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A SINGLE ADMINISTRATION OF DEPOBUPIVACAINE INTRAOPERATIVELY PROVIDES ANALGESIA AND REDUCTION IN USE OF RESCUE OPIATES COMPARED WITH BUPIVACAINE HCL IN PATIENTS UNDERGOING TOTAL KNEE ARTHROPLASTY

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ABSTRACT

Background: DepoBupivacaine (DB) is a controlled-release formulation of bupivacaine contained within multivesicular liposomal [DepoFoam®] particles that release bupivacaine over several days, prospectively designed to provide three days of analgesia following a single administration to patients undergoing surgery.

Objectives: In this study, we sought to evaluate the efficacy, safety, and comparative systemic bioavailability of a single administration of DB compared with bupivacaine HCl with epinephrine (Bup/epi) in patients undergoing unilateral total knee arthroplasty (TKA).

Methods: We compared three doses of DB to commercial Bup/epi in the first two cohorts of an ongoing, randomized, double-blind, parallel-group, dose-ranging study. During surgery, 60 mL of DB or Bup/epi was infiltrated into the tissue surrounding the wound. Ketorolac 30 mg was administered to all subjects at the end of surgery. Subjects also received acetaminophen 1000 mg orally three times a day for at least 24 h preoperatively and for 96 h postoperatively. Rescue medication consisted of parenteral opioid followed by oral oxycodone. In the first cohort, 15 subjects were randomized into three groups: Bup/epi 150 mg, or DB 150 mg, or DB 300 mg. Following review by an unblinded safety and efficacy committee, an additional 10 subjects were randomized into each of the three groups, and a fourth group of 25 subjects received DB 450 mg. After surgery, the following decision-making top-line results were assessed by an unblinded safety and efficacy committee: safety, pain, and total opiate rescue.

Results: DB administration was associated with wound-healing scores equivalent to Bup/epi over the first five days following surgery and was not associated with clinical signs of cardiac or CNS adverse events. DB 150 mg was ineffective in reducing pain compared with an equivalent dose of Bup/epi. DB at 450 mg statistically significantly reduced pain ($P<0.05$) when assessed at the end of general anesthesia (mean 7.0, 6.2, and 5.0 for DB at 150, 300, and 450 mg, respectively, compared with 7.0 Bup/epi). DB 300 mg and 450 mg statistically significantly reduced pain at the time of first rescue opioid use (mean 7.7, 6.4, and 6.1 for DB at 150, 300, and 450 mg, respectively, compared with Bup/epi, 7.8). DB 450 mg reduced opioid rescue (cumulative mg morphine equivalents) throughout the observation period:

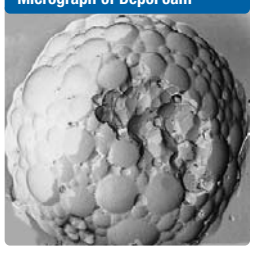
Treatment	Mean Cumulative Morphine Equivalents				
	N	Day 2	Day 3	Day 4	Day 5
Bup/epi	27	39	58	73	84
DB 150 mg	25	57	75	88	99
DB 300 mg	26	43	58	67	74
DB 450 mg	25	34	44	53	60

Conclusion: A single administration of DB intraoperatively was demonstrated to be safe at doses up to 450 mg and dose-dependently achieved analgesia and reduction in opioid rescue in subjects.

INTRODUCTION

- Bupivacaine extended-release liposome injection [DepoBupivacaine; DB; also known as EXPAREL™] uses multivesicular liposomal [DepoFoam®] technology to release bupivacaine over several days (Figure 1).
- Bupivacaine with epinephrine (Bup/epi) is a short-acting local anesthetic widely used in perioperative setting and for postoperative analgesia and has been shown to decrease morphine consumption, but is limited by a duration of action of only a few hours.[1,2]
- Opioids are used extensively for the relief of postoperative pain, but may be associated with a wide range of complications including nausea, vomiting, pruritus, and respiratory depression.[3,4]
- Nonsteroidal anti-inflammatory drugs (NSAIDs) are also effective for management of postoperative pain and may decrease opioid use.[4,5]
- DB was designed to provide prolonged analgesia for 72 hours after a single infiltration in surgical patients.
- This study evaluated the safety and efficacy of DB for prolonged postoperative analgesia in subjects undergoing total knee arthroplasty (TKA).

Figure 1. Scanning Electron Micrograph of DepoFoam®



METHODS

Study Design

- Multicenter, randomized, double-blind, parallel-group, active-control, dose-ranging study to evaluate the efficacy of a single administration of DB via local infiltration for prolonged postoperative analgesia in subjects undergoing TKA.

Subjects

- Male or female, ≥18 and ≤75 years of age
- Scheduled to undergo primary unilateral TKA under general anesthesia
- Classified as American Society of Anesthesiology (ASA) Physical Class 1–3
- Provided written informed consent, and were able and willing to comply with all study visits and procedures

Procedures

- During surgery, 60 mL of DB or Bup/epi was infiltrated into the tissue surrounding the wound:
  - In the first cohort, 15 subjects were randomized into three groups:
    - Bup/epi 150 mg
    - DB 150 mg
    - DB 300 mg
  - Following review by an unblinded safety and efficacy committee, an additional 10 subjects were randomized into each of the above three groups, and a fourth group of 25 subjects received DB 450 mg.
  - Ketorolac 30 mg was administered to all subjects at the end of surgery and all subjects also received acetaminophen 1000 mg orally three times a day for at least 24 hours preoperatively and for 96 hours postoperatively.
  - Rescue medication consisted of parenteral opioid followed by oral oxycodone.

