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Letters

Shock Reduction With Long-Term Quinidine in Patients With Brugada Syndrome and Malignant Ventricular Arrhythmia Episodes

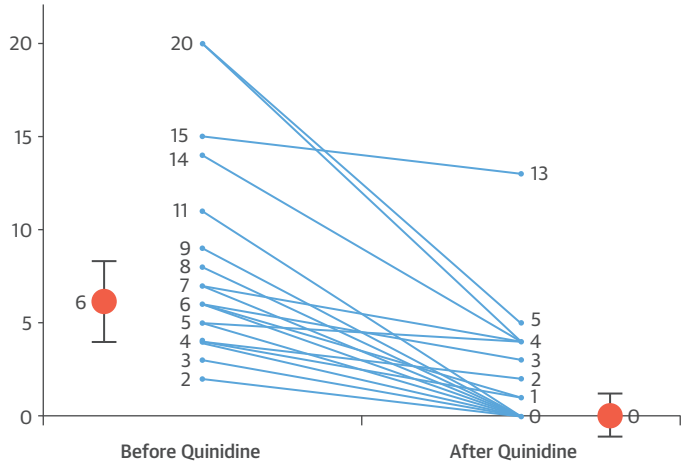
High-risk Brugada syndrome (BrS) is treated with an implantable cardioverter-defibrillator (ICD). However, ventricular arrhythmias (VA) and high-energy shocks may be frequent events after ICD implantation (1), resulting in an impact on quality of life. Quinidine, a class Ia antiarrhythmic agent that inhibits outward transient K current (I_{to1}), has been proposed as an adjuvant treatment in BrS patients (2-4), but there are limited data about its long-term effectiveness. We sought to describe the experience in Spain with quinidine in patients with BrS and frequent appropriate ICD shocks.

We conducted a nationwide observational survey in all centers in Spain that contribute to the national registry of ICD implants. Electrocardiogram patterns were considered diagnostic of BrS if a coved-type ST-segment elevation of >2 mm was documented in ≥1 lead from V_1 to V_3 in the presence or absence of a sodium-channel blocker. Statistical analyses were performed using SPSS (version 18.3 for Windows, IBM Inc., Armonk, New York). Continuous variables are presented as means ± SD or medians (interquartile range [IQR]) and categorical variables as numbers and percentages. Comparisons between groups (patients with or without recurrent shocks) were undertaken using the Student *t* test or Wilcoxon rank-sum test for continuous variables and chi-squared test or Fisher exact test for categorical variables. The median number of shocks per patient before and after treatment was evaluated by a Wilcoxon matched-pairs signed-rank test. We assessed the relation of covariates with recurrent shocks by univariate cox regression analysis and then determined hazard ratios (HR).

We received information from 48 centers, representing 91% of all centers with ICD implantation and follow-up programs from Spain. A total of 820 BrS patients with ICD were identified. Of these, 29 (3.5%) were prescribed quinidine for recurrent VA and are the subject of the present investigation. The majority of patients were male (n = 25) and mean age was 39 ± 14 years. ICD had been implanted for secondary prevention after sudden death in 16 patients (55%). Spontaneous ST-segment elevation (type 1 pattern) was recorded in 24 patients (83%). Indication for quinidine was electrical storm in 9 patients (31%) and frequent ICD shocks in 20 (69%). Ten patients received quinidine bisulfate (mean dose 591 ± 239 mg/day), and hydroquinidine (19 patients), mean dose 697 ± 318 mg/day.

After a mean period of 60 ± 41 months under quinidine treatment, 19 patients (66%) remained free of appropriate ICD discharges. Figure 1 shows the reduction in the median number of ICD shocks before and after quinidine for each patient. A significant reduction in total number of shocks and in median number of shocks per patient was observed, from 203 to 41 shocks and from 6 shocks per patient IQR (4 to 9) to 0 shocks per patient IQR (0 to 2.5), p < 0.0001, respectively. A total of 10 patients (34%) experienced at least 1 recurrent shock (in 4, shocks were related to a reduction in the dose of quinidine due to side effects [n = 2] or to temporary discontinuation of treatment by the patient

FIGURE 1 ICD Shocks Before and After Quinidine



The chart shows the median number of implantable cardioverter-defibrillator (ICD) shocks before and after quinidine administration for each patient. The number of shocks was reduced by quinidine use.

[n = 2]). Predictors of recurrent shock in the univariate analysis were a temporary discontinuation of quinidine (HR: 4.6; 95% confidence interval [CI]: 1.28 to 16.6; p = 0.02) and the number of shocks prior to quinidine initiation (HR: 1.13; 95% CI: 1.01 to 1.26; p = 0.03). The mean dose of quinidine was not different in patients with and without recurrent shocks, except for those with temporary suppression of treatment (due to side effects or by patient decision).

During quinidine therapy, QT intervals corrected for heart rate increased by a mean of <10% (413 ± 18 to 442 ± 35; p = 001) without episodes of torsade-de-pointes. Side effects appeared in 5 patients (17%): diarrhea (n = 4) and cutaneous lupus erythematosus (n = 1). These were managed with reduction of quinidine doses.

This study reports on the largest series of very high-risk BrS patients. Quinidine administration in BrS patients with life-threatening VA was associated with a very significant reduction in ICD shocks. Even those patients who continued to receive shocks experienced a clinically relevant reduction in the VA burden for the long term. Several studies have documented that quinidine is effective in preventing ventricular fibrillation induction in BrS patients during electrophysiologic study (2,3), but only anecdotal reports had documented its beneficial effects in symptomatic BrS patients (secondary prevention patients).

We found that a temporary reduction in the dose of quinidine due to side effects or discontinuation of treatment by the patient were important factors predicting recurrent shocks. Side effects were seen in 5 patients (17%) and diarrhea was the most frequent, which is similar to previous reports (2,3). Careful assessment of factors that might affect compliance in individual patients might also be useful in the long-term management of quinidine-treated patients.

Some patients are relatively resistant to quinidine and may require higher doses to control VA. Also, there may be genetic and phenotypic heterogeneity and some patients may have a worse outcome with quinidine. Monitoring of quinidine plasma levels has been proposed. Unfortunately, this was not available for our patients and could help in the management of these patients.

The relatively small number of patients and the retrospective nature of the study with no control subjects are the main limitations of our study. Additionally, patients with recurrent shocks or arrhythmic storms may remain free of arrhythmias for years, and so it is difficult to know how much of the benefit we found can be attributed to the use of quinidine.

In conclusion, quinidine administration in patients with BrS and recurrent ventricular arrhythmias is effective in the majority of cases and contributes to a clinically relevant reduction in the number of ICD shocks. Predictors of recurrent shock were a temporary discontinuation of quinidine and the number of shocks prior to quinidine initiation.

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Restarting Dabigatran Etexilate 24 h After Reversal With Idarucizumab and Redosing Idarucizumab in Healthy Volunteers

Idarucizumab is a specific reversal agent that rapidly neutralizes dabigatran's anticoagulant activity (1–3). We investigated restoration of dabigatran