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Research paper

Efficacy and safety of mexiletine in non-dystrophic myotonias: A randomised, double-blind, placebo-controlled, cross-over study

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Abstract

The MYOMEX study was a multicentre, randomised, double-blind, placebo-controlled, cross-over study aimed to compare the effects of mexiletine vs. placebo in patients with myotonia congenita (MC) and paramyotonia congenita (PC). The primary endpoint was the self-reported score of stiffness severity on a 100 mm visual analogic scale (VAS). Mexiletine treatment started at 200 mg/day and was up-titrated by 200 mg increment each three days to reach a maximum dose of 600 mg/day for total treatment duration of 18 days for each cross-over period. The modified intent-to-treat population included 25 patients (13 with MC and 12 with PC; mean age, 43.0 years; male, 68.0%). The median VAS score for mexiletine was 71.0 at baseline and decreased to 16.0 at the end of the treatment while the score did not change for placebo (81.0 at baseline vs. 78.0 at end of treatment). A mixed effects linear model analysis on ranked absolute changes showed a significant effect of treatment ($p < 0.001$). The overall score of the Individualized Neuromuscular Quality of Life questionnaire (INQoL) was significantly improved ($p < 0.001$). No clinically significant adverse events were reported. In conclusion, mexiletine improved stiffness and quality of life in patients with nondystrophic myotonia and was well tolerated.

Keywords: Clinical trials; Muscle channelopathy; Nondystrophic myotonias; Myotonia congenita; Paramyotonia congenita; Mexiletine.

1. Introduction

Myotonia is a delayed muscle relaxation after voluntary contraction which is usually described as stiffness [1–3]. The intensity of myotonia can vary and is associated with pain, fatigue and weakness that may have a significant detrimental effect on daily activities, mobility, physical functioning and quality of life [4].

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Nondystrophic myotonias are due to ion channel dysfunction. They classically include Myotonia Congenita (MC), Paramyotonia Congenita (PC) and sodium channel myotonias (SCM). Recent data from electrophysiological and molecular biological studies led to a new classification of these disorders and they are now classified as chloride or sodium channel diseases. The chloride channel disorders include autosomal-recessive myotonia congenita (Becker's disease) and autosomal-dominant myotonia congenita (Thomsen's disease) which are characterized by clinical myotonia with warm-up phenomenon [5]. Sodium channel disorders are all autosomal-dominantly inherited diseases and they comprise PC and SCM. In PC patients, myotonia is said paradoxical because it is induced and exacerbated by continued exercise or cold exposure [6].

In daily practice, mexiletine – a non-selective voltage-gated sodium channel blocker – is one of the most effective treatment available for patients with nondystrophic myotonia. Its use for the management of myotonic disorders has been reported for more than 30 years [7]. No standardized treatment has been developed for nondystrophic myotonia and the current therapeutic strategies are mainly based on clinical experience and selective case reports [7–16].

In 2010, mexiletine has been approved in France for the "symptomatic treatment of myotonic syndromes (myotonic dystrophies and nondystrophic myotonias or channelopathies)" based on a literature review. At that time, only few clinical studies have assessed the efficacy of mexiletine in these disorders [17–19]. Following the request of the French health authority, the present MYOMEX clinical study was conducted to investigate the efficacy and safety of mexiletine in nondystrophic myotonias [20].

2. Materials and methods

2.1. Study design

The MYOMEX study was a multicentre, double-blind, placebo-controlled, cross over (2 treatment periods of 18–22 days) study with a 4–8 days wash-out period. The objectives were to determine the efficacy and safety of mexiletine for the symptomatic treatment of nondystrophic myotonias.

The study could not be restricted to mexiletine-naïve patients because nondystrophic myotonias are rare diseases. Moreover, patients already treated with mexiletine were hesitant stopping treatment for a long period. Consequently, a crossover design with two short periods of treatment was chosen rather than a design with two parallel groups.

The study was conducted in accordance with the Declaration of Helsinki and was approved by an independent Ethics Committee ("*Comité de Protection des Personnes Île de France I*"). Written informed consent was obtained from each patient. This trial is registered with EudraCT, number 2010–020,923–37.

2.2. Patients

Male and female patients, aged between 18 and 65 years, were included if they had genetically definite myotonia congenita (MC) or paramyotonia congenita (PC), were able to comply with the study conditions and experienced myotonic symptoms severe enough to justify treatment. Myotonia was assessed by physicians according to a clinical standardized process which evaluated the presence and the severity of myotonia in 8 regions (eyelids, eyes movements, jaw and throat, upper limbs, lower limbs and respiratory muscles) and the disability in 7 daily activities (talking, writing, feeding, hygiene, getting dressed, walking, climbing stairs). The clinical exam included 5 contraction-relaxation (with a maximal contraction of 2 s) of the eyelids, the jaws, the hands and the toes, the research of a lid-lag sign and the percussion of the deltoids, thenar eminences, thighs and calves. Symptoms were considered severe enough when myotonia involved at least two segments (upper limb, lower limb or face) and had an impact on at least three of the seven daily activities. If patients were not drug naive, they must agree to stop treatment at least four days before inclusion. A normal cardiac examination performed by a cardiologist including ECG and cardiac ultrasound was required (done within three months before trial). Patients were excluded in case of intercurrent event which could interfere with the muscle function (infection, trauma, fracture, etc.), disease that contraindicated mexiletine or interfered with clinical evaluation, use of any medication that could interfere with muscle function (diuretics, anti-epileptics (sodium channel blockers), anti-arrhythmics, corticosteroids and beta-blockers) or allergy to mexiletine. Women of childbearing potential not using a medically-accepted contraceptive regimen were excluded.

