The PK Profile of SABER®-Bupivacaine in Humans Across Surgical Models Demonstrates Sustained 72-Hour Drug Delivery

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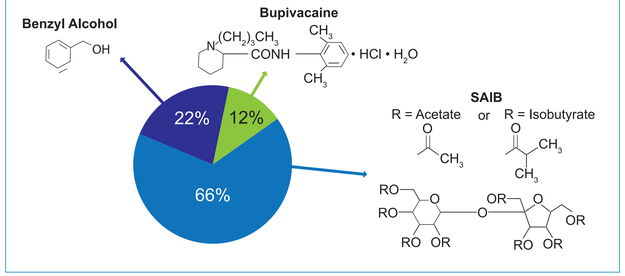
INTRODUCTION

- Local anesthetics, such as bupivacaine, an amide-type anesthetic that blocks the generation and conduction of nerve impulses, mitigate serious acute pain after surgery and limit the reliance on opioids; however, they provide only short periods of pain relief
- There is an unmet need for an extended-release formulation of bupivacaine that provides reliable postsurgical pain relief during the first 72 hours
- SABER-Bupivacaine was developed to meet this need and contains 132 mg bupivacaine base/mL (660 mg in a 5-mL dose)
- SABER-Bupivacaine is a sustained-release formulation of bupivacaine base (12%) in a controlled-release matrix composed of a fully esterified sugar derivative, sucrose acetate isobutyrate (SAIB), and benzyl alcohol, administered together as a solution[1] **(Figure 1)**

Figure 1. SABER-Bupivacaine formulation.



- SABER-Bupivacaine is easily administered through a single instillation directly into the surgical incision where the solvent rapidly diffuses and leaves an in situ depot
- This analysis was conducted to evaluate the pharmacokinetic profile of SABER®-Bupivacaine across multiple surgical models

METHODS

STUDY DESIGN AND TREATMENT

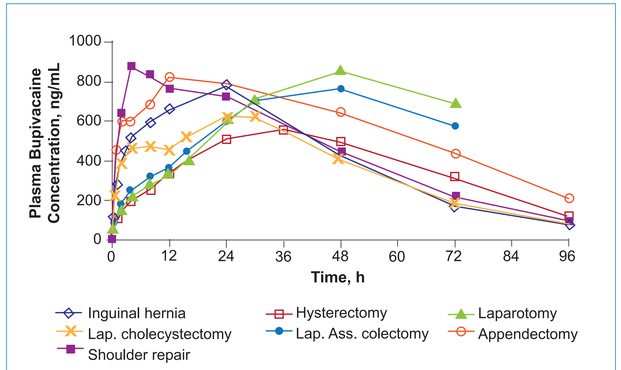
- Eleven clinical trials have evaluated the clinical pharmacokinetics of SABER-Bupivacaine
  - — Two trials in healthy subjects (subcutaneous administration)
  - — Nine trials in patient populations undergoing various surgical procedures (such as inguinal hernia repair, hysterectomy, laparotomy, laparoscopic cholecystectomy, laparoscopically assisted colectomy, appendectomy, and shoulder repair)
- In each clinical study, following baseline blood sample collection, additional PK samples were collected at specified time points until 72 to 96 hours after dosing with SABER-Bupivacaine
- These samples were analyzed for determination of bupivacaine concentration using a validated liquid chromatography/tandem mass spectrometry method

RESULTS

ABSORPTION/BIOAVAILABILITY

- Absorption of bupivacaine in all surgical models was rapid; measurable drug concentrations were observed at the first evaluated time points (0.5 or 1 hour), followed by a gradual increase in concentration in all evaluated surgical models, demonstrating lack of dose dumping with the formulation[1] **(Figure 2)**

Figure 2. Mean plot of bupivacaine concentration after administration of 5 mL SABER-Bupivacaine by surgery type.



- Across abdominal surgery types, the mean maximum plasma concentration (C_{max}) varied from 625 to 989 ng/mL, and time to maximum observed plasma concentration (T_{max}) ranged from 24 to 48 hours[1]
  - — Differences could be attributed to interpatient variability, surgery type, and variation in localized blood flow at the site of administration[1] **(Table 1)**
- In shoulder surgery, the mean maximum plasma concentration (C_{max}) was 731 ng/mL, and the time to maximum observed plasma concentration (T_{max}) was 8 hours

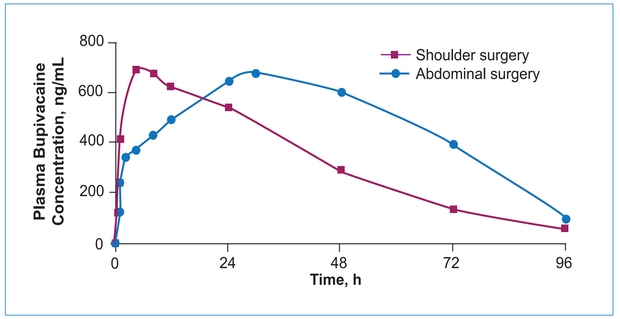
Table 1. Pharmacokinetic Parameters of Bupivacaine After Administration of 5 mL SABER-Bupivacaine Across Surgery Types

