Mexiletine (NaMuscla) for the treatment of myotonia in non-dystrophic myotonic disorders

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Abstract

Introduction

NaMuscla, (mexiletine), is the first licensed treatment for the Non-Dystrophic Myotonias (NDM). NDM are categorised by genetic ion channel dysfunction and cause significant morbidity. To date, off-license mexiletine, although less costly, has sometimes been subject to breaches in supply causing significant regional and national variation in availability.

Areas covered

The evidence supporting mexiletine use in NDM, its mechanism of action, chemistry and pharmacodynamics is reviewed. The evidence for other, unlicensed medications, used to treat myotonia as well as new antimyotonic compounds in development is also reviewed.

Expert opinion

Mexiletine is an effective and safe treatment for NDM. However, whilst mexiletine is very effective in reducing muscle stiffness, it is less effective at treating the pain associated with NDM and some *SCN4A* genotypes may not respond to mexiletine treatment. In addition, gastrointestinal discomfort is frequent and may prevent adequate dose titration.

Since the designation of mexiletine as an orphan drug for NDM, level 1 evidence for the antimyotonic effect of lamotrigine has emerged. However, no superiority trials have been completed. A head-to-head trial to compare the efficacy of mexiletine and lamotrigine in reducing both muscle stiffness and pain and to determine variation in genotype response would facilitate greater precision medicine in NDM.

1. Introduction

The non-dystrophic myotonias (NDM) are part of a group of disorders known as skeletal muscle channelopathies that are caused by genetic ion channel dysfunction. In NDM, ion channel dysfunction results in skeletal muscle hyperexcitability that can be detected on electromyogram as myotonia and patients experience as muscle stiffness which may be painful.

NDM has traditionally been divided into three categories: Myotonia Congenita (MC), Paramyotonia Congenita (PMC), and Sodium Channel Myotonia (SCM). MC occurs in two major forms: autosomal dominant and autosomal recessive both associated with mutations in the muscle chloride channel gene, *CLCN1* [1]. PMC and SCM are autosomal dominant disorders associated with missense mutations in the muscle sodium channel gene, *SCN4A* [2,3]. Although NDM can be caused by mutations in muscle sodium (NaV1.4) or chloride channels (ClC-1), the end result for both is that muscle fibres are hyperexcitable. Thus treatments aimed at reducing excitability are applied to all forms of NDM.

NDM can be distinguished from myotonic dystrophy by the lack of systemic organ involvement and the fact that severe weakness is not a common feature of the condition [4]. However, the non-dystrophic title is a misnomer as in addition to pain and stiffness, muscle weakness can develop [5]. In a series of 49 genetically confirmed PMC cases, 'myopathic muscle biopsy findings' were reported in 33% of those biopsied [6]. It is not known if treatment of myotonic symptoms prevents muscle weakness or myopathic features developing in NDM.

NDM is a rare disease. The point prevalence of genetically confirmed NDM was 0.75/100,000 of a UK population [7]. This could be broken down into 0.52/100,000 for MC, 0.17/100,000 for PMC and 0.06/100,000 for SCM [7]. This is similar to that reported in other European populations.

There is no study of mortality or cause of death in people with NDM, but several published reports confirm the debilitating nature of the symptoms. In a two month period, stiffness was reported in over 89% of patients and occurred on a median of 5 days per week causing a significant impact on life [8]. Stiffness limits patients' mobility and activities of daily living: some are greatly restricted in function with consequences on their participation in education, employment and social activity. Trip et al's study of NDM symptoms found patients primarily had difficulty in climbing stairs, running and getting up from sitting, all causing marked morbidity [9].

A further study also found that people with NDM reported significantly worse ratings for physical scores of the SF-36 Health Questionnaire compared with the normal population and that these findings closely resembled the scores of other chronic diseases like type-II diabetes mellitus or ischaemic heart disease [10].

One of the most debilitating aspects of NDM is the pain it causes [11]. Many case reports describe how severe the pain of NDM can be [12–14]. One study, that examined 62 patients with NDM, found pain to be present in 42% and excess fatigue in 53% [9]. Pain and fatigue were found to be the best predictors of poor general health perception and physical function in patients with NDM [10,15].

