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Open-Label Trial of Ranolazine for the Treatment of Paramyotonia Congenita

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Abstract

Introduction: Paramyotonia congenita (PMC) is a non-dystrophic myotonic disorder that is believed to be caused by a defect in Na_v1.4 sodium channel inactivation. Ranolazine, which acts by enhancing slow inactivation of sodium channels, has been proposed as a therapeutic option, but *in vivo* studies are lacking.

Methods: We conducted an open-label, single-center trial of ranolazine to evaluate efficacy and tolerability in patients with PMC. Subjective symptoms of stiffness, weakness, and pain, as well as clinical and electrical myotonia, were evaluated. Baseline measures were compared with those after 4 weeks on ranolazine.

Results: Ranolazine was tolerated well without any serious adverse events. Both subjective symptoms and clinical myotonia were significantly improved. EMG myotonia duration was reduced, but this change was not statistically significant in all muscles tested.

Discussion: Our findings support the use of ranolazine as a treatment for myotonia in PMC and suggest that a randomized, placebo-controlled trial is warranted.

Keywords

myotonia; paramyotonia; ranolazine; electromyography; stiffness; channelopathy

Author contributions

Design or conceptualization of the study: A.A.H., A.B., M.M.R., J.T.K., W.D.A. Analysis or interpretation of the data: S.L., D.K., M. F., J.A., A.A.H., M.M.R., W.D.A., Statistical analysis: D.K. and W.D.A. Drafting or revising the manuscript for intellectual content: S.L., D.K., A.B., M.F., J.A., M.M.R., J.T.K., W.D.A.

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Introduction

Paramyotonia congenita (PMC) is a rare autosomal-dominant, non-dystrophic myotonic disorder characterized by clinical myotonia and symptoms of muscle stiffness, pain, and a feeling of fatigue or weakness. PMC results from missense mutations in *SCN4A* that lead to a gain-of-function in skeletal muscle Na_v1.4 sodium channels, usually caused by a defect of channel inactivation.^{1,2}

Several sodium channel blockers have been clinically tested in myotonic disorders; however, only mexiletine and lamotrigine have been shown to effectively reduce myotonia in randomized, placebo-controlled trials.^{3,4} There are currently no FDA-approved treatments for myotonia, and some patients do not tolerate or show poor response to treatments such as mexiletine.⁵ Recently, ranolazine (Ranexa®, Gilead Sciences, Foster City, CA), which was approved in 2006 for the indication of chronic angina, has been proposed as a possible therapeutic option due to its mechanism of enhancing slow inactivation of sodium channels.⁶ One study of PMC mutants *in vitro* showed ranolazine to be effective in stabilizing the inactivated state in both mutant and wild-type sodium channels.⁷ Due to its potential benefit and favorable safety profile, we conducted an open-label, single-center trial of ranolazine in patients with PMC.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the institutional review board at The Ohio State University Wexner Medical Center and registered at www.clinicaltrials.gov (NCT02251457). Written informed consent was obtained from each participant.

Study Design

This single-center, open-label trial evaluated the efficacy and tolerability of ranolazine in participants with PMC. Participants were age 18 years or older, had a diagnosis of PMC established by genetic testing of the participant or a first-degree relative, and had clinically evident myotonia. Those taking mexiletine, lacosamide, acetazolamide, phenytoin, quinine, procainamide, Saint John's wort, or tocainide were only allowed to participate after discontinuing the medication for a time period of 7 half-lives. Individuals taking CYP3A inducers or potent inhibitors, simvastatin exceeding 20 mg daily, metformin exceeding 1700 mg daily, P-glycoprotein inhibitors or substrates, or QTc-prolonging drugs were excluded. Other exclusion criteria included hypersensitivity to the study drug, hepatic cirrhosis, creatinine clearance < 30 mL/min, prolonged QTc (> 470 ms for men and > 480 ms for women), pregnancy, history of malignancy or adenomatous polyps, or direct family history of sudden cardiac death. Lamotrigine was not an exclusion criterion, but no participant took lamotrigine during the study period.

All participants were assessed at baseline and weeks 2, 4, and 5. After the baseline assessment, patients received a 500 mg dose of ranolazine twice daily and continued until week 4 (patients did not receive any anti-myotonia treatments at baseline and week 5). The

dose was increased to 1000 mg twice daily as tolerated after the week 2 visit. During each assessment, a 12-lead EKG was performed.

