Title: Mechanistic Population Pharmacokinetics of Total and Unbound Paclitaxel for a New Nanodroplet Formulation vs. Taxol in Cancer Patients – A New Class of Models Based on Solubility Limited Drug Disposition

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Objectives: To compare the disposition and in vivo release of paclitaxel between a tocopherol-based cremophor-free formulation (TOCOSOL Paclitaxel®) and Cremophor® EL-formulated paclitaxel (Taxol®) in human subjects. To develop a mechanistic model for unbound and total paclitaxel pharmacokinetics. To compare various classes of models with linear or nonlinear drug disposition.

Methods: Thirty-five patients (average ± SD age: 59±13 yr) with advanced non-hematological malignancies were studied in a randomized two-way crossover trial. Patients received 175 mg/m² paclitaxel as 15 min (TOCOSOL Paclitaxel) or 3 h (Taxol) intravenous infusion in each study period. Eighteen blood samples were taken between pre-dose and 120 h post dose and paclitaxel was determined by LC-MS/MS in plasma ultrafiltrate and whole blood. The FOCE method with the interaction option in NONMEM VI was used for population pharmacokinetics. Models with first-order, mixed-order, or first-order and mixed-order elimination, and first-order or mixed-order distribution were considered. The limited aqueous solubility of paclitaxel for release from TOCOSOL paclitaxel nanodroplets into plasma and release of a fraction of dose into a peripheral compartment were considered (Fig. 1).

Results: A linear disposition model with three compartments for unbound paclitaxel and a one-compartment model for cremophor were applied. Total clearance of unbound paclitaxel was 845 L/h (variability: 25% CV). The prolonged release with TOCOSOL Paclitaxel was explained by the limited solubility of unbound paclitaxel of 405 ng/mL (estimated) in plasma. Models based on limited solubility of paclitaxel had the best predictive performance (Fig 2) and objective function. The 15 min TOCOSOL Paclitaxel infusion yielded a mean time to 90% cumulative input of 1.14 ± 0.16 h. TOCOSOL Paclitaxel was estimated to release 9.8% of the dose directly into the deep peripheral compartment. The model accounted for the presence of drug-containing nanodroplets in blood.

Conclusions: Population pharmacokinetic analysis indicated linear disposition and a potentially higher bioavailability of unbound paclitaxel following TOCOSOL Paclitaxel administration due to direct release at the target site. The prolonged release of TOCOSOL Paclitaxel supports 15 min paclitaxel infusions. This mechanistic model may be important for development of prolonged release formulations that distribute in the systemic circulation.

Topic area: Mechanistic Modeling/Systems Biology

Figure 1: Structural model accounting for the solubility limit (C_Sol) of paclitaxel in plasma
Figure 2: Visual predictive check for paclitaxel concentrations in plasma ultrafiltrate and in whole blood based on 10,000 simulated, virtual patients. Data are median, 25-75% percentile (dotted line), and 10-90% percentile (dashed line). Ideally, 20% of the observations should fall outside the 10-90% percentile of simulated concentrations at each time point.