Pharmacokinetics and Safety of Different Bupivacaine Formulations and Administration Techniques in Augmentation Mammoplasty

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BACKGROUND

- Augmentation mammoplasty, a common cosmetic surgery, often includes the use of a local anesthetic such as bupivacaine hydrochloride (HCl) for postoperative analgesia[1]
- High plasma concentrations of local anesthetics may cause serious neurologic and cardiac complications known as local anesthetic systemic toxicity (LAST)[2]
  - LAST is more common with unintentional intravascular injection or rapid systemic absorption from highly vascular areas[2]
- HTX-011 is a novel, extended-release (ER), dual-acting, fixed-dose combination local anesthetic comprising bupivacaine and low-dose meloxicam, incorporated in a proprietary Biochronomer® polymer
  - HTX-011 is administered by instillation through a needle-free application into the surgical site as a single dose; the Biochronomer polymer enables the controlled-release of bupivacaine and meloxicam simultaneously over approximately 3 days
  - Approximately 50% of the bupivacaine is released from HTX-011 over the first 24 hours
- Herein are a subset of results from two clinical studies in patients undergoing bilateral submuscular augmentation mammoplasty, a highly vascular procedure, to report the pharmacokinetics (PK) and safety of HTX-011 (400 mg bupivacaine/12 mg meloxicam) and bupivacaine HCl (150 mg)

OBJECTIVES

- To characterize the bupivacaine PK profile and safety and tolerability of HTX-011 applied into the surgical site by instillation compared with bupivacaine HCl administered via instillation and injection

METHODS

- This analysis included cohorts from 2 studies evaluating subjects undergoing bilateral submuscular augmentation mammoplasty. The entry criteria were identical for both studies (**Table 1**)
  - A phase 2b randomized study (NCT03011333) included a cohort of subjects receiving HTX-011 400 mg bupivacaine/12 mg meloxicam administered via instillation
  - A phase 4 open-label study (NCT03705065) included 2 cohorts of subjects who were randomly assigned in a 1:1 ratio to receive bupivacaine HCl 150 mg via instillation or injection
- Subjects in both studies were kept in an inpatient facility for 72 hours postoperatively for study assessments

Table 1. Key Inclusion and Exclusion Criteria for Both Studies

Key inclusion criteria	Key exclusion criteria
• Females ≥18 years old who were not pregnant, lactating, or planning to become pregnant • Provide written informed consent • Scheduled to undergo bilateral submuscular augmentation mammoplasty with saline or silicone smooth implants with a volume of 300-500 cc • ASA Physical Status classification system category I-III	• Pre-existing concurrent acute or chronic painful/restrictive condition (unrelated to the augmentation mammoplasty) that may require analgesia during the postoperative period • Use of NSAIDs, long-acting opioids, any opioids, bupivacaine, or any local anesthetic for ≤10 days, ≤3 days, ≤24 hours, ≤5 days, or ≤72 hours prior to scheduled surgery, respectively • BMI >35 kg/m^2

ASA, American Society of Anesthesiologists; BMI, body mass index; NSAIDs, nonsteroidal anti-inflammatory drugs.

Outcome Measures

- PK parameters in both studies included maximum observed plasma concentration (C_{max}), area under the curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$), time to maximum plasma concentration (T_{max}), and apparent terminal elimination half-life ($t_{1/2}$)
- Secondary endpoints included incidence of adverse events (AEs) including potential LAST symptoms

Assessments

- Blood samples to determine the plasma concentrations of bupivacaine were collected from bupivacaine HCl subjects every 15 minutes for the first 1.5 hours and at hours 2, 3, 4, 6, 8, 12, 24, 48, and 72 and were collected from HTX-011 subjects at hours 1, 2, 4, 6, 8, 12, 20, 22, 24, 26, 28, 36, 48, 60, 72, and 120
- Plasma concentrations of bupivacaine were determined using validated liquid chromatography tandem-mass spectrometry assays. Concentrations were calculated by interpolation from a calibration curve. The lower limit of quantitation for bupivacaine in human plasma was 0.100 ng/mL

Statistical Analysis

- PK parameters for bupivacaine were calculated using Phoenix® WinNonlin® version 6.3 (Certara Inc., Princeton, NJ, US) using actual sampling times
- PK parameters were calculated using noncompartmental analysis and reported for the PK analysis population using descriptive statistics
- AEs were analyzed using descriptive statistics

RESULTS

Baseline Demographics

- The safety analysis included 50 subjects who received HTX-011 by instillation in the phase 2b study and 30 subjects who received bupivacaine HCl (15 instillation, 15 injection) in the phase 4 study
- The baseline characteristics were generally well-balanced across studies; mean age was 32.0 and 30.5 years and mean body mass index was 24.1 and 23.5 kg/m^2 in the phase 2b and phase 4 study, respectively

