Long-term Safety and Efficacy of Mexiletine for Patients With Skeletal Muscle Channelopathies

The skeletal muscle channelopathies include the nondystrophic myotonias and the periodic paralyses. Myotonia is the core clinical feature of the nondystrophic myotonias and may be a feature of hyperkalemic periodic paralysis. It is caused by mutations in the skeletal muscle voltage-gated chloride channel gene CLCN1 or sodium channel gene 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 gastrointestinal2,3 but minor neurological effects (eg, tremor) are also reported.4,5 Two randomized clinical trials have demonstrated the efficacy of mexiletine for the short-term treatment of myotonia2,3 but long-term safety and efficacy data outside a trial setting are lacking. We performed a retrospective review of our large skeletal muscle channelopathy patient cohort to address this.

Methods | All patients with genetically confirmed nondystrophic myotonia or hyperkalemic periodic paralysis prescribed mexiletine with a minimum of 6 months follow-up in our clinic were included. Study data were collected as part of a clinical audit registered with the hospital audit committee. This study received ethical approval from the National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Research Ethics committee. Because data were collected as part of a clinical audit, such evaluations do not require patient consent.

The standard dose titration was increments of 50 to 100 mg of mexiletine per week until symptoms resolved or a total daily dose of 600 mg was reached. Efficacy was determined by patient report. Any symptom or adverse event not clearly attributable to an alternative cause was included. All available electrocardiograms (ECGs) were reexamined. 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. The corrected QT interval was calculated using Medcalc (http://www.medcalc.com/qtc.html). Significance was assessed using paired t test or 1-way analysis of variance then unpaired t test.

Results | A total of 122 patients were identified; 63 met inclusion criteria. Forty patients had mutations in CLCN1, 21 in SCN4A, and 2 in both CLCN1 and SCN4A (subsequently analyzed with the SCN4A group). The mean length of follow-up was 4.8 years (range, 6 months to 17.8 years).

There were no serious adverse events. Paired assessment of ECG parameters while not taking mexiletine and at the highest dose at which an ECG was recorded for each individual revealed no significant change in heart rate (71 beats per minute vs 71 beats per minute; P = .97), PR interval (154 ms vs 154 ms; P = .97), PR interval (154 ms vs 154 ms; P = .97), and corrected QT interval (440 ms vs 440 ms; P = .97).

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A, Any symptom or adverse event reported while taking mexiletine was included unless there was a clear alternative precipitant. Because some patients reported more than 1 adverse event, the total exceeds 100%. B, Distribution of adverse events by genotype. Because some patients reported more than 1 adverse event, in some cases, the total exceeds the total number of patients in that category. CLCN1 missense indicates all patients with CLCN1 missense mutations only (dominant or recessive myotonia congenita); heterozygous (Het) NMD, patients with recessive myotonia congenita with 1 CLCN1 missense mutation and 1 CLCN1 mutation associated with nonsense mediated decay; homzygous (Hom) NMD, patients with recessive myotonia congenita with 2 mutations associated with nonsense mediated decay; and SCN4A missense, all patients with SCN4A mutations. * 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 the inability to focus (1.5%).
Figure 2. Mexiletine Efficacy and Mean Effective Dose by Genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>SCNA4 Missense</th>
<th>CLCN1 Missense</th>
<th>CLCN1 Hom NMD</th>
<th>CLCN1 Het NMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective dose</td>
<td>SCNA4 Missense</td>
<td>CLCN1 Missense</td>
<td>CLCN1 Hom NMD</td>
<td>CLCN1 Het NMD</td>
</tr>
<tr>
<td>Mean (SD) [mg]</td>
<td>331 (177) [21]^a</td>
<td>550 (85) [10]^a</td>
<td>463 (160) [8]</td>
<td>420 (175) [10]</td>
</tr>
</tbody>
</table>

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) or mexiletine was stopped because of concern over potential but not actual adverse events (n = 1, Hom NMD). B, To enable analysis of effective dose, those patients who found mexiletine ineffective (n = 12) were also excluded. CLCN1 missense indicates all patients with CLCN1 missense mutations only (dominant or recessive myotonia congenita); heterozygous (Het) NMD, patients with recessive myotonia congenita with 1 CLCN1 missense mutation and 1 CLCN1 mutation associated with nonsense mediated decay; homozygous (Hom) NMD, patients with recessive myotonia congenita with 2 mutations associated with nonsense mediated decay; and SCNA4 missense, all patients with SCNA4 mutations. One-way analysis of variance P = .007.

* Post hoc unpaired t test P = .001.

milliseconds vs 166 milliseconds; P = .23), QRS duration (89 milliseconds vs 89 milliseconds; P = .52), automatically calculated QTc (406 milliseconds vs 405 milliseconds; P = .88), or manually calculated QTc (386 milliseconds vs 392 milliseconds; P = .30). All 16 patients referred to cardiology because of cardiac concern were advised it was safe to start or continue mexiletine.

A total of 33 of 63 patients (52.4%) reported 1 or more adverse events (Figure 1). Sixteen of the 23 patients (69.6%) who reported dyspepsia required dyspeptic therapy, despite which 4 stopped taking mexiletine.

Patients with CLCN1 missense mutations required significantly more mexiletine than those with SCNA4 mutations (Figure 2). Eight of 11 patients (72.7%) who stopped mexiletine previously because of inefficacy or intolerable adverse events found it effective and tolerable on retrial. Twelve patients were refractory to mexiletine treatment.

Discussion | The limitations of this study included 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 center.

