A review of the use of mexiletine in patients with myotonic dystrophy and non-dystrophic myotonia

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ABSTRACT

Introduction Myotonia is found in a number of muscle diseases, including myotonic dystrophy and non-dystrophic myotonia. The resulting symptoms of myotonia can interfere with daily activities such as walking or climbing the stairs. Due to the rarity of both these conditions, pharmacological treatment of myotonia is largely anecdotal and is led by specialist clinicians who tend to favour the use of mexiletine, a class 1b antiarrhythmic sodium antagonist.

Objective To identify and review randomised controlled trials in order to assess the efficacy and safety of use of mexiletine in myotonic dystrophy and non-dystrophic myotonia for two different patient cases.

Search methods The literature search was conducted using MEDLINE, EMBASE and The Cochrane Library (from January 1990 to December 2014). Specialist neurology centres were also contacted.

Selection criteria All randomised controlled trials between January 1990 and December 2014 which compared the use of mexiletine for the treatment of myotonia in patients who suffer from myotonic dystrophy and non-dystrophic were included in this review. Primary outcome: reduction of clinical myotonia.

Results Two randomised controlled trials were included for review. Both studies are underpowered; however, there is evidence to support the use of mexiletine for the improvement of clinical myotonia.

Conclusions Larger randomised controlled trials are required, which look at the functional effect of myotonia as a primary outcome (ie, stair test) and the long-term use of mexiletine. This is needed to establish the ongoing efficacy and safety of the long-term use of mexiletine in the management of myotonia.

INTRODUCTION

Myotonia is defined as a delay in the relaxation of muscles after contraction. It is found in a number of muscle diseases such as myotonic dystrophy and non-dystrophic myotonia (NDM).¹ The resulting symptoms of myotonia can include stiffness, pain, fatigue and weakness,² which can interfere with daily activities such as walking or climbing the stairs.¹ The severity of symptoms can vary from mild to disabling, which can have a major impact on quality of life.

NDM differs from myotonic dystrophy in that there is a lack of progressive muscular weakness over time and eventual wasting of the muscle tissue.³ Myotonic dystrophy is divided into two types: type 1 and type 2. Myotonic dystrophy type 1 (DM1) is the most common form of muscular dystrophy in adults.⁴ It is caused by the expansion of cytosine-thymine-guanine (CTG) trinucleotide

repeat in the DMPK gene on chromosome 19q. Myotonic dystrophy type 2 (DM2) is caused by an increased cytosine-cytosine-thymine-guanine (CCTG) repeat in the ZNF9 gene on chromosome 3.⁵ Both types can appear at any age and can affect men and women equally. It affects at least 1 in 8000 people worldwide.³

The NDMs, which include myotonia congenita and paramyotonia congenita, are inherited skeletal muscle ion channel disorders. They are rare disorders estimated to affect 1 in 100 000 people worldwide.⁶ Most cases are associated with mutations in the gene (CLCN-1) encoding the major skeletal muscle chloride channel CIC-1^{7 8} and the gene (SCN4A) encoding the skeletal muscle sodium channels.^{9–11} This affects the muscle contraction process whereby a single nerve stimulus results in repetitive firing of action potentials. It is the enhanced excitability of the muscle fibre membrane that results in symptoms of myotonia as muscles are slow to relax after contraction.

Current treatment options

Due to the rarity of both DM1 and NDM, pharmacological treatment of myotonia is largely anecdotal and is led by specialist clinicians. Medicines such as mexiletine, quinine, procainamide, carbamazepine and phenytoin have been used to manage symptoms; however, a Cochrane review conducted in 2006 concluded that there was limited evidence thus far to support a licensed treatment for this condition.¹ Many specialist clinicians have favoured the use of mexiletine, a class 1b antiarrhythmic sodium antagonist, as the first-line treatment for myotonia in DM1 and NDM. Thus, there is a need to identify any randomised placebo-controlled trials to establish efficacy and safety of use in this area.

CASE STUDIES

Two patient cases will be presented for the purpose of this review—one patient (patient A) with DM1 and one patient (patient B) with NDM.

1. Patient A who is 30 years old has been diagnosed with DM1. He had been experiencing whole body spasms which have now resolved and has percussion myotonia. He also has significant painful tongue and jaw myotonia and this is affecting his quality of life. When asked to produce a sustained hand grip, his hand release time was 10 s on the first attempt, 5 s on the second attempt and 1.5 s on the third attempt.
2. Patient B who is 25 years old has persistent and severe symptoms of NDM. Significant myotonia affecting the tongue, hands, arms and legs has caused significant impairment of speech, hand

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tasks and mobility. The severity of his symptoms meant that he was unable to undertake manual labour as required for his job and had subsequently been made redundant. His symptoms had also prevented him from undertaking some day-to-day activities.