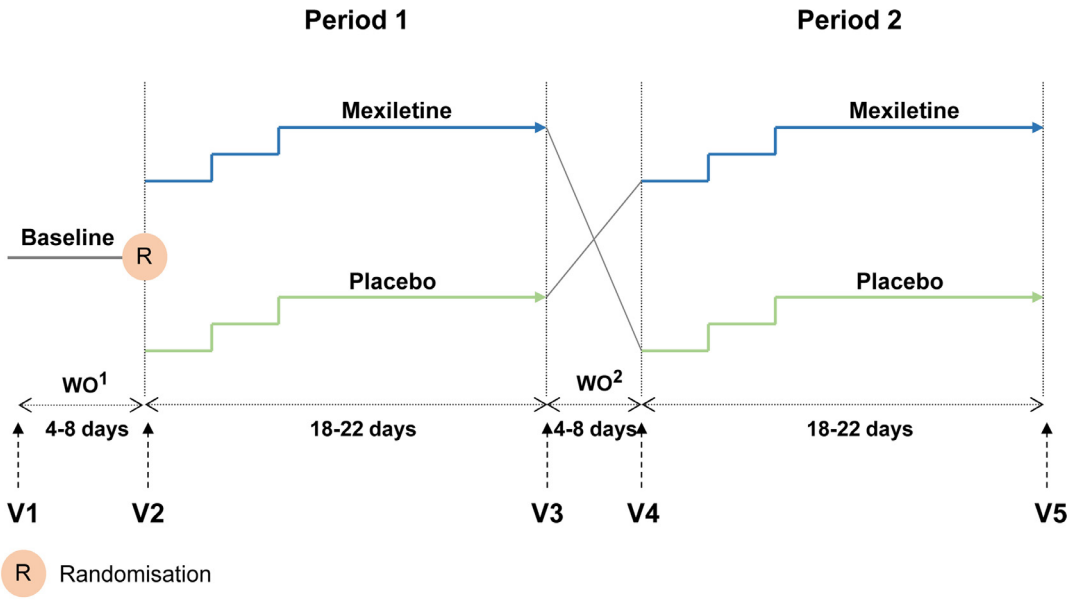
2.3. Randomisation and masking

Patients were randomly assigned (1:1) to receive either mexiletine followed by placebo or vice versa (Fig. 1). Randomisation was stratified according to diagnosis (myotonia congenita and paramyotonia congenita) and generated by computer list. Patients, sponsor and study personnel were blinded to the treatment (mexiletine or placebo) and their sequence allocation. The placebo tablets looked identical to mexiletine and were administered with the same schedule as mexiletine.

2.4. Treatments

Patients attended screening visit and then baseline visit 4–8 days after (Fig. 1). This time period allowed the elimination of residual blood mexiletine in patients who had received mexiletine before study entry.

The study drug mexiletine or the placebo was started at 200 mg/day and titrated by increments of 200 mg every three days to reach a maximum dose of 600 mg/day in one week. In case of intolerable adverse events, the dose of the study



V, visit at center
WO[1], wash-out before randomization for patients who were treated by mexiletine before study
WO[2], wash-out between treatment periods

Fig. 1. Study overview.

medication could be reduced by decrements of 200 mg/day and stopped for the ongoing period if the adverse event persisted. The mexiletine or placebo capsules were to be taken at the beginning of a meal.

2.5. Study procedures and assessments

Demographics, medical history, molecular results, results of a complete cardiac examination (<3 months) were recorded at screening visit. Blood samples for clinical chemistry and haematology tests were collected at screening and at the end of each period.

To avoid triggers, all subjects were placed for 15 min in a room at controlled temperature (22 °C) and remained completely relaxed for 30 min. For women, tests were not performed during menses. A 15-min interval between tests was considered sufficiently long to avoid warm up.

2.5.1. Primary end-point

The score of stiffness severity self-reported by the patients on a 100-mm visual analogic scale (VAS) ranging from "no stiffness at all" (0 mm) and "worst possible stiffness" (100 mm) was assessed at the beginning (Visits 2 and 4) and at the end (Visits 3 and 5) of each period.

2.5.2. Secondary efficacy end-points

The second efficacy outcomes were assessed at baseline (Visit 2) and at the end of each period (Visits 3 and 5):

- Time needed to stand up from a chair, walk around the chair and sit down again (chair test).Impact of the disease on health-related quality of life evaluated using the validated Individualized Neuromuscular Quality of Life (INQoL) auto-questionnaire which comprises four main domains divided into 12 subdomains [21,22].
- EMG tests were performed to evaluate the decline of the compound muscle action potential (CMAP) amplitude recorded from the abductor digiti minimi (ADM) muscle after repeated short exercises (3 ADM contractions of 10 s each, with 50 s intervals) performed on the left hand at room temperature and on the right hand after cooling (7-min cold exposure using ice bag of the ADM), according to the standardized EMG protocol previously described by Fournier et al. [23,24].
- The Clinical Global Impression (CGI) for efficacy was assessed at the end of each period. The efficacy was rated on a 4-point rating scale (good, fair, poor, none) by the patients and the investigator.
- At the end of the study, patients were asked on their preference for one or the other study period and for their willingness to continue mexiletine.

2.5.3. Safety assessments

Adverse events were assessed at each visit by direct questioning of the patient and by the review of the patient diary booklet, through clinical examination (vital signs) and from the clinical laboratory values. The investigator evaluated the severity of the adverse event using the following categories: mild, moderate or severe and the adverse event relation to the treatment.

12-lead ECG was performed at screening visit (all patients), baseline visit (non-naive patients only before study medication intake), at the end of each period. Recording using portable ECG device was performed before and two hours after the first study medication intake of each period, once at home on day 8 of each period (under 600 mg/day) and at the end of each period. Parameters of the ECG (HR, PR, QRS and QTc) were analysed and reviewed on live and systematically by a cardiologist (each time an ECG was performed) and a feed-back was immediately transmitted to the investigator.

Concomitant medications and compliance were recorded at each visit. The CGI scale for tolerability was assessed at the end of each period on a 4-point rating scale by the patients and the investigator.

