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HTX-011: Predictable Release Rates of Bupivacaine and Meloxicam for 72 Hours

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INTRODUCTION

- HTX-011 is an investigational dual-acting local anesthetic comprising bupivacaine and meloxicam in an extended-release polymer
  - HTX-011 has demonstrated superiority over bupivacaine hydrochloride (HCl) for managing postoperative pain over 72 hours in multiple surgical procedures, including bunionectomy, herniorrhaphy, and total knee arthroplasty (TKA)[1-3]
  - Meloxicam, a non-steroidal anti-inflammatory drug, normalizes the local pH at the site of HTX-011 administration, enhancing the penetration of bupivacaine into pain-transmitting neurons and generating a synergistic analgesic effect[4]
- Tissue vascularity of the surgical site affects the speed of absorption of local anesthetics into the plasma, resulting in higher maximal plasma concentrations (C_{max}) of injected anesthetic (eg, bupivacaine HCl)
- The extended release of bupivacaine and meloxicam from HTX-011 occurs via release from a proprietary triethylene glycol-based poly(orthoester) polymer, termed Biochronomer™, which allows for the diffusion of active ingredients over 72 hours[4]
  - Although the efficacy of HTX-011 over 72 hours has been previously demonstrated, the kinetics of the ingredient release from the polymer have only been described in preclinical models[4]
- Bupivacaine plasma concentrations above 2000 ng/mL can result in local anesthetic systemic toxicity (LAST),[5] a group of rare but potentially life-threatening adverse events[6,7]
- Here we present in vitro release (IVR) data for HTX-011 and compare them with the in vivo pharmacokinetic (PK) data from clinical studies in bunionectomy, herniorrhaphy, TKA, and augmentation mammoplasty

METHODS

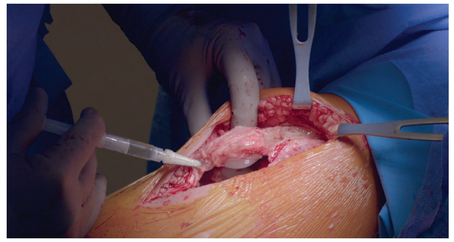
In Vitro Studies

- A validated IVR assay measured bupivacaine and meloxicam released from HTX-011 into the surrounding dissolution medium at 37°C
  - Bupivacaine and meloxicam concentrations in the dissolution medium were measured by a validated high-performance liquid chromatography method

In Vivo Studies

- In vivo PK data presented in this analysis were collected across several clinical studies evaluating HTX-011 in bunionectomy (NCT02762929; NCT03295721), herniorrhaphy (NCT02504580; NCT03237481), TKA (NCT03015532), and augmentation mammoplasty (NCT03705065 [Bupivacaine HCl only]; NCT03011333)
  - A single intraoperative dose of HTX-011 was administered without a needle to the surgical site and surrounding tissues prior to closure (**Figure 1**)
    - 60 mg bupivacaine/1.8 mg meloxicam (bunionectomy)
    - 300 mg bupivacaine/9 mg meloxicam (herniorrhaphy)
    - 400 mg bupivacaine/12 mg meloxicam (TKA and mammoplasty)
  - Bupivacaine HCl was administered via injection with commonly used doses in these surgical models
    - 50 mg bupivacaine HCl (bunionectomy)
    - 75 mg bupivacaine HCl (herniorrhaphy)
    - 125 mg bupivacaine HCl (TKA)
    - 150 mg bupivacaine HCl (mammoplasty)
  - Plasma samples were collected at study protocol–specified time points and concentrations of bupivacaine and meloxicam were measured with validated liquid chromatography tandem-mass spectrometry assays
  - In vivo release rates of bupivacaine and meloxicam were derived for HTX-011 using population PK modeling based on plasma concentrations

Figure 1. HTX-011 is Administered Without a Needle Into the Surgical Site

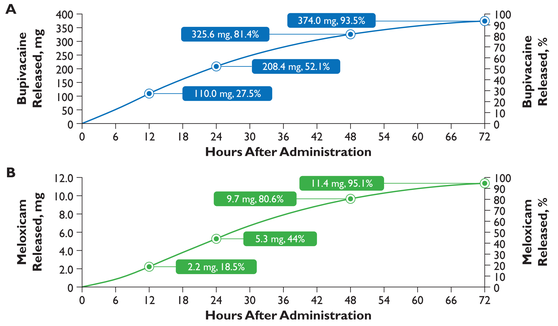


RESULTS

In Vitro Release Rates of Bupivacaine and Meloxicam From HTX-011

- The proportion of the total bupivacaine dose released from HTX-011 was 28%, 52%, 81%, and 94% over 12, 24, 48, and 72 hours, respectively (**Figure 2A**)
- The proportion of the total meloxicam dose released was 19%, 44%, 81%, and 95% after 12, 24, 48, and 72 hours, respectively (**Figure 2B**)
- For the highest recommended dose of HTX-011 (400 mg bupivacaine/12 mg meloxicam in mammoplasty and TKA), these in vitro release rates equate to ~200 mg bupivacaine and ~5.3 mg meloxicam released in the first 24 hours
  - These amounts are well below the respective recommended 24-hour maximums for bupivacaine (400 mg) and meloxicam (30 mg)[8,9]