Thus treatment is often necessary for the symptoms of NDM. However, until recently there has been no licensed treatment for myotonia. The recommended therapeutic approach has been that patients with mild symptoms are encouraged to avoid triggers such as cold or strenuous exercise and make use of the warm up phenomena with an emphasis on gentle warm up and warm down prior to activity and avoidance of sudden movements whenever possible. When pharmacological intervention is required, the recommended first line treatment for myotonia has been off-license use of mexiletine [16], or more recently, lamotrigine [17]. Recommended second line treatments include other anticonvulsants or antiarrhythmics such as carbamazepine, phenytoin and flecainide but these have varying efficacy [18,19].

The lack of licensed treatments for myotonia has limited the availability of pharmacological therapy due to a limited number of physicians experienced enough in these rare disorders to be able to prescribe off-license and intermittent availability in mexiletine supply. This has sometimes created an inequity in access to treatment for some patients and created significant regional variation in availability.

2. Mexiletine and antimyotonic agents

2.1. Overview of the market

NaMuscla mexiletine received marketing authorisation throughout the EU on 18th December 2018 for the treatment of NDM. Mexiletine has level 1 evidence of its efficacy versus placebo in the treatment of NDM. There are two registered double blind RCTs for mexiletine use in NDM. The trial of 'Mexiletine for symptoms and Signs of Myotonia in Nondystrophic Myotonia' organised by the Consortium for Clinical Investigation of Channelopathies is published [20] and the 'MYOMEX' trial organised by Assistance Publique – Hospitaux de

Paris (AP-HP) is ongoing (https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-020923-37/FR). There has also been one series of Bayesian aggregated placebo-controlled n-of-1 trials of mexiletine in patients with NDM [21,22] which achieved similar results to the published RCT.

Lamotrigine also has level 1 evidence as an antimyotonic agent [17]. The primary outcome measure in the lamotrigine trial was reduction of the myotonia behaviour score. This score focuses on muscle stiffness and does not measure changes in pain or fatigue. Although the effect of lamotrigine on pain and fatigue was not directly measured, patients did report improved SF-36 scores suggesting it does have an effect. Lamotrigine was suggested as a first line drug for treatment naïve patients given its efficacy for muscle stiffness, high availability and low cost. However, the potential for severe life-threatening side effects such as Stevens-Johnson syndrome should be borne in mind and is reported to occur in 0.03% to 0.08% of adult populations [23].

In terms of drugs in development, ranolazine has preclinical evidence of its efficacy and has undergone two recent open label studies providing class IV evidence of its efficacy for the treatment of NDM [24,25]. In the PMC study, ranolazine significantly improved all subjective measures of muscles stiffness, weakness and pain [25]whilst for the MC study significant improvement was limited to muscle stiffness only[24]. Tocainamide is known to be a very effective anti-myotonic agent [18] but its use is precluded by reports of fatal agranulocytosis [26]. Therefore, research has looked at developing tocainamide analogues [27]. The leading compound, To042, is 100 times more potent then mexiletine at reducing muscle stiffness in a rat model of myotonia [27]. Additional preclinical studies are now needed to progress To042 to human studies [19].

Other sodium channel blocking agents such as phenytoin, carbamazepine, flecainide and disopyramide also have level 4 evidence of antimyotonic efficacy in NDM patients [12,18]. These agents tend to be used off license. However, it is worth noting that there is level 4 evidence that flecainide may be effective in some patients that are refractory to mexiletine [19,28,29].

2.2. Prevalence

The maximum prevalence of NDM (9/100,000) has been recorded in Scandinavian countries where there is known to be a founder effect for MC [30,31]. This is much higher than the 0.75/100,000 point prevalence

estimated for the UK population [7]. However, the prevalence required for the definition of an orphan disease is 5/10,000. Therefore, even if the prevalence of NDM is estimated based on the higher prevalence data from Scandinavia, the prevalence of NDM would still equate to 9/100,000, well under the 5/10,000 requirement for orphan disease designation.

2.3. History of orphan drug designation

The first marketing authorisation for Mexitil mexiletine as an anti-arrythmic medicinal product was granted in 1975 to Boehringer Ingelheim. However, in 2008 Boehringer Ingelheim stopped Mexitil production as it was no longer commercially viable.

