PK-PD model of morphine, pregabalin and their combination to assess the opioid-sparing effect

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Introduction

Chronic pain (CP) causes major discomfort and is highly prevalent [1]. Opioids are currently the most effective class of analgesics, but lead to a plethora of adverse effects such as cognitive impairment, sedation and even risk of death due to opioid overdose. Therefore there is a strong need for improved treatments. As part of the QSPainRelief consortium our goal is to identify novel analgesic drug combinations that are complementary or synergistic with each other and could be superior to current treatments.

To that end a clinical trial was performed to study combining morphine and pregabalin for the treatment of pain. Treatment effect was assessed by multiple nociceptive tests, which included the 'cold pressor test' where subjects placed their hand for 2 minutes in a 35°C water bath followed by a 1.0°C bath. A pharmacodynamic (PD) endpoint is the time in seconds from immersion to hand withdrawal from the water bath indicating that the pain is no longer tolerable (pain tolerance threshold, PTT).

Objectives

- Describe the clinical trial results by a PK-PD model
- To determine if the combined treatment effect is antagonistic, additive or synergistic

Methods

Clinical trial:

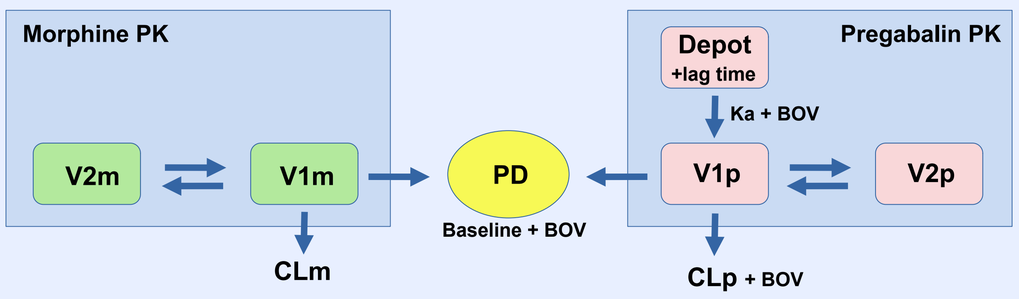
Clinical trial design and power analysis based simulations were previously supported by us [2]. Combined treatment effect of morphine and pregabalin was assessed in a double-blind, placebo controlled clinical trial in 12 male and 15 female healthy volunteers. In four identical study periods with 7 days wash-out in-between, subjects (20-64 years) received a single oral dose of 300 mg (t = 0 h) pregabalin, 3 mg (t = 2 h) + 7 mg (t = 5 h) morphine as a bolus infused intravenously, a combination of these two (double-dummy) or placebo in randomized order.

Model development:

The effect of pregabalin on ColdPTT was previously modelled by van Esdonk et al. [3]. We took this model as the starting point for our modelling process using NONMEM 7.5.1. Between occasion variability (BOV) was examined for both PK and PD models. Model selection was based on objective function value (OFV), diagnostic plots, model stability and relative standard error (RSE), among others.

Results

Combined PK-PD turnover model:



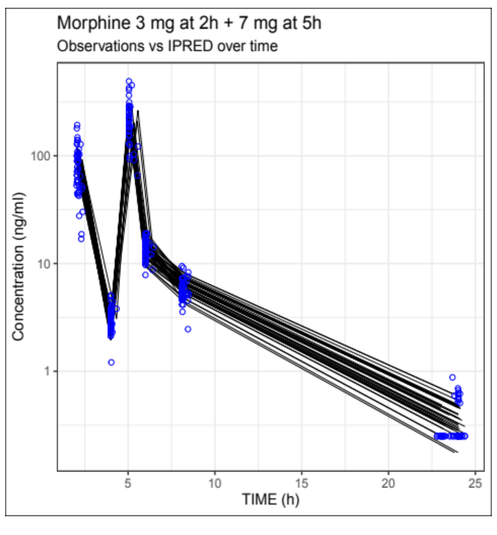
PD was described by a turnover model. BOV on the baseline (13.98 seconds) improved the OFV over 100 points. A declining slope of the baseline (from the placebo occasion) further improved the fit (a). To describe all treatments, individual PD compartments were folded into one PD compartment with a single turnover (kout) for both morphine and pregabalin. The combined pregabalin + morphine treatment was best fitted by modulation of the pregabalin effect (2.1-fold increase) when morphine and pregabalin were present within the system (b)+(e). This translates into an approximate 55% improvement over the additive (1+1) case for the ColdPTT test in healthy subjects.

(a) $SL_{PLB} = SLOPE_{PLB_{OCC}} * TIMEAFTERDOSE$

(b) $COMBI_p = 1 \quad IF\left(CP_m.\mathrm{GT}.0.\mathrm{AND}.CP_p.\mathrm{GT}.0\right) COMBI_p = THETA_c$

(c) $EFF_m = CP_m * SLOPE_m$ (d) $EFF_p = CP_p * SLOPE_p * COMBI_p$

(e) $\frac{DA(PD)}{DT} = \left(Kin + SL_{PLB}\right) * \left(1 + EFF_{m+p}\right) - Kout * A(PD)$



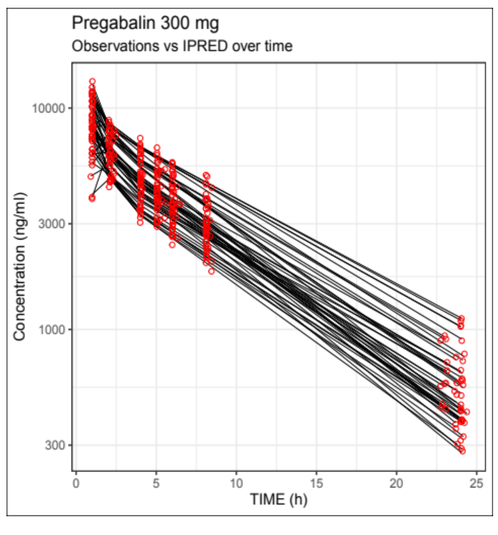


Figure 1: PK fits of morphine and pregabalin. With the circles representing the observations and the black lines the individual predictions of the PK models.

