The Pharmacokinetic and Pharmacodynamic Evaluation of Multilamellar Vesicles Formulated Ropivacaine, TLC590, Administered by Local Injection in Rats

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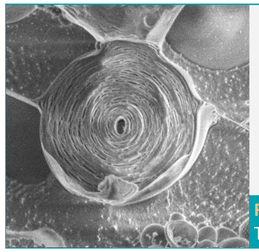
Introduction

Improvement in postoperative pain control plays an important role in the quality of patient recovery and satisfaction. Single administration of a sustained-release local anesthetic may provide prolonged pain relief and minimize opioid use. Multilamellar vesicles formulated ropivacaine, TLC590 (Figure 1), is being developed to sustain the release of ropivacaine *in situ* to maintain the local concentration within the therapeutic window. The objective of the present study is to demonstrate its sustained-release profile and the prolonged analgesia by pharmacokinetic and pharmacodynamic studies after local injection in rats.



TLC590 is a two-vial system comprising of one vial of sterile TLC590 lyophilized cake and one vial of sterile TLC590 reconstitution solution. The major components include ropivacaine, 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine and cholesterol.

Figure 1 Electron microscopic image of TLC590, a multilamellar vesicle structure.

Materials and Methods

Twelve female Sprague-Dawley rats (randomly divided into two groups, six rats per group) were used in the pharmacokinetic study following the subcutaneous injections of TLC590 (19 mg of ropivacaine/kg) and ropivacaine solution (19 mg of ropivacaine/kg), respectively (Table 1). At designated time points (0.25, 1, 2, 4, 8, 24, 48 and 72 h post-injection), ropivacaine plasma concentrations were determined by a LC-MS/MS and the pharmacokinetic parameters were obtained with Phoenix WinNonlin.

Table 1 The study design of pharmacokinetic study

Group	Dose of API (mg/kg)	Injection Route	Time Point (h)
TLC590	19	SC	0.25, 1, 2, 4, 8, 24, 48 and 72
Ropivacaine solution	19	SC	0.25, 1, 2, 4, 8, 24, 48 and 72

API, active pharmaceutical ingredient; SC, subcutaneous injections.

A pharmacodynamic study employing the incisional pain model was performed in twenty male Sprague-Dawley rats (randomly divided into four groups, five rats per group) (Table 2). After intraplanar injection of TLC590 (1.9 mg of ropivacaine/rat), ropivacaine solution (1.9 mg of ropivacaine/rat), Exparel® (1.3 mg of bupivacaine/rat) or normal saline (as a control group) along a 1-cm incision line, the 50% paw withdrawal threshold (g) and percentage of maximum possible effects (%MPE) were measured using the von Frey test at preselected times post-injection.

Table 2 The study design of pharmacodynamic study

Group	Dose of API (mg/kg)	Injection Volume (μL)	Injection Route	Time Point (h)
TLC590	1.9	100	IP	BL, 0*, 0.5, 1, 2, 3, 4, 5, 6, 7 and 24
Ropivacaine solution	1.9	100	IP	
Exparel®	1.3	100	IP	
Normal saline	0	100	IP	

API, active pharmaceutical ingredient; IP, intraplantar injection; BL, baseline threshold.
*Baseline threshold of post-surgery time point.

Results and Discussion

Ropivacaine concentration in plasma versus time profiles of both groups following a single subcutaneous injection is illustrated in Figure 2. The half-life ($t_{1/2}$) of ropivacaine after subcutaneous injection of TLC590 (26.1 h) was significantly prolonged (about 22-fold) compared with that of ropivacaine solution (1.19 h). While the maximum plasma concentration (C_{max}) of ropivacaine after subcutaneous injection of TLC590 (142 ng/mL) was only around one-ninth (1/9) of that after subcutaneous administration of ropivacaine solution (1290 ng/mL), and the exposure of ropivacaine ($AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$) was similar between two groups (3410 vs. 3910 ng × h/mL for $AUC_{0\text{-last}}$; 3940 vs. 3970 ng × h/mL for $AUC_{0\text{-}\infty}$) (Table 3).

