Concentrations of Bupivacaine and Meloxicam in Breast Milk after Exposure to HTX-011

Amy Yamamoto[1], Clynn Wilker[1], Adrienne Griffith[1], Scott Brantley[2], Craig Saffer[3]

[1]Heron Therapeutics, Inc, San Diego, CA; [2]Nuventra Pharma Sciences, Durham, NC; [3]West Coast OB/GYN, Inc., San Diego, CA

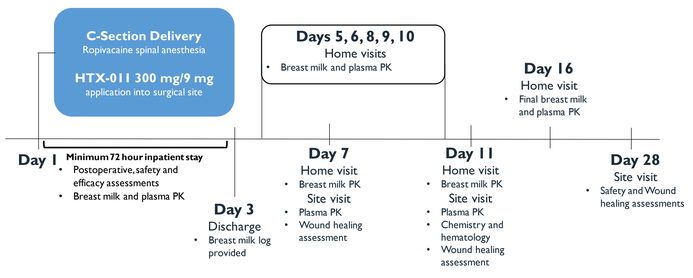
INTRODUCTION AND OBJECTIVES

- HTX-011, an investigational drug, has been developed for application into the surgical site to reduce postoperative pain for up to 72 hours and the need for opioid analgesics
- HTX-011 is a dual-acting local anesthetic (DALA) comprising the active ingredients bupivacaine and low-dose meloxicam in an FDA-approved polymer designed for controlled diffusion of ingredients over 72 hours
- Following HTX-011 administration, the polymer enables extended and simultaneous release of bupivacaine and meloxicam using a proprietary vehicle formulation in combination with different excipients approved for human use (dimethyl sulfoxide [DMSO], glycerol triacetate [triacetin], and maleic acid)
- After bupivacaine and meloxicam have been released from HTX-011 and are absorbed systemically, their distribution, metabolism, and excretion is expected to be the same as for other bupivacaine or meloxicam formulations
- The primary objective of this Phase 2, open-label study was to measure concentrations of bupivacaine, meloxicam and DMSO present in expressed breast milk and plasma from women undergoing a planned Cesarean section who were administered a single dose of HTX-011 postpartum

METHODS

- Enrolled women undergoing a planned Cesarean section (N=11) with ropivacaine spinal anesthesia (NCT03955211)
- **Inclusion Criteria:** Expected to deliver a single neonate, scheduled to undergo a planned Cesarean section surgery with a low transverse skin incision (e.g. Pfannenstiel), has American Society of Anesthesiologists (ASA) Physical Status of I, II, or III and agrees to refrain from the use of breast milk from this pregnancy in any manner
- **Exclusion Criteria:** Has planned to breastfeed her neonate at any time during the 28-day period after HTX-011 administration, had a prior full-term pregnancy with unsuccessful breast milk expression, administered bupivacaine within 5 days, any local anesthetic within 72 hours prior to the scheduled surgery, has been administered systemic steroids within 5 half-lives or 10 days prior to administration of study drug
- Following delivery of the neonate, after chord clamp and prior to skin closure, HTX-011 (300 mg bupivacaine/9 mg meloxicam) was applied without a needle to the surgical site and surrounding tissues. Samples of maternal blood and complete expression of breast milk were collected through postpartum Day 16
- Plasma and breast milk concentrations of bupivacaine, meloxicam, and DMSO were measured using validated liquid chromatography tandem-mass spectrometry assays and pharmacokinetic (PK) parameters were calculated using a standard noncompartmental analysis method

STUDY DESIGN



RESULTS

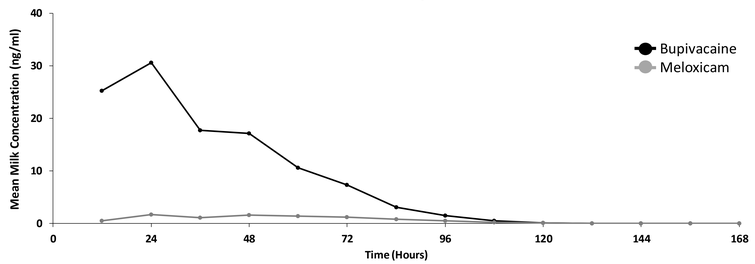
- On average, ≤ 0.01% of the HTX-011 dose was excreted in breast milk with quantifiable levels at microgram concentrations observed for ≤ 6 days postpartum
- Mean total amounts of bupivacaine, meloxicam and DMSO detected in breast milk were 4.90 µg, 0.92 µg, and 48.30 µg, respectively. Median time to maximum concentration (T_{max}) in breast milk was 48 hours for bupivacaine, 60 hours for meloxicam, and 12 hours for DMSO (**Table 1**)
  - For reference, in a nonclinical model using neonatal pigs administered bupivacaine 0.25 mg/kg/day, meloxicam 12 mg/kg/day, and DMSO 80 mg/kg/day (≈237-, 48,600-, and 3,500-times greater, respectively, than the maximum daily infant dose from breast milk based on body surface area) no toxicity was observed (Data on File)
- Mean maximum plasma concentration (C_{max}) was 235 ng/mL for bupivacaine and 75.9 ng/mL for meloxicam. Mean C_{max} of DMSO was 3690 ng/mL. Median plasma T_{max} was 24 hours for bupivacaine, 36 hours for meloxicam, and 2 hours for DMSO (**Table 2**)

