

Pharmacokinetics of a sustained-release ropivacaine depot vs. ropivacaine HCl for peripheral nerve block in rat and pig

Kelsey Pflepsen, PhD[1]; William Taylor[1]; Mark Ereth, MD[1]; Jacob Hutchins, MD, MHA[2]

[1]InSitu Biologics, Inc., Oakdale, MN, USA [2]University of Minnesota, Minneapolis, MN, USA

INTRODUCTION

- Postoperative pain management increasingly favors regional nerve block over systemic opioids.
- Standard immediate-release local anesthetics, such as ropivacaine HCl, provide analgesia for less than 24 hours[1] and are rapidly absorbed.[2]
- The ropivacaine depot is an investigational sustained-release formulation of ropivacaine base designed to extend single-injection block duration while attenuating peak systemic exposure.
- These studies characterized plasma concentration-time profiles and pharmacokinetic (PK) parameters for the depot relative to ropivacaine HCl across ascending doses in rat and pig.

METHODS

- Nonclinical studies only[3]; IACUC-approved at each performing facility. No IND was required.
- Single ropivacaine depot (INSB200) dose, three ascending levels: pig 36.39, 48.10, and 53.53 mg/kg (perineural + subcutaneous); rat 72.71, 95.61, and 118.35 mg/kg (intramuscular at the sciatic nerve + subcutaneous).
- Ropivacaine HCl comparator, separate studies: pig, 3.5 mg/kg perineural, male (n=2) and female (n=2); rat, 4 mg/kg intramuscular at the sciatic nerve, male only (n=3).
- Plasma (ropivacaine depot) or serum (ropivacaine HCl) ropivacaine quantified by LC-MS/MS through 336 hours.
- PK parameters (C_{max}, T_{max}, $t_{½}$, AUC_{last}) derived by extravascular non-compartmental analysis, combined-sex where applicable. Pig ropivacaine HCl values as noted in Table 1.

RESULTS

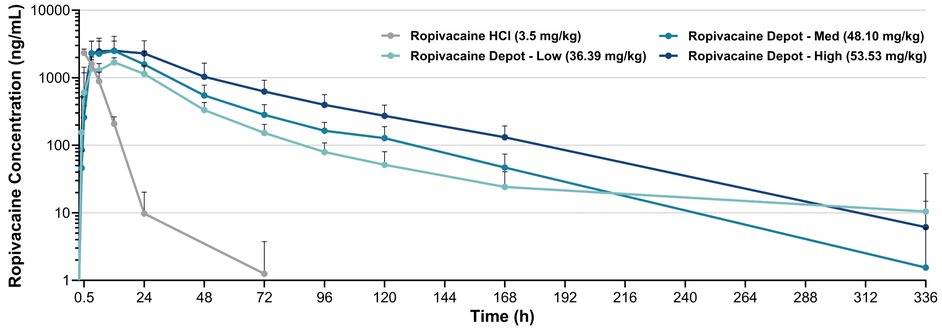
- Ropivacaine HCl peaked at 0.5 h in both species and was last quantifiable at 72 h (pig) and 48 h (rat). Ropivacaine depot peaked later (T_{max} 9.38–11.3 h pig; 3.50–4.50 h rat) and remained quantifiable through 168 h (rat) and 336 h (pig).
- C_{max} increased approximately in proportion to dose in pig and approximately or slightly less than proportionally to dose in rat.
- AUC increased generally more than proportionally to dose in pig and approximately in proportion to dose in rat.
- Terminal half-life increased moderately with dose, consistent with prolonged release from the depot.
- Despite much higher depot doses, C_{max} stayed comparable to or lower than ropivacaine HCl in pig, and higher in rat (~2.8- to 3.4-fold), though far less than proportional to the 18- to 30-fold higher dose.

1–2 weeks
Quantifiable ropivacaine after one dose vs. ≤48–72 h for ropivacaine HCl (rat/pig)

0.7–1.2×
Pig C_{max} vs. ropivacaine HCl, at a 10–15× higher depot dose

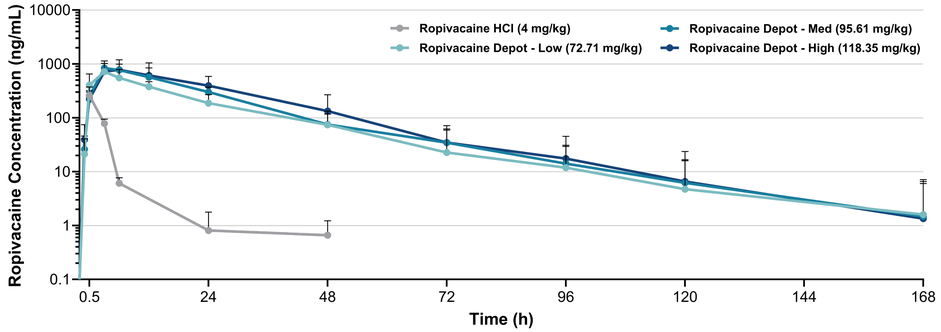
2.8–3.4×
Rat C_{max} vs. ropivacaine HCl, at an 18–30× higher depot dose

