from only 5 countries (Argentina, China, Czech Republic, Norway, and Sweden) and was mostly attributable to discrepancies in classification of the availability of quinidine as either “not available” or “available with restrictions.”

Quinidine is readily and immediately available in only 19 countries (14%). In contrast, this medication is unavailable in 99 countries (76%) and is available but only through restrictive regulatory processes that require 4 to 90 days to complete in 13 countries (10%) (Fig. 1). Of the 273 physicians responding to our survey, 71 (26%) had at least one patient in need of quinidine therapy because of idiopathic VF or Brugada syndrome. Importantly, 28 physicians (representing 10% of all survey responders and 39% of physicians who treated patients with Brugada syndrome or idiopathic VF) reported having one or more patients who developed arrhythmic events related to inaccessibility to quinidine when prescribed. Within 4 months (June to September 2012),
we were able to gather detailed information concerning 22 patients who had serious arrhythmic complications (mainly recurrent appropriate ICD shocks for spontaneous VF) because of inaccessibility of quinidine. The reports included serious adverse events considered probably (10 cases) or possibly (12 cases) related to the absence of quinidine and included reports of 2 patients who possibly died because of lack of quinidine therapy (Table 1).

Discussion

Quinidine was the most commonly used medication for the prevention of ventricular and atrial arrhythmias as recently as 2 decades ago (29,30). However, several factors led to a gradual decrease in the use of this drug. First, the potential for QT prolongation and torsades de pointes provocation by quinidine became clearly evident in the 1980s (31–33); then, in 1989, the CAST (Cardiac Arrhythmia Suppression Trial) revealed that the use of class I antiarrhythmic drugs for the prevention of sudden death in patients with asymptomatic ventricular arrhythmias and impaired left ventricular function actually resulted in increased mortality (34). Finally, in 1990, an extensively quoted meta-analysis suggested that use of quinidine is associated with increased mortality even in the setting of atrial fibrillation therapy (35). The decline in use of quinidine was perpetuated by the introduction of new antiarrhythmic drugs considered safe at the time. By 2006, AstraZeneca (the main manufacturer of quinidine) discontinued its production (26). Although discontinuation of mass production of quinidine might be perceived as inevitable given modern pharmaceutical market forces, it was clearly problematic from an ethical point of view because the unique effectiveness of quinidine for prevention of VF (15–18) and for controlling arrhythmic storms in patients with idiopathic VF (19,20) had been known for more than 2 decades at that time. Moreover, the laboratory (36) and clinical (6–8) evidence establishing the high efficacy of quinidine in the management of patients with Brugada syndrome, particularly for arrhythmic storms (9–13), were well known at the time production of quinidine was discontinued.

Our study shows that quinidine is entirely unavailable or available only with delay in 86% of all countries for which data were obtainable. Interestingly, quinidine is produced in France by a large manufacturer (Sanofi) but is not readily available in neighboring countries such as Germany. Lack of fiscal incentives, driven by low pricing and the low prevalence of the conditions for which the drug is indicated, is potentially one explanation for the variations in availability of quinidine noted between countries. Ironically, one of the brands of quinidine available in the United States is made in India, although it is not marketed in its country of origin. As a consequence of this absurdity, a 10-year-old Indian girl with arrhythmic storm due to Brugada syndrome is
Quinidine Shortage for Brugada Syndrome

