Is mexiletine ready for prime time in patients with Type 2 Long QT Syndrome?

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Background: Mexiletine has been proven effective in shortening the duration of ventricular repolarization and reducing the arrhythmic events in type 3 Long QT Syndrome (LQT3). Initial reports indicate that mexiletine might also be effective in patients with type 2 Long QT Syndrome (LQT2, caused by loss-of-functions variants on KCNH2 gene, coding for HERG potassium channel), but this issue has not been investigated in detail.

Purpose: We quantified the electrocardiographic (ECG) effects of mexiletine in a cohort of LQT2 patients.

Methods: Twelve-lead ECGs were collected before and after the administration of mexiletine to evaluate the drug's effect on the heart rate-corrected QT interval (QTc). QTc intervals were classified as being (1) at "high-risk" if >500 ms or (2) "normal" if <460 ms, before and after the administration of the drug. KCNH2 variants were defined as (1) trafficking-deficient or (2) non-trafficking-deficient, based on functional studies.

Results: We tested the maximum tolerated dose of mexiletine in 20 patients (11 males, 55%), who were 17±16 years old at diagnosis, affected by genetically established LQT2. The mean age at the beginning of mexiletine administration was 23±15 years and the mean daily dose administered was 9±2 mg/kg/day.

Before mexiletine, the mean QTc interval was 527±53 ms and 10/20 (50%) patients had high-risk QTc values (i.e. QTc >500 ms).

After mexiletine, the mean QTc interval shortened to 484±47 ms in the overall population (p=0.001). In the majority of patients (18/20, 90%; Figure 1) QTc interval shortened, with a mean shortening of 42±28 ms, and a high-interindividual variability (range of shortening from 86 ms to 8 ms). Just 2 (10%) patients did not show any reduction of the QTc, despite receiving the highest adult dosages of mexiletine in our cohort (up to 10 mg/kg/day).

As compared to baseline conditions, after mexiletine the proportion of patients with high risk QTc values (>500 ms) decreased non-significantly from 50% to 35% (p=0.52). Furthermore, in only 6/20 (30%) patients the QTc normalized (i.e. QTc <460 ms) after the initiation of treatment.

The effect of mexiletine was not influenced by gender (p=0.89) or by the functional effect of the KCNH2 mutation (trafficking-deficient vs. non-trafficking-deficient variants, p=0.41).

The effect of mexiletine in LQT2 patients was inferior to the one previously observed in a cohort of 34 LQT3 patients, who had similar QTc values at baseline and received similar dosages of mexiletine, but showed a significantly higher reduction of the average QTc interval (63±37 ms in LQT3 vs. 42±28 ms in LQT2, p=0.02).

Conclusions: Mexiletine induces a reduction of the QTc interval in most LQT2 patients, but many patients remain with high-risk QTc values after receiving the drug. The demonstration that an average QTc shortening of 42 ms is enough to reduce arrhythmic events is necessary, before the introduction of mexiletine in clinical practice for LQT2.

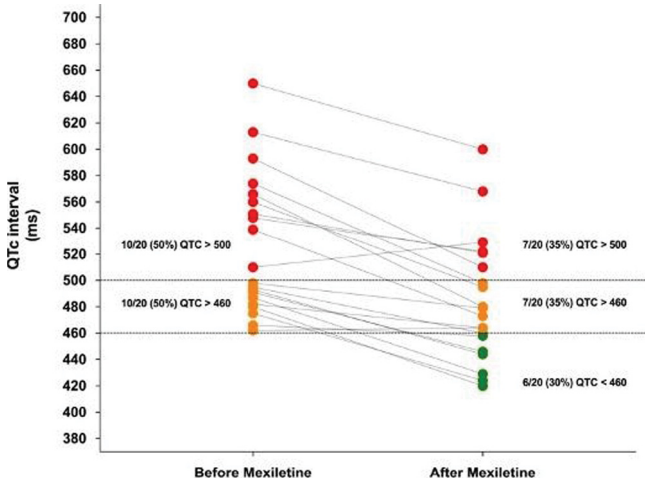

Figure 1