Drug-induced QT-interval shortening following antiepileptic treatment with oral rufinamide

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BACKGROUND The arrhythmogenic potential of short QT intervals has recently been highlighted in patients with a short QT syndrome. Drug-induced QT-interval prolongation is a known risk factor for ventricular tachyarrhythmias. However, reports on drug-induced QT-interval shortening are rare and proarrhythmic effects remain unclear.

OBJECTIVE Recently, rufinamide, a new antiepileptic drug for the add-on treatment of Lennox-Gastaut syndrome, was approved in the European Union and the United States. Initial trials showed drug-induced QT-interval shortening. The aim of our study was to evaluate the effects of rufinamide on QT intervals in patients with difficult-to-treat epilepsies.

METHODS Nineteen consecutive patients with Lennox-Gastaut syndrome and other epilepsy syndromes were included (n = 12 men; mean age 41 ± 12 years). QRS, QT, and T_{peak}-T_{end} intervals were analyzed before and during rufinamide treatment.

RESULTS The mean QT interval shortened significantly following rufinamide administration (QT interval 349 ± 23 ms vs 327 ± 17 ms; corrected QT interval 402 ± 22 ms vs 382 ± 16 ms; $P = .002$). T_{peak}-T_{end} intervals were 79 ± 17 ms before and 70 ± 20 ms on treatment ($P = .07$). The mean reduction of the corrected QT interval was 20 ± 18 ms. During follow-up (3.04 ± 1.09 years), no adverse events including symptomatic cardiac arrhythmias or sudden cardiac deaths were observed.

CONCLUSION QTc-interval shortening following oral rufinamide administration in a small patient group was not associated with significant clinical adverse effects. These observations nothwithstanding, the ability of rufinamide to significantly shorten the QT interval portends a potential arrhythmogenic risk that may best be guarded against by periodic electrocardiographic recordings.

KEYWORDS Drug-induced QT-interval shortening; Short QT syndrome; SUDEP; sudden cardiac death; Proarrhythmia; Rufinamide

ABBREVIATIONS **AED** = antiepileptic drugs; **ECG** = electrocardiogram/electrocardiographic; $\mathbf{I_{Kr}}$ = delayed rectifier potassium current; $\mathbf{I_{Na}}$ = sodium channel current; **LGS** = Lennox-Gastaut syndrome; **SCD** = sudden cardiac death; **SQTS** = short QT syndrome; **SUDEP** = sudden unexpected death in epilepsy

(Heart Rhythm 2012;9:776–781)

Introduction

The short QT syndrome (SQTS) represents a primary electrical disease characterized by a substantial shortening of the QT interval, atrial and ventricular effective refractory periods, and a risk for atrial and ventricular tachyarrhythmias.[1,2] Up to now, gain-of-function mutations of cardiac potassium channels as well as loss-of-function mutations of cardiac L-type calcium channels have been described in SQTS with an increased risk for sudden cardiac death (SCD).[3–5] However, the yield of genetic screening in familial SQTS is only 23% in index patients.[6]

Bellet et al[7] reported for the first time drug-induced QT-interval prolongation in 1951 (quinidine). Meanwhile a variety of drugs have been identified to prolong the QT interval. The risk for proarrhythmia (torsades de pointes) significantly increases with a corrected QT (QTc) interval of >500 ms.[8] The regulatory consequence of the potential life-threatening proarrhythmic side effects of drugs led to the implementation of a thorough QT/QTc analysis during the development of new drugs (International Conference on Harmonisation 2005, ICH E14).[9] However, drug-induced QT-interval shortening is a rarely observed phenomenon.[10] Furthermore, proarrhythmic effects of drug-induced QT-interval shortening have been shown only with digitalis.[11]

Recently, rufinamide, probably the first QT-interval-shortening drug in the post–ICH E14 period, was approved in the European Union by the European Medicines Agency (in 2007) and in the United States by the Food and Drug Administration (in 2008).[10] Rufinamide is structurally distinct from other antiepileptic drugs (AEDs) and is used as an adjunctive treatment for seizures associated with Lennox-

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1547-5271/$ -see front matter doi:10.1016/j.hrthm.2012.01.006

Gastaut syndrome (LGS) in children older than 4 years as well as in adults. This severe epileptic encephalopathy is characterized by multiple types of generalized seizures, especially drop attacks and tonic seizures, delayed psychomotor development, and behavioral and personality disorders. Clinical trials with rufinamide showed a concentration-dependent degree of QT-interval shortening.[10,12] Although the underlying mechanism and safety relevance of this finding is not known, the European labeling advises clinicians to use their clinical judgment when prescribing rufinamide to patients at risk for further QT-interval shortening (SQTS).[13] However, data on proarrhythmic side effects of drug-induced QT-interval shortening were not reported.[10,12,13]

The aim of our study was to assess the first clinical experience of the new drug rufinamide in the treatment of LGS in a tertiary epilepsy center in Germany with regard to changes in the QT interval and cardiovascular events during follow-up.

