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A SINGLE ADMINISTRATION OF DEPOBUPIVACAINE™ INTRAOPERATIVELY RESULTS IN PROLONGED DETECTABLE PLASMA BUPIVACAINE AND ANALGESIA IN PATIENTS UNDERGOING INGUINAL HERNIA REPAIR

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ABSTRACT

Background: DepoBupivacaine (DB) is a controlled-release formulation of bupivacaine contained within multivesicular liposomal DepoFoam®. DB was designed to provide 3 days of analgesia after a single wound infiltration in surgical patients.

Objective: To evaluate the efficacy, safety, and pharmacokinetics (PK) of a single administration of DB compared with bupivacaine HCl (Bup) in patients undergoing open inguinal hernia repair.

Methods: We compared 4 doses of DB with commercial Bup in a randomized, double-blind, sequential-cohort, dose-ranging study. During surgery, 40 mL of DB or Bup was infiltrated into the tissue surrounding the wound. Rescue medication consisted of parenteral opiate followed by oral opioid. The doses evaluated were DB 175, 225, 300, and 350 mg and Bup 100 mg. After surgery, we assessed pain at rest and with activity (cough) within a calendar day; time to first opioid rescue; total opioid rescue; and fraction of subjects requiring opioid rescue.

Results: DB administration led to prolonged plasma concentrations of bupivacaine (>100 ng/mL through 72 h post administration) compared with Bup (100 ng/mL at 24 h), although C_{max} was similar to that of Bup, even at the highest DB doses studied.

Compared with Bup, DB significantly reduced pain with activity 8–24 h after administration of all doses studied. Pain scores in all groups were low beyond 24 h.

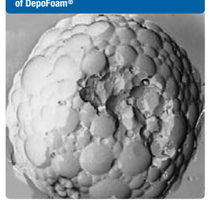
DB showed trends of decrease in the fraction of subjects using opioid, increase in the time to first opioid rescue, and decrease in total opioid consumption compared with Bup; none of these findings were statistically significant. No serious adverse events (SAEs) were attributable to DB. Wound healing was normal.

Conclusions: A single administration of DB intraoperatively resulted in sustained plasma bupivacaine concentration (>100 ng/mL) in subjects undergoing inguinal hernia repair. Pain with activity was significantly lower in subjects who received DB compared with those who received Bup in the more painful, first 8–24 h following surgery. Thereafter, resolution of wound pain in all groups made detection of differences between groups difficult. Although this dose-finding and PK study was not powered to detect differences, there was a non-significant trend to lower opioid rescue in all DB groups compared with the Bup group. Wound healing was normal, and no SAEs were attributable to DB.

INTRODUCTION

- Inadequately controlled postoperative pain remains one of the greatest challenges in the management of surgical patients.
- Bupivacaine is a short-acting local anesthetic widely used in perioperative and postsurgical settings.[1] Bupivacaine has been shown to reduce postoperative pain and decrease morphine consumption but is limited by a duration of action of only a number of hours when administered by wound infiltration.[2]
- DepoBupivacaine, also known as EXPAREL™ (DB; bupivacaine extended-release liposome injection), uses multivesicular DepoFoam® technology to release bupivacaine over several days (Figure 1).

Figure 1. Scanning Electron Micrograph of DepoFoam®



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- Opioids are used extensively for the relief of postoperative pain, but may be associated with a wide range of complications, including nausea, vomiting, dysphoria, pruritus, and respiratory depression.[3,4,5]
- Nonsteroidal anti-inflammatory drugs (NSAIDs) are also effective for management of postoperative pain and may decrease opioid use.[4,6] However, these drugs may be associated with increased gastrointestinal, renal, and cardiovascular risk in some patients.[7]
- Multimodal analgesia, which relies on the additive and synergistic effects of different analgesics, helps to achieve appropriate pain management and decrease the use and the associated adverse events (AEs) of opioids.[8]
- DB was designed to provide 72 hours of analgesia after a single local administration in surgical patients.
- This phase 2 dose-ranging study in patients undergoing open inguinal hernia repair evaluated pharmacokinetics and safety at the doses tested; efficacy data was also assessed.

METHODS

Study Design

- Phase 2, multicenter, randomized, double-blind, dose-escalating/de-escalating study to evaluate the safety, efficacy, and pharmacokinetics of a single dose of DB in the management of postoperative pain in subjects undergoing inguinal hernia repair.