2.5.4. Mexiletine plasma concentrations

Blood samples for assessment of mexiletine plasma concentrations were collected on the first day of each period, before the first dose of treatment, and at the end of each period, before and two hours after the morning dose intake (mexiletine or placebo). A 7 mL blood sample was collected per timepoint in heparinized tubes, immediately centrifuged at 4 °C (10 min at 1500 g) and stored frozen at -20 °C until analysis. Blood samples for mexiletine levels assessment were sent at the end of the study to the Department of Pharmacology of Pitié-Salpêtrière Hospital for a blinded analysis using ultraperformance liquid chromatography with MS/MS detection (method validated according to the United States Food and Drug Administration criteria).

2.6. Statistical analysis

The primary endpoint was the score of stiffness severity as self-reported by the patients on the VAS. Difference between treatments was evaluated using a mixed effect linear model on ranks. The difference between the two treatments for the absolute change from baseline was estimated with the following parameters: diagnosis strata, treatment, period and sequence as fixed effects, subject as random factor and baseline value as fixed covariate. A potential carry-over effect was first explored. Since no significant effect of the treatment × sequence interaction was evidenced ($p = 0.845$), the data from the two periods were combined.

The ITT population included all randomised patients. The modified ITT population (mITT) included all randomised patients with at least one available evaluation pertaining to the primary criterion or with a VAS value at the end of each period. The safety population included patients who received at least one study treatment dose.

The main secondary endpoints were the changes of chair test score, INQoL score and CGI-efficacy score during each period and patient's preference at the end of the study. The changes from baseline of the results of the chair test were compared using Wilcoxon test. The changes from baseline of the INQoL score were analysed using a mixed effect linear model. The CGI-efficacy data were transformed as binary variables (efficient for good/fair and not efficient for poor/none) and treatment groups were compared using the McNemar test. Patient's preferences for one or the other study period were compared using a binomial test.

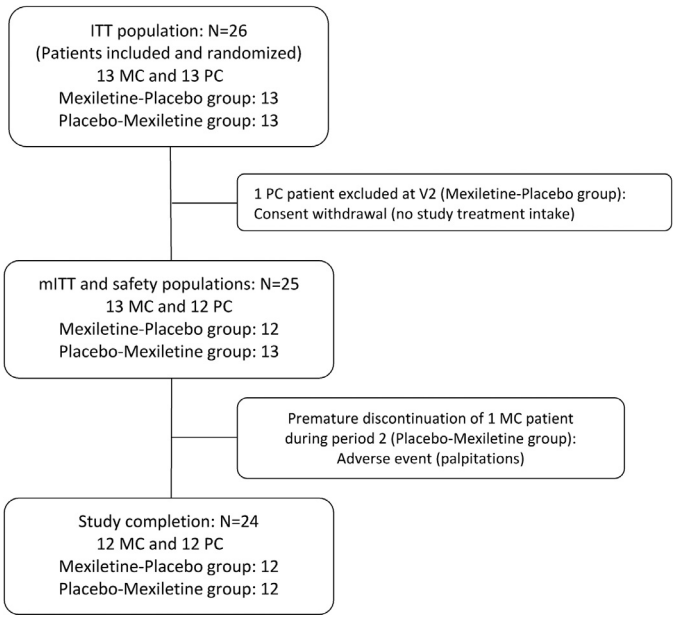


Fig. 2. Flow chart.

Changes from baseline in ECG parameters were described for each visit and the treatment effect was assessed using a mixed effect linear model.

The estimation of the sample size was based on the number of patients ($n = 200$) identified by molecular analysis in the study centres and according to clinical experience, 40 to 50% of patients required symptomatic treatment for myotonia. It was postulated that a 50% reduction of the primary outcome (stiffness VAS score) would be a clinically significant goal. In order to obtain 24 patients (which represents 12% of the identified population in France) with two analysable periods of treatment, it was estimated that up to 40 patients had to be screened. No previous data was available to enable calculation of power and sample size.

3. Results

3.1. Patient disposition

A total of 26 patients (13 with MC and 13 with PC) were enrolled in six centres. One patient withdrew consent after randomisation but before any study treatment intake (Fig. 2). Therefore, the mITT population was composed of 25 patients (13 MC and 12 PC).

3.2. Patient characteristics at inclusion

In the mITT population, the mean age was 43.0 years (40.3 years for MC and 46.0 for PC) with a range from 20 to 66 years (Table 1). A majority of patients (68.0%) were male

Table 1
Patient characteristics at inclusion (mITT population).

	Myotonia congenita ($n=13$)	Paramyotonia congenita ($n=12$)	Total ($n=25$)
Age			
Mean (SD)	40.3 (12.2)	46.0 (10.2)	43.0 (11.4)
Median (range)	40.9 (20.2; 66.0)	48.9 (21.8; 59.6)	44.9 (20.2; 66.0)
Male gender, n (%)	11 (84.6)	6 (50)	17 (68.0)
Body mass index, kg/m^2, mean (SD)	26.2 (4.0)	23.8 (3.6)	25.1 (3.9)
Mexiletine treatment, n (%)			
Treated at screening	9 (69.2)	2 (16.7)	11 (44.0)
Previously treated	1 (7.7)	2 (16.7)	3 (12.0)
Treatment naive	3 (23.1)	8 (66.7)	11 (44.0)
Chair test time, s, mean (SD)	9.1 (3.7)	5.3 (1.9)	7.3 (3.5)
INQoL score, mean (SD)			
Weakness	61.9 (27.1)	64.9 (28.2)	63.4 (27.1)
Locking	65.2 (25.8)	73.2 (19.4)	69.0 (22.9)
Pain	34.0 (31.4)	43.4 (32.3)	38.5 (31.5)
Fatigue	58.7 (25.5)	49.1 (38.6)	54.1 (32.1)
Activities	56.6 (24.2)	65.8 (11.6)	61.0 (19.4)
Independence	25.2 (25.3)	41.2 (20.7)	33.2 (24.0)
Social relationship	24.2 (23.5)	38.4 (23.8)	31.0 (24.3)
Emotions	46.8 (26.1)	56.5 (26.1)	51.5 (26.0)
Body image	49.8 (30.0)	53.5 (21.5)	51.6 (25.8)
Overall quality of life	43.3 (22.2)	52.2 (18.2)	47.8 (20.4)
Randomised treatment sequence, n (%)			
Placebo-mexiletine	6 (46.2)	7 (58.3)	13 (52.0)
Mexiletine-placebo	7 (53.8)	5 (41.7)	12 (48.0)

INQoL, individualized neuromuscular quality of life.