At each time point, participants rated severity of stiffness, weakness, and pain symptoms on a 0–9 scale with 9 being the most severe.³ Eyelid and handgrip myotonia were assessed by having participants squeeze their eyes shut or make a tight fist for 5 seconds and then rapidly opening. Five consecutive trials of each maneuver were performed and time to full opening was measured. One trial of Timed-up-and-go (TUG) was performed at each visit.⁸ At baseline and week 4, EMG myotonia was measured in the tibialis anterior (TA) and abductor digiti minimi (ADM) muscles, and the short exercise test of the ADM (SET) was performed as previously described.^{9,10} The presence or absence of myotonia following 15 needle movements (EMG frequency) and the duration of the longest sustained myotonic discharge (EMG duration) were assessed in the TA and ADM. Maximum ADM CMAP decrement was assessed during three trials of the SET. All assessments were performed blinded to results from prior assessments. Drug compliance was quantified using a drug diary and pill counts.

Statistical Analysis

The primary objective was to compare outcomes at week 4 to baseline. Linear mixed effects models included an indicator of visit and a random intercept for each participant. EMG duration, TUG, eyelid opening, and hand opening were log transformed to better satisfy model assumptions. The sign test was used to compare EMG frequencies at week 4 to baseline. To control the familywise error rate at 0.1, we used the Bonferroni correction and thus conducted each test comparing outcomes at week 4 to baseline at the 0.01 level. We secondarily explored longitudinal changes for outcomes measured at multiple time points and compared EKG QTc and SET decrement using a paired t test. Based on our prior study in myotonia congenita (MC), we calculated that with 10 patients, we would have 80% power to detect a change from baseline to week 4 of 1.33 standard deviations at the 0.01 level with a two-sided paired t-test.¹⁰

Results

Baseline Demographics, Safety, and Medication Tolerance

A total of 12 potential participants were screened and 10 (4 men and 6 women with a mean age of 44.7 years) were enrolled. Two individuals were excluded due to negative genetic testing. Enrolled participants had confirmed *SCN4A* mutations (Supplementary Table 1) and all had clinical and EMG myotonia. All participants tolerated the drug and remained on it for the duration of the study. Average medication compliance was 99.6%. There were no serious adverse events. QTc at week 4 (407 ± 21 ms, mean $\pm$ standard deviation) was not changed from baseline (402 ± 27 ms, mean $\pm$ standard) ($p=0.368$). Mild constipation, which required no medication for treatment, was reported in 3 participants. Additionally, 2 participants reported transient lightheadedness. All but one participant tolerated the 1000 mg twice daily dose due to reported side effects of insomnia, constipation, mental fog, and malaise.

Subjective Symptoms

Subjective symptoms of stiffness, pain, and weakness were significantly improved at week 4 compared to baseline (Table 1 and Figure 1a). This improvement was also significant by week 2. After ranolazine was stopped at week 5, there was no longer a significant difference in symptoms compared to baseline in any parameter.

Clinical Myotonia

Clinical myotonia improved after treatment with ranolazine. TUG, eyelid opening, and hand opening times all improved significantly at week 4 compared to baseline (Table 1 and Figure 1b). This improvement was also significant by week 2 in all three clinical measures. At week 5, there was no longer a significant difference compared to baseline.

EMG Myotonia and SET

Participants also showed improvement in EMG myotonia after treatment with ranolazine (Table 1 and Figure 1c). TA EMG myotonia duration was significantly reduced at week 4 compared to baseline. ADM EMG myotonia duration showed a 60% reduction at week 4 but this was not significant. The change in TA and ADM EMG myotonia grades at week 4 was not significant. Maximum SET amplitude decrement was similar at week 4 ($94.4 \pm 11.2\%$ mean $\pm$ standard deviation) and baseline ($89.6 \pm 11.2\%$) ($p=0.113$).

Discussion

Our results showed that ranolazine was well-tolerated and led to improvement in clinical, and to a lesser extent, EMG myotonia in patients with PMC. These findings are aligned with preclinical data and support the use of ranolazine as a treatment for myotonia. The results of this study are similar to our previous findings showing the effect of ranolazine in patients with MC.¹⁰ Both PMC and MC patients showed a greater reduction in EMG myotonia duration than EMG myotonia frequency. We suggest that this finding is a result of ranolazine's use-dependent block of sodium current, thereby causing a reduction in the duration of myotonia without eliminating the initiation of myotonia.¹⁰

In the current study, patients showed significant improvement in all subjective measures, i.e. stiffness, weakness, and pain. This is in contrast to patients with MC, who only showed a statistically significant improvement in subjective stiffness.¹⁰ It has been proposed that mutations in *SCN4A* cause an increase in sodium persistent inward current, resulting in muscle depolarization and weakness in individuals with PMC.^{7,10–11} Treatment with ranolazine has been shown to decrease the amplitude of the inward sodium current in PMC, suggesting that ranolazine directly targets the pathologic current responsible for both weakness and muscle stiffness.¹¹ While sodium persistent inward current does play a central role in triggering muscle stiffness in MC, the primary defect is a reduction in chloride current,^{12–14} which is not reversed by treatment with ranolazine. The mechanism of action of ranolazine is more closely linked to the underlying defect in PMC, which may explain its greater efficacy in PMC compared to MC.