Subjects

- Males ≥18 years of age
- Scheduled to undergo unilateral inguinal hernia repair under general anesthesia, using an open, tension-free procedure
- Classified as American Society of Anesthesiology (ASA) Physical Class 1 or 2
- Provided written informed consent, and were able and willing to comply with all study visits and procedures

Treatment and Cohorts

- DB or Bup was injected into the surgical wound in a 40 mL volume by infiltration immediately before closure.
- Four subject cohorts:
  - Cohort 1: 25 subjects (12 DB 175 mg; 13 Bup 100 mg)
  - Cohort 2: 16 subjects (12 DB 225 mg; 4 Bup 100 mg)
  - Cohort 3: 16 subjects (12 DB 300 mg; 4 Bup 100 mg)
  - Cohort 4: 19 subjects (14 DB 350 mg; 5 Bup 100 mg)

Assessments

- Pharmacokinetics: plasma samples were obtained at baseline and for up to 96 hours posttreatment and standard pharmacokinetic parameters (maximum plasma concentration [C_{max}], area under the curve [AUC], time to maximum plasma concentration [t_{max}], and apparent terminal elimination half-life [$t_{1/2}$]) were determined.
- Efficacy
  - Time to first use and number of subjects taking no supplemental pain medication (opioid or nonopioid)
  - Total use of supplemental opioid medication
  - Pain intensity at rest and with activity over 96 hours
  - Subject rating of pain control
- Safety
  - AEs
  - Serious AEs (SAEs)
  - Wound healing
  - Application site reaction
  - Clinical laboratory values
  - Electrocardiograms (ECGs)

RESULTS

Subjects

- A total of 76 subjects were enrolled and all completed the study. Demographic characteristics are summarized in Table 1.

Table 1. Subject Demographic Characteristics

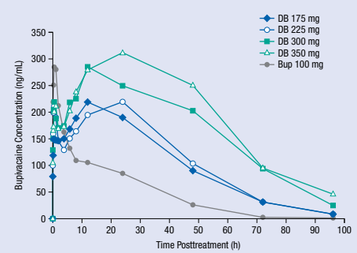
Characteristic	DB 175 mg n=12	DB 225 mg n=12	DB 300 mg n=12	DB 350 mg n=14	DB All Doses n=50	Bup 100 mg n=26
Age, y; mean (SD)	62.9 (15.7)	48.0 (20.4)	55.2 (12.5)	54.6 (13.0)	55.1 (16.0)	51.3 (12.6)
Gender, n (%)						
Male	12 (100)	12 (100)	12 (100)	14 (100)	50 (100)	26 (100)
Female	0	0	0	0	0	0
Ethnic Group, n (%)						
White	12 (100)	11 (91.7)	12 (100)	12 (85.8)	47 (94.0)	24 (92.3)
Black	0	0	0	0	0	1 (3.8)
Asian/ Pacific Islander	0	1 (8.3)	0	1 (7.1)	2 (4.0)	1 (3.8)
Other	0	0	0	1 (7.1)	1 (2.0)	0
Weight, kg; mean (SD)	82.0 (10.4)	72.8 (9.0)	81.4 (10.8)	76.7 (9.8)	78.2 (10.4)	84.4 (14.8)
Height, cm; mean (SD)	177.3 (7.0)	172.6 (7.9)	177.1 (9.0)	174.7 (8.9)	175.4 (8.2)	178.6 (8.4)

Abbreviations: Bup=bupivacaine HCl; DB=DepoBupivacaine.

Pharmacokinetics

- A graph of bupivacaine concentration over time is shown in Figure 2.

Figure 2. Bupivacaine Concentration Over Time



Abbreviations: Bup=bupivacaine HCl; DB=DepoBupivacaine.

- Pharmacokinetic parameters for bupivacaine after administration of DB are summarized in Table 2.
- There was a dose-proportional increase in plasma bupivacaine concentrations with increasing DB dose, but both t_{max} and $t_{1/2}$ were dose independent.
- The $t_{1/2}$ for DB was approximately double that of Bup.

Table 2. Pharmacokinetic Parameters for Bupivacaine After Administration of DB and Bup

Pharmacokinetic Parameter	DB 175 mg n=12	DB 225 mg n=12	DB 300 mg n=12	DB 350 mg n=14	Bup 100 mg n=26
C_{max} (ng/mL)*	241.4 (88.6)	303.3 (83.8)	365.2 (129.8)	414.8 (121.7)	336.4 (155.6)
t_{max} (h)†	12.0	10.1	12.1	12.1	0.6
$AUC_{0\text{-}tlast}$ (ng•h/mL)*	9250.8 (4068.4)	9958.2 (4195.5)	16027.6 (5455.1)	18127.0 (6931.1)	4371.5 (1560.1)
$t_{1/2}$ (h)*	15.9 (6.7)	14.1 (5.1)	14.6 (4.6)	18.9 (6.2)	8.5 (2.9)

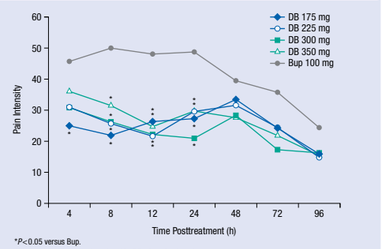
*Mean (SD); †median.

Abbreviations: $AUC_{0\text{-}tlast}$=area under the curve from time to t hours after drug administration where tlast is the time the last plasma sample was collected; Bup=bupivacaine HCl; C_{max}=maximum plasma concentration; DB=DepoBupivacaine; $t_{1/2}$=apparent terminal elimination half-life; t_{max}=time to C_{max}.

Efficacy

- Pain intensity with activity was lower with DB versus Bup and these differences were statistically significant for all DB doses at 8–24 hours after dosing (Figure 3).