In the UK, during this time, generic mexiletine has been imported from Teva Pharmaceuticals Canada and used off-license for the treatment of myotonia. In Italy, since 2010, Mexiletine can be obtained from the Military Chemical Pharmaceutical Plant of Florence (Stabilimento Chimico Farmaceutico Militare di Firenze) as a "named-patient" drug. Costs are entirely covered by the Italian National Health System. In France, using a national procedure, Assistance Publique – Hopiteux de Paris (APHP), had the marketing authorisation for mexiletine transferred. Thus France has been the only European country with an authorised antimyotonic treatment.

In an attempt to secure an ongoing supply, mexiletine has been a designated orphan drug in the EU since the 9th November 2014. We obtained orphan designation initially and it was initially granted to Temmler Pharma GmbH & Co. KG, Germany, then transferred to Hormosan Pharma GmbH, Germany, in October 2015, then to Lupin (Europe) Limited, United Kingdom, in August 2016 and finally to Lupin Europe GmbH in May 2018.

Mexiletine hydrochloride has been authorised in the EU as Namuscla since 18 December 2018. Namuscla mexiletine is an orally active antimyotonic agent. It is licensed for use in adult patients with non-dystrophic myotonic disorders only i.e. the license does not include use for the treatment of myotonic dystrophy.

2.4. Chemistry

Namuscla mexiletine is the licensed mexiletine treatment available in the EU. It is a white powder encapsulated in hard gelatine capsules. Capsules contain a mexiletine dose of 166.6mg equivalent to a

mexiletine hydrochloride dose of 200 mg. This is the dose used in the published randomised trials [20,21] as well as other case reports [32].

NaMuscla is freely soluble in water, has a dissociation constant (PKa) of 8.4 and a molecular weight of 215.73. The chemical name of the active substance is (2RS)-1-(2,6-dimethylfenoxy)propan-2-amine hydrochloride ($C_{11}H_{17}NO \cdot HCl$).

2.5. Pharmacokinetics, pharmacodynamics and Metabolism

Mexiletine is primarily absorbed in the upper portion of the small intestine. Peak plasma levels are reached 2 - 3 hours after administration to normal subjects. Mexiletine shows a fast distribution phase, a slow distribution phase and a slow elimination phase. Tissue uptake is substantial. Bioavailability is about 80 ± 8 %. Renal clearance varies with urine pH but this is unlikely to have clinical significance. In patients the elimination half-life is 5 - 17 hours [33].

2.6. Mechanism of action

In vitro data confirms sodium channel mutations seen in PMC and SCM are gain of function mutations that alter the kinetics of NaV1.4 muscle sodium channels. These mutations tend to increase NaV1.4 activity by impairing fast inactivation rather than enhancing activation [29] In MC, it is loss of the stabilising chloride conductance that results in muscle hyperexcitability manifesting as myotonia [34]. Therefore, in MC, mexelitine is effective by targeting wild-type sodium channels, whilst in myotonia caused by NaV1.4 mutations mexiletine may act on mutant and/or wild-type channels. However, for all forms of NDM, the overall effect of mexiletine is to reduce skeletal muscle hyperexcitability.

Mexiletine is particularly suited for the treatment of myotonia as it has high affinity for NaV1.4 and preferentially binds to channels in the open or fast-inactivated state [29,35]. The IC_{50} of mexiletine is 3.3µM for NaV1.4 in the open state, 67.8 µM for the inactivated state and 431 µM for the resting state[35]. This means that whilst the IC_{50} for tonic (0.1Hz stimulation) block of wild-type NaV1.4 is 256±25µM the IC_{50} for phasic block (10Hz stimulation) is 46±5µM [29]. Thus rapidly firing myotonic muscle is more sensitive to mexiletine block than resting or normally contracting muscle.

However, *SCN4A* mutations may alter NaV1.4 sensitivity to mexiletine. Heterologously expressed human NaV1.4 V445M, A444W, L443C and R1448H channels are more sensitive than wild-type channels to mexiletine block [35–37], whilst other variants including G1306E and P1158L are less sensitive than wild-type [29,38,39]. This difference in sensitivity may occur because of altered state-dependent affinity of NaV1.4 mutant channels for mexiletine or because of alterations in gating that affect mexiletine's use-dependent block of mutant channels[37]

2.7. Clinical Efficacy

Mexiletine has been used off license for the treatment of NDM since at least the 1990s. The strongest data is with regards its effect on muscle stiffness in patients with NDM. Mexiletine has consistently demonstrated its efficacy in reducing muscle stiffness on objective and subjective measures. In the published RCT examining the effects of mexiletine in 59 adults with NDM, patient reported severity score for stiffness was reduced by 1.68 during the mexiletine period (p<0.01), time taken for eye opening after forced closure was reduced by 0.3 seconds (p<0.01), for hand opening after forced closure was 0.748 seconds (p<0.01) and to relax from 90% hand-grip force to 5% hand grip force was 0.518 seconds (p<0.01) [20].

