Effects of two selective sodium channel blockers with distinct mechanisms of action on axonal excitability

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Introduction

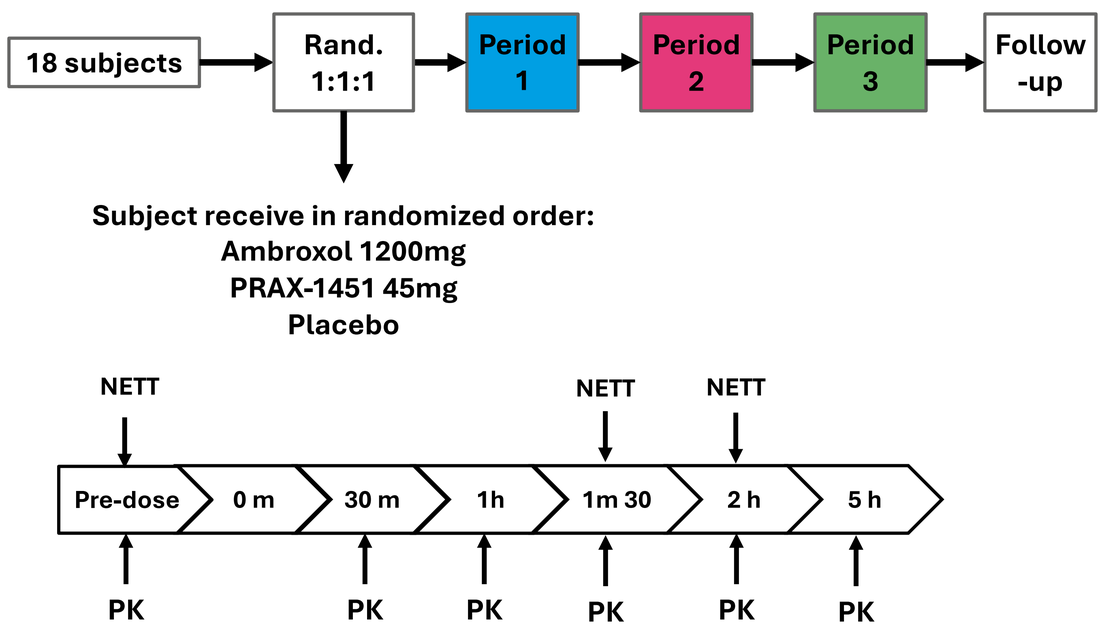
The sensitivity of Nerve Excitability Threshold Tracking (NETT) for non-selective Na_v blockers has previously been demonstrated[1]. Interest in the use of selective Na_v blockers has recently increased for a multitude of indications (ie. pain). Yet direct measurement of axonal excitability as a biomarker to explore mechanisms of action (MoAs) of Na_v blockers is rarely performed in early-phase clinical trials.

Aim

We aimed to investigate NETT effects of two distinct selective Na_v blockers with unique MoAs to determine the specificity of NETT and further investigate its potential in early-phase drug development of drugs that modulate axonal excitability.