Pharmacokinetics

- The PK analysis included all subjects who received bupivacaine HCl and 49 evaluable subjects for HTX-011
- The bupivacaine PK profiles for bupivacaine HCl administered via instillation and injection were comparable; differences in T_{max} and $t_{1/2}$ were not clinically significant (**Table 2**)
- Mean bupivacaine plasma C_{max} was lower with HTX-011 via instillation compared with bupivacaine HCl administered via instillation or injection (**Table 2, Figure 1**)
- One subject receiving bupivacaine HCl and no subjects receiving HTX-011 had bupivacaine plasma values above 2000 ng/mL, a bupivacaine exposure level with which LAST has been reported to occur[3-7]

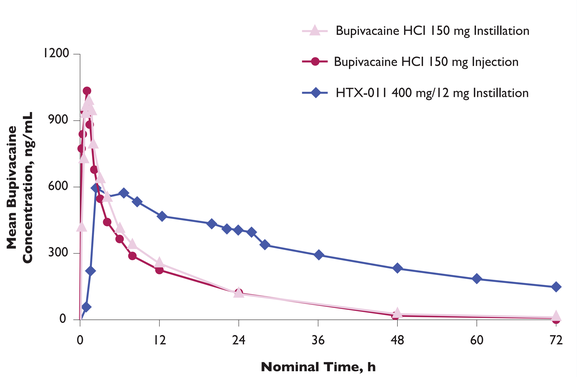
Table 2. Summary Plasma Pharmacokinetics of Bupivacaine Following Administration of HTX-011 and Bupivacaine HCl

	HTX-011 400 mg/12 mg instillation N = 49[a,b]	Bupivacaine HCl 150 mg	
		Instillation n = 15	Injection n = 15
C_{max}, min-max, ng/mL	368-1550	256-1480	415-2170
C_{max}, mean (SD), ng/mL	710 (246)	1110 (347)	1110 (469)
T_{max}, median (range), h	3.58 (1.27-34.58)	1.03 (0.53-1.58)	0.73 (0.18-1.25)
$AUC_{0-\infty}$, mean (SD), h·ng/mL	27,000 (8960)	9850 (6760)	8710 (2340)
$t_{1/2}$, mean (SD), h	19.0 (4.40)	13.5 (5.03)	7.69 (2.33)

$AUC_{0-\infty}$, area under the curve from time 0 extrapolated to infinity; C_{max}, maximum observed plasma concentration; HCl, hydrochloride; SD, standard deviation; $t_{1/2}$, apparent terminal elimination half-life; T_{max}, time to maximum plasma concentration.

[a]n = 39 for $AUC_{0-\infty}$ and $t_{1/2}$; 10 subjects did not exhibit a terminal log linear phase.
[b]One subject was excluded from summary statistics due to a bupivacaine pre-dose concentration >5% C_{max}.

Figure 1. Mean Plasma Exposure Profiles of Bupivacaine Following Administration of HTX-011 or Bupivacaine HCl



HCl, hydrochloride.

Safety

- The most common AEs were nausea, vomiting, headache, and constipation (**Table 3**)
- There was no evidence of LAST in either study
  - One subject who received bupivacaine HCl via injection had a bupivacaine plasma concentration of 2170 ng/mL and had mild hypotension at 1 hour postdose. The hypotension resolved at 2 hours postdose and the subject's bupivacaine plasma concentration had decreased below 1000 ng/mL by 4 hours postdose

Table 3. Most Common AEs (incidence >10%) After Administration of HTX-011 or Bupivacaine HCl

Preferred term, n (%)	HTX-011 400 mg/12 mg instillation N = 50	Bupivacaine HCl 150 mg	
		Instillation n = 15	Injection n = 15
Subjects reporting at least one AE	48 (96)	15 (100)	14 (93)
Nausea	37 (74)	10 (67)	10 (67)
Vomiting	19 (38)	9 (60)	6 (40)
Headache	7 (14)	3 (20)	3 (20)
Constipation	7 (14)	2 (13)	1 (7)
Dizziness	6 (12)	1 (7)	1 (7)
Hypotension	6 (12)	3 (20)	3 (20)
Tachycardia	6 (12)	3 (20)	1 (7)
Pyrexia	6 (12)	–	–
Pruritus generalized	1 (2)	2 (13)	1 (7)

AE, adverse event; HCl, hydrochloride.

CONCLUSIONS

- In augmentation mammoplasty, a highly vascular procedure:
  - Bupivacaine mean C_{max} was lower with HTX-011 than with bupivacaine HCl, despite a higher administered dose of bupivacaine in HTX-011
  - The HTX-011 extended-release formulation was dose-proportional to the AUC observed with bupivacaine HCl
  - The most common AEs with the different bupivacaine formulations and administration techniques were the same: nausea, vomiting, headache, and constipation
  - No subjects receiving HTX-011 and one subject receiving bupivacaine HCl via injection had a bupivacaine plasma level over 2000 ng/mL; the risk of LAST may be lower for HTX-011 given the lower peak systemic exposure of bupivacaine and unique needle-free application

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