The aggregated n-of-1 trial on mexiletine in NDM used Bayesian analysis to provide probabilities of reaching clinically meaningful treatment effect instead of frequentist analysis to refute a null hypothesis [21]. This trial provided similarly convincing results for mexiletine's effects on muscle stiffness with a 100% probability of reaching a clinically meaningful effect on the patient reported muscle stiffness severity score for the NDM group overall. When broken down by genotype, the *CLCN1* subgroup also had a 100% probability whilst the *SCN4A* subgroup had 93% probability. It has previously been reported that patients with *CLCN1* missense mutations require a higher dose of mexiletine for efficacy [16]. Therefore, it should be noted that the standard dose in both the RCT and the aggregated n-of-1 trial was 200mg three times a day.

There is also good evidence of mexiletine's effect on weakness in NDM. In the RCT the patient reported weakness severity score reduced whilst on mexelitine by 1.26 (p<0.01) whilst in the aggregated n-of-1 trial the probability of a clinically meaningful reduction in weakness was 87%. This effect is also supported by neurophysiological studies. The neurophysiological correlate of weakness in NDM is a drop in compound muscle action potential (CMAP) on exercise testing. CMAP drop is cold-induced and exacerbated by repetition

in PMC, improved by repetition in recessive MC and tends not to alter significantly during short exercise testing in dominant MC and SCM [4]. In 1994 Jackson and Barohn demonstrated increased compound muscle action potentials (CMAP) on the short exercise test following mexiletine therapy in a patient with PMC [32]. Maintenance of CMAP amplitude has also been reported in response to repetitive stimulation in MC patients taking mexiletine [40], implying that mexiletine is effective at reducing the transient weakness that can be associated with recessive MC.

However, it was pain and fatigue that were found to be the best predictors of poor general health perception and physical function in patients with NDM [10,15]. Mexiletine is effective against pain, but its effect on pain appears smaller than its effect on muscle stiffness. In the aggregated n-of-1 trials mexiletine had a 45% chance of reaching a clinically meaningful treatment effect for pain compared with 100% chance for stiffness [21].

Mexiletine's effect on fatigue is more impressive. Mexiletine significantly reduced patient reported tiredness severity score (p<0.01) and INQOL fatigue score (p=0.07) in the RCT[20] and had a 74% chance of reaching a clinically meaningful treatment effect on fatigue in the aggregated n-of-1 trial [21].

However, not all patients respond to mexiletine. In clinical practice, approximately 20% of patients find mexelitine ineffective or only partially effective [16]. In the aggregated n-of-1 trial, all 16 MC patients found mexiletine effective. In contrast, 3 of 11 patients with *SCN4A* mutations found mexiletine ineffective. This is interesting as some NaV1.4 variants are less sensitive than wild-type channels to mexiletine block *in vitro*. It is worth considering flecainide in these patients, as demonstrated by the case reports of patients with G1306A and P1158L mutations in *SCN4A* who found mexiletine ineffective and were changed to flecainide based on data from *in vitro* expression studies with good therapeutic effect [28,39].

2.8. Safety and tolerability

Mexiletine is contraindicated in patients with evidence of ventricular or atrial arrhythmia, heart block or ECG changes that may progress to heart block or with acute or past myocardial infarction [33] (Table 1). There have been no serious cardiac adverse events associated with mexiletine use in NDM [16,20,21]. However, all patients must have cardiac history, examination and a baseline ECG reviewed prior to initiation of the drug (figure 1) [20,21].

There was only 1 serious adverse event in the n-of-1 trial. This was an allergic skin reaction. However, 90% of patients in the n-of-1 trial had at least 1 adverse reaction [21]. By far the most frequent adverse reaction is gastrointestinal discomfort. This was true for the RCT [20], n-of-1 trial [21] and a retrospective case series review [16]. Gastrointestinal symptoms may require dyspeptic therapy in order to achieve adequate dose titration of mexiletine [16]. Other adverse effects of mexiletine include headache, nausea, palpitations, insomnia, and tremor [16,20,21].

