Open-label trial of ranolazine for the treatment of myotonia congenita

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ABSTRACT

Objective: To determine open-label, pilot study whether ranolazine could improve signs and symptoms of myotonia and muscle stiffness in patients with myotonia congenita (MC).

Methods: Thirteen participants were assessed at baseline and 2, 4, and 5 weeks. Ranolazine was started after baseline assessment (500 mg twice daily), increased as tolerated after week 2 (1,000 mg twice daily), and maintained until week 4. Outcomes included change from baseline to week 4 in self-reported severity of symptoms (stiffness, weakness, and pain), Timed Up and Go (TUG), hand grip and eyelid myotonia, and myotonia on EMG.

Results: Self-reported severity of stiffness ($p < 0.0001$) and weakness ($p < 0.01$) was significantly improved compared with baseline. TUG and grip myotonia times were reduced ($p = 0.03$, $p = 0.01$). EMG of the abductor digiti minimi and tibialis anterior showed significantly reduced myotonia duration ($p < 0.001$, $p < 0.01$) at week 4. No participant discontinued ranolazine because of side effects.

Conclusions: Ranolazine appeared to be well tolerated over a period of 4 weeks in individuals with MC, and ranolazine resulted in improvement of signs and symptoms of muscle stiffness. The findings of this study suggest that ranolazine should be investigated in a larger controlled study.

Classification of evidence: This study provides Class IV evidence that ranolazine improves myotonia in myotonia congenita. **Neurology® 2017;89:710-713**

GLOSSARY

ADM = abductor digiti minimi; **MC** = myotonia congenita; **NDM** = nondystrophic myotonic disorder; **TA** = tibialis anterior; **TUG** = Timed Up and Go.

Myotonia congenita (MC) is a nondystrophic myotonic disorder (NDM) caused by *CLCN1* chloride channel mutations resulting in a reduction of chloride conductance. MC results in impairment due to symptoms of muscle stiffness without altering the life span, and among the NDMs, MC has the greatest detrimental effect on patients' perceived quality of life.¹

Several medications are used to treat myotonia, but only mexiletine has evidence from a randomized, placebo-controlled, double-blind study.² Recently, ranolazine (Ranexa, Gilead Sciences, Foster City, CA) was shown to reduce myotonia in an MC mouse model and was possibly superior to mexiletine.³ On the basis of these encouraging data, we designed this pilot study to investigate whether ranolazine could improve signs and symptoms of muscle stiffness and myotonia in MC.

METHODS Standard protocol approvals, registrations, and patient consents. This study was registered on clinicaltrials.gov (NCT02251457) and was approved by an ethics standards committee on human experimentation (The Ohio State University). Written informed consent was obtained from all participants.

Study design. This was a single-center, open-label trial (NCT02251457) to test tolerability and efficacy of ranolazine in MC (Class IV evidence). Participants had genetically confirmed MC or genetic confirmation in a first-degree relative. Individuals treated with mexiletine, lacosamide, acetazolamide, phenytoin, quinine, procainamide, Saint John's wort, or tocainide were permitted to participate after discontinuation for 7 half-lives of each medication. Other exclusionary agents included CYP3A inducers of potent inhibitors, simvastatin >20 mg daily, metformin >1,700 mg daily, and P-glycoprotein inhibitors or substrates. Because ranolazine can prolong QT interval, individuals with prolonged QT (QTc: men >470 milliseconds, women >480 milliseconds) or taking QTc-prolonging

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drugs were excluded. Individuals with creatinine clearance <30 mL/min were excluded because of the risk of renal failure in the setting of renal insufficiency. Patients with cirrhosis were excluded.

Intervention and study visits. Assessments occurred at baseline and weeks 2, 4, and 5. At baseline and week 5, patients were not receiving antimyotonia treatments. Ranolazine was initiated after baseline and continued until week 4. Ranolazine was

initiated at 500 mg twice daily and increased as tolerated to 1,000 mg twice daily after the week 2 visit. A 12-lead ECG was performed at each visit.

Clinical assessment. Severity of stiffness, weakness, and pain symptoms was graded by participants (0–9, with 9 being the most severe) similar to a previously used symptom diary.² Hand grip myotonia was assessed by timing hand opening with a stopwatch after tight hand closure for 5 seconds. Five consecutive trials were

Table Results of symptom diary, clinical measures of muscle stiffness and mobility, and electrophysiology