The absence of any significant change in ECG parameters or serious adverse events 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.

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Conflict of Interest Disclosures: None reported.

Funding/Support: This work was supported by Medical Research Council Centre grant 512225 and the UCL Biomedical Research Centre. University College London’s National Muscle Channelopathy Service is supported by National Health Service England specialist commissioning (http://www.nclm.ac.uk). Dr Suetterlin has received funding from the European Community’s Seventh Framework Programme (FP7/2007-2013) under grant agreement 2012-305121, Integrated European-omics Research Project for Diagnosis and Therapy in Rare Neuromuscular and Neurodegenerative Diseases (NEUROMICS). Dr Matthews has a research fellowship from the National Institute for Health Research (NIHR). Dr Hanna is supported by a Medical Research Council Centre grant (512225), the UCL Biomedical Research Centre, the National Centre for Research Resources, and the National Highly Specialised Service (HSS) Department of Health UK. Dr Fialho is supported by the HSS Department of Health UK.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.


IKBKG Mutation With Incontinentia Pigmenti and Ring-Enhancing Encephalopathy

Incontinentia pigmenti (IP, Bloch-Sulzberger syndrome) is an X-linked dominant genodermatosis affecting skin and other organs, including the brain, with variable expressivity. Incontinentia pigmenti results from mutations in the inhibitor of κ-β kinase-γ gene (IKBKG), which is located on Xq28. Deletions in this gene result in loss of function, leading to a wide variety of manifestations. This mutation is often lethal in males, resulting in miscarriage of male fetuses. Previously proposed revised diagnostic criteria included as major criteria any of 4 types of IP skin lesions and several minor criteria including anomalies of the brain, eyes, oral cavity, breasts, nipples, hair, and nails in a typical context of multiple male miscarriages and characteristic skin histopathology findings.

Report of a Case | An infant girl, the product of consanguineous parents, presented at birth with erythematous vesicles on her hands, progressing to scaly, erythematous plaques on her head, neck, trunk, and extremities in a blaschkoid pattern. There were no neurological symptoms. Initial concern for infection led to several investigations. Results from blood culture and herpes simplex virus culture of a vesicle were negative. Cerebrospinal fluid showed elevated protein level of 0.063 g/dL (range, 0.015-0.06 g/dL; to convert to grams per liter, multiply by 10), glucose level of 52 mg/dL, and 0.004 nucleated cells/L, with negative herpes simplex virus polymerase chain reaction results. Aspartate aminotransferase level was elevated to 1355 U/L (range, 10-80 units/L; to convert to microkatals per liter, multiply by 0.0167), and the alanine aminotransferase level was elevated to 807 U/L (range, 10-50 U/L; to convert to microkatals per liter, multiply by 0.0167).

Fundoscopy revealed bilateral preretinal and retinal hemorrhages, extending to the maculae, as commonly seen in vaginally delivered infants. Brain magnetic resonance imaging showed multiple areas of restricted diffusion and intraparenchymal and leptomeningeal enhancement resembling hemophagocytic lymphohistiocytosis (Figure). DNA sequencing for a panel of genes associated with hemophagocytic lymphohistiocytosis was negative. Skin histopathological examination revealed dense inflammatory infiltrate with a myriad of eosinophils, prominent spongiosis with intraepidermal vesicles containing eosinophils, and several necrotic keratinocytes, consistent with the inflammatory stage of IP. The child harbored a common known pathogenic deletion in IKBKG, also known as activator of NF-κ-β or NEMO.

This study was approved by the University of Texas Southwestern Medical Center institutional review board.

Discussion | Skin manifestations are commonly the first symptom and occur in nearly all patients with IP. They follow Blaschko lines. Our patient had inflammatory lesions (Figure). Eye abnormalities include retinal anomalies, such as telangiectasia, hemorrhage, arteriovenous anastomoses, neovascularization, and retinal avascularity, or anomalies involving vitreous and lens, microphthalmia, and cataracts. Minor criteria include skin appendage abnormalities including the absence of pilosebaceous glands; alopecia; sparse, wooly hair; anomalies of eyebrows and eyelashes; nail pitting; dystrophy; and subungual or periungual tumors. Nipple and dental anomalies may also be present. Neurological manifestations occur in the first month of life in two-thirds of cases with neurological involvement, which comprise as much as one-third of all IP cases. They range from a single seizure to psychomotor delay, learning disabilities, hemiplegia, epilepsy, cerebellar ataxia, microcephaly, childhood encephalomyelitis, and stroke-like episodes. Magnetic resonance imaging may reveal white matter and corpus callosum abnormalities, cortical malformations, cerebro atrophy, and cerebral or cerebellar hemorrhage. Although stroke-like lesions secondary to focal cortical and white matter necrosis in a nonvascular distribution have been reported in IP, ring enhancement is unusual. Our patient manifested ring enhancement in areas of restricted diffusion together with subtle, diffuse intraparenchymal, cerebellar, and leptomeningeal enhancement.

Conclusions | The rarity of IP together with its myriad clinical presentations poses a significant diagnostic challenge. The presentation of IP may mimic other blashkoid pigmentary disorders such as hypomelanosis of Ito, focal dermal hypoplasia (Goltz syndrome), or herpes simplex virus infection. The neurological syndrome of IP is even less specific. In the absence of cerebral Citrobacter or fungal infection, the diffuse radially distributed ring-enhancement appearance of our case by magnetic resonance imaging is most suggestive of cellular loss along migrational trajectories.

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Letters