

Modeling of Pain Intensity and Informative Dropout in a Dental Pain Model after Naproxcinod and Naproxen Administration

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Objectives:

The objective of this work was to describe the pain intensity (PI), measured on a visual analogue scale (VAS), and dropout due to request of rescue medication after administration of naproxcinod, naproxen or placebo after wisdom tooth removal.

Methods:

Patients (n=242) that requested pain relief after removal of mandibular wisdom teeth were randomised to naproxcinod 375, 750, 1500 or 2250 mg, naproxen 500 mg, or placebo [1]. Plasma was collected for analysis of total and unbound naproxen plasma concentrations, and PI was measured on a 100 mm VAS for up to 8 hours post-dose. Patients needing additional pain relief could request rescue medication. The pharmacokinetic/pharmacodynamic (PK/PD) analysis was performed using NONMEM VI.

Results:

A one-compartment model with transit compartment absorption and saturable protein binding described the naproxen concentrations after naproxen or naproxcinod administration. An exponential model described the placebo response on the PI, and the drug effect was described using a sigmoid $E_{\max}$ model.

$$PI = PI_{baseline} \cdot (1 - Placebo) \cdot (1 - Drug)$$

$$Placebo = P_{\max} \cdot (1 - e^{-k_{pl} \cdot t})$$

$$Drug = \frac{E_{\max} \cdot C_u^{\gamma}}{EC_{50}^{\gamma} + C_u^{\gamma}}$$

Typical maximal placebo effect was a decrease in PI by 20.2 %, and the rate constant k_{pl} was 0.237 h⁻¹. EC_{50} was 0.135 µmol/L and the shape factor γ was 1.61.

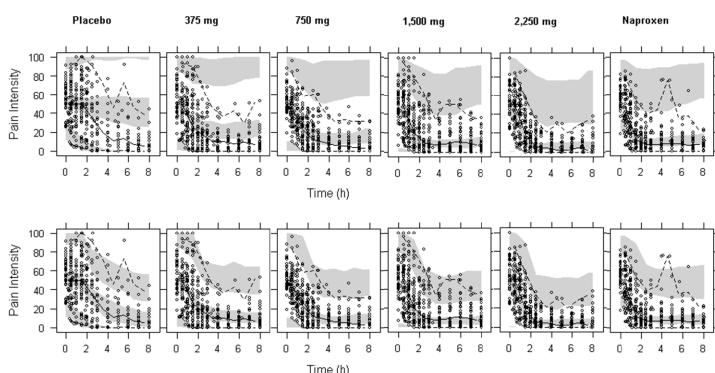


Figure 1. Visual predictive check of pain intensity (PI) versus time based on the final PK/PD model. The top row is simulated without dropout and the bottom row is simulated with dropout. Open circles represent the observations and the lines represent the median, 2.5th and 97.5th percentile of the observations. The shaded areas represent the 95 % confidence intervals for the simulated median and 2.5th and 97.5th percentiles

The dropout was modelled using a Weibull time-to-event model, where the hazard was dependent on the model predicted PI as well as baseline PI.

$$h(t) = h_0 \cdot \exp(COV)$$

$$h_0 = \lambda \cdot \alpha \cdot t^{(\alpha-1)}$$

$$COV = \theta_{PI} \cdot (1 + \theta_{baseline} \cdot (PI_{baseline} - 55)) \cdot PI_t$$

λ was 0.00999, α was 0.729, θ_{PI} was 0.0782 and $\theta_{baseline}$ was -0.00261.

Since the dropout was not at random, it was necessary to include the simulated dropout in the VPCs of PI.

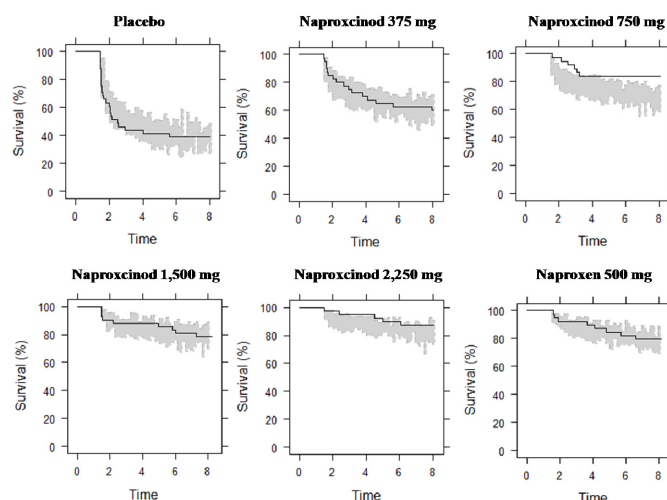


Figure 2. Visual predictive check of time to request of rescue medication based on the final PK/PD model. Solid line represents the observed Kaplan-Meier curve and the shaded area represents the 90% prediction interval for the simulated Kaplan-Meier curve

Conclusions:

This model provides a pharmacometric platform that describes the placebo effects and relationship between PI measured on a VAS and dropout after dental extraction. VPCs created by simultaneous simulations of a continuous variable and time to event provide a good way of assessing the goodness of fit when there is informative dropout.

References:

[1] Hill et al., Clinical Therapeutics 2006; 28:1279-1295