Variable	Visit	n	Raw mean/median	SD/quartiles	Comparison to baseline	95% Confidence interval	p Value
Self-reported stiffness (0–9, 9 = worst) ^a	Baseline	13	5.46	2.18	0		
	Week 2	13	3.46	2.37	–2	–3.42 to –0.58	0.0073
	Week 4 ^b	12	2.08	1.73	–3.53	–4.99 to –2.07	<0.0001
	Week 5	13	6	2.45	0.54	–0.89 to 1.96	0.4476
Self-reported weakness (0–9, 9 = worst) ^a	Baseline	13	4.15	2.67	0		
	Week 2	13	3.23	2.45	–0.92	–2.03 to 0.19	0.1005
	Week 4 ^b	12	2.5	2.15	–1.81	–2.95 to –0.67	0.0028
	Week 5	13	5.08	2.6	0.92	–0.19 to 2.03	0.1005
Self-reported pain (0–9, 9 = worst) ^a	Baseline	13	4.08	3.01	0		
	Week 2	13	2.92	2.66	–1.15	–2.42 to 0.11	0.0732
	Week 4 ^b	12	2.42	2.61	–1.73	–3.03 to –0.43	0.0107
	Week 5	13	3.92	3.01	–0.15	–1.42 to 1.11	0.8069
Hand grip opening time, s ^c	Baseline	13	2.16	1.53	1		
	Week 2	13	1.75	0.47	0.91	0.74 to 1.13	0.4045
	Week 4 ^b	12	1.45	0.37	0.76	0.61 to 0.93	0.0109
	Week 5	13	1.91	0.89	0.94	0.76 to 1.16	0.5928
Eyelid opening time, s ^c	Baseline	13	1.94	1.50	1		
	Week 2	13	1.81	0.90	1.000	0.75 to 1.32	0.9919
	Week 4 ^b	12	1.40	0.57	0.811	0.60 to 1.08	0.1459
	Week 5	13	1.73	0.66	0.980	0.73 to 1.30	0.8747
TUG, s ^c	Baseline	12	9.99	3.36	1		
	Week 2	12	9.08	1.78	0.942	0.84 to 1.04	0.2147
	Week 4 ^b	11	8.68	1.59	0.887	0.80 to 0.99	0.0318
	Week 5	12	9.86	3.25	0.99	0.90 to 1.11	0.8895
EMG duration ADM, μs ^c	Baseline	11	10,082.73	13,932.3	1		
	Week 4 ^b	11	8,582.55	14,121.37	0.48	0.35 to 0.66	0.0008
EMG duration TA, μs ^c	Baseline	11	7,159.09	7,022.78	1		
	Week 4 ^b	11	6,288.27	6,881.83	0.48	0.29 to 0.78	0.0088
EMG frequency ADM (0–15 insertions) ^d	Baseline	13	13	8–15	0		
	Week 4 ^b	12	13	2.5–14	1	0 to 3	0.125
EMG frequency TA (0–15 insertions) ^d	Baseline	13	12	6–14	0		
	Week 4 ^b	12	11.5	4–14.5	0.5	–1 to 3	1

Abbreviations: ADM = abductor digiti minimi; TA = tibialis anterior; TUG = Timed Up and Go.

Raw means and SDs are presented for each variable except EMG frequency, which presents the median and the first and third quartiles. All p values are presented at the nominal level.

^aThe comparison to baseline is estimated by the mean difference.

^bPrimary comparison.

^cThe comparison to baseline is estimated by the ratio of geometric means.

^dThe comparison to baseline is estimated by the median difference.

performed. Eyelid myotonia was tested in a similar manner. A single trial of the Timed Up and Go (TUG) was performed.⁴

EMG assessment. EMG myotonia was assessed in the tibialis anterior (TA) and abductor digiti minimi (ADM) muscles at baseline and week 4. Presence or absence of myotonia after 15 needle movements (EMG frequency) and the duration of the longest sustained myotonic run (EMG duration) were quantified in each muscle.

Statistical analysis. Sample size was set at 12 to have at least 80% power to detect an effect size of 0.9 SD in the difference of EMG myotonia comparing the posttreatment at 4 weeks to baseline at 2-sided $\alpha = 0.05$. The main comparison for each outcome was the change from baseline to week 4, but changes were also assessed from baseline to weeks 2 and 5 as available. Paired *t* test was used to compare QTc intervals on ECG between baseline and week 4. EMG duration and frequency were analyzed with the sign test, and all other outcomes were analyzed with linear mixed models that included an indicator of visit and a random intercept for each participant. EMG duration, TUG, and hand/eyelid opening times were log transformed to satisfy model assumptions. To account for multiplicity, we use a Bonferroni correction to preserve an overall type I error rate of 0.1. Thus, each comparison of baseline to week 4 is tested at the 0.01 level. Longitudinal comparisons are exploratory.

RESULTS Study demographics, safety, and medication tolerance. Thirteen potential participants with MC

were screened and enrolled from our clinic or by self-referral (3 men and 10 women; mean age 47.5 ± 16.2 years, range 18–67 years). This cohort included autosomal dominant ($n = 12$) and recessive ($n = 1$) MC, all with clinically evident muscle stiffness and myotonia on EMG. There were no serious adverse events. The most common adverse event was constipation, noted in 4 of 13 participants. Constipation was mild and either did not require treatment or was managed with increased fiber intake. Week 4 ECG QTc (415 ± 22 milliseconds) was not significantly different compared with baseline QTc (412 ± 26 milliseconds, $p = 0.5$). No participant discontinued because of side effects. One participant mistakenly stopped ranolazine before the week 4 visit, and thus, 13 total participants were enrolled. All participants but 1 increased to 1,000 mg twice daily. This participant had a history of migraines and experienced a migraine when starting the medication and opted not to increase the dose.