Table 1. Pharmacokinetic Analyses in Breast Milk Following HTX-011 Exposure

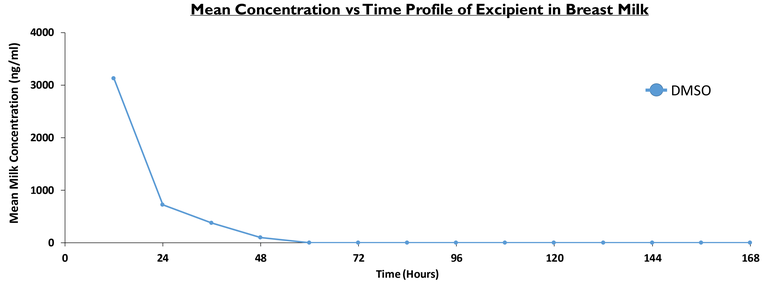
Matrix	Treatment	Analyte	Dose (mg)	N	T_{max} (hr)	T_{last} (hr)	C_{max} (ng/mL)	$Ae_{0\text{-}360h}$ (µg)	$fe_{0\text{-}360h}$ (%)	Dose Margins*
Breast Milk	HTX-011 300 mg/ 9 mg	BPV	300	11	48	120	22.0	4.90	0.00163	~237x
		MLX	9	11	60	102	1.71	0.92	0.0103	~48,600x
		DMSO	1,200	8	12	42	2410	48.3	0.00403	~3,500x

BPV, bupivacaine; MLX, meloxicam; DMSO, dimethyl sulfoxide; Ae, amount excreted; fe, fraction excreted
*Dose margins (fold increase of doses in neonatal pigs vs exposure in humans) calculated based on body surface area

Mean Concentration vs Time Profiles of Bupivacaine and Meloxicam in Breast Milk



Mean Concentration vs Time Profile of Excipient in Breast Milk



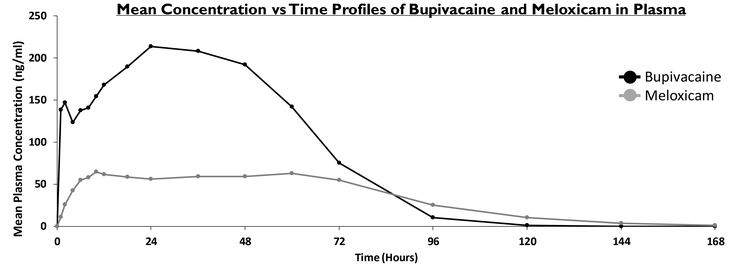
RESULTS

Table 2. Pharmacokinetic Analyses in Plasma Following HTX-011 Exposure

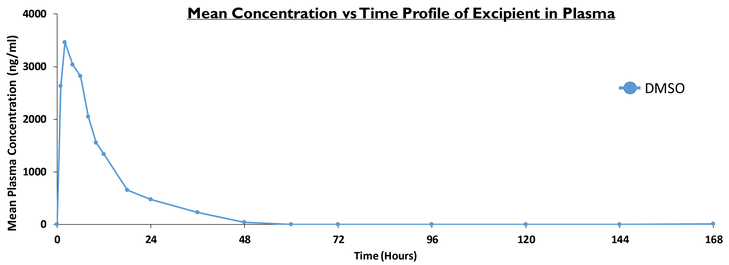
Matrix	Treatment	Analyte	Dose (mg)	N	T_{max} (hr)	T_{last} (hr)	C_{max} (ng/mL)	$AUC_{0\text{-}24}$ (h·ng/mL)	AUC_{last} (h·ng/mL)	$t_{1/2}$ (hr)
Plasma	HTX-011 300 mg/ 9 mg	BPV	300	11	24	96	235	3,930	12,900	9.21
		MLX	9	11	36	144	75.9	1,260	5,600	17.9
		DMSO	1,200	11	2	36	3,690	36,700	41,000	11.0

BPV, bupivacaine; MLX, meloxicam; DMSO, dimethyl sulfoxide

Mean Concentration vs Time Profiles of Bupivacaine and Meloxicam in Plasma



Mean Concentration vs Time Profile of Excipient in Plasma



DISCUSSION AND CONCLUSIONS

- A single postpartum dose of HTX-011 (300 mg bupivacaine/9 mg meloxicam) in women undergoing Cesarean section resulted in very low (microgram) levels of bupivacaine and meloxicam in breast milk. Levels of the well-known excipient DMSO were barely detectable by 48 hours
- Linear extrapolation of these data to an HTX-011 dose of 400 mg/12 mg would be expected to lead to an approximate 33% higher concentration of these components in breast milk
- Nonclinical studies confirm a high dose margin of the bupivacaine, meloxicam and DMSO exposures observed in human breast milk
- This suggests a low risk for potential adverse effects on the breastfed child from maternal postpartum administration of HTX-011

ACKNOWLEDGMENTS

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