2.9. Regulatory affairs

As mexiletine hydrochloride was available in 50, 100 and 200mg doses, there are some issues with patients that were on lower doses of mexiletine than the 200mg equivalent dose of NaMuscla. As a result, for these patients, unlicensed prescription of mexiletine hydrochloride in the UK has been recommended to continue in certain regions.

3. Conclusion

Namuscla secures the supply of mexiletine to treat patients with non-dystrophic myotonia. However, the licensed use comes at a higher cost and might reduce its availability within public healthcare systems. Mexiletine is a safe and effective treatment for myotonia. There may be genotype differences in its efficacy. It would be useful to demonstrate its superiority over lamotrigine, the only other medication with level 1 evidence as an antimyotonic.

4. Expert opinion:

Namuscla mexiletine is now licensed in the EU for the treatment of myotonia. The major effect of this will be to secure a licensed source of medication for patients with non-dystrophic myotonia. However, the risk may be that not all patients can access this as the cost of Namuscla is somewhat prohibitive and there are alternative, unlicensed but readily available medications (lamotrigine) that now have level I evidence of efficacy. However, although generally well tolerated, lamotrigine can be associated with rare but life-threatening side effects (table 1) whilst this has not been reported for mexiletine. In addition, mexiletine has class 1 evidence of its efficacy in myotonic dystrophy type 1 [41] and despite the association of myotonic dystrophy type 1 with cardiac arrhythmia, when prescribed with the appropriate precautions (figure 1),

mexiletine was found to be safe and well-tolerated in this patient group[41].   In our experience, mexiletine is also safe and well tolerated in patients with myotonic dystrophy type 2. This means that mexiletine is a particularly good choice of therapy if initiating treatment for a probable genetic myotonia that is not yet genetically confirmed. However, although mexiletine's effect on muscle stiffness is excellent, it is not very effective in treating the pain associated with NDM [21]. In our experience, the pain associated with NDM can be very refractory to available treatment and yet it is pain and fatigue that have been reported to have the greatest impact on NDM patients' quality of life[10,15]. Moreover, the mechanism of pain in NDM is not well understood. Therefore, research to identify the molecular pathways involved and develop therapy that has a greater impact on the pain associated with NDM is a key challenge for the future.

The use of novel trial design will be necessary to facilitate and accelerate development of such therapies. RCT trials are difficult to complete with sufficient power in rare diseases because of the limited numbers of patients available for recruitment and the significant heterogeneity in phenotype. This heterogeneity is particularly prominent in NDM. For example, in achieve adequate power the RCT in NDM was an international, multi-centre trial [20] This complicates logistics and significantly increases the expense.

Bayesian aggregated n-of-1 trials are uniquely suited to the NDM patient group as they represent a chronic, symptomatic condition, "where period effects (i.e. changes in disease state) and carry over effects (i.e. lingering drug effect) are small"[22]. In aggregated n-of-1 trials the patient act as their own control and less patients are required to power the study sufficiently to detect clinically meaningful differences. For example, Bayesian analysis of the results from the first 11 consecutive NDM patients undergoing n-of-1 trials on mexiletine was sufficient to determine with greater than 95% probability that mexiletine reduces myotonia with a clinically meaningful difference [21]. In contrast, a sample size of 54 was estimated as necessary for 93% power to detect change in the RCT[20]. Moreover, in Bayesian aggregated n-of-1 trials, the effect of a medication on pain and/or muscle stiffness in the same individual may be more easily differentiated[21].

Thus, in future, for NDM, or other rare diseases, where multiple medications that provide symptomatic relief are being used off-license, Bayesian aggregated n-of-1 trials could be used to determine treatment superiority for individual symptoms and mutation-specific response to therapy. Thus, not only would n-of-1 design make

trials of new antimyotonic medication more affordable it would do so whilst facilitating greater precision medicine.

Drug Summary Box

Drug Name: Mexiletine
Phase: Solid
Indication: Non-dystrophic Myotonia
Pharmacology description/mechanism of action: Use-dependent block of sodium channels that reduces aberrant excitability and myotonic firing of muscle.
Route of administration: Oral
Pivotal trials: The trial of 'Mexiletine for symptoms and Signs of Myotonia in Non-dystrophic Myotonia' organised by the Consortium for Clinical Investigation of Channelopathies demonstrated the efficacy and tolerability of mexiletine for the treatment of Non-dystrophic Myotonia.

