Pharmacokinetic Characteristics of SABER®-Bupivacaine in Humans Demonstrate Sustained Drug Delivery for up to 72 Hours in a Variety of Surgical Models

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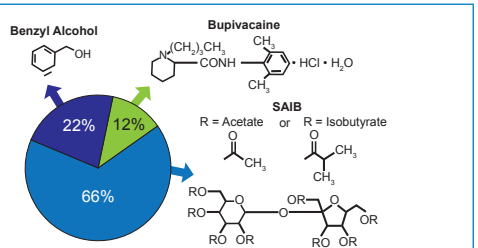
INTRODUCTION

- Bupivacaine is a locally acting, amide-type anesthetic that blocks the generation and conduction of nerve impulses through the inhibition of neuronal voltage-gated Na^+ channels
- To develop an extended-release formulation of bupivacaine that could provide prolonged postsurgery local analgesia up to 72 hours after single-dose administration, a formulation of SABER-Bupivacaine was developed containing 132 mg bupivacaine base/mL (660 mg in a 5-mL dose)[1]
- 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 instilled into the surgical incision before wound closure
  - After administration, the solvent rapidly diffuses, leaving a sustained-release matrix of bupivacaine and SAIB
- Clinical pharmacokinetics of SABER-Bupivacaine have been evaluated in healthy subjects and in target patient populations undergoing various surgical procedures[1]

METHODS

Study Design and Treatment

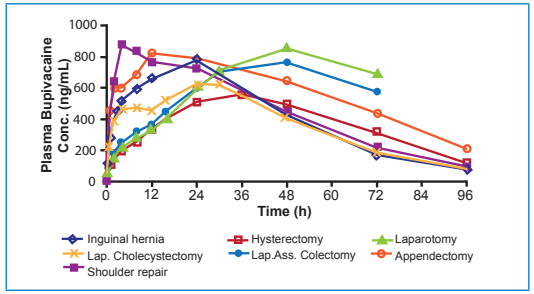
- Eleven clinical trials have evaluated the clinical pharmacokinetics of SABER-Bupivacaine
  - Two trials in healthy subjects (subcutaneous administration)
  - Nine trials in patient populations who underwent various surgical procedures (such as inguinal hernia repair, hysterectomy, laparotomy, laparoscopic cholecystectomy, laparoscopically assisted colectomy, appendectomy, and shoulder repair)

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**)

Table 1. Pharmacokinetic Parameters of Bupivacaine After Administration of 5 mL SABER-Bupivacaine in Abdominal Surgery

Parameter	Hernia Repair N = 19	Appendectomy N = 14	Hysterectomy N = 60	Laparotomy N = 30	LC N = 30	LAC N = 129
C_{max}, ng/mL[a]	762 ± 94.3	988.5 ± 150.8	625 ± 40	956 ± 88.5	752.1 ± 56	849.6 ± 42
T_{max}, h	23.9	24	36	48.1	24.3	46.6
$AUC_{0\text{-last}}$, ng·h/mL[a]	39,886 ± 4385	61,016 ± 7261	35,230 ± 2440	41,942 ± 4445	30,997 ± 2315	39,602 ± 2117

LC, laparoscopic cholecystectomy; LAC, laparoscopically assisted colectomy.
[a] Mean ± SEM.

Comparison of Pharmacokinetics After SABER-Bupivacaine and Standard Bupivacaine HCl Administration

- On a dose-adjusted basis, the cumulative exposure of bupivacaine was similar between SABER-Bupivacaine administration and bupivacaine HCl administration (mean $AUC_{0\text{-last}}$ between the 2 treatments was roughly proportional), suggesting comparable bioavailability[1]
  - Time to maximum observed plasma concentration (T_{max}) was significantly extended for SABER-Bupivacaine compared with bupivacaine HCl[1] (**Table 2**)

Table 2. Bupivacaine Plasma Pharmacokinetic Parameters

Parameter	5 mL SABER-Bupivacaine 660 mg	Bupivacaine HCl 150 mg
	N = 335	N = 38
C_{max}, ng/mL[a]	792.5 ± 23.8	313.7 ± 36.8
T_{max}, h[b]	30.1	1.2
$AUC_{0\text{-last}}$, ng·h/mL[a]	37,409.0 ± 1221.4	7172.8 ± 921.9

[a] Mean ± SEM. [b] Median.