(84.6% for MC and 50% for PC). Nine patients with MC (four in the placebo-mexiletine sequence and five in the mexiletine-placebo sequence) and two patients with PC (one in each treatment sequence) were currently treated with mexiletine at screening.

3.3. Primary outcome measure: stiffness score

The median stiffness VAS score for patients receiving mexiletine was 71.0 at baseline and decreased to 16.0 at the end of the treatment period while median VAS score for placebo did not change (81 at baseline vs. 78 at end of treatment) (Table 2). This corresponded to a median change of -78% of the stiffness VAS score compared to baseline for subjects under mexiletine and a +2% median change for placebo. The individual variations according to diagnosis and period are presented in Fig. 3.

The comparison between the two treatments regarding the stiffness VAS absolute change from baseline was performed using a mixed effects linear model on ranks. The model showed a significant effect of treatment ($p < 0.001$) and baseline value ($p=0.002$) in mITT population (Table 2). There was no significant effect for diagnosis MC or PC ($p=0.716$), period ($p=0.133$) and treatment × diagnosis interaction ($p=0.357$).

3.4. Secondary efficacy outcome measures

3.4.1. Chair test

At baseline, the mean time for the chair test was longer for the patients with MC compared to patients with PC (9.1 s vs. 5.3 s, respectively) (Table 3). For the overall population, the mean (SD) change for performing the chair test was significantly reduced after mexiletine treatment: 5.2 (1.6) s vs. 7.5 (4.1) in placebo group ($p=0.0007$).

3.4.2. Neuromuscular Quality of Life (INQoL)

Participants answered each sub-domain of the INQoL auto-questionnaire by using a seven-point Likert scale. They assessed the degree of impact of a symptom and of the disease on some aspects of their life. They also evaluated the importance that they give to each item.

Prior to treatment, almost all patients reported weakness and muscular locking. Pain was reported by 60% of patients and fatigue by 80% (Table 4). After treatment with placebo, the percentages of patients with symptoms were comparable to baseline values. In contrast, after treatment with mexiletine, the percentage of patients with symptoms was lower compared to baseline values for all symptoms at the exception of muscular locking.

The mean scores of INQoL for symptoms subdomains with the highest negative impact on quality of life were for locking (69.1) and weakness (63.4) (Table 4). After placebo treatment, the mean scores of the four symptoms (weakness, locking, pain and fatigue) remained stable while they were all improved with mexiletine. The mean scores of INQoL for locking and weakness were greatly improved (decreasing to 30.5 for both). There was also a significant improvement of fatigue and pain with a mean reduction from 54.1 to 23.8 and 38.5 to 12.9, respectively.

For the Life domain (activities, independence, social relationships, emotions and body image), the greatest impact

Table 2
Evolution of stiffness (100 mm visual analogic scale) before treatment and at the end of treatment (mITT population).

	Placebo		Mexiletine	
	Before treatment	End of treatment	Before treatment	End of treatment
Myotonia congenita ($n=13$)				
Mean (SD)	70.0 (20.6)	62.7 (32.4)	66.1 (24.7)	29.2 (17.6)
Median [range]	74.0 [27;91]	69.0 [0;98]	73.0 [11;100]	25.0 [9;72]
Absolute change				
Mean (SD)	−7.3 (23.7)		−36.9 (30.2)	
Median [range]	2.0 [−63;14]		−32.0 [−78;35]	
Paramyotonia congenita ($n=12$)				
Mean (SD)	80.8 (13.7)	69.9 (32.4)	65.8 (20.5)	19.0 (20.8)
Median [range]	83.5 [54;98]	86.5 [4;96]	67.0 [17;96]	12.0 [1;54]
Absolute change				
Mean (SD)	−10.8 (36.9)		−46.8 (25.1)	
Median [range]	1.0 [−94;35]		−50.0 [−93;−3]	
Total ($n=25$)				
Mean (SD)	75.2 (18.1)	66.2 (31.9)	66.0 (22.3)	24.3 (19.5)
Median [range]	81.0 [27;98]	78.0 [0;98]	71.0 [11;100]	16.0 [1;72]
Absolute change				
Mean (SD)	−9.0 (30.1)		−41.7 (27.7)	
Median [range]	2.0 [−94;35]		−42.0 [−93;35]	

of the disease at baseline was on the subdomain "activities" (mean score, 61.0). Placebo treatment had no effect (60.7) on this subdomain, but mexiletine treatment improved it (28.1). The mean score of the overall quality of life (aggregation of the five life subdomains) was significatively improved after mexiletine treatment (from 47.8 to 27.1, $p < 0.001$).

A mixed effects linear model showed a significant treatment effect for each domain of the INQoL questionnaire except for the domain "Expected treatment effect".

3.4.3. Clinical global impression of efficacy

The investigators reported that the mexiletine treatment was efficient in 92% of patients and that the placebo was poorly efficient in 80% of patients ($p < 0.001$). Similarly, 92% of patients reported that mexiletine treatment was efficient and 76% considered that the placebo was poorly efficient ($p < 0.001$).

3.4.4. Patient's preference and willingness to continue treatment

Twenty (80%) patients significantly preferred the mexiletine treatment period ($p=0.0041$; binomial test). All but two patients (92%) were willing to continue taking mexiletine after the study.

