

Muscle velocity recovery cycles - A biomarker for pharmacological effects on muscle excitability

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Introduction

Muscle velocity recovery cycles (MVRC) is a method to obtain information on excitability of the muscle cell membrane, independent of neuromuscular transmission. This could be an interesting pharmacodynamic (PD) biomarker for drugs targeting muscle excitability.

Aim

As a proof-of-concept, we evaluated the sensitivity of MVRC to detect effects of mexiletine, a voltage-gated sodium channel (Nav) blocker. Thereby, this study aimed to develop and validate the method for implementation as a PD biomarker in early phase drug development in healthy subjects, and patients with neuromuscular disease.

Methods

In a double-blind, two-way crossover study, effects of a single oral dose of mexiletine 333 mg was compared to placebo in 12 healthy male subjects. MVRC was performed pre-dose, and 3h and 5h post-dose. Stimulation was guided by QTRACS. Treatment effects were calculated using an ANCOVA, with baseline as covariate.

Results

Compared to placebo, mexiletine had significant effects on MVRC endpoints:

↓ Early supernormality after 5 conditioning stimuli (5ESN)

Difference -2.78% (95%CI: -4.16, -1.40; p=0.0003) (Fig. 1A)

↓ Late supernormality after 5 conditioning stimuli (5XLSN)

Difference -1.46% (95%CI: -2.26, -0.65; p=0.001) (Fig. 1B)

These results indicate that mexiletine decreases the percentage increase in velocity of the muscle action potential after 5 vs. 1 conditioning stimuli, at long and short interstimulus intervals. These results correspond to a decrease in muscle membrane excitability after 5 conditioning stimuli. This can be explained by use-dependent Nav1.4 inhibition by mexiletine.

Conclusions

This study shows that effects of mexiletine can be detected using MVRC in healthy subjects. This indicates that MVRC can be used as a tool in early phase drug development, to demonstrate proof-of-mechanism of novel drugs targeting muscle excitability.

