

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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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).

FIGURE 1: Paclitaxel concentrations in plasma ultrafiltrate and in whole blood

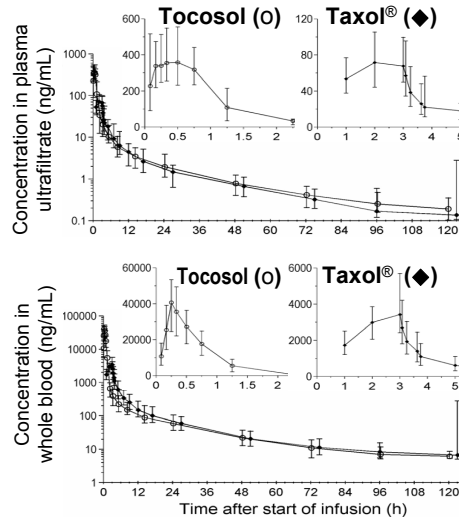


FIGURE 2: Structural model for both formulations

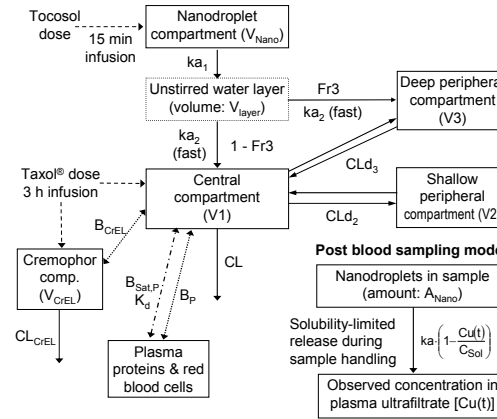


TABLE: Final estimates from bootstrap (n=500)

Parameter	Symbol	Unit	Estimate (90% CI)	Variability (90% CI) [†]	ΔObj [‡]
Disposition of paclitaxel					
Total clearance	CL	L h ⁻¹	845 (793 - 910)	25% (15 - 36%)	
Volume of central compartment [§]	V1	L	610 (430 - 718)	27% (0.3 - 39%)	
Volume of shallow peripheral compartment [¶]	V2	L	1480 (1260 - 1710)	19% (3.8 - 26%)	
Volume of deep peripheral compartment [¶]	V3	L	6830 (6080 - 7561)	23% (16 - 29%)	
Intercompartmental clearance to V2 [¶]	CLD ₂	L h ⁻¹	724 (631 - 918)	22% (0.2 - 32%)	
Intercompartmental clearance to V3 [¶]	CLD ₃	L h ⁻¹	317 (274 - 371)	23% (14 - 31%)	
Release from TOCOSOL nanodroplets					
Relative extent of bioavailability for TOCOSOL Paclitaxel	F _{TOCOSOL}		0.940 (0.882 - 0.997)	(F _{TOCOSOL} fixed to 1)	9.9 [‡]
Fraction of dose directly entering the deep peripheral compartment from nanodroplets	Fr3		0.098 (0.0443 - 0.153)		32
Maximum rate of release from nanodroplets	V _{max}	mg h ⁻¹	356 (301 - 424)		
Amount of drug in nanodroplets for that the release rate is half-maximal	A _{Nano}	mg	50.0 (27.7 - 78.8)	45% (33 - 58%)	233 [‡]
Solubility of unbound paclitaxel in plasma	C _{sol}	ng mL ⁻¹	405 (368 - 452)		155 [‡]
Volume of distribution of nanodroplets [¶]	V _{Nano}	L	6.66 (6.03 - 7.35)	21% (16 - 24%)	29 [‡]
Half-life of release during sample handling if no saturation [¶]	t _{1/2} (ka)	min	26.8 [‡] (19.8 - 36.2)	73% (52 - 94%)	936 [‡]
Disposition of cremophor					
Total clearance of cremophor [¶]	CL _{CrEL}	L h ⁻¹	0.583 (0.257 - 0.970)	128% (81 - 169%)	491
Volume of distribution of cremophor [¶]	V _{CrEL}	L	6.01 (fixed)		
Paclitaxel binding					
Linear binding to plasma proteins and red blood cells	B _p		21.0 (19.0 - 22.6)	13% (4.1 - 17%)	51
Maximum binding capacity divided by K _d	B _{satP} /K _d		8.01 (3.72 - 13.0)	85% (46 - 127%)	51
Dissociation constant	K _d	ng mL ⁻¹	4.38 (3.02 - 6.99)		
Linear binding of paclitaxel to cremophor	B _{CrEL}	L g ⁻¹	6.61 (5.65 - 7.93)		491

[†]: Apparent coefficients of variation; [‡]: Per 1.73 m² body surface area; [§]: Increase in objective function after estimation of the simplified model, if the parameter mean was fixed to zero (or other appropriate values). Final model used as reference. A ΔObj. of 3.84 corresponds to an alpha of 0.05 for 1 degree of freedom. [¶]: Release from nanodroplets during sample handling assumed to be saturable due to solubility of paclitaxel.

FIGURE 3: Visual predictive check

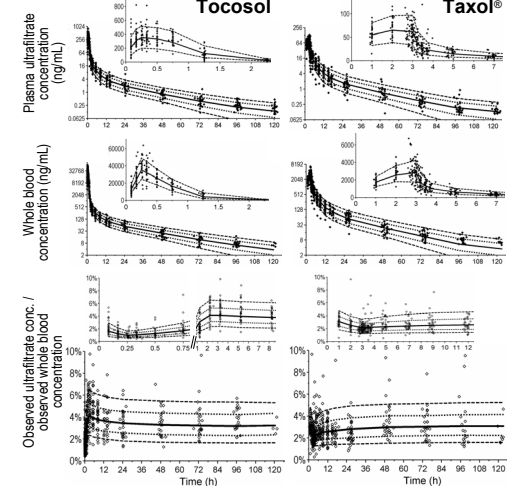
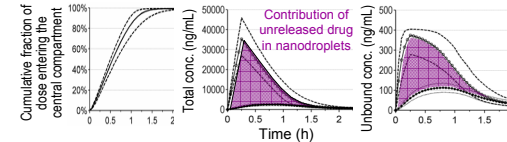


FIGURE 4: In vivo release profile of TOCOSOL



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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