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Table 1

<table>
<thead>
<tr>
<th>Country</th>
<th>City</th>
<th>Hospital</th>
<th>Case Description</th>
</tr>
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<tbody>
<tr>
<td>Mexico</td>
<td>Mexico City</td>
<td>Instituto Nacional de Cardiología</td>
<td>A 30-year-old man with Brugada syndrome presented with VF storm that responded immediately to quinidine therapy. He received quinidine for more than 5 years without events until marketing of quinidine was discontinued in Mexico. Shortly thereafter, he received one appropriate ICD shock for VF. It took 8 days to receive supplies of quinidine. Once administration of quinidine was restarted, he remained free of arrhythmias for the remaining follow-up period (6 months).</td>
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<tr>
<td>Philippines</td>
<td>Manila</td>
<td>Philippine Heart Center</td>
<td>Frequent ICD shocks leading to premature ICD battery depletion, probably due to inaccessibility of quinidine. A 52-year-old man with Brugada syndrome underwent ICD implantation for recurrent syncope in 2002. He then developed several VF storms leading to multiple appropriate ICD shocks (the most frequent was 20 in 1 day). Because of the frequent ICD shocks, the patient quit his job and would stay outside the emergency department of the hospital for fear of recurrence. He had innumerable episodes and countless shocks. He was treated with metoprolol and amiodarone, alone and in combination, without success. Because of the numerous appropriate ICD shocks, he required ICD replacement for battery depletion only 3 years after implantation. Quinidine was prescribed, but the drug was not available in the Philippines. Years later, a relative sent supplies of quinidine from Guam. Treatment with quinidine led to complete suppression of arrhythmias. The patient has remained free of arrhythmias for the past 7 years, ever since treatment with quinidine was started.</td>
</tr>
<tr>
<td>India</td>
<td>New Delhi</td>
<td>All India Institute of Medical Sciences</td>
<td>Recurrent ICD shocks in a child, probably due to inaccessibility of quinidine. A 10-year-old girl with Brugada syndrome presented with VF storm. She was originally treated with the intravenous antimalarial agent quinine because quinidine was not available (38). Over the years, she was treated with oral quinidine. Although quinidine is produced in India, it is not marketed there. Consequently, physician colleagues in the United States periodically mail supplies of quinidine back to India for the treatment of this child. Over the years, she has received ICD shocks definitively linked to temporary lack of quinidine availability.</td>
</tr>
<tr>
<td>Thailand</td>
<td>Bangkok</td>
<td>Bhumibol Adulyadej Hospital</td>
<td>Death from VF storm possibly related to inaccessibility of quinidine and isoproterenol. A 67-year-old man was hospitalized with VF storm. He had diabetes and hypertension and presented with chest pain but had no significant coronary artery disease during emergency catheterization. He went into incessant VF within 30 min. He failed to respond to antiarrhythmic therapy, including intravenous amiodarone. The diagnosis of idiopathic VF was considered, and therapy with intravenous isoproterenol and oral quinidine was prescribed. However, neither of these medications was available. After multiple DC shocks, cardiogenic shock developed and an intra-aortic balloon pump was placed. The patient ultimately died of cardiogenic shock due to intractable arrhythmic storm.</td>
</tr>
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*A complete list of patients who experienced serious adverse events because of the unavailability of quinidine appears as Online Table 1.

ICD—implantable cardioverter-defibrillator; VF—ventricular fibrillation.

desperately dependent on an Indian-made medication that is shipped to her from the United States, thanks to the collaboration between colleagues in these 2 countries (Table 1). The unavailability of quinidine in southeast Asian countries such as Thailand and the Philippines is intolerable because Brugada syndrome is highly prevalent in that region (37). Through our survey, we identified 22 patients who experienced serious adverse events (mainly recurrent ICD shocks for VF) that were attributed to inaccessibility of quinidine, including 2 fatalities possibly due to this problem.

Study limitations. The fact that 10% of physicians responding to our inquiry could provide detailed information regarding patients in urgent need of quinidine therapy could represent selection bias; in other words, it is possible that physicians with patients in need of quinidine were more likely to respond to our survey and were therefore overrepresented. Nevertheless, the fact that within a very short period we were able to collect data for so many adverse events in so many countries suggests that the lack of quinidine availability is a serious medical hazard at the international level.

Our study has important clinical implications. Professional medical organizations, in particular the Heart Rhythm Society, the European Heart Rhythm Association, and the Asia Pacific Heart Rhythm Society, must work in unison with national healthcare authorities to ensure expedited access and reduce the price of the processes required to make quinidine readily and legally available in all countries. Until that happens, arrhythmia centers (at least in referral hospitals) should ensure an adequate supply of quinidine for immediate access in medical emergencies. Also, drug manufacturers must assume responsibility for an adequate and continuous supply of irreplaceable medications proven valuable even when their marketing is no longer profitable. Legislative measures to prevent independent and unilateral discontinuation of crucial drug production by manufacturers, pending the availability of efficacious substitutes, should be considered at the national level.

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