Methods

Nineteen consecutive patients (n = 11 men; mean age 41 ± 12 years) with LGS and other epilepsy syndromes treated in the Bethel Epilepsy Center, Bielefeld, Germany, were included since the introduction of rufinamide in 2008. The mean duration of epilepsy in these patients was 40 ± 11 years. In 9 patients, the diagnosis was LGS. The other patients had other focal epilepsy (n = 5) or epilepsy with focal or generalized seizures (n = 5). They were treated off-label because of severe drug-refractoy epilepsies, mostly with drop attacks. Three patients had an implanted vagal nerve stimulator. At the time of electrocardiographic (ECG) recording, the neurostimulator was not active. Non-AED comedication with potential effects on the QT interval included digitalis (n = 1 patient) and promethazine (n = 2 patients). AEDs used were acetazolamide (n = 2), clobazam (n = 4), clonazepam (n = 3), carbamazepine (n = 4), diazepam (n = 1), ethosuximide (n = 1), felbamate (n = 1), lacosamide (n = 4), lamotrigine (n = 12), levetiracetam (n = 11), lorazepam (n = 1), methsuximide (n = 1), oxcarbazepine (n = 2), phenobarbital (n = 1), phenytoin (n = 2), pregrabalin (n = 1), topiramate (n = 3), valproic acid (n = 14), and zonisamide (n = 2). Thus, the most common baseline therapy of our patients included lamotrigine, levetiracetam, and valproic acid. Rufinamide was administered in all patients exclusively as an adjunctive treatment to a baseline therapy. Before the initiation of the drug in each patient, a 12-lead ECG was recorded and repeated during titration. Drug monitoring of all AEDs was performed in the fasting state and after no change in the dosage of the drug at least for >3 days.[14]

All ECGs were scanned and analyzed digitally (Adobe Acrobat Professional 8.0, Adobe Systems Inc, San Jose, CA). A standardized method was used to exactly measure the QT interval. The end of the T wave was defined as the intersection of a tangent to the steepest slope of the last limb of the T wave and the baseline preferably in lead II.[15] The mean of the QT interval of 3 consecutive QT intervals was calculated. The QTc interval was defined as QT/$\sqrt{}$RR from the RR interval between the measured and the preceding complex (Bazett). Two cardiologists performed the ECG measurements without the knowledge of the underlying medication. ECGs with heart rates below 60 beats/min and above 100 beats/min were excluded from the QT/QTc analysis owing to imprecision of Bazett's correction. Furthermore, T_{peak}-T_{end} intervals were calculated as the difference of the interval of the Q wave to the peak of the T wave (QT_{peak}) and the interval of the Q wave to the end of the T wave (QT_{end}), representing a surrogate marker of the transmural dispersion of repolarization (T_{peak}-T_{end} interval).[16] Finally, QRS width has been determined before and during treatment. Clinical information with respect to symptomatic cardiac arrhythmias and adverse events such as syncope and sudden unexpected death in epilepsy (SUDEP) was assessed during follow-up. All parameters were expressed as mean values ± SD. A Student *t* test was performed to test for statistical differences between 2 unpaired mean values. A *P* value of <.05 was considered to be statistically significant (Microsoft Excel 2008 for Macintosh, v.12.2.5, Redmond, WA).

Results

The follow-up was 3.6 ± 0.67 years, and on medication, 3.04 ± 1.09 years. In 7 patients, rufinamide was stopped owing to lack of clinical benefit. The final dosage of rufinamide in all patients was 2779 ± 410 mg (Table 1). The maximal serum concentration was 18.4 ± 8.9 μg/mL (therapeutic range 5–30 μg/mL; serum concentrations in adults according to data from routine therapeutic drug monitoring 15.9 ± 8.5 μg/mL).[14] The most frequent comedications with the maximal dosage and blood level during follow-up were as follows: lamotrigine (n = 12; 344 ± 113 mg; 11 ± 2.1 μg/mL), levetiracetam (n = 11; 3091 ± 1136 mg; 25.4 ± 23.4 μg/mL), and valproic acid (n = 14; 1689 ± 1160 mg; 64.8 ± 23.4 μg/mL).

QT intervals were 349 ± 23 ms (QTc interval 402 ± 22 ms) before the initiation of therapy and significantly decreased to 327 ± 17 ms (QTc interval 382 ± 16 ms) after steady state (*P* = .002; Figure 1). T_{peak}-T_{end} intervals averaged 79 ± 17 ms before therapy and were nonsignificantly decreased to 70 ± 20 ms (*P* = .07). The mean reduction in the QTc interval was −20 ± 18 ms, and the change in the T_{peak}-T_{end} intervals was −8 ± 16 ms. QRS duration did not change before and after treatment (95 ± 11 ms vs 94 ± 10 ms; *P* = .89). The heart rates were not different between baseline and rufinamide treatment (81 ± 11 beats/min vs 82 ± 8 beats/min; *P* = .54).

The maximal individual difference in the QTc interval in a single patient between baseline and rufinamide treatment was −54 ms (QTc interval 411 ms vs 357 ms; 3200 mg of rufinamide; serum level 41.1 μg/mL). The QTc interval of <320 ms was not recorded in any patient, as observed in patients with SQTS (SQTS 1−3). However, drug-induced QT-interval shortening to QTc values of 350 ms occurred in 2 patients. A drug-induced reduction in the QTc interval to ≥30 ms (range 30–54 ms) was observed in 6 of the 19 (32%) patients (Figure 2). Furthermore, QTc-interval