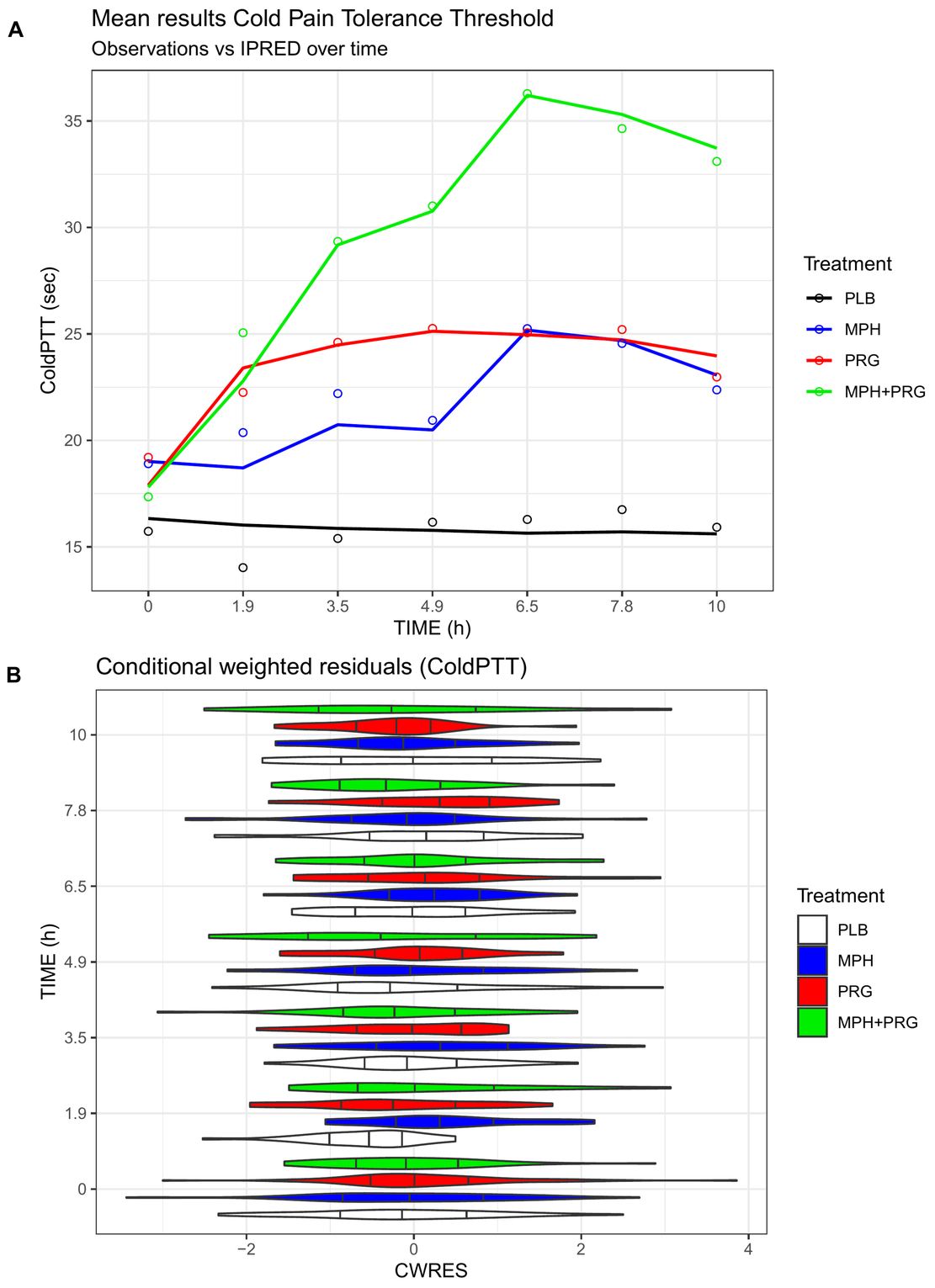


*Figure 2: **A**; PD fits of morphine, pregabalin and their combined treatment. With the circles representing the mean observations and the lines the mean individual predictions of the PD model. Morphine was given at t=2h + t=5h. Pregabalin was given at t=0h. **B**; CWRES of the PD fits including 0.25, 0.5 and 0.75 quantiles. **C**; Visual Predictive Check (VPC) of the model. MPH; morphine, PRG; pregabaline, MPH+PRG; morphine+pregabalin, PLB; placebo.*

Conclusions

- Both PK and PD models described the data adequately.
- Combining morphine and pregabalin indicated a synergistic analgesic effect on the ColdPTT test associated with a significant improvement of model fit statistics.
- These results suggest that pain patients could benefit from the combined treatment of pregabalin and morphine, allowing for lower doses of the opioid morphine to achieve the same treatment effect, and therefore to an important reduction in opioid-induced side effects and abuse potential.

References

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[3] van Esdonk, Michiel J., et al. "Population Pharmacokinetic/Pharmacodynamic Analysis of Nociceptive Pain Models Following an Oral Pregabalin Dose Administration to Healthy Subjects." *CPT: pharmacometrics & systems pharmacology* 7.9 (2018): 573-580.

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