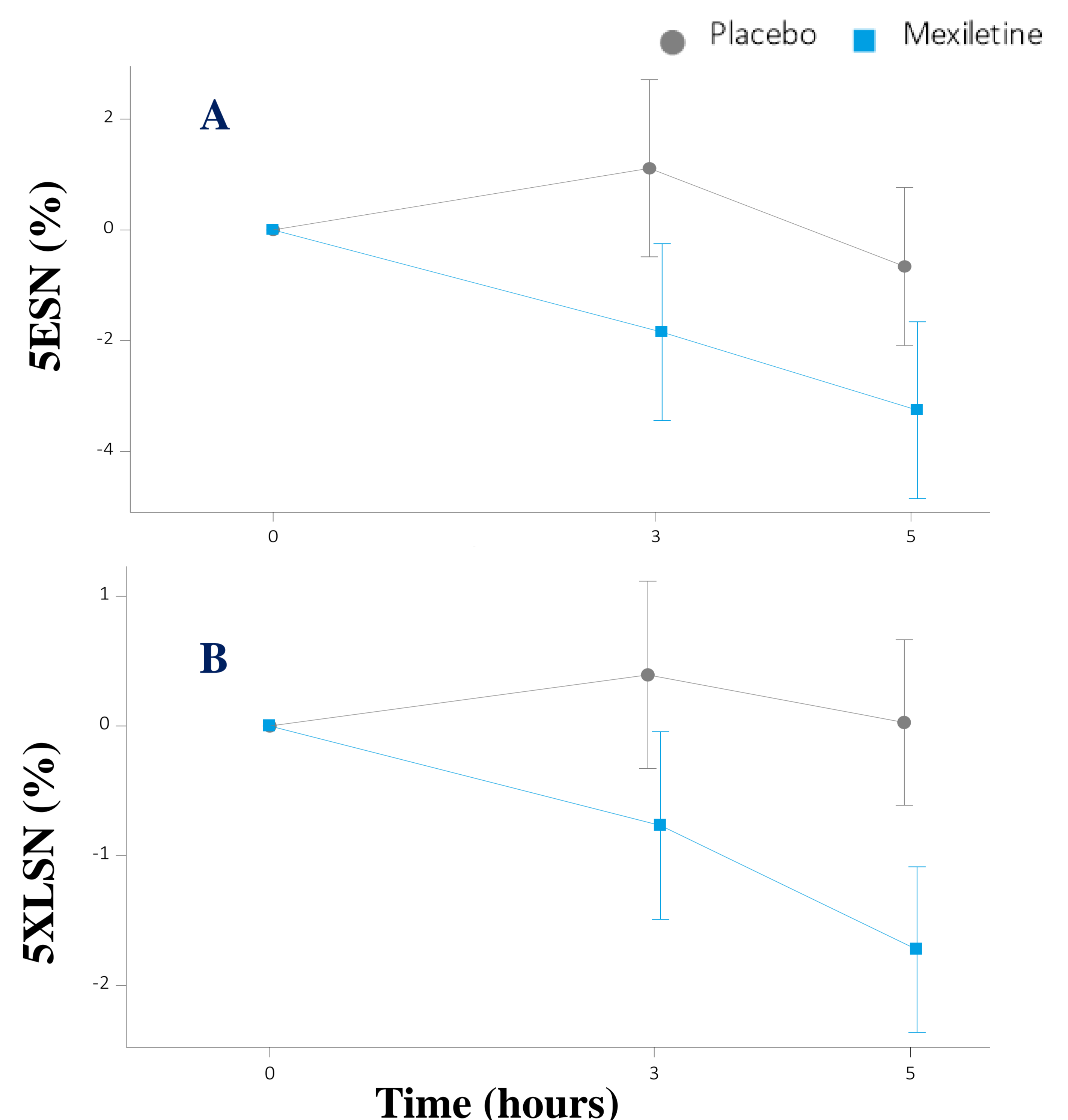


Fig. 1: Change from baseline effects of mexiletine and placebo on MVRC endpoints.

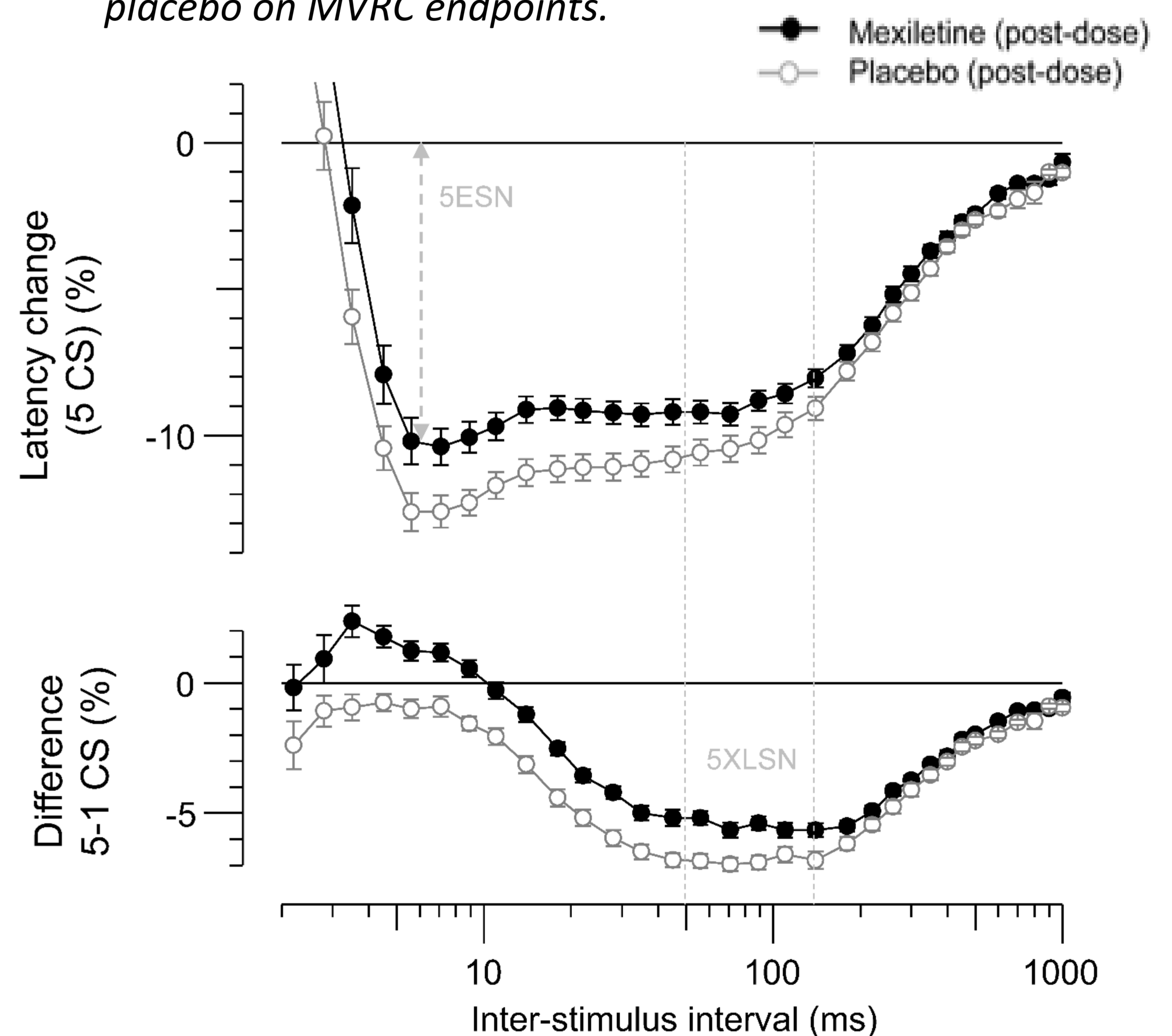


Fig. 2: Average post-dose MVRC recordings of mexiletine and placebo.