3.5. Electroneuromyography (ENMG) examinations

In patients with MC, the mean compound muscle action potential (CMAP) amplitude decreased after the first short exercise, but returned to normal values after exercise cessation. At room temperature, CMAP amplitudes recovered with repeated exercise and approached normal values (warm-up phenomenon) whereas after cold exposure, decrease in CMAP amplitudes remained more pronounced (Fig. 4A). Overall, the decrease in CMAP amplitude was less pronounced in subjects receiving mexiletine than in those receiving placebo (Table 5).

In patients with PC, the expected patterns were observed, i.e. an aggravation of myotonia with repeated exercises and after cold exposure (Fig. 4B). Here also, the decrease in CMAP amplitudes was less pronounced in subjects receiving mexiletine than in those receiving placebo (Table 6).

3.6. Mexiletine plasma concentrations

After 18 days of treatment, mexiletine plasma concentrations were within the therapeutic range usually described for mexiletine (0.5 to 2.0 µg/mL). Mexiletine was not detected in the plasma of any patient during the placebo period at any timepoint. Before the first mexiletine intake, plasma concentration was null or below the detection threshold for all patients in both periods, regardless of treatment sequence, thus indicating that the wash-out period was sufficient.

3.7. Safety

The mean duration of treatment was 18.7 (1.8) days for placebo and 19.0 (2.4) days for mexiletine. Overall, the compliance of patients with the study treatment was high, with 100% of patients taking the placebo treatment according to protocol and 88% for mexiletine.

No serious adverse event was reported. Adverse events were more commonly reported in patients receiving mexiletine: 40 events reported for 15 (60%) patients under mexiletine and 14 events reported for nine (36%) patients under placebo. Adverse events were more frequently reported in the Gastrointestinal Disorders SOC (8 events in 7 patients overall, 24% of subjects in the mexiletine period

Table 3
Evolution of score (in seconds) for chair test before treatment and at the end of treatment (mITT population).

	Before treatment ($n=25$)	End of treatment	
		Placebo ($n=25$)	Mexiletine ($n=25$)
Myotonia congenita ($n=13$)			
Mean (SD)	9.1 (3.7)	9.5 (4.8)	5.7 (1.8)
Median [range]	9.0 [4;16]	9.0 [4;20]	6.0 [3;10]
Absolute change			
Mean (SD)	–	0.5 (1.9)	−3.4 (3.3)
Median [range]	–	0.0 [−2;4]	−3.0 [−11;0]
P-value [a]	–	0.008	
Paramyotonia congenita ($n=12$)			
Mean (SD)	5.3 (1.9)	5.3 (1.5)	4.6 (1.0)
Median [range]	5.0 [3;10]	6.0 [3;7]	5.0 [3;6]
Absolute change			
Mean (SD)	–	0.0 (1.3)	−0.8 (1.5)
Median [range]	–	0.0 [−3;2]	0.0 [−5;0]
P-value [a]	–	0.021	
Total ($n=25$)			
Mean (SD)	7.3 (3.5)	7.5 (4.1)	5.2 (1.6)
Median [range]	6.0 [3;16]	6.0 [3;20]	5.0 [3;10]
Absolute change			
Mean (SD)	–	0.2 (1.6)	−2.1 (2.9)
Median [range]	–	0.0 [−3;4]	−1.0 [−11;0]
P-value [a]	–	0.0007	

[a] Wilcoxon signed-rank test.

Table 4
Individualized Neuromuscular Quality of Life (INQoL) before and after treatment (mITT population).

	Before treatment ($n=25$)	End of treatment	
		Placebo ($n=25$)	Mexiletine ($n=25$)
Patients with symptoms, n (%)			
Weakness	24 (96.0)	23 (92.0)	19 (76.0)
Locking	24 (96.0)	23 (92.0)	24 (96.0)
Pain	15 (60.0)	18 (72.0)	8 (32.0)
Fatigue	20 (80.0)	20 (80.0)	13 (52.0)
INQoL, mean (SD)			
Symptoms			
Weakness	63.4 (27.1)	61.7 (28.8)	30.5 (24.3) [a]
Locking	69.1 (22.9)	66.1 (30.8)	30.5 (20.3)
Pain	38.5 (31.5)	46.3 (34.3)	12.9 (22.8)
Fatigue	54.1 (32.1)	55.8 (36.1)	23.8 (30.2)
Life			
Activities	61.0 (19.4)	60.7 (24.7)	28.1 (23.9)
Independence	33.2 (24.0)	34.4 (22.9)	16.2 (21.0)
Social relationship	31.0 (24.3)	35.6 (27.5)	17.2 (17.9)
Emotions	51.4 (26.0)	50.0 (28.0)	22.6 (19.1)
Body image	51.6 (25.8)	50.2 (26.3)	27.4 (22.7)
Overall quality of life [b]	47.8 (20.4)	49.9 (22.7)	27.1 (21.6)
Treatment effects			
Perceived treatment effect	13.7 (19.4)	26.0 (27.3)	47.0 (39.0)
Expected treatment effect	18.7 (28.2)	32.3 (31.4)	43.0 (44.3)

INQoL, Individualized Neuromuscular Quality of Life.
[a] $p < 0.001$ for each domain of INQoL, except $p=0.002$ for perceived treatment effect and $p=0.077$ for expected treatment effect.
[b] Aggregation of the five Life domains.

and 8% of subjects in the placebo period). The adverse events reported in at least two patients during mexiletine treatment which were considered as related to mexiletine were upper abdominal pain ($n=2$), nausea ($n=2$) and insomnia ($n=3$), all reported in patients with PC. An adverse event (palpitations) led to mexiletine discontinuation in one MC patient. It occurred in a stressful context and resolved spontaneously in few hours. No significant variations were observed in 12-lead ECG or in the portable ECG device parameters (HR, PR, QRS, QTc) between baseline and the end of the treatment period, either with placebo or mexiletine.