In both cases, patient A and patient B were not on any current treatment for myotonia and both consultants wished to use mexiletine therapy at a dose of 200 mg twice a day or three times a day (TDS), as this is considered standard treatment. The intended treatment outcome would be for an improvement in symptoms with minimal restriction on activities of daily living and work-related tasks.

Mexiletine is an unlicensed drug and as such, needs formulary approval before it is prescribed. The aim of this therapeutic review is to appraise the available evidence for the use of mexiletine in both patients and to find an appropriate dose.

LITERATURE SEARCH

A literature search was performed on 21 January 2015, using the databases EMBASE and MEDLINE (see online supplementary appendix) to identify all relevant and recent clinical trials between January 1990 and December 2014, which evaluated the use of mexiletine in patients who have myotonia. The Cochrane Library was also used as a secondary source (see online supplementary appendix). From each of the identified papers, citations were checked to ensure that no trials were missed.

The following Medical Subject Headings (MeSH) terms were used: Mexiletine, myotonia and myotonia congenital.

Selection criteria

All randomised controlled trials comparing the use of mexiletine in myotonia (in patients who suffer from dystrophic myotonia or NDM), which looked at patients who are aged 18 and above, were included for therapeutic review.

Please see [figure 1](#) for a summary of the selection process.

GUIDELINES

A search for national guidelines was conducted using the National Institute for Health and Care Excellence (NICE) website, which yielded no results. Local guidelines in specialist centres such as the National Hospital for Neurology and Neurosurgery; Salford Royal Hospital NHS Foundation Trust and St George's University Hospitals NHS Foundation Trust were accessed by calling the respective medicine information departments. All hospitals contacted had no formal guidelines.

CRITICAL EVALUATION OF THE LITERATURE

The studies selected for review have been summarised in [table 1](#).

Randomisation and blinding

Computer-generated block randomisation was used by both studies to ensure an equal number of patients were allocated to either the intervention group or the control group. Stratification was not carried out according to patient characteristics although in the Statland 2012 trial stratification by centre took place.

Overall, the baseline characteristics of the two crossover trials in both studies were balanced, except in the Statland 2012 trial where there were more men in the placebo than the mexiletine group.

Figure 1 A summary of the selection process.

Table 1 Studies evaluating the use of mexiletine for the treatment of myotonia

	Logigian <i>et al</i> ¹³	Statland <i>et al</i> ²
Study type	A single-centre, two randomised, double-blind, placebo-controlled crossover trials	Multicentre (seven centres in four countries), randomised, double-blind, placebo-controlled crossover study
Number of patients	20 patients	59 patients
Patient population	Participants who were between the ages of 18 and 80 met the standard clinical criteria for the presence of myotonia and had a diagnosis of myotonic dystrophy type 1	Participants who were at least 16 years old and had clinical symptoms or signs of NDM and myotonic potentials on electromyography
Study design	<i>First trial:</i> mexiletine 150 mg (TDS) versus placebo for 7 weeks, followed by a 4–8 week washout period and then the opposite intervention <i>Second trial:</i> mexiletine 200 mg (TDS) versus placebo for 7 weeks, followed by a 4–8 week washout period and then the opposite intervention	Mexiletine 200 mg or placebo (TDS) for 4 weeks, followed by the opposite intervention for 4 weeks, with 1 week washout between periods
Primary outcome	This study looked at the time for isometric grip force to relax from 90% to 5% of peak force after a 3 s maximum grip contraction ^{12 13}	This study looked at the severity score of muscle stiffness reported by patients during the third and fourth week of each treatment period via the interactive voice response (IVR) diary
Secondary outcomes	ECG outcomes and adverse effects were monitored	This study looked at pain, weakness and tiredness as reported by patients; clinical myotonia bedside assessment; a quantitative measure of hand grip myotonia; myotonia on needle electromyography. It also looked at the response of patients who filled out the short-form health survey (SF-36) and the individualised quality of life questionnaire for neuromuscular disorders (INQoL)
Findings	A significant reduction in grip relaxation times, hence an improvement in myotonia	Improved patient-reported stiffness on the IVR in both treatment periods

NDM, non-dystrophic myotonia.

In the Logigian 2010 trial, most patients included were men, Caucasian and had symptoms of myotonia for over 20 years. patient A matches the demographics of this study—male and Caucasian but his myotonia symptoms have occurred recently. He is also on average 14 years younger than the patients included in this study. Blinding was considered adequate in this trial as only the pharmacist and the biostatistics programmer, who was unblinded, had access to the treatment assignments and was not involved in patient assessments.