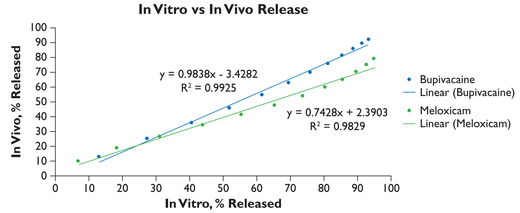
Figure 2. Calculated In Vitro Release Rates of Bupivacaine and Meloxicam From HTX-011 (400 mg bupivacaine/12 mg meloxicam)



Pharmacokinetics of Bupivacaine In Vivo

- The in vitro release rates of HTX-011 strongly correlated with patient PK data (R^2 >0.98; **Figure 3**)

Figure 3. In Vitro Versus In Vivo Release of Bupivacaine and Meloxicam From HTX-011



R^2, coefficient of determination; Y, y-axis intercept.

- As expected, times to maximum plasma concentrations (T_{max}) of bupivacaine released from HTX-011 were delayed compared with those observed after bupivacaine HCl injection in same type of surgical procedure (**Table 1**)
  - Characteristic of extended-release products, HTX-011 produced a long plateau in bupivacaine concentration-time profile and resulted a wider range of median T_{max} values across surgeries
- The mean bupivacaine C_{max} after HTX-011 application at its highest dose was 710 ng/mL (augmentation mammoplasty) and 672 ng/mL (TKA, **Table 1**), well below the level associated with toxicity (2000 ng/mL)
- The mean C_{max} for a 150 mg bupivacaine HCl injection in augmentation mammoplasty was 1110 ng/mL (**Table 1**), 4x the bupivacaine C_{max} for HTX-011 in the same procedure when normalized to the dose given (**Figure 4**)

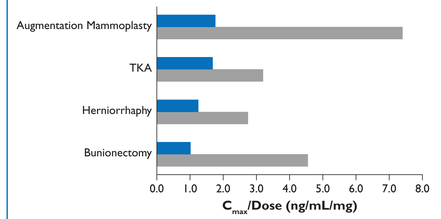
Table 1. Maximum Plasma Concentration (C_{max}) and Time to Reach C_{max} (T_{max}) Across Studies

	HTX-011 Application				Bupivacaine HCl Injection			
		Bupivacaine				Bupivacaine		
	n	Dose (mg)	Mean C_{max} (ng/mL)	Median T_{max} (h)	n	Dose (mg)	Mean C_{max} (ng/mL)	Median T_{max} (h)
Augmentation Mammoplasty	49	400	710	3.58	15	150	1110	0.73
TKA[a]	109	400	672	20.87	65	125	399	1.03
Herniorrhaphy	177	300	371	22.00	32	75	206	0.73
Bunionectomy	174	60	62	4.00	25	50	228	1.32

C_{max}, maximum plasma concentration; HCl, hydrochloride; TKA, total knee arthroplasty; T_{max}, time to reach maximum plasma concentration.
[a]Includes patients who received HTX-011 with or without additional injection of ropivacaine.

- Consistent with the known effect of local tissue vascularity on the C_{max} of injected bupivacaine HCl, increased dose-normalized C_{max} (C_{max}/dose) were observed for injected bupivacaine HCl with increasing vascularity (eg, in mammoplasty, **Figure 4**)
- In contrast, bupivacaine released from HTX-011 did not exhibit the same broad variability and remained within a C_{max}/dose range of 1.2-1.8 ng/mL/mg compared with 2.7-7.4 ng/mL/mg for bupivacaine HCl, demonstrating consistent and predictable absorption across surgical procedures (**Figure 4**)
- Across all surgical procedures evaluated, the dose-normalized C_{max} was reduced with HTX-011 application compared with bupivacaine HCl injection (**Figure 4**)

Figure 4. Dose-Normalized C_{max} (C_{max}/Dose) of Bupivacaine Following Administration of Bupivacaine HCl or HTX-011 Across Surgical Procedures



C_{max}, maximum plasma concentration; HCl, hydrochloride; TKA, total knee arthroplasty.

CONCLUSIONS

- Patient PK data strongly correlated with the in vitro release rates of bupivacaine and meloxicam
- The maximum plasma concentration with HTX-011 was several-fold lower than the literature-based toxicity levels
  - For a detailed analysis of the absence of potential LAST across clinical studies evaluating HTX-011, please see ePoster A4279 (Viscusi et al.)
- The extended release of bupivacaine and meloxicam from HTX-011 over 72 hours demonstrated consistent dose-proportional C_{max} values not impacted by vascularity
- Unlike the dose-normalized C_{max} range for bupivacaine HCl, the dose-normalized C_{max} range for bupivacaine released from HTX-011 is consistent and predictable across surgical procedures regardless of site vascularity

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HERON THERAPEUTICS

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