

A Pharmacokinetic Study of a Novel Sphingomyelin/Cholesterol Liposomal Topotecan and Non-Liposomal Topotecan in Rats

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Abstract

Introduction. Optosomal topotecan (Topotecan Liposomes Injection, TLI) is a novel sphingomyelin/cholesterol liposomal (OPTISOME™) encapsulation of topotecan HCl (TPT). TPT, a semi-synthetic derivative of camptothecin (CPT), is approved for the treatment of refractory ovarian, small cell lung (SCLC), and cervical cancers. The cytotoxicity of TPT and other CPT analogues is related to duration of systemic exposure to drug. OPTISOMES have been designed to prolong drug circulation time in blood, increase drug delivery to the tumor, and improve the therapeutic index of the encapsulated drug. Additionally, optosomal encapsulation is designed to maintain TPT in the active lactone form. The pharmacokinetic (PK) disposition of OPTISOME encapsulated drug is dictated by the liposome, which alters the plasma PK profile and tissue distribution of the drug. Once the drug is released from the liposome, the PK disposition will be the same as after administration of the non-liposomal formulation of the drug. The objectives of this study were to evaluate the plasma PK disposition of TLI compared with non-liposomal TPT (NL-TPT) in the plasma of rats and to evaluate the potential gender differences in the PK disposition of TLI and NL-TPT.

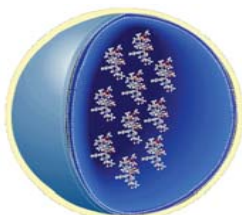
Methods. TLI and NL-TPT were administered at 0.93 mg/kg intravenously over one (1) minute via a bilateral jugular vein cannula (JVC) in male and female Sprague-Dawley Rats. Drug administration and blood sampling were performed in separate cannulas. Blood (0.5 mL) samples were obtained in 6 cohorts (n = 3 rats per gender per cohort). Cohorts consisted of: 1) pre-dose, 1 and 3 minutes post-dose; 2) 5, 10, and 20 minutes post-dose; 3) 0.5, 1, and 2 hours post-dose; 4) 4, 8, and 12 hours post-dose; 5) 24, 36, and 48 hours post-dose; 6) 60 and 72 hours post-dose. Plasma samples were processed via methanolic extraction to measure the total (lactone + hydroxy acid) form of sum total (encapsulated + released) TPT via liquid chromatography/mass spectrometry (LC/MS). The area under the concentration versus time curves from 0 to infinity (AUC_{0-∞}), clearance (CL), maximum concentration (C_{max}), time of C_{max} (T_{max}), and time of last detectable concentration (T_{last}) were estimated.

Results. The AUC after administration of TLI and NL-TPT was 41.2 and 0.40 mcg·h/mL, respectively. The CL after administration of TLI and NL-TPT was 0.38 and 38.8 mL/min/kg, respectively. The C_{max} after administration of TLI and NL-TPT was 13.1 and 0.61 mcg/mL, respectively. The T_{max} after administration of TLI and NL-TPT was 0.02 h. The T_{last} after administration of TLI and NL-TPT was 24 h and 2 h, respectively. The results were similar in male and female rats.

Conclusions. The higher and prolonged exposure of TPT in plasma after administration of TLI compared with NL-TPT is consistent with OPTISOME formulations and provides PK advantages over non-liposomal formulations of CPT analogues, including TPT, with similar PK results being expected in male and female patients.

Introduction

- Optosomal topotecan (Topotecan Liposomes Injection, TLI) is a novel sphingomyelin/cholesterol liposomal (OPTISOME™) encapsulation of topotecan HCl (TPT).
- TPT, a semi-synthetic derivative of camptothecin (CPT), is approved for the treatment of refractory ovarian, small cell lung (SCLC), and cervical cancers.
- The cytotoxicity of TPT and other CPT analogues is related to duration of systemic exposure to drug.
- OPTISOMES have been designed to prolong drug circulation time in blood, increase drug delivery to the tumor, and improve the therapeutic index of the encapsulated drug.
- Optosomal encapsulation, with a core pH of 4.0, is designed to maintain TPT in the active lactone form.
- The pharmacokinetic (PK) disposition of OPTISOME encapsulated drug is dictated by the liposome, which alters the plasma PK profile and tissue distribution of the drug.
- Once the drug is released from the liposome the PK disposition will be the same as after administration of the non-liposomal formulation of the drug.