In the Statland 2012 trial, most patients included were Caucasian and all had clinical symptoms or signs of NDM. Although the mean age of participants were in their 40s, the demographics of this study are overall applicable to patient B. Blinding was considered inadequate for this trial because even though participants, physicians and evaluators were blinded, there were a number of patients who were taking mexiletine at baseline, and therefore could potentially recognise the side effects of this drug.

Patient withdrawal and follow-up

Only 20 patients were enrolled into each trial for the Logigian 2010 study. Two patients dropped out of the 150 mg three times a day (TDS) trial and did not complete the study due to time commitments. The stage at which these patients decided to discontinue was mentioned; however, these patients were not followed up.

In the Statland 2012 trial, two patients were excluded from analysis due to failure to call the interactive voice response system to report stiffness in either period. Three patients dropped out of the study—two patients due to side effects and one due to failure to comply with study visits. It is difficult to say whether adverse effects reported were attributed to the study medication

Patient compliance

In the Logigian 2010 trial, three patients had a trough mexiletine blood level of 0 µL/mL. These patients, who were non-

compliant, were removed from the assessment of the plasma concentration of mexiletine but not from the study. Nonetheless, only 76% of patients had achieved the therapeutic range for treating arrhythmias (0.5–2.0 µL/mL) on 200 mg TDS and 59% on 150 mg TDS. The mexiletine drug levels for Statland 2012 were taken at baseline, at the end of the washout period and at the end of both placebo arms and were not detectable. This proves that the washout period was sufficient. This meets the recommendation that was given by the Cochrane review—a randomised controlled trial with a sufficient washout period. Compliance to drug treatment was high, with over 90% of capsules taken in both periods.

Power calculation

Power calculations for both studies were carried out to calculate appropriate sample sizes. However, due to patient withdrawal, both studies are underpowered.

RESULTS

Tables 2 and 3 show that treatment with mexiletine results in a significant reduction in hand grip relaxation time, which is what patient A has been struggling with. There seems to be a larger treatment effect for the 150 mg TDS trial. Adverse events were reported, with gastrointestinal distress the most common in

Table 2 Hand grip relaxation time for the 150 mg TDS trial (Logigian 2010)

Relaxation of peak force after maximal voluntary contraction	Relaxation time (s)		Treatment effect (s)	95% CI	p Value
	Mexiletine	Placebo			
90–5%	1.32	2.55	–1.23	(–1.81 to –0.64)	0.0004
90–10%	0.92	1.76	–0.84	(–1.35 to –0.33)	0.003
50–5%	0.98	2.18	–1.19	(–1.79 to –0.60)	0.0006

Table 3 Hand grip relaxation time for the 200 mg TDS trial (Logigian 2010)

Relaxation of peak force after maximal voluntary contraction	Relaxation time (s)				
	Mexiletine	Placebo	Treatment effect (s)	95% CI	p Value
90–5%	1.27	2.63	–1.36	(–2.09 to –0.63)	0.001
90–10%	0.98	1.98	–1.00	(–1.63 to –0.37)	0.004
50–5%	0.92	2.19	–1.27	(–1.96 to –0.57)	0.001

both trials. Respiratory effects were the second most common; but what respiratory symptoms the patients experienced are unclear. There were no significant effects of mexiletine on ECG measurements. The results for all the outcomes in this study were stated and discussed.

Table 4 shows that mexiletine was associated with significantly improved stiffness in both treatment periods; for patient B, this was a symptom that was most debilitating.

Overall, period 1 had a bigger treatment effect than period 2. The most common adverse drug reactions were gastrointestinal. As discussed in the study, the reported symptoms and therefore results could have been affected because patients noticed that they were experiencing side effects (or they noticed a treatment effect); hence, they might have exaggerated the score to a lower or higher value, depending on whether they believed they were taking mexiletine or placebo. The main flaw with this study is that the primary outcome is dependent on the patient's perception of their symptoms and is largely subjective. This is in contrast to the Logigian 2010 study where the primary outcome is a quantitative measure of hand grip myotonia and thus the results are more reliable.

One known problem with reporting myotonia is the warm-up phenomenon, where myotonia improves after repeated contractions, as seen with patient A. Logigian 2010 describes how the relaxation time was calculated from the initial contraction, but Statland 2012 does not give any details of how the hand grip myotonia was assessed. This could have a significant effect on how myotonia is reported.