Figure 3. Pain Intensity With Activity

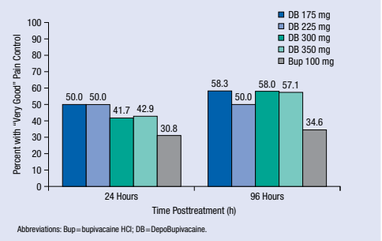


*$P<0.05$ versus Bup.

Abbreviations: Bup=bupivacaine HCl; DB=DepoBupivacaine.

- Subject ratings of pain control were generally better with DB versus Bup (Figure 4), although none of these differences achieved statistical significance.

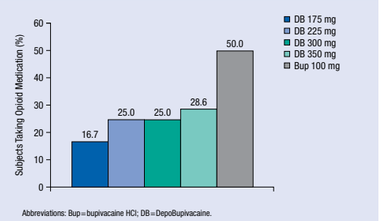
Figure 4. Subject Ratings of Pain Control at 24 and 96 Hours



Abbreviations: Bup=bupivacaine HCl; DB=DepoBupivacaine.

- The percentage of DB-treatment subjects who required supplemental opioid pain medication was generally lower than the percentage who received Bup (Figure 5).

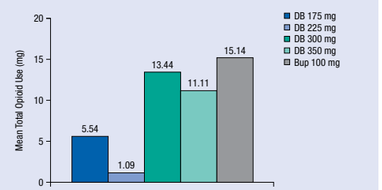
Figure 5. Percentage of Subjects Taking Supplemental Opioid Pain Medication



Abbreviations: Bup=bupivacaine HCl; DB=DepoBupivacaine.

- Total use of opioid pain medication was lower with all DB doses than with Bup, although these differences were not statistically significant (Figure 6).

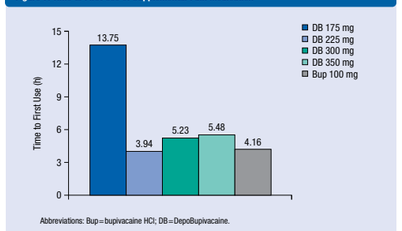
Figure 6. Total Opioid Use



Abbreviations: Bup=bupivacaine HCl; DB=DepoBupivacaine.

- There were no statistically significant differences among groups with respect to time to first use of supplemental pain medication (Figure 7).

Figure 7. Time to First Use of Supplemental Pain Medication



Abbreviations: Bup=bupivacaine HCl; DB=DepoBupivacaine.

Safety

- All AEs judged as being related to study medication are summarized in Table 3. There were no discontinuations due to AEs.
- Nearly all AEs related to DB were mild or moderate in severity.
- Two subjects who received DB experienced SAEs (hematoma in 1, and both urinary retention and benign prostatic hyperplasia in another, both nonfatal). None were considered related to the study drug. No patients in the Bup group experienced SAEs.

Table 3. Adverse Events Considered to Be Related to Study Medication

AE, n (%)	DB 175 mg n=12	DB 225 mg n=12	DB 300 mg n=12	DB 350 mg n=14	DB Combined n=50	Bup 100 mg n=26
Any event	3 (25.0)	1 (8.3)	1 (8.3)	2 (14.3)	7 (14.0)	3 (11.5)
Constipation	1 (8.3)	0	0	0	1 (2.0)	0
Dry mouth	1 (8.3)	0	0	0	1 (2.0)	0
Nausea	1 (8.3)	0	0	0	1 (2.0)	0
Application site edema	1 (8.3)	0	0	0	1 (2.0)	0
Pyrexia	0	1 (8.3)	0	0	1 (2.0)	0
Burning sensation	0	0	0	1 (7.1)	1 (2.0)	0
Headache	1 (8.3)	0	0	0	1 (2.0)	0
Hypoesthesia	0	0	1 (8.3)	0	1 (2.0)	0
Syncope vasovagal	0	0	0	1 (7.1)	1 (2.0)	0
Urinary retention	0	0	0	0	0	1 (3.8)
Hypertension	1 (8.3)	0	0	0	1 (2.0)	0
Hypotension	0	0	0	0	0	1 (3.8)

Abbreviations: AE=adverse event; Bup=bupivacaine HCl; DB=DepoBupivacaine.

- Overall, 20% of subjects treated with DB and 19.2% of those who received Bup had local reactions. There were no significant differences among groups for wound healing.
- There were no wound infections in the DB study groups; 2 wound infections occurred in the Bup group.
- Shifts in laboratory parameters were minimal, expected in this population, and similar across groups.
- Vital signs were similar among groups at baseline and at all posttreatment time points evaluated.
- Three subjects had abnormal ECGs both before and after study drug administration.

CONCLUSIONS

- A single intraoperative administration of DB, a controlled-release formulation of bupivacaine contained within multivesicular liposomal DepoFoam®, resulted in pain with activity scores that were significantly lower than those for subjects who received Bup in the first 8–24 hours following surgery.
- There was a trend toward lower opioid use in all DB groups compared with the Bup group.
- A single administration of DB intraoperatively resulted in sustained plasma bupivacaine concentrations (>100 ng/mL) in subjects undergoing inguinal hernia repair.
- DB was safe and well tolerated.
- Wound healing was normal in subjects who received DB.

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