Methods

Figure 1: Study design



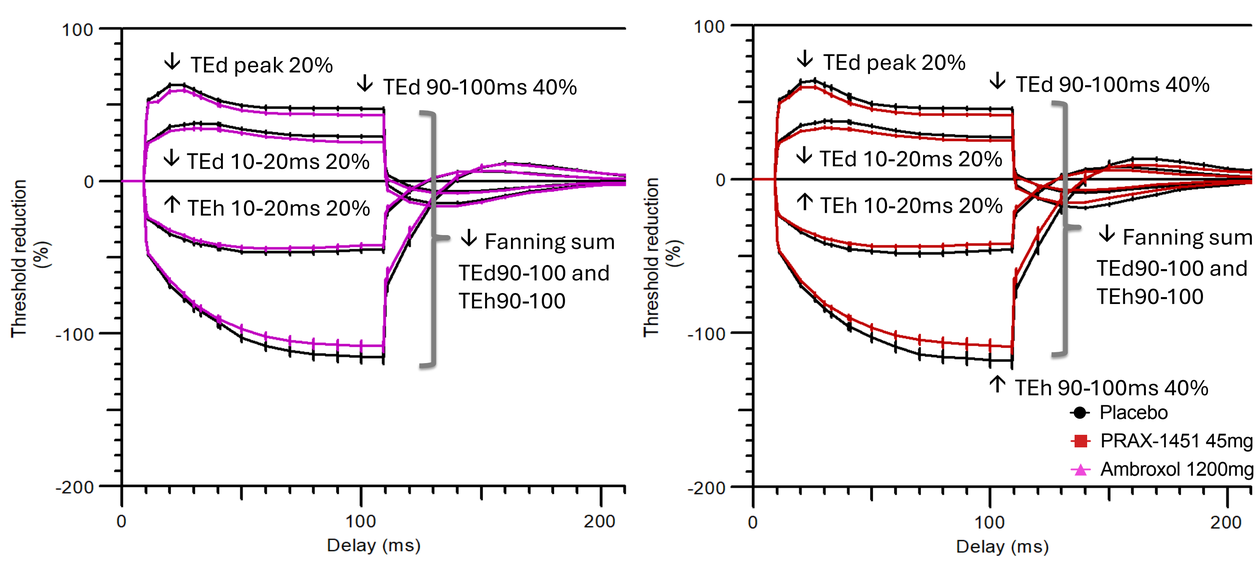
Randomized, double-blind, placebo-controlled, three-way cross-over study with single doses of:

- Ambroxol (Na_v 1.7/1.8 blocker)
- PRAX-1451 (I_{NA} modulator)
- Motor and Sensory NETT at the median nerve
- TROND + Latent Addition (LA) protocol using QTRAC-S
- Constant skin temperature monitoring
- Mixed effects model analysis of variance with 2+5h timepoints combined and baseline as covariate