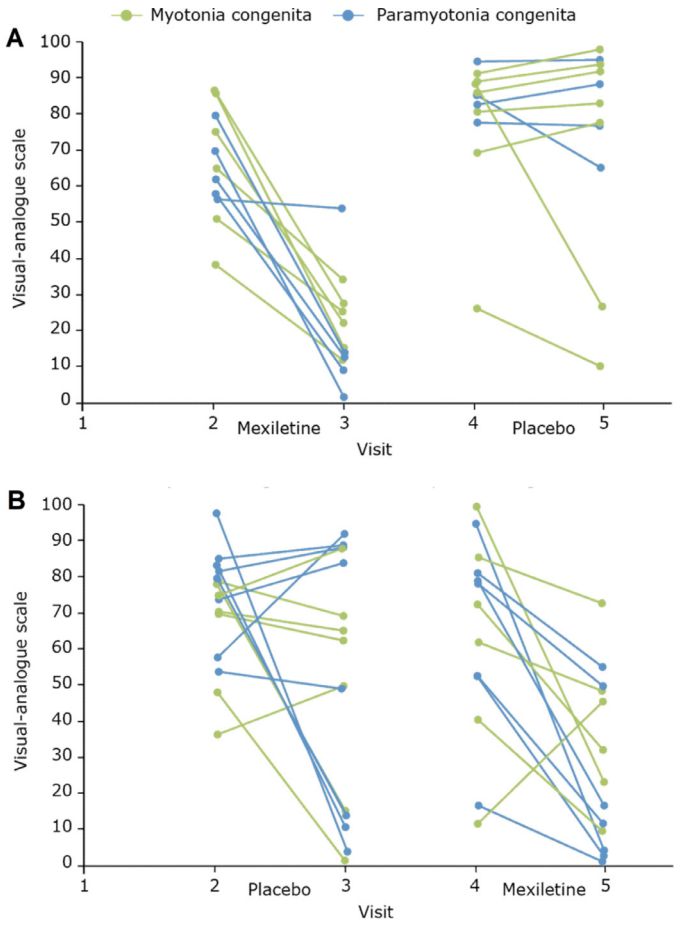


Fig. 3. Stiffness 100 mm VAS score by treatment sequence: (A) mexiletine-placebo or (B) placebo-mexiletine (mITT population).

Investigators and patients considered the tolerability (CGI) to mexiletine treatment as good except for the MC patient who prematurely withdrawn.

4. Discussion

This study demonstrated a significant effect of mexiletine versus placebo in patients with nondystrophic myotonia. The primary criterion was stiffness self-reported by patients and it was significantly improved in both periods of the cross-over study. Overall, the median absolute change from baseline on VAS was –42 mm for mexiletine and +2 mm for placebo. This represents a median change of –78% of the stiffness VAS score compared to baseline for subjects under mexiletine vs. a +2% median change for placebo. The effect of mexiletine over placebo was highly significant ($p < 0.001$).

The other efficacy tests confirmed the positive impact of mexiletine on symptoms of nondystrophic mytonias. After mexiletine treatment, the mean time for chair test was improved in both diagnostic groups, but this change was mainly due to patients with MC who presented a higher score at baseline compared to PC (9.1 vs. 5.3 s). Indeed, the time was already short for patients with PC at baseline and it was difficult to improve it further.

This clinical improvement with mexiletine was reflected in quality of life with a significant treatment effect on all domain of the INQoL questionnaire.

The treatment periods were correctly identified by most patients and investigators under blind conditions. The fact that a high rate of patients could correctly guess their treatment could be regarded as a partial unblinding, thus introducing a possible bias in the trial. One can also consider that this high rate of correct answers simply highlights the obvious clinical efficacy of mexiletine. Our clinical results are consistent with those of Statland et al. which provided preliminary evidence of the efficacy of mexiletine on the symptoms of nondystrophic myotonias in a study with a comparable design [17]. A cohort of 59 patients with nondystrophic myotonias was randomised in a double-blind cross-over study. Treatment consisted of oral 200 mg mexiletine or placebo capsules three times daily for four weeks followed by the opposite intervention for four weeks with one-week washout in between. Mexiletine significantly improved patient-reported severity score stiffness (on a scale from one to nine): difference between mexiletine and placebo was –1.68 ($p < 0.001$) for period 1 and −3.68 ($p = 0.04$) for period 2. Mexiletine improved also the INQoL global score (difference, −2.69; $p < 0.001$) and decreased handgrip myotonia on clinical examination (difference, −0.33 s; $p < 0.001$). In the study of Statland et al., there was nevertheless a statistically significant interaction between treatment and period for the primary criterion which, according to the authors, could be related to an unintentional unblinding of participants during period 2. In our study, there was no significant interaction between treatment and period and mexiletine was not detectable in blood after the wash-out period thus ruling out difficulties in the interpretation of the data.

In a recent study, Stunnenberg et al., investigated the efficacy of mexiletine in nondystrophic mytonia using an aggregated N-of-1 trials design and compared the results with those of the randomised clinical trial of Statland et al. A series of double-blind, randomised, placebo-controlled N-of-1-trials included in one centre 30 adult patients with nondystrophic myotonia who received mexiletine (600 mg daily) vs. placebo during multiple treatment periods of four weeks [19]. Mexiletine compared with placebo resulted in a mean reduction in daily-reported muscle stiffness of 3.12 (on a scale from one to nine), which was consistent with the previous effect of the randomised clinical trial of Statland et al. who reported a treatment effect of 2.69.

In the retrospective review of Suetterlin et al. of a cohort of 63 patients with nondystrophic myotonias, the efficacy of mexiletine was classified based on subjective patient report. Patients with genetically confirmed skeletal muscle channelopathy (nondystrophic myotonia or hyperkalemic periodic paralysis) with mexiletine treatment were included [18]. Mexiletine was effective or partially effective for a majority of patients.