Table 1 Comparison of the Indications, Side Effects and Contraindications of Mexiletine and Lamotrigine

|	Mexiletine[20,21,33,41]	Lamotrigine [17,23,42]
Indications	Non-dystrophic myotonia Dystrophic Myotonia	Non-dystrophic Myotonia[17]
Common Side Effects	Dyspepsia, headache, paraesthesia, vision blurred, vertigo, insomnia	Headache, skin rash, Fatigue, Muscle/joint pain/oedema, Sore throat, nausea
Contraindications	Cardiac: any arrhythmia (atrial, ventricular or heart block), acute or past myocardial infarction or symptomatic coronary artery disease.	Myoclonic seizures Parkinsons' disease
Severe life-threatening side effect	Not reported	Stevens-Johnson Syndrome (0.03% to 0.08% of adult population); toxic epidermal necrolysis, aplastic anaemia, bone marrow depression & pancytopenia reported [23]
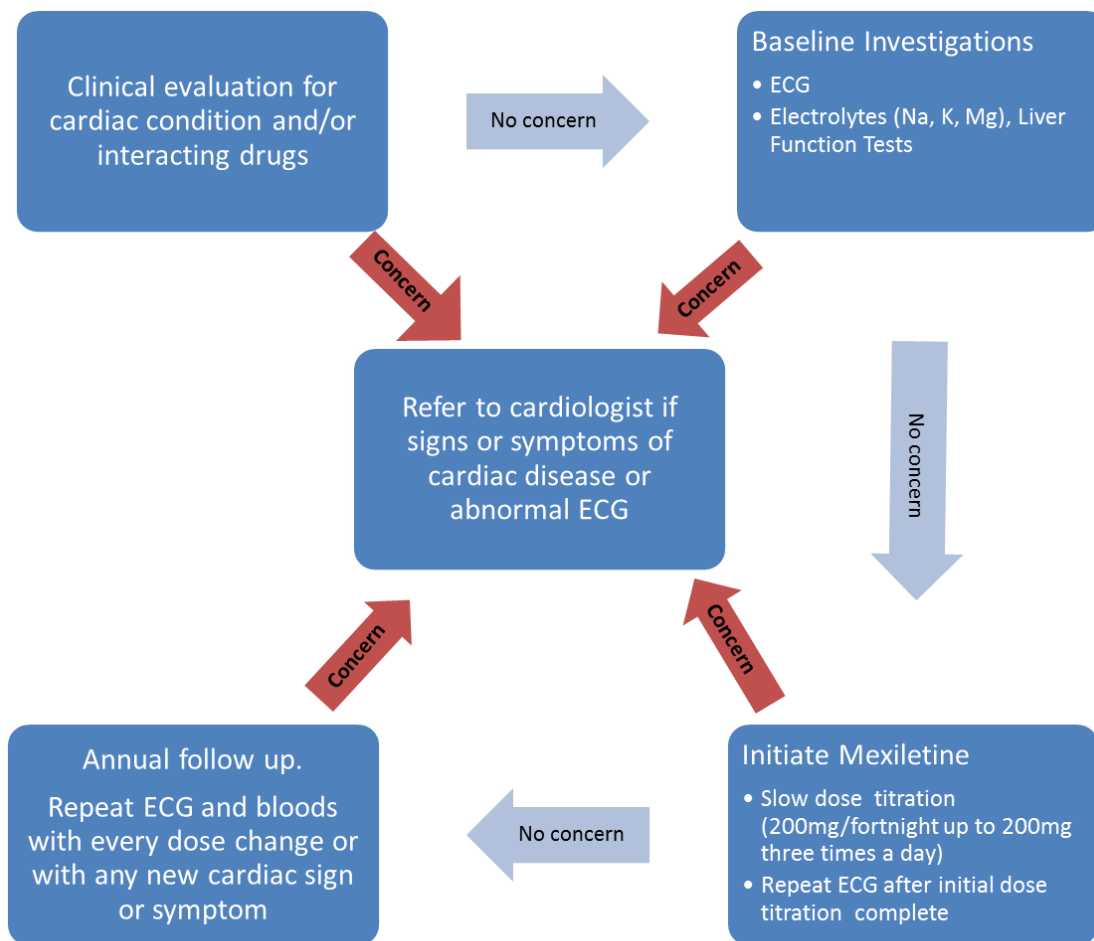
Figure 1 Suggested approach to initiation and monitoring of mexiletine treatment in patients with non-dystrophic myotonia

References

[1]   Koch M, Steinmeyer K, Lorenz C, et al. The skeletal muscle chloride channel in dominant and recessive human myotonia. Science. 1992;257:797–800.