Results

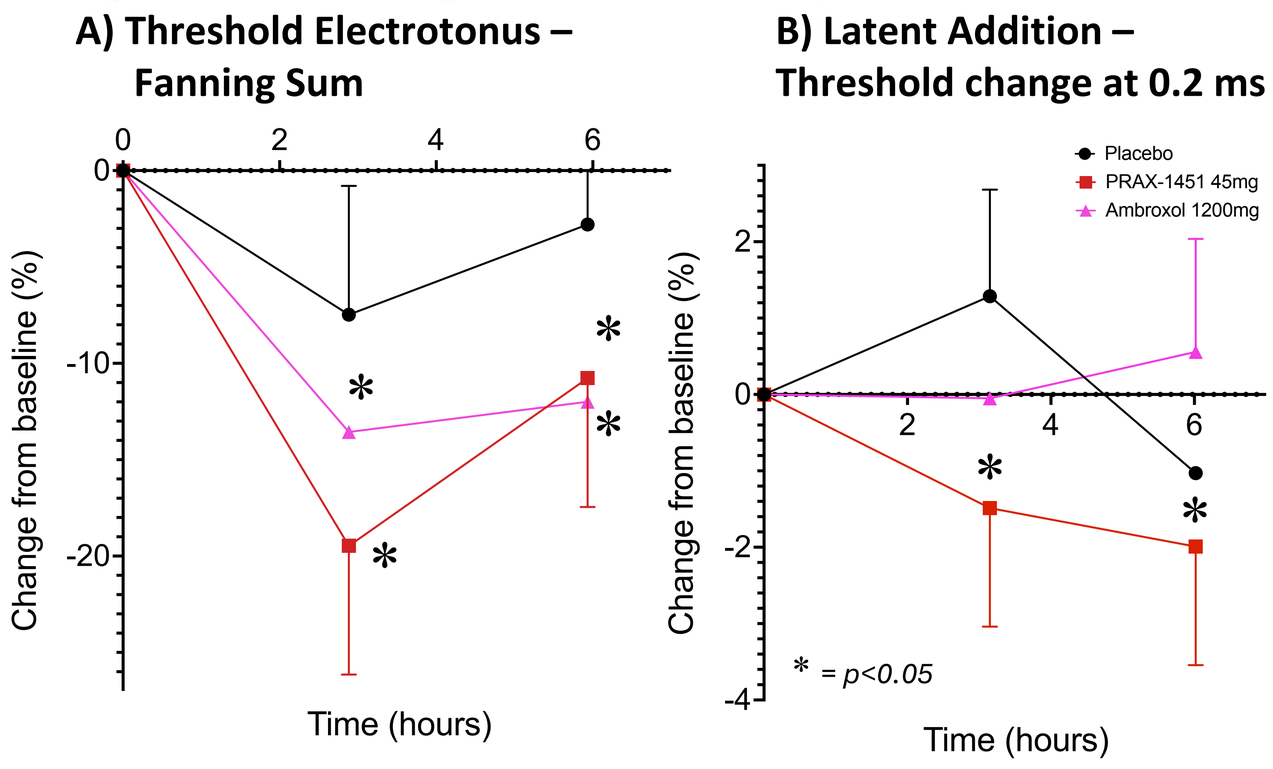
- 20 participants received all treatments
- **Main results Ambroxol & PRAX-1451**
  Sensory threshold electrotonus (TE) (Figure 2 & 3A)
  - ↓ Depolarizing TE (all $p < 0.05$)
  - ↑ Hyperpolarizing TE (all $p < 0.05$)
  - ↓ Fanning sum ($p < 0.05$)
- **Additional results PRAX-1451 (Figure 3B)**
  - ↓ Latent Addition (LA) Threshold change at 2 ms ($p < 0.05$)
- Additional significant results, not reported
  1. ↓ Current-Threshold (I/V) parameters PRAX-1451 sensory
  2. ↓ Recovery Cycle (RC) parameters PRAX-1451 sensory
  3. Ambroxol motor results generally in line with sensory results
- PRAX-1451 did not exhibit motor effects

Figure 2: SNAP Threshold Electrotonus TROND Graphs



Description: TROND graphs for sensory Threshold Electrotonus (TE) parameters (mean ± standard error): baseline in black vs. 2+5 h post-dose combined for A) ambroxol in purple and B) PRAX-1451 in red. The TE paradigm consists of a40% and 20% depolarizing or hyperpolarizing conditioning pulse during which a test pulse is given (10-100 ms after) measuring the neuron's compensatory ability.

Figure 3: SNAP Change from Baseline Graphs



Description: Change from baseline (including 95% confidence interval error bars) for sensory parameters A) TE Fanning sum and B) LA Threshold Change at 0.2 ms. The fanning sum is a sum of the depolarizing and hyperpolarizing conditioning pulse (CP) at 90 - 100 ms. The LA consists of a 90% hyperpolarizing CP pulse where the neuronal recovery is specific for persistent sodium current (I_{NA}).

Conclusions

- Both ambroxol and PRAX-1451 significantly decreased axonal excitability across multiple endpoints
- We confirmed NETT's sensitivity for demonstrating drug effects of selective ion channel modulators, supporting its potential use as a proof-of-mechanism biomarker
- TE was the most sensitive biomarker for sodium channel modulation, irrespective of MoA
- PRAX-1451's distinct effects on the LA confirm its MoA on the I_{NA} current, supporting LA as a specific biomarker for I_{NA} modulation

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References: 1. Ruijs et al. Effects of Mexiletine and Lacosamide on Nerve Excitability in Healthy Subjects: A Randomized, Double-Blind, Placebo-Controlled, Crossover Study. Clin Pharmacol Ther. 2022 Nov;112(5):1008–19.

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