No significant adverse events or ECG conduction abnormalities were reported during the short time use of mexiletine in our study. Adverse events appeared to be

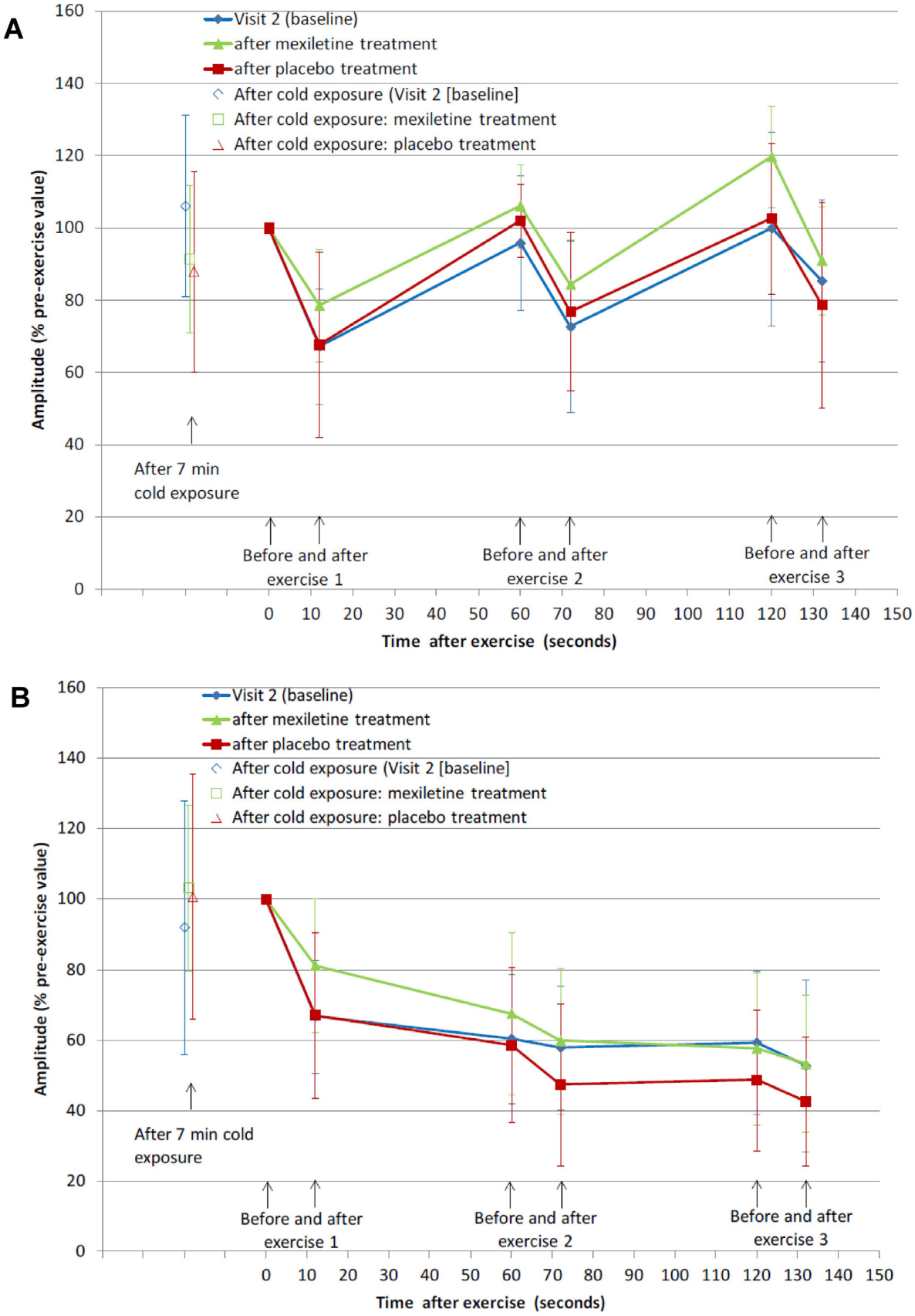


Fig. 4. Compound muscle action potential (CMAP) after repeated exercise (expressed as percentage of pre-first exercise) after cold exposure: (A) patients with myotonia congenita or (B) paramyotonia congenita (mITT population).

Table 5
CMAP amplitude after cold exposure (% pre-test) and repeated exercises (% pre-first exercise) in patients with MC before any treatment (V2) and at the end of each treatment period (V3 or V5) – mITT population.

Treatment		Before (V2) [a] % of pre-exercise value [c]	Placebo [b] % of pre-exercise value [c]	Mexiletine [b] % of pre-exercise value [c]
After cold exposure [d]		$N=11$	$N=13$	$N=13$
(no test)	Mean (SD)	106.1 (25.1)	88.0 (27.9)	91.4 (20.5)
	Med [range]	103.8 [68.7;159.8]	94.0 [42.2;138.0]	86.9 [62.7;143.8]
Short exercise 1		$N=13$	$N=13$	$N=12$
after cold exposure	Mean (SD)	67.2 (15.9)	67.7 (25.7)	78.6 (15.5)
After test	Med [range]	72.4 [27.2;90.0]	63.0 [18.2;105.2]	79.8 [47.7;103.9]
Short exercise 2		$N=13$	$N=13$	$N=12$
after cold exposure	Mean (SD)	95.8 (18.5)	102.0 (10.2)	106.1 (11.5)
Before test	Med [range]	100.0 [63.2;130.3]	103.4 [85.6;116.1]	106.9 [80.8;126.0]
Short exercise 2		$N=13$	$N=13$	$N=12$
after cold exposure	Mean (SD)	72.6 (23.7)	76.8 (21.8)	84.4 (12.3)
After test	Med [range]	79.2 [27.9;104.5]	79.3 [41.3;103.2]	83.9 [59.9;107.0]
Short exercise 3		$N=13$	$N=13$	$N=12$
after cold exposure	Mean (SD)	99.9 (26.8)	102.6 (20.9)	119.7 (14.0)
Before test	Med [range]	103.9 [36.8;149.4]	103.4 [59.7;136.4]	117.8 [104.5;145.0]
Short exercise 3		$N=13$	$N=13$	$N=12$
after cold exposure	Mean (SD)	85.3 (22.4)	78.7 (28.4)	91.0 (15.0)
After test	Med [range]	89.6 [38.2;129.2]	91.0 [9.1;110.3]	93.7 [49.6;113.0]

CMAP: compound muscle action potential; MC: myotonia congenita; Med: median; mITT: modified intention-to-treat; SD: standard deviation.
[a] Tests were performed at V2 on the right hand.
[b] Tests were performed on the right hand, either at V3 or V5 according to the treatment period.
[c] Value relative to value recorded before short exercise test 1 except for "After cold exposure", for which the value is relative to value before cold exposure.
[d] 5–7 min of cold exposure.