Subjective stiffness, weakness, and pain. Participant-rated severity scores for stiffness, weakness, and pain improved with ranolazine (table). Stiffness was significantly reduced by 3.53 points at week 4 (figure 1A). At week 4, weakness and pain were reduced but not

Figure 1 Patient-reported stiffness, hand grip, and TUG

Treatment with ranolazine improves patient-reported severity of stiffness (A), hand opening time (B), and TUG (C) at week 4 compared with baseline. TUG = Timed Up and Go.

statistically significantly (figures e-1A and e-1B at Neurology.org). As expected, these changes disappeared off ranolazine (week 5).

Clinical and EMG myotonia. Clinical myotonia and EMG myotonia were improved with ranolazine (table). ADM EMG duration at week 4 was significantly reduced by 52% (figure e-2A). TA EMG duration was significantly reduced by 52% at week 4 (figure e-2B). In contrast, EMG frequency showed no significant change for the ADM or TA (figure e-2C and e-2D). At week 4, reductions were noted in hand opening time (24%) and TUG (11%), but they were not statistically significant (figure 1, B and C). In contrast, eyelid opening time did not show a change at week 4.

DISCUSSION Our results show improvement in clinical and EMG assessments of myotonia. Assessment of EMG myotonia frequency has been used as an outcome in antimyotonia trials.² We quantified EMG frequency and duration of myotonia, and ranolazine showed an effect on duration but not frequency. This fits with the mechanism of action of ranolazine in that it reduces Na current most effectively during periods of depolarization of the mean membrane potential (as occur during myotonia). Thus, it is expected that the duration of EMG myotonia can be reduced but not eliminated.

Mexiletine is the treatment of choice in MC, but $\approx 25\%$ of patients with NDM do not respond to mexiletine.^{2,5,6} While this study does not allow comparison of ranolazine and mexiletine, having an alternative to mexiletine may be beneficial. Mexiletine may not be tolerated because of gastrointestinal side effects.⁶ An additional theoretical advantage of ranolazine is that mexiletine can easily block sodium current completely and induce loss of muscle excitability and weakness.^{7,8} Ranolazine does not directly block sodium current but instead causes a hyperpolarized shift in the voltage dependence of slow inactivation.³ Because the voltage dependence of $\text{Na}_v1.4$ slow inactivation is shallow, ranolazine is unlikely to completely eliminate sodium current and thus may be less prone to cause muscle weakness.^{9,10} In the prior NDM mexiletine trial, subjective weakness improved with mexiletine, but strength was not quantitatively assessed.²

This study should be interpreted with caution because of the lack of blinding and placebo control, but the findings suggest that ranolazine is well tolerated over a period of 4 weeks and has possible benefit in MC, suggesting the need for investigation in a randomized controlled trial. There is preclinical evidence that ranolazine may also benefit NDM related to sodium channel mutations.¹⁰ A similar, parallel pilot study of ranolazine in paramyotonia congenita is ongoing (NCT02251457).

AUTHOR CONTRIBUTIONS

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

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DISCLOSURE

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REFERENCES

1. Sansone VA, Ricci C, Montanari M, Apolone G, Rose M, Meola G. Measuring quality of life impairment in skeletal muscle channelopathies. *Eur J Neurol* 2012;19:1470–1476.
2. Statland JM, Bundy BN, Wang Y, et al. Mexiletine for symptoms and signs of myotonia in nondystrophic myotonia: a randomized controlled trial. *JAMA* 2012;308:1357–1365.
3. Novak KR, Norman J, Mitchell JR, Pinter MJ, Rich MM. Sodium channel slow inactivation as a therapeutic target for myotonia congenita. *Ann Neurol* 2015;77:320–332.
4. Podsiadlo D, Richardson S. The timed “Up & Go”: a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991;39:142–148.
5. Kwieciński H, Ryniewicz B, Ostrzycki A. Treatment of myotonia with antiarrhythmic drugs. *Acta Neurol Scand* 1992;86:371–375.
6. Trivedi JR, Cannon SC, Griggs RC. Nondystrophic myotonia: challenges and future directions. *Exp Neurol* 2014;253:28–30.
7. Desaphy JF, Carbonara R, Costanza T, Conte Camerino D. Preclinical evaluation of marketed sodium channel blockers in a rat model of myotonia discloses promising antimyotonic drugs. *Exp Neurol* 2014;255:96–102.
8. Courtney KR. Comparative actions of mexiletine on sodium channels in nerve, skeletal and cardiac muscle. *Eur J Pharmacol* 1981;74:9–18.
9. Rich MM, Pinter MJ. Crucial role of sodium channel fast inactivation in muscle fibre inexcitability in a rat model of critical illness myopathy. *J Physiol* 2003;547:555–566.
10. El-Bizri N, Kahlig KM, Shyrock JC, George AL Jr, Belardinelli L, Rajamani S. Ranolazine block of human Nav1.4 sodium channels and paramyotonia congenita mutants. *Channels* 2011;5:161–172.