The analgesic action attributed to the local anesthetic effect of the TLC590 after paw incision in rats is shown in Figure 3. The anesthetic effect of a single-dose of TLC590 was shown to have as quick an onset as ropivacaine solution but prolonged postoperative analgesia compared to ropivacaine solution. Furthermore, the analgesic effect of TLC590 lasted for 6 hours which was significantly longer than that of Exparel® (<5 hours).

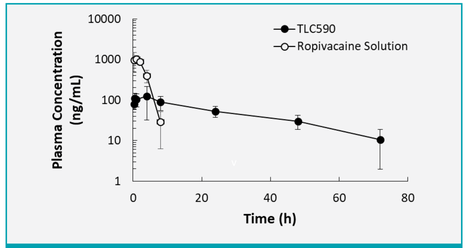


Figure 2 Mean plasma concentration versus time in rats after subcutaneous administration of ropivacaine solution and TLC590 at 19 mg of ropivacaine/kg.

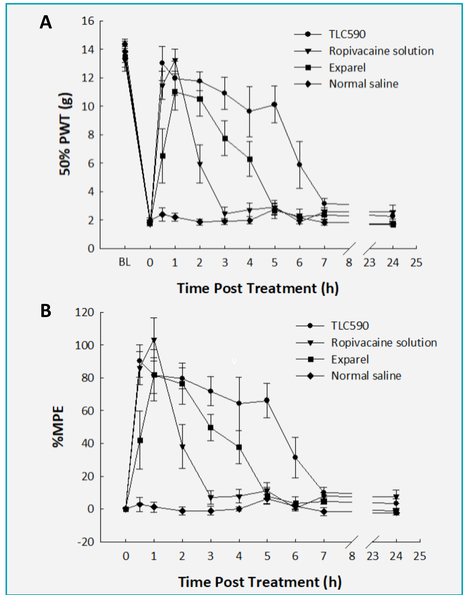


Figure 3 Changes in 50% paw withdrawal threshold (g) (A) and percentage of maximum possible effects (%MPE) (B) in rats with intraplanar injection of TLC590, ropivacaine solution, Exparel® and normal saline. BL, baseline threshold, was measured before surgery.

Table 3 The pharmacokinetic parameters after subcutaneous injection of TLC590 and ropivacaine solution in rats

Parameters	Unit	TLC590 (n = 5)[1]	Ropivacaine solution (n = 5)[1]
C_{max}	ng/mL	142 ± 94.4	1290 ± 280
t_{max}	h	1.30 ± 1.56	0.700 ± 0.411
$t_{1/2}$	h	26.1 ± 7.31	1.19 ± 0.299
$AUC_{0\text{-last}}$	ng × h/mL	3410 ± 824	3910 ± 311
$AUC_{0\text{-}\infty}$	ng × h/mL	3940 ± 1020	3970 ± 355
MRT_{inf}	h	35.2 ± 10.4	2.28 ± 0.446

[1], pharmacokinetic parameters of one rat could not be reported due to insufficient data points under Phoenix WinNonlin analyzing.
Data represent mean value ± standard deviation.

Summary

- TLC590 is a lipid-based, multilamellar vesicles formulated ropivacaine, that produces the prolonged analgesic effect in postoperative pain management.
- The $t_{1/2}$ of TLC590 was approximately 22-fold longer than that of ropivacaine solution.
- The C_{max} of TLC590 was only 1/9 of that of ropivacaine solution at the same dosage, which promotes the drug safety improvement by a formulated ropivacaine.
- TLC590 was shown to have as quick an onset as ropivacaine solution but prolonged postoperative analgesia compared to ropivacaine solution.
- The onset of TLC590 was faster than Exparel® but the sustained analgesic effect of TLC590 was longer than Exparel®.

Conclusions

TLC590 exhibited a sustained release profile in pharmacokinetic properties and pharmacodynamic effects after a single administration. These preclinical data indicate that a single administration of TLC590 is a promising candidate for improving postoperative pain management. The safety of TLC590 in different species is further disclosed in another ePoster (ID# 6921).

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