[2]   L.J. P, R. T, R.C. G, et al. Linkage of atypical myotonia congenita to a sodium channel locus. Neurology. 1992;42:431–433.

[3]   Ptacek LJ, Trimmer JS, Agnew WS, et al. Paramyotonia congenita and hyperkalemic periodic paralysis map to the same sodium-channel gene locus. Am. J. Hum. Genet. 1991;49:851–854.

[4]   Suetterlin K, Männikkö R, Hanna MG. Muscle channelopathies: recent advances in genetics, pathophysiology and therapy. Curr. Opin. Neurol. 2014;27:583–590.

[5]   Nagamitsu S, Matsuura T, Khajavi M, et al. A "dystrophic" variant of autosomal recessive myotonia congenita caused by novel mutations in the CLCN1 gene. Neurology. 2000;55:1697–1703.

[6]   M. R. D da S, Miller HA, Kwiecinski H, et al. Correlating phenotype and genotype in the periodic paralyses. Neurology. 2004;63:1647–1655.

[7]   Horga A, Raja Rayan DL, Matthews E, et al. Prevalence study of genetically defined skeletal muscle channelopathies in England. Neurology. 2013;80:1472–1475.

[8]   Statland JM, Wang Y, Richesson R, et al. An interactive voice response diary for patients with non-dystrophic myotonia. Muscle Nerve. 2011;44:30–35.

[9]   Trip J, Drost G, Ginjaar HB, et al. Redefining the clinical phenotypes of non-dystrophic myotonic syndromes. J. Neurol. Neurosurg. Psychiatry. 2009;80:647–652.

[10]   Trip J, de Vries J, Drost G, et al. Health status in non-dystrophic myotonias: close relation with pain and fatigue. J. Neurol. 2009;256:939–947.

[11]   Matthews E, Fialho D, Tan SV, et al. The non-dystrophic myotonias: Molecular pathogenesis, diagnosis and treatment. Brain. 2010;133:9–22.

[12]   Rosenfeld J, Sloan-Brown K, George AL. A novel muscle sodium channel mutation causes painful congenital myotonia. Ann. Neurol. 1997;42:811–814.

[13]   Nam T-S, Choi S-Y, Park D-J, et al. The Overlap between Fibromyalgia Syndrome and Myotonia Congenita. J. Clin. Neurol. 2015;11:188.

[14]   Fialho D, Schorge S, Pucovska U, et al. Chloride channel myotonia: Exon 8 hot-spot for dominant-negative interactions. Brain. 2007;130:3265–3274.

[15]   Sansone VA, Ricci C, Montanari M, et al. Measuring quality of life impairment in skeletal muscle channelopathies. Eur. J. Neurol. 2012;19:1470–1476.

[16]   Suetterlin KJ, Bugiardini E, Kaski JP, et al. Long-term Safety and Efficacy of Mexiletine for Patients With Skeletal Muscle Channelopathies. JAMA Neurol. 2015;72:1531.

[17] Andersen G, Hedermann G, Witting N, et al. The antimyotonic effect of lamotrigine in non-dystrophic myotonias: a double-blind randomized study. Brain. 2017;140:2295–2305.

[18] Kwieciński H, Ryniewicz B, Ostrzycki A. Treatment of myotonia with antiarrhythmic drugs. Acta Neurol. Scand. 1992;86:371–375.

[19] De Bellis M, Camerino DC, Desaphy J-F. Toward precision medicine in myotonic syndromes. Oncotarget. 2017;8:14279–14280.

[20] Statland JM. Mexiletine for Symptoms and Signs of Myotonia in Nondystrophic Myotonia: A Randomized Controlled Trial. JAMA. 2012;308:1357.

[21] Stunnenberg BC, Raaphorst J, Groenewoud HM, et al. Effect of Mexiletine on Muscle Stiffness in Patients With Nondystrophic Myotonia Evaluated Using Aggregated N-of-1 Trials. JAMA. 2018;320:2344–2353.

