A Two Part, Randomised, Double-blind, Placebo-controlled, Four-way Cross-over, Single Dose Study to Pharmacologically Validate a Pain Model Battery Suitable for Early Phase Clinical Drug Development

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INTRODUCTION

■No single experimental model can replicate the complex nature of analgesics and their efficacy. Although a single pain model can be used to demonstrate the pharmacological mechanism of action of a compound, one single model can not reliably mimic clinical pain.

■ This was the first time that an integrated battery of experimental pain models was executed in combination with the administration of different analgesic drugs.

AIM

To investigate the ability of a battery of pain models to detect analgesic properties of commonly used analgesics in healthy subjects.

METHODS

■ The test battery consists of a sequence of tests eliciting cutaneous electrical-, mechanical (pneumatic)-, and thermal (cold pressor)-pain, and measuring pain detection threshold (PDT), pain tolerance thresholds (PTT) and area under the VAS-time curve (AUC). Furthermore, the battery included the UVB model to measure hyperalgesia.

■). In part I of the study, subjects received fentanyl 50 µg/kg, phenytoin 300 mg, (s)-ketamine 10 mg or placebo (sodium chloride 0.9%) as an intravenous infusion over 30 minutes. In part II, subjects were administered imipramine 100 mg, pregabalin 300 mg, ibuprofen 600 mg or placebo capsules as a single oral dose. In each part, subjects received all four treatments.

■ Pharmacodynamic outcome variables were analysed using a mixed model analysis of variance.

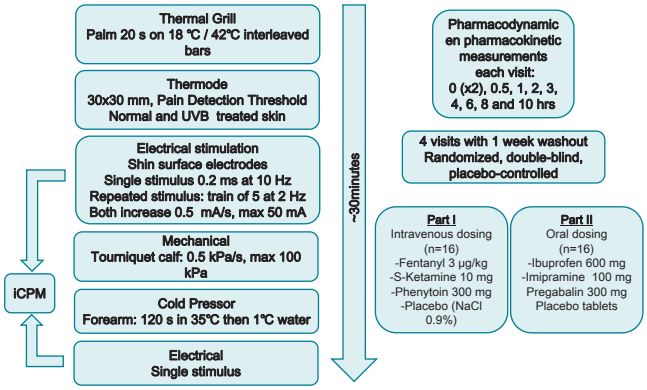


Figure 1: Overview of study design.

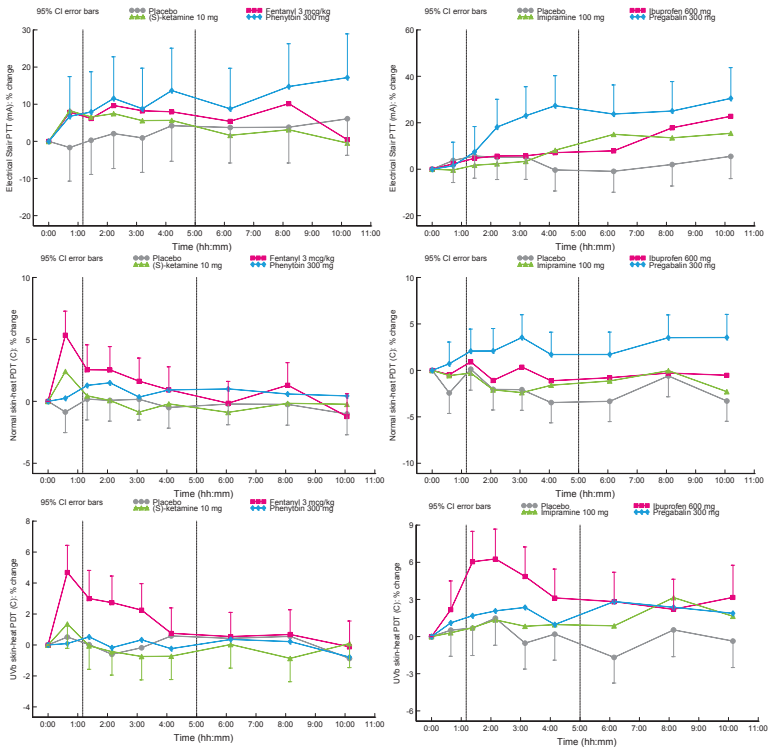


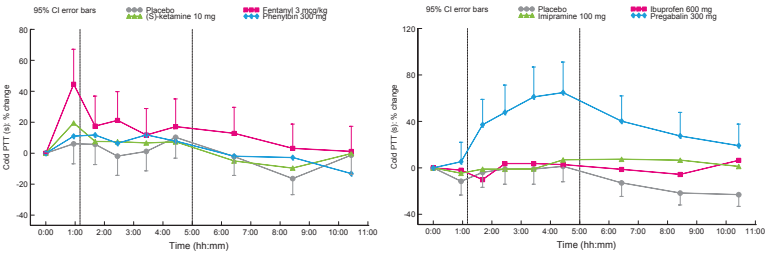
Figure 2: Least Square Mean change from baseline (±95% CI) in pharmacodynamic tests. PTT=Pain Tolerance Threshold.

RESULTS

■ 22 healthy subjects participated in part I and 17 in part II. 16 subjects completed all treatments periods in part I and 16 in part II (8 females in each part).

■ Overall pharmacokinetic parameters measured in this study were relatively consistent with the known pharmacokinetic data for these compounds.

■ Adverse events reported in the study were all mild or moderate in severity and in line with their known pharmacological profile



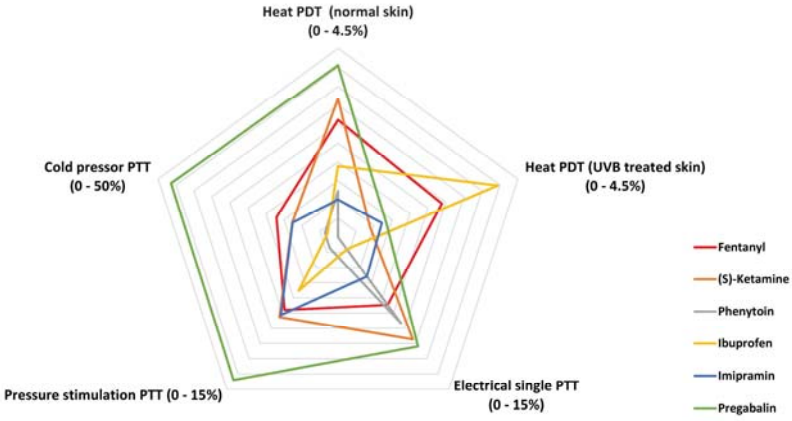


Figure 3: Contrast of compounds compared to placebo in the pharmacodynamic tests. PDT= Pain Detection Threshold, PTT=Pain Tolerance Threshold.

CONCLUSIONS

■The battery of pain models is able to detect changes in pain detection and pain tolerance thresholds after administration of different classes of analgesic compounds in healthy male and female subjects.

■ The analgesic compounds all showed a unique profile in their effects on the pain tasks administered. These profiles were in most cases compatible with the expected pharmacology.

■ This battery of pain models can be used to benchmark analgesic properties of new drugs against established analgesics in early phase clinical studies in healthy subjects.

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