Table 6
CMAP amplitude after cold exposure (% pre-test) and repeated exercises (% pre-exercise) in patients with PC before any treatment (V2) and at the end of each treatment period (V3 or V5) – mITT population.

Treatment		Before [a] % of pre-exercise value [c]	Placebo [b] % of pre-exercise value [c]	Mexiletine [b] % of pre-exercise value [c]
After cold exposure [d]		$N=11$	$N=12$	$N=11$
(no test)	Mean (SD)	92.0 (36.0)	100.7 (34.8)	103.2 (23.6)
	Med [range]	91.4 [37.2;174.1]	103.6 [4.9;149.5]	101.5 [66.3;133.9]
Short exercise 1		$N=12$	$N=12$	$N=12$
after cold exposure	Mean (SD)	66.7 (16.10)	67.1 (23.5)	81.2 (18.8)
After test	Med [range]	68.4 [31.3;93.5]	61.8 [35.3;103.4]	84.6 [54.2;113.1]
Short exercise 2		$N=12$	$N=12$	$N=12$
after cold exposure	Mean (SD)	60.4 (18.3)	58.6 (22.0)	67.5 (23.0)
Before test	Med [range]	64.0 [34.0;86.0]	59.7 [16.3;89.2]	59.9 [25.4;106.0]
Short exercise 2		$N=12$	$N=12$	$N=12$
after cold exposure	Mean (SD)	57.9 (17.7)	47.3 (22.9)	59.8 (20.7)
After test	Med [range]	59.9 [27.9;94.4]	44.1 [5.1;80.3]	53.6 [27.1;94.0]
Short exercise 3		$N=12$	$N=12$	$N=12$
after cold exposure	Mean (SD)	59.3 (20.12)	48.7 (20.1)	57.6 (21.6)
Before test	Med [range]	60.5 [27.7;100.0]	47.9 [14.3;85.5]	57.9 [22.0;103.8]
Short exercise 3		$N=12$	$N=12$	$N=12$
after cold exposure	Mean (SD)	52.8 (24.3)	42.6 (18.3)	53.3 (19.45)
After test	Med [range]	44.9 [25.3;102.8]	38.4 [16.3;72.2]	54.2 [18.6;92.0]

CMAP: compound muscle action potential; Med: median; mITT: modified intention-to-treat; PC: paramyotonia congenita; SD: standard deviation.
[a] Tests were performed at V2 on the right hand.
[b] Tests were performed on the right hand either at V3 or V5 according to the treatment period.
[c] Value relative to value recorded before short exercise test 1 except for "After cold exposure", for which the value is relative to value before cold exposure.
[d] 5–7 min of cold exposure.

slightly more common with mexiletine treatment than with placebo, but no serious adverse event was reported.

In ENMG examinations, there were large inter- and intra-individual variations from one visit to the other. In both diagnosis groups, our results suggest that the decrease in CMAP amplitude was less pronounced in subjects receiving mexiletine than in those receiving placebo, even if these changes were not statistically significant. This non-significance could be in part explained by an inter-centre variability and perhaps also by some protocol design

limitations (short treatment period duration, small population or a too low maximal dosage of mexiletine) and is a limit to the conclusions which can be drawn from the EMG tests results for this study. This results trend is consistent with the results of Lo Monaco et al. who reported previously a significant reduction of the CMAP amplitude transitory depression after the beginning of mexiletine treatment in a cohort of 21 patients with MC [25]. Nevertheless, the different profiles of MC and PC were evidenced as expected, supporting that repeated short exercise tests are highly sensitive to discriminate between PC or MC and therefore remain an essential tool for diagnosis.

Our study has some limitations. One of them is the short duration of treatment due to the unwilling of patients already treated with mexiletine to discontinue their treatment for a too long period of time. Nevertheless, a 18-day duration was sufficient to demonstrate with confidence the efficacy of mexiletine compared to placebo. Taken together with the short duration of treatment, unfrequent adverse events had a low chance to be detected. There was no extension phase to the MYOMEX study but some long-term follow-up data are available for 8 patients out of 25 enrolled and were collected after informed consent during the 94 months after the study completion. Their stiffness VAS scores remained low and each of them remained under treatment indicating a sustained treatment effect and good tolerability. Another consequence of the rarity of the disease in France was the need to include both chloride channelopathy and sodium channelopathy to achieve a sufficient sample size. Indeed, patients with MC or PC have different clinical, genetic and electrophysiological characteristics. Nevertheless, both MC and PC patients appeared to have benefited from mexiletine treatment as demonstrated by the highly significant overall difference. However the study was not sufficiently powered due to the rarity of the diseases to further analyse differences according to the type of channelopathy.

In conclusion, mexiletine significantly improved stiffness and quality of life in patients with nondystrophic myotonia and was well tolerated over the 18-day treatment period.

Declaration of Competing Interests

S. Vicart reports serving on scientific advisory boards and being a consultant for Lupin starting after the end of the study. Y. Péréon reports personal fees from Lupin, outside the submitted work. B. Fontaine reports grants from AFM-Telethon during the conduct of the study. The other authors did not report conflicts of interest.

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