Unbound (Free) Plasma Bupivacaine

- Given that free bupivacaine (particularly C_{max}) provides more relevant information regarding potential central nervous system and electrocardiography adverse events than total bupivacaine concentrations, unbound bupivacaine was measured in the pharmacokinetic samples from hysterectomy patients[1]
  - Mean free bupivacaine plasma concentrations closely paralleled the total bupivacaine concentration—approximately 5% to 6% for both SABER-Bupivacaine and bupivacaine HCl[1] (**Figure 3, Table 3**)
  - Delayed T_{max} for total bupivacaine and free bupivacaine was 36 hours with SABER-Bupivacaine and 1 hour with bupivacaine HCl[1] (**Table 3**)

Figure 3. Mean (SEM) free bupivacaine plasma concentrations.

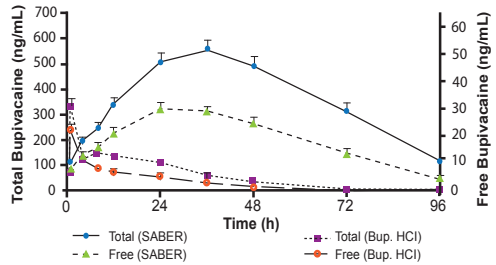


Table 3. Plasma Pharmacokinetic Parameters of Total and Free Bupivacaine (Study BU-001-IM)[1]

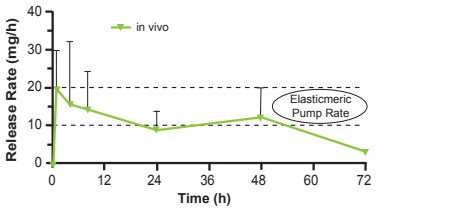
Parameter	5 mL SABER-Bupivacaine 660 mg		Bupivacaine HCl 100 mg	
	Total N = 59	Free N = 59	Total N = 27	Free N = 27
C_{max}, ng/mL[a]	625 ± 40	39 ± 3	342 ± 27	23 ± 2
T_{max}, h[b]	36	36	1.0	1.0
AUC_t, ng·h/mL[a]	35,230 ± 2440	1824 ± 125	5650 ± 450	286 ± 22

[a] Mean ± SEM. [b] Median.

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 4**)
  - 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[2]

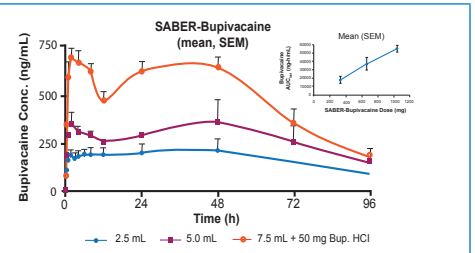
Figure 4. In vivo release rate of bupivacaine from SABER-Bupivacaine.



Dose Proportionality of SABER-Bupivacaine

- After the administration of SABER-Bupivacaine, the systemic concentration of bupivacaine increased proportionally to the dose administered within the range 2.5 to 7.5 mL (330-990 mg)[1] (**Figure 5**)

Figure 5. Dose proportionality of SABER-Bupivacaine in patients undergoing open inguinal hernia repair.



SAFETY

- No treatment-related instances were reported 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 showed that SABER-Bupivacaine provides 72 hours of sustained delivery of bupivacaine in a variety of surgical models, from a variety of injection/instillation sites, in a dose-linear fashion
  - Bioavailability was 100%
  - Absorption of bupivacaine after SABER-Bupivacaine administration in all surgical models was rapid and demonstrated a lack of dose dumping
  - Pharmacokinetics of SABER-Bupivacaine were dose linear from 2.5 to 7.5 mL
  - T_{max} was significantly prolonged for SABER-Bupivacaine compared with bupivacaine HCl
  - Differences in local blood perfusion and type of tissue and patient-to-patient variability can impact pharmacokinetics
- SABER-Bupivacaine administration was well tolerated

REFERENCES

1. Data on file. Cupertino, CA: DURECT Corporation.
2. Liu SS et al. *J Am Coll Surg.* 2006;203:914-932.

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