The Long Term Safety and Efficacy of Mexiletine for Patients with Skeletal Muscle Channelopathies

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Author contributions

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Juan Kaski – design of study, revision of manuscript.

Jasper Morrow – analysis of data, revision of manuscript.

Emma Matthews – design of study, analysis of data, revision of manuscript.

Michael Hanna – conceptualisation of study, revision of manuscript.
Doreen Fialho – design and conceptualisation of study, analysis of data, revision of
manuscript.

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Introduction

The skeletal muscle channelopathies include the Non-Dystrophic Myotonias (NDM) and the Periodic Paralyses. Myotonia is the core clinical feature of NDM and may be a feature of Hyperkalaemic periodic paralysis. It is caused by mutations in the skeletal muscle voltage-gated chloride channel gene \textit{CLCN1} or sodium channel gene \textit{SCN4A}. Adequate treatment of myotonia is important for quality of life, mobility and functional independence (1).

Mexiletine acts on voltage gated sodium channels. Its most frequent adverse effect is gastrointestinal (2, 3) but minor neurological effects (e.g. tremor) are also reported (4,5).

Two randomised controlled trials have demonstrated the efficacy of mexiletine for the short term treatment of myotonia (2, 3), but long-term safety and efficacy data outside a trial setting is lacking. We performed a retrospective review of our large skeletal muscle channelopathy patient cohort to address this.

Methods

All patients with genetically confirmed NDM or Hyperkalaemic periodic paralysis prescribed mexiletine with a minimum of 6 months follow up in our clinic were included. The standard dose titration was increments of 50 to 100mg mexiletine per week until symptoms resolved or a total daily dose of 600mg was reached. Efficacy was determined by patient report. Any symptom or adverse event not clearly attributable to an alternative cause was included. All available ECGs were re-examined. Heart rate, PR interval (P wave to beginning of QRS complex), QRS duration (Q wave to end of S wave) and corrected QT interval (QTc) were noted or calculated manually. QTc was calculated using http://www.medcalc.com/qtc.html.

Significance was assessed using paired student’s t-test or one way ANOVA then unpaired student’s t-test.

Results
122 patients were identified. 63 met inclusion criteria. 40 had mutations in \textit{CLCN1}, 21 in \textit{SCN4A} and 2 in both \textit{CLCN1} and \textit{SCN4A} (subsequently analysed with the \textit{SCN4A} group). The mean length of follow up was 4.8 years (6 months to 17.8 years).

There were no serious adverse events. Paired assessment of ECG parameters off mexiletine and at the highest dose at which an ECG was recorded for each individual revealed no significant change in heart rate (71bpm Vs 71bpm p=0.97), PR interval (154ms Vs 166ms p=0.23), QRS duration (89ms Vs 89ms p=0.52), automatically calculated QTc (406ms Vs 405ms p=0.88) or manually calculated QTc (386ms Vs 392ms p=0.30). All 16 patients referred to cardiology because of cardiac concern were advised it was safe to start or continue mexiletine.

33 out of 63 patients reported one or more adverse effect (see figure 1). 16 of the 23 patients who reported dyspepsia required dyspeptic therapy despite which four stopped mexiletine. Patients with \textit{CLCN1} missense mutations required significantly more mexiletine than those with \textit{SCN4A} mutations (see figure 2). 8 of 11 patients who stopped mexiletine previously because of inefficacy or intolerable side effects found it effective and tolerable on retrial. 12 patients were refractory to mexiletine treatment.

\textbf{Discussion}

Limitations of this study include the retrospective design and lack of quantitative myotonia measures. Although the level of medication adherence is unknown it is likely to be high as mexiletine is taken purely for symptom control with quick onset of effect and usually obtained from our centre.

The absence of any significant change in ECG parameters or serious adverse event within a total of 302.4 years of patient follow up demonstrates the long term safety of mexiletine and
suggests that frequent routine ECG monitoring of patients on maintenance dose may not be necessary.

An adequate treatment trial of mexiletine requires slow dose titration and dyspeptic therapy where indicated. Clinicians should be particularly mindful of this in patients with missense mutations in CLCN1 as they required significantly higher mexiletine doses.
Acknowledgments

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Dr Doreen Fialho, the principal investigator had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, approval of the manuscript; and decision to submit the manuscript for publication was independent of funding organization or sponsor.


Figure Titles and Legends

Figure 1. Percentage of Patients reporting adverse effects whilst taking mexiletine

A. Any symptom or adverse effect reported whilst taking mexiletine was included unless there was a clear alternative precipitant. As some patients reported more than one adverse effect the total exceeds 100%. B. Distribution of adverse effects by genotype. As some patients reported more than one adverse effect, in some cases the total exceeds the total number of patients in that category. SCN4A missense = all patients with SCN4A mutations. CLCN1 missense = all patients with CLCN1 missense mutations only (Dominant or Recessive MC). Hom Nmd = Recessive MC patients with 2 CLCN1 mutations predicted to lead to nonsense mediated decay. Het Nmd = Recessive MC patients with one missense mutation and one mutation predicted to lead to nonsense mediated decay.

*‘Other’ adverse effects were breathlessness (3.1%), vivid dreams (1.5%), tremor and dizziness (1.5%), loose stool, change in ejaculate and fatigue (1.5%), blepharospasm and inability to focus (1.5%).
A.

B.

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>SCN4A</th>
<th>CLCN1 missense</th>
<th>CLCN1 hom NMD</th>
<th>CLCN1 het NMD</th>
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<tbody>
<tr>
<td>Palpitatons</td>
<td>3</td>
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<td>1</td>
<td>0</td>
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<tr>
<td>Dyspepsia</td>
<td>11</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
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<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
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<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Syncope</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unspecified SE</td>
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<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
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<td>2</td>
<td>0</td>
</tr>
<tr>
<td>None</td>
<td>9</td>
<td>7</td>
<td>5</td>
<td>9</td>
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</table>
**Figure 2. Mexiletine Efficacy and Mean Effective Dose by Genotype**

Efficacy was classified based on subjective patient report as documented by the clinician. **A.** Patient reported mexiletine efficacy according to genotype. **B.** Mean effective dose of mexiletine by genotype. In A and B patients were excluded if the effective dose was unknown (n=1, *CLCN1* missense) mexiletine was stopped because of concern over potential but not actual side effects (n=1, Hom NMD). In B, to enable analysis of effective dose, those patients who found mexiletine ineffective (n=12) were also excluded. *SCN4A* missense = all patients with *SCN4A* mutations. *CLCN1* missense = all patients with *CLCN1* missense mutations only (Dominant or Recessive MC). Hom Nmd = Recessive MC patients with 2 *CLCN1* mutations predicted to lead to nonsense mediated decay. Het Nmd = Recessive MC patients with one missense mutation and one mutation predicted to lead to nonsense mediated decay. One way ANOVA p = 0.007 *post hoc unpaired student’s t-test p = 0.001.

![Diagram showing efficacy and effective dose by genotype](image-url)
<table>
<thead>
<tr>
<th></th>
<th>SCN4A missense</th>
<th>CLCN1 missense</th>
<th>CLCN1 Hom NMD</th>
<th>CLCN1 Het NMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective dose of mexiletine (mg) mean ± SD (n)</td>
<td>333* ± 177 (21)</td>
<td>550* ± 85 (10)</td>
<td>463 ± 160 (8)</td>
<td>420 ± 175 (10)</td>
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