OPTISOME, Sphingomyelin/Cholesterol Liposome Encapsulated Drug

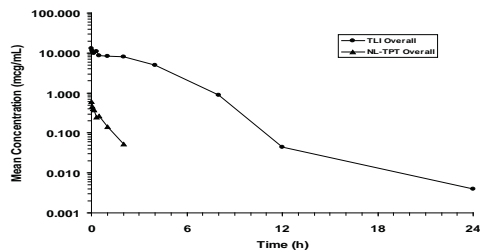
Study Objectives

- To evaluate the plasma PK disposition of TLI compared with non-liposomal TPT (NL-TPT) in the plasma of rats.
- To evaluate potential gender differences in the PK disposition of TLI and NL-TPT.

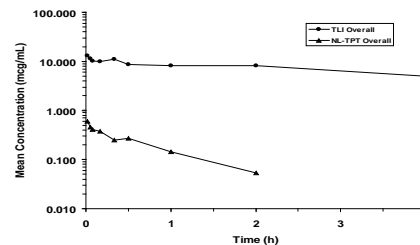
Methods & Materials

- **Dose and Administration:**
 - TLI and NL-TPT were administered at 0.93 mg/kg IV x 1 over 1 minute via a bilateral jugular vein cannula (JVC) in male and female Sprague-Dawley rats.
- **Pharmacokinetic Studies:**
 - Drug administration and blood sampling were performed in separate cannulas. Blood (0.5 mL) samples were obtained in 6 cohorts (n = 3 rats per gender per cohort).
 - Cohorts consisted of: 1) pre-dose, 1 minute and 3 minutes post-dose; 2) 5 minutes, 10 minutes, and 20 minutes post-dose; 3) 0.5 hour, 1 hour, and 2 hours post-dose; 4) 4 hours, 8 hours, and 12 hours post-dose; 5) 24 hours, 36 hours, and 48 hours post-dose; 6) 60 hours and 72 hours post-dose.
 - Plasma samples were processed via methanolic extraction to measure the total (lactone + hydroxy acid) form of sum total (encapsulated + released) topotecan via LC/MS.
 - The LC/MS assay was linear and acceptable from 10 ng/mL to 600 ng/mL. The lower limit of quantitation (LLQ) for sum total topotecan in plasma was 10 ng/mL (0.01 mcg/mL).
- **Pharmacokinetic Analysis:**
 - The PK analysis of TLI and NL-TPT in male rats, female rats, and overall (male + female rats) was performed using non-compartmental methods.
 - The presented data for TLI and NL-TPT is based on the mean value from the samples obtained at each time point in each rat.
 - The clearance (CL), elimination half-life (t_{1/2}), and volume of distribution (V_{dss}) were calculated using standard equations.
 - The areas under the plasma concentration versus time curve from 0 to 4 h (AUC_{0-4h}), 0 to last measurable sample (AUC_{0-last}), and 0 to infinity (AUC_{0-∞}) were calculated using the log trapezoidal method.
 - The areas under the mean concentration versus time curve from 0 to 4 h (AUMC_{0-4h}), 0 to last measurable sample (AUMC_{0-last}), and 0 to infinity (AUMC_{0-∞}) were calculated using standard equations.
 - The mean residence time from 0 to 4 h (MRT_{0-4h}) and 0 to infinity (MRT_{0-∞}) were calculated using standard equations.

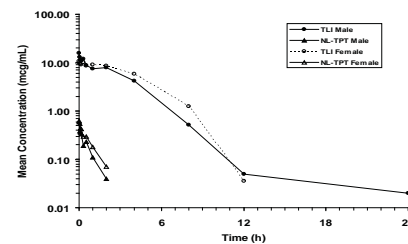
Results



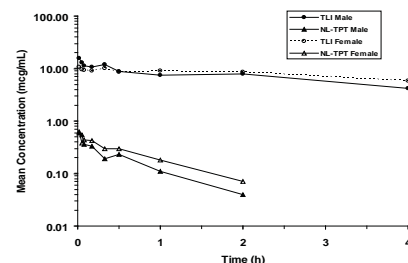
Mean Concentration versus Time Profiles of the Total Form of Sum Total Topotecan after Administration of TLI and NL-TPT in Overall Rat Plasma from 0 to 24 hours