Parameter	Hernia Repair N = 19	Appendectomy N = 14	Hysterectomy N = 60	Laparotomy N = 30	LC N = 30	LAC N = 129	Shoulder Surgery N = 54
C_{max}, ng/mL[a]	762 ± 94	989 ± 151	625 ± 40	956 ± 89	752 ± 56	850 ± 42	731 ± 55
T_{max}, h	24	24	36	48	24	47	8
$AUC_{0\text{-last}}$, ng·h/mL[a]	39,886 ± 4385	61,016 ± 7261	35,230 ± 2440	41,942 ± 4445	30,997 ± 2315	39,602 ± 2117	28,601 ± 2713

LC, laparoscopic cholecystectomy; LAC, laparoscopically assisted colectomy; SEM, standard error of the mean.

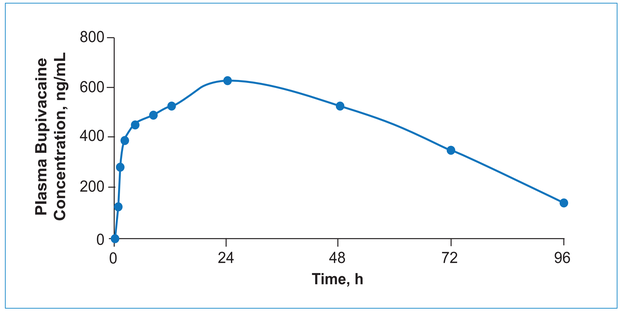
[a]Mean ± SEM.

Figure 3. Mean plasma bupivacaine profile: average time-matched plasma concentration across the various abdominal surgeries vs shoulder surgery.



- There is no evidence of dose dumping either in the abdominal surgery or the shoulder surgery cohorts following administration of SABER-Bupivacaine
- In the shoulder surgery cohort, a shorter T_{max} is observed as compared with the abdominal surgery cohorts, possibly due to the confinement of the administered drug in a smaller space, resulting in rapid systemic absorption
- Sustained delivery of bupivacaine is observed for prolonged duration in all surgical models

Figure 4. Mean plasma bupivacaine profile: average time-matched plasma bupivacaine concentration across all surgical models (abdominal and shoulder).

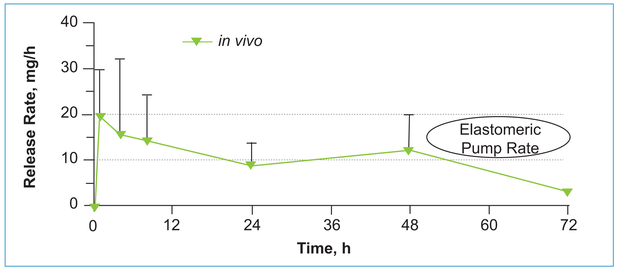


- Overall mean plasma concentrations are sustained between 400 to 600 ng/mL from 12 to 72 hours postoperatively following administration of SABER-Bupivacaine

Release Rate of Bupivacaine From SABER-Bupivacaine *in Vivo*

- The absorption rate or release rate of bupivacaine from the SABER-Bupivacaine depot was calculated from the plasma concentration-time profile using deconvolution analysis
- Deconvolution analysis of crossover data of healthy subjects showed that the *in vivo* release rate was 10 to 20 mg/h during the first 48 hours and then tapered gradually **(Figure 5)**
  - — Delivery was completed by 72 to 96 hours after drug administration
  - — Delivery of SABER-Bupivacaine was in the target range of the recommended delivery rate for the elastomeric pump, which has been found efficacious in a variety of surgical models

Figure 5. *In vivo* release rate of bupivacaine from SABER-Bupivacaine.



SAFETY

- There were no reported treatment-related instances of serious central nervous system or cardiac adverse events traditionally associated with bupivacaine toxicity[1]
- No treatment-related changes in heart rate, conduction, or repolarization or treatment-emergent ventricular arrhythmias were detected by Holter monitoring[1]

CONCLUSIONS

- This pharmacokinetic analysis demonstrates that SABER-Bupivacaine provides immediate and continuous 72-hour delivery of bupivacaine in a variety of surgical models from a variety of injection/instillation sites
  - — Complete delivery of the drug was observed with SABER-Bupivacaine
  - — Absorption of bupivacaine after SABER-Bupivacaine administration in all surgical models was rapid and demonstrated a lack of dose dumping
  - — Overall mean bupivacaine concentration was between 400 to 600 ng/mL for an extended duration from 12 to 72 hours
  - — Differences in local blood perfusion, type of tissue, and patient-to-patient variability can impact pharmacokinetics
- SABER-Bupivacaine administration was well tolerated

REFERENCE

1. Data on file. Cupertino, CA: DURECT Corporation.

Financial Disclosure

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http://myqr.co/xhDc

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