Effects of sodium channel blockers on “nerve excitability threshold tracking”

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Introduction

Selective voltage gated sodium channel blockers are of growing interest as treatment for pain. For drug development of such compounds, it would be critical to have a biomarker that can be used for proof-of-mechanism and dose selection for patient studies.

Aim

To evaluate whether drug-induced changes in sodium conductance can be detected using nerve excitability threshold tracking in 18 healthy subjects.

Methods

In a randomized, double-blind, three-way crossover study, effects of single oral doses of mexiletine and lacosamide were compared to placebo. On each study visit, motor- and sensory nerve excitability measurements of the median nerve were performed (pre-dose; 3- and 6-hours post-dose). Stimulation was guided by QTRAC-S. Treatment effects were calculated using an ANCOVA, with baseline as covariate.

Results

Mexiletine and lacosamide had significant effects on a multitude of motor- and sensory nerve excitability parameters. Including:

↓ **TEd40-60ms** (motor nerve) (*Fig. 2a)*
MEX: -1.37% (95%CI: -2.20, -0.55; p=0.002)
LAC: -1.27% (95%CI: -2.0968, -0.4430; p=0.004)

↑ **Superexcitability** (motor nerve) (*Fig. 2b)*
MEX: 1.74% (95%CI: 0.61, 2.87; p=0.004)
LAC: 1.47% (95%CI: 0.34, 2.60; p=0.013)

↓ **Strength-duration time constant** (sensory nerve) (*Fig. 2c)*
LAC: -0.08ms (95%CI: -0.12, -0.05; p<0.001)

Conclusions

Mexiletine and lacosamide significantly decrease excitability of motor and sensory nerves, in line with their mechanism of action. This study shows that threshold tracking can be a sensitive biomarker in early phase pharmacological studies. The method would therefore be a valuable tool in drug development, to help identify target engagement in healthy subjects and possibly guide dose selection for patient studies.

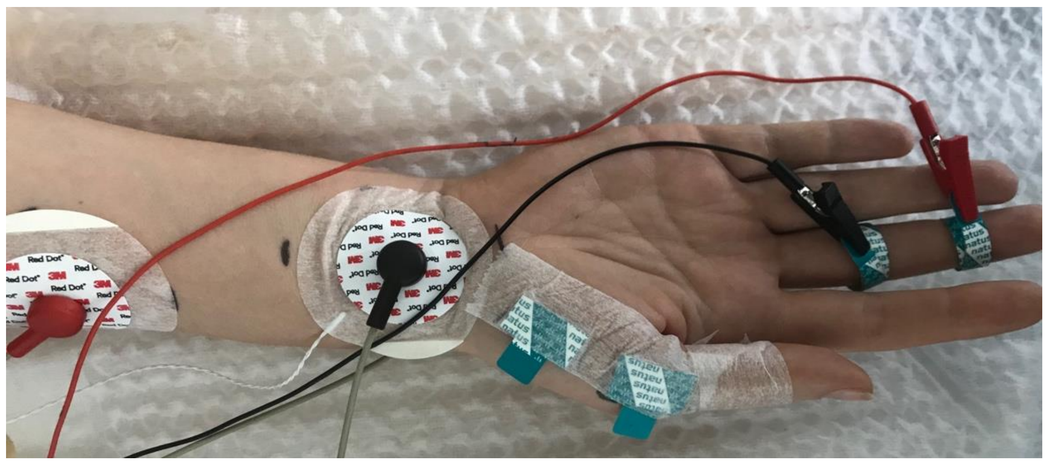

Fig. 1: Nerve excitability threshold tracking set-up.

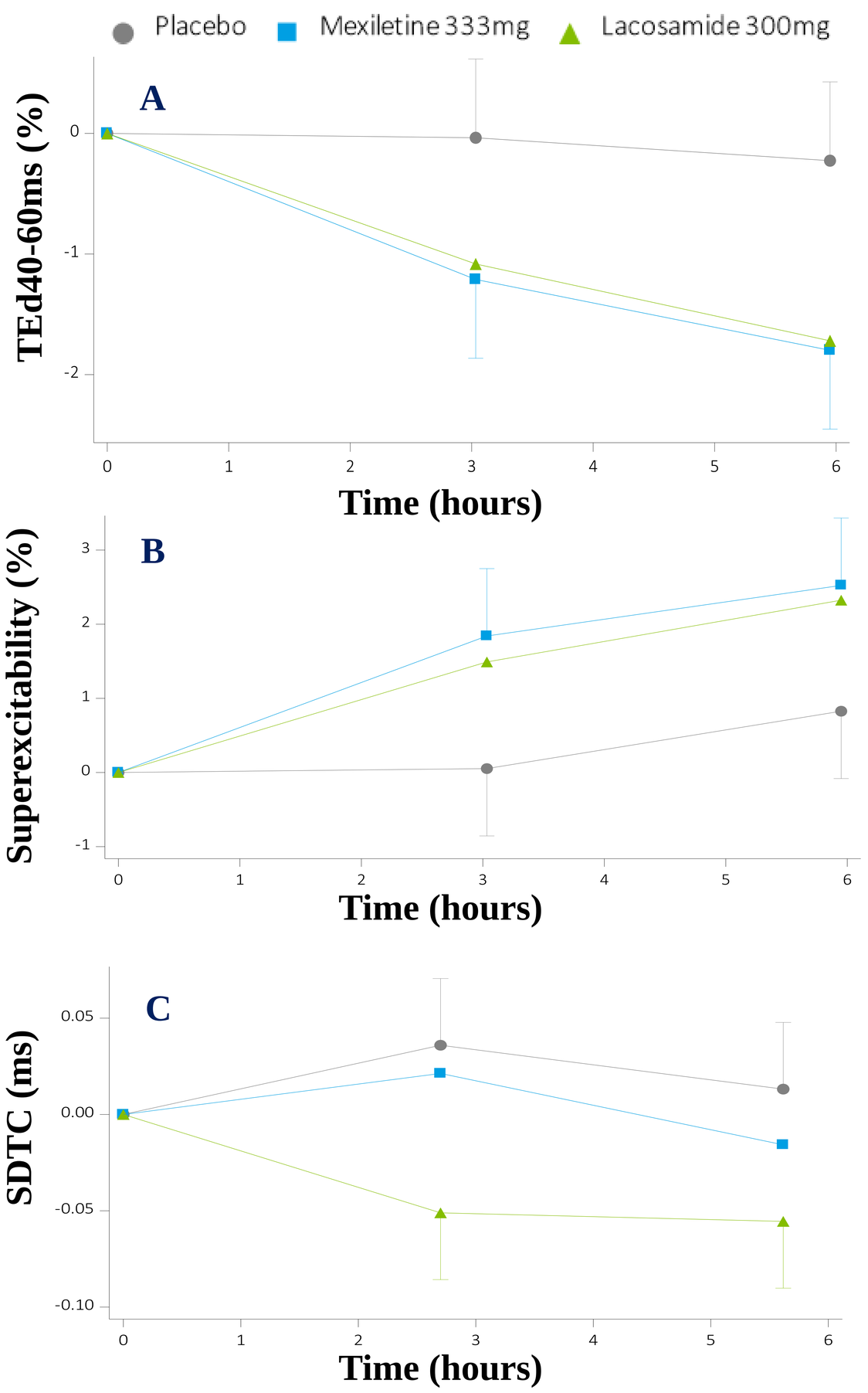

Fig. 2: Change from baseline (CFB) effects of mexiletine, lacosamide and placebo on threshold tracking endpoints. SDTC = strenght duration time constant.

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