[22] Stunnenberg BC, Woertman W, Raaphorst J, et al. Combined N-of-1 trials to investigate mexiletine in non-dystrophic myotonia using a Bayesian approach; study rationale and protocol. BMC Neurol. 2015;15:43.

[23] Betchel NT, Saadabadi A. Lamotrigine. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 [cited 2020 Feb 21]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK470442/.

[24] Arnold WD, Kline D, Sanderson A, et al. Open-label trial of ranolazine for the treatment of myotonia congenita. Neurology. 2017;89:710–713.

[25] Lorusso S, Kline D, Bartlett A, et al. Open-label trial of ranolazine for the treatment of paramyotonia congenita: Ranolazine for Paramyotonia. Muscle Nerve. 2019;59:240–243.

[26] Volosin K, Greenberg RM, Greenspon AJ. Tocainide associated agranulocytosis. Am. Heart J. 1985;109:1392–1393.

[27] De Bellis M, Carbonara R, Roussel J, et al. Increased sodium channel use-dependent inhibition by a new potent analogue of tocainide greatly enhances in vivo antimyotonic activity. Neuropharmacology. 2017;113:206–216.

[28] Desaphy J-F, Modoni A, LoMonaco M, et al. Dramatic improvement of myotonia permanens with flecainide: a two-case report of a possible bench-to-bedside pharmacogenetics strategy. Eur. J. Clin. Pharmacol. 2013;69:1037–1039.

[29] Farinato A, Altamura C, Imbrici P, et al. Pharmacogenetics of myotonic hNav1.4 sodium channel variants situated near the fast inactivation gate. Pharmacol. Res. 2019;141:224–235.

[30] Sun C, Tranebjaerg L, Torbergsen T, et al. Spectrum of CLCN1 mutations in patients with myotonia congenita in Northern Scandinavia. Eur. J. Hum. Genet. EJHG. 2001;9:903–909.

[31] Baumann P, Myllylä VV, Leisti J. Myotonia congenita in northern Finland: an epidemiological and genetic study. J. Med. Genet. 1998;35:293–296.

[32] Jackson CE, Barohn RJ, Ptacek LJ. Paramyotonia congenita: abnormal short exercise test, and improvement after mexiletine therapy. Muscle Nerve. 1994;17:763–768.

[33] Namuscla 167 mg hard capsules - Summary of Product Characteristics (SmPC) - (emc) [Internet]. [cited 2019 Dec 19]. Available from: https://www.medicines.org.uk/emc/product/9838/smpc.

[34] Bryant SH, Morales-Aguilera A. Chloride conductance in normal and myotonic muscle fibres and the action of monocarboxylic aromatic acids. J. Physiol. 1971;219:367–383.

[35] Wang GK, Russell C, Wang S-Y. Mexiletine block of wild-type and inactivation-deficient human skeletal muscle hNav1.4 Na $^+$ channels: Mexiletine block of persistent late Na $^+$ currents. J. Physiol. 2004;554:621–633.

[36] Weckbecker K, Würz A, Mohammadi B, et al. Different effects of mexiletine on two mutant sodium channels causing paramyotonia congenita and hyperkalemic periodic paralysis. Neuromuscul. Disord. NMD. 2000;10:31–39.

[37] Takahashi MP, Cannon SC. Mexiletine block of disease-associated mutations in S6 segments of the human skeletal muscle Na+ channel. J. Physiol. 2001;537:701–714.

[38] Desaphy JF, De Luca A, Tortorella P, et al. Gating of myotonic Na channel mutants defines the response to mexiletine and a potent derivative. Neurology. 2001;57:1849–1857.

[39] Desaphy J-F, Carbonara R, D'Amico A, et al. Translational approach to address therapy in myotonia permanens due to a new SCN4A mutation. Neurology. 2016;86:2100–2108.

[40] Lo Monaco M, D'Amico A, Luigetti M, et al. Effect of mexiletine on transitory depression of compound motor action potential in recessive myotonia congenita. Clin. Neurophysiol. 2015;126:399–403.

[41] Logigian EL, Martens WB, Moxley RT, et al. Mexiletine is an effective antimyotonia treatment in myotonic dystrophy type 1(LOE Classification). Neurology. 2010;74:1441–1448.

[42] Cohen-Israel M, Berger I, Martonovich EY, et al. Short- and long-term complications of in utero exposure to lamotrigine. Br. J. Clin. Pharmacol. 2018;84:189–194.