This study had several limitations as it was unblinded, not placebo-controlled, performed at a single center, and made no comparison to an alternate treatment such as lamotrigine or mexiletine. Given that the results show clinical benefit with ranolazine, a larger, randomized, placebo-controlled trial is warranted. Additionally, comparison of different potential therapeutics in differing phenotypes and mutations may be needed as genotype and phenotype could drive therapeutic effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. Mark Rich received grant funding from MDA (MDA 378033). John T. Kissel and W. David Arnold received support from Gilead Sciences as noted above. The remaining authors have no conflicts of interest to disclose.

Abbreviations

ADM	abductor digiti minimi
EKG	electrocardiogram
SET	Short exercise test
EMG	electromyography
MC	myotonia congenita
PMC	Paramyotonia congenital
TA	tibialis anterior
TUG	timed-up-and-go

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Figure 1.

(a) Patient-reported symptoms of stiffness, pain, and weakness were reduced at week 4 compared to baseline; (b) Clinical measures of Timed-Up-And-Go, eyelid opening time, and hand grip were significantly reduced at week 4 compared to baseline; (c) electromyography (EMG) myotonia duration in the tibialis anterior (TA), but not in the abductor digit minimi (ADM), was significantly reduced at week 4 compared to baseline.

Table 1:

Self-reported symptom severity rating, clinical hand grip and eyelid myotonia assessments, and electromyographic (EMG) myotonia testing

Subjective Symptoms							
Variable	Visit	N	Mean	Standard Deviation	Comparison to Baseline (Difference)	99% Confidence Interval (Difference)	p-value
Self-reported Stiffness (0-9, 9=worst)	Baseline	10	6	1.25			
	Week 2	10	2.1	1.6	-3.9	(-5.76, -2.04)	<0.0001
	Week 4	10	1.4	1.58	-4.6	(-6.46, -2.74)	<0.0001
	Week 5	10	6.5	2.88	0.5	(-1.36, 2.36)	0.4627
Self-reported Weakness (0-9, 9=worst)	Baseline	10	4	1.41			
	Week 2	10	1.5	1.27	-2.5	(-4.69, -0.31)	0.0039
	Week 4	10	1	1.49	-3	(-5.19, -0.81)	0.0008
	Week 5	10	4.5	3.14	0.5	(-1.69, 2.69)	0.5327
Self-reported Pain (0-9, 9=worst)	Baseline	10	4.6	2.5			
	Week 2	10	1.6	1.65	-3	(-5.03, -0.97)	0.0003
	Week 4	10	0.9	1.37	-3.7	(-5.73, -1.67)	<0.0001
	Week 5	10	4.5	3.14	0.3	(-1.73, 2.33)	0.6857
Clinical Myotonia/EMG Duration							
Variable	Visit	N	Mean	Standard Deviation	Comparison to Baseline (Ratio)	99% Confidence Interval (Ratio)	p-value
Hand Grip Opening Time (seconds)	Baseline	10	9.27	14.68			
	Week 2	10	4.43	9.52	0.47	(0.25, 0.90)	0.0030
	Week 4	10	3.54	7.17	0.42	(0.23, 0.80)	0.0009
	Week 5	10	9.9	15.26	0.96	(0.51, 1.80)	0.8601
Eyelid Opening Time (seconds)	Baseline	10	10.76	11.96			
	Week 2	10	8.07	13.85	0.60	(0.34, 1.06)	0.0193
	Week 4	10	3.57	4.27	0.47	(0.26, 0.83)	0.0010
	Week 5	10	14.33	18.8	1.12	(0.63, 1.99)	0.5869
Timed Up and Go (seconds)	Baseline	9	11.43	4.84			
	Week 2	9	9.44	3.25	0.84	(0.74, 0.96)	0.0012
	Week 4	9	8.76	2.36	0.79	(0.70, 0.90)	<0.0001
	Week 5	9	10.83	5.01	0.93	(0.82, 1.06)	0.1683
EMG Duration ADM (milliseconds)	Baseline	10	108247	228651			
	Week 4	10	16750	14749	0.40	(0.09, 1.77)	0.0760
EMG Duration TA (microseconds)	Baseline	10	40031	32453			
	Week 4	10	23981	38138	0.34	(0.15, 0.78)	0.0023

EMG Frequency							
Variable	Visit	N	Median	Quartiles (Q1, Q3)	Comparison to Baseline (Median Difference)	99% Confidence Interval (Median Difference)	p-value
EMG Frequency ADM (0-15 insertions)	Baseline	10	15	(13, 15)			
	Week 4	10	12.5	(10, 15)	-1.5	(-6, 1)	0.1250
EMG Frequency TA (0-15 insertions)	Baseline	10	15	(15, 15)			
	Week 4	10	12.5	(13, 15)	0.0	(-9,0)	0.1250

ADB, abductor digiti minimi; TA, tibialis anterior