DISCUSSION

The Cochrane review called for larger, well-designed randomised controlled trials to look at drug treatment for myotonia.¹ The aim of this review is to establish whether mexiletine would be a safe and effective treatment option in both patient cases.

Both studies had crossover trials included in their study design with a sufficient washout period. This was demonstrated through mexiletine drug levels that were taken before the start of each treatment and were found to be zero. However, the primary outcome of the Statland 2012 trial is to look at patient-

reported outcomes and in the survey conducted most patients were able to guess what treatment they were assigned to. As patients may have been exposed to mexiletine at some point in the study, they could have potentially experienced side effects, thus enabling them to identify which treatment they were taking. This is backed up by the study's survey where 79% of patients in the second period guessed correctly that they were taking mexiletine and 80% of patients guessed correctly they were taking placebo. This ultimately introduces bias into the results. Blinding was also deemed inadequate, as 44.1% of patients had been taking mexiletine at baseline.

In conclusion, Logigian 2010 shows us there is some evidence that mexiletine has an effect on myotonia. The significance of the results is somewhat limited by its small sample size; however, the results are promising. The primary outcome for Statland 2012 will have to be discounted, as it is both subjective and non-quantitative. In addition, the methodology should be robust in order to eliminate bias. For instance, its quantitative measure on the hand grip myotonia assessment may be flawed if the relaxation time was calculated on repeated contractions.

RECOMMENDATIONS

Patient A has been struggling with his myotonia, especially his hand release time. Both studies have shown that mexiletine can improve hand grip myotonia and that 150–200 mg TDS is an effective dose. Therefore, a starting dose of 150 mg TDS is an appropriate dose for patient A, titrating to 200 mg TDS if needed. Mexiletine drug levels should be taken to ensure that a therapeutic level is reached. Although patient A does not suffer from cardiovascular disease, an ECG should be performed on a regular basis; first, at baseline (as patients with DM1 are at risk of developing cardiac symptoms) and at regular intervals to monitor for any cardiac side effects. It is worth noting that both studies were conducted for a short period of time, and therefore the long-term cardiac effects are unknown. Therefore, a periodic review of patient A's response and tolerability to mexiletine is recommended.

Evidence from the Statland 2012 trial shows some positive evidence to support a trial of mexiletine at a dosage of 200 mg TDS in patient B, provided there are no contraindications to therapy. Overall, the use of mexiletine therapy showed improvements in symptoms such as reduction of muscle stiffness, pain, weakness and tiredness, which patient B has been experiencing. Given the severity of symptoms that patient B has reported and the favourable safety profile shown in the Statland study, a trial of mexiletine would be justified. If effective, it could help improve mobility and ability to perform activities of daily living. Overall, this would improve quality of life. Monitoring should be carried out as described above.

Larger randomised controlled trials are needed in future, which include the stair test (the time taken to climb 10 stairs) as an outcome. This is the best method to assess the functional effect of myotonia.¹ Patients should be randomised to either

Table 4 Patient-reported outcomes via IVR* and hand grip relaxation time (Statland 2012)

Endpoint	Mean mexiletine treatment (95% CI)	Mean placebo treatment (95% CI)	Treatment effect estimate	Effect size	p Value
IVR stiffness (first period)	2.53 (1.80 to 3.17)	4.21 (3.40 to 5.20)	–1.68 (–2.66 to –0.706)	–1.36	<0.001
IVR stiffness (second period)	1.60 (1.04 to 2.20)	5.27 (4.44 to 6.27)	–3.68 (–3.85 to –0.139)	–2.97	0.04
Clinical assessment: hand grip (s)	0.164 (0.0858 to 0.294)	0.494 (0.281 to 0.872)	–0.330 (–0.633 to –0.142)	–0.748	<0.001

*IVR—interactive voice response diary—patient-reported severity score of stiffness (scale of 1=minimal to 9=worst ever experienced) as a primary endpoint. Changes in pain, weakness and tiredness are measured as secondary endpoints.²

mexiletine or placebo, with no crossover. This will prevent patients from guessing their treatment allocation. As part of the selection criteria, patients should only be enrolled into the study if they have never taken mexiletine before. This will ensure that adequate blinding is maintained throughout the study. However, due to the rarity of these conditions, especially in NDM, it may be difficult to identify such patients.

In both trials, minimal adverse events were recorded. However, long-term safety on the use of mexiletine in DM1 and NDM is yet to be demonstrated and assessed. Safety and scope for titration of mexiletine dosages are also unknown; therefore, clinicians may choose to stop treatment if the drug does not demonstrate improvement in symptoms of DM1 or NDM.

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