BACKGROUND
Paclitaxel is active against a wide array of cancers. The most commonly used paclitaxel formulation (Taxol®) contains Cremophor® EL that is associated with hypersensitivity reactions and peripheral sensory neuropathy. Cremophor EL also causes nonlinear pharmacokinetics (PK) of total, but not of unbound paclitaxel. We compared a new tocopherol-based, cremophor-free paclitaxel formulation (TOCOSOL Paclitaxel®) with Taxol®. TOCOSOL Paclitaxel encapsulates paclitaxel in nanodroplets that can be dosed as a 15 min intravenous infusion and that release paclitaxel over time. 

OBJECTIVES
1) To compare the disposition and in vivo release of paclitaxel between two formulations.
2) To develop a mechanism-based PK model for unbound and total paclitaxel.
3) To compare various classes of models with linear or nonlinear drug disposition.

METHODS
Randomized 2-way crossover study:
- Thirty-five patients (average ± SD age: 59±13 yr) with advanced non-hematological malignancies
- Dose: 175 mg/m² paclitaxel as 15 min (TOCOSOL Paclitaxel) or 3 h (Taxol®) intravenous infusion
- Eighteen blood samples from 0 to 120 h post dose
- Paclitaxel analysis by LC-MS/MS in plasma ultrafiltrate and whole blood.

Population PK in NONMEM VI (method: FOCE+I):
- Nonparametric bootstrap with 500 replicates
- Models with first-order, mixed-order, or first-order and mixed-order elimination, and first-order or mixed-order distribution were considered.
- Limited aqueous solubility of paclitaxel for release from TOCOSOL paclitaxel nanodroplets into plasma

RESULTS
Paclitaxel concentrations in plasma ultrafiltrate showed a plateau between 0.25 and 0.75 h for TOCOSOL Paclitaxel, whereas total concentrations showed a pronounced peak (Fig. 1). The final model (Fig. 2 & Table) included three compartments for unbound paclitaxel with linear disposition. The prolonged release of 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. 3) and objective function. The 15 min TOCOSOL Paclitaxel infusion yielded a mean time to 90% cumulative input of 1.14 ± 0.16 h (Fig. 4).

CONCLUSIONS
1. Population PK analysis indicated linear disposition and a potentially higher bioavailability of unbound paclitaxel following TOCOSOL Paclitaxel administration due to direct release at the target site.
2. The prolonged release of TOCOSOL Paclitaxel supports 15 min paclitaxel infusions.
3. The proposed mechanism-based model may be important for development of prolonged release formulations that distribute in the systemic circulation.

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