Mean Concentration versus Time Profiles of the Total Form of Sum Total Topotecan after Administration of TLI and NL-TPT in Overall Rat Plasma from 0 to 4 hours



Mean Concentration versus Time Profiles of the Total Form of Sum Total Topotecan after Administration of TLI and NL-TPT in Male and Female Rat Plasma from 0 to 24 hours



Mean Concentration versus Time Profiles of the Total Form of Sum Total Topotecan after Administration of TLI and NL-TPT in Male and Female Rat Plasma from 0 to 4 hours

Pharmacokinetic Parameters for the Total Form of Sum Total Topotecan after Administration of TLI and NL-TPT

Compound	Gender	Rat No.	RatID	Lipid dose (mg/kg)	AUC (0-4h) (mcg·h/mL)	AUC (0-∞) (mcg·h/mL)	AUC (0-∞) (mcg·h/mL)	AUMC (0-4h) (mcg·h ² /mL)	AUMC (0-∞) (mcg·h ² /mL)	AUMC (0-∞) (mcg·h ² /mL)	MRT (0-4h) (h)	MRT (0-∞) (h)
TLI ^a	Male	Mean		9.3	28.7	369	37.2	47.6	98	145	1.65	3.90
	Female	Mean			32.0	45.1	45.2	57.0	131.8	132.4	1.78	2.93
	Overall ^c	Mean			30.4	41.2	41.2	52.6	118.5	118.5	1.73	2.88
NL-TPT ^a	Male	Mean		N/A	N/A	0.29	0.33	N/A	0.18	0.34	N/A	1.03
	Female	Mean			N/A	0.41	0.49	N/A	0.28	0.89	N/A	1.19
	Overall ^c	Mean			N/A	0.35	0.40	N/A	0.23	0.58	N/A	1.45

^a Pharmacokinetic studies of TLI and NL-TPT performed in 6 cohorts (n=3 rats per cohort); presented data based on mean value from samples obtained in each rat
^b Time of last detectable concentration for TLI and NL-TPT in males rats was 24 hours and 2 hours, respectively
^c Time of last detectable concentration for TLI and NL-TPT in female rats was 12 hours and 2 hours, respectively
^d Overall pharmacokinetic results generated by combining concentration versus time results from male and female rats

Compound	Gender	Rat No.	RatID	Lipid dose (mg/kg)	C _{max} (mcg/mL)	T _{max} (h)	t _{1/2} ^b (h)	CL (mL/min/kg)	V _{dss} (L/kg)
TLI ^a	Male	Mean		9.3	15.6	0.02	3.47	0.417	0.0974
	Female	Mean			10.6	0.02	1.00	0.343	0.0601
	Overall ^c	Mean			13.1	0.02	2.89	0.376	0.0649
NL-TPT ^a	Male	Mean		N/A	0.60	0.02	2.48	46.97	2.90
	Female	Mean			0.62	0.02	2.57	31.63	3.40
	Overall ^c	Mean			0.61	0.02	2.48	38.75	3.37

^a Pharmacokinetic studies of TLI and NL-TPT performed in 6 cohorts (n=3 rats per cohort); presented data based on mean value from samples obtained in each rat
^b t_{1/2} = terminal half-life
^c Overall pharmacokinetic results generated by combining concentration versus time results from male and female rats

Conclusions

- The larger and prolonged exposure of TPT in plasma after administration of TLI compared with NL-TPT is consistent with OPTISOME formulations and provides PK advantages over non-liposomal formulations of CPT analogues including TPT.
- The plasma pharmacokinetic disposition of sum total TPT after administration of TLI is consistent with the drug remaining encapsulated in the liposome for a prolonged period of time.
- The pharmacokinetic disposition of TLI and NL-TPT was similar in male and female rats.

Future Studies

- Pharmacologic studies evaluating the plasma and tumor disposition of liposomal encapsulated and released TPT after TLI in preclinical models and in patients are planned.
- Clinical trials to evaluate the safety and efficacy of TLI are being planned.