Figure 1. Pig Concentration-Time Profiles



Mean (+SD) plasma (ropivacaine depot) and serum (ropivacaine HCl) ropivacaine concentration vs. time, semi-logarithmic scale. Ropivacaine depot doses are 36.39 (light blue, n = 7* (4 male, 3 female)), 48.10 (teal, n = 8 (4 male, 4 female)), and 53.53 mg/kg (dark blue, n = 8 (4 male, 4 female)); ropivacaine HCl dose is 3.5 mg/kg (gray, n = 4 (2 male, 2 female)).
*One animal in the 36.39 mg/kg group died during the dosing procedure (attributed to anesthesia). No PK samples were collected.

Figure 2. Rat Concentration-Time Profiles



Mean (+SD) plasma (ropivacaine depot) and serum (ropivacaine HCl) ropivacaine concentration vs. time, semi-logarithmic scale. Ropivacaine depot doses are 72.71 (light blue, n = 12 (6 male, 6 female)), 95.61 (teal, n = 12 (6 male, 6 female)), and 118.35 mg/kg (dark blue, n = 12 (6 male, 6 female)); ropivacaine HCl dose is 4 mg/kg (gray, n = 3 (3 male)).

RESULTS (continued)

Table 1. Pig and Rat Pharmacokinetic Parameters

Species	Test Article	Dose (mg/kg)	C_{max} (ng/mL)	T_{max} (h)	$t_{½}$ (h)	AUC_{last} (h·ng/mL)
Pig	Ropivacaine HCl	3.5	2340	0.50	2.68*	13,300*
	Depot - Low	36.39	1730	10.4	27.2	63,600
	Depot - Med	48.10	2790	9.38	37.7	98,300
	Depot - High	53.53	2730	11.3	43.4	151,000
Rat	Ropivacaine HCl	4.0	262	0.50	1.03	697
	Depot - Low	72.71	744	3.50	14.3	14,000
	Depot - Med	95.61	890	4.25	17.5	19,300
	Depot - High	118.35	901	4.50	24.2	21,400

*Pig ropivacaine HCl AUC_{last} and $t_{½}$ calculated from reported concentrations (linear trapezoidal method to last quantifiable timepoint; log-linear terminal-phase regression, n=4 animals with ≥3 declining terminal points, $R^2 \geq 0.85$).

DISCUSSION

- The depot produced a distinct, far more prolonged profile than ropivacaine HCl, with delayed T_{max} and quantifiable ropivacaine for at least 1–2 weeks post-dose.
- Despite higher doses, peak levels were comparable to or lower than ropivacaine HCl in pig and within a modest multiple in rat, indicating lower dose-normalized peak systemic concentrations than ropivacaine HCl.
- Findings support further evaluation of the depot for prolonged single-injection nerve block.

REFERENCES

1. Maagaard M, Albrecht E, Mathiesen O. Prolonging peripheral nerve block duration: current techniques and future perspectives. *Acta Anaesthesiol Scand*. 2025;69(4):e70010. doi:10.1111/aas.70010
2. Naropin (ropivacaine hydrochloride) injection, for epidural, perineural, or infiltration use. Prescribing information. Fresenius Kabi USA, LLC; 2022. Accessed September 30, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/020533s038lbl.pdf
3. Data on file. InSitu Biologics, Inc., Oakdale, MN.
4. Pflepsen K, Taylor W, Ereth M, Hutchins J. Pharmacokinetics of a sustained-release ropivacaine peripheral nerve block formulation (INSB200) across rat and porcine models: comparison to ropivacaine HCl. Poster presented at: PAINWeek 2026; September 8–11, 2026; Las Vegas, NV. Abstract P078. Posted online August 4, 2026.

ACKNOWLEDGMENTS

All studies described were sponsored and funded by InSitu Biologics, Inc. No government or other third-party funding was received. K. Pflepsen and W. Taylor are employees of InSitu Biologics, Inc. M. Ereth serves as Chief Medical Officer under a consulting arrangement, and J. Hutchins serves as a paid consultant to InSitu Biologics, Inc.'s medical advisory board. All authors hold equity interests, including stock options, in InSitu Biologics, Inc. Portions of these data were presented at PAINWeek 2026.[4]

CORRESPONDING AUTHOR

Kelsey Pflepsen, PhD
InSitu Biologics, Inc.
3510 Hopkins Place North, Bldg 4, Oakdale, MN 55128
kelsey.pflepsen@insitubiologics.com