Assessments

- Pharmacokinetic (PK) parameters
- Pain intensity at rest
- Pain intensity with activity
- Total opioid consumption
- Safety parameters included adverse events (AEs), serious AEs, plasma laboratory values, electrocardiograms (ECGs), and wound-healing assessment

RESULTS

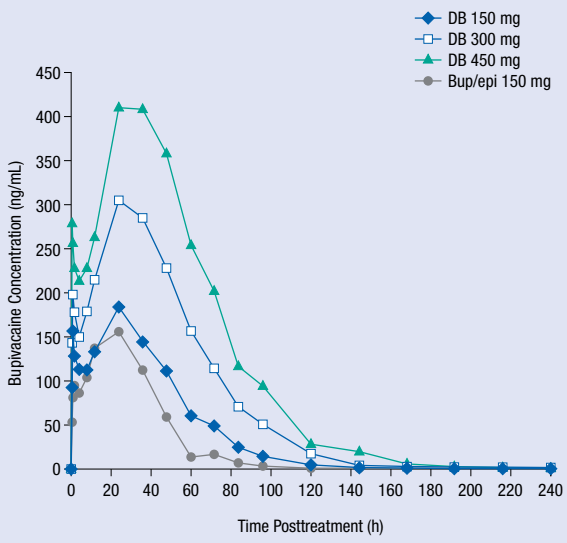
Subjects

- A total of 103 subjects were included in the trial.

Pharmacokinetics

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

Figure 2. Bupivacaine Concentration Over Time



Abbreviations: Bup/epi=bupivacaine HCl with epinephrine; DB=DepoBupivacaine.

- A summary of PK parameters is shown in Table 1.

Table 1. Pharmacokinetic Parameters for Bupivacaine After Administration of DB and Bup/epi

Pharmacokinetic Parameter	DB			Bup/epi 150 mg
	150 mg	300 mg	450 mg	
C_{max} (ng/mL)*	217 (86.3)	351 (123)	500 (173)	170 (102)
t_{max} (h)†	24	24	24	24
AUC_{∞} (ng•h/mL)*	8337 (3378)	20103 (9332)	27630 (12939)	6622 (4838)
$t_{1/2}$ (h)*	12.2 (2.65)	17.9 (6.58)	18.8 (5.09)	10.9 (2.41)

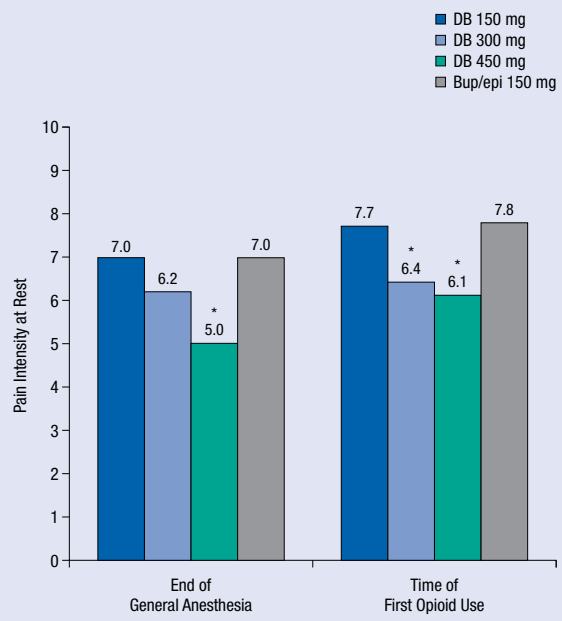
*Mean ± (SD)
†median

Abbreviations:
AUC_{∞} = area under the curve from time 0 to infinity; Bup/epi=bupivacaine HCl with epinephrine;
C_{max} = maximum plasma concentration; DB=DepoBupivacaine;
$t_{1/2}$ = terminal elimination half-life; t_{max} = time to reach C_{max}.

Pain Reduction

- DB 450 mg statistically significantly reduced pain versus Bup/epi 150 mg ($P<0.05$) when assessed at the end of general anesthesia and at the time of first opioid use (Figure 3).

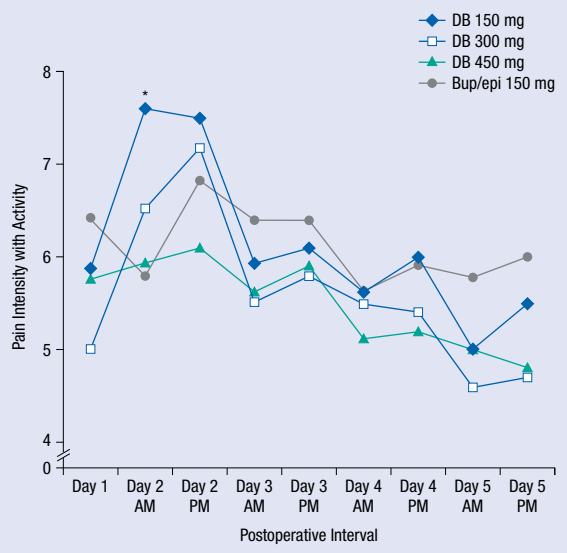
Figure 3. Pain Intensity at the End of General Anesthesia and Time of First Opioid Use



*$P<0.05$ versus Bup/epi 150 mg.
Abbreviations: Bup/epi=bupivacaine HCl with epinephrine; DB=DepoBupivacaine.

- Pain intensity at rest was generally lower with DB 450 mg than with Bu/epi 150 mg at all postoperative intervals evaluated.
- Pain intensity with activity was generally lower with DB 450 mg than with Bup/epi 150 mg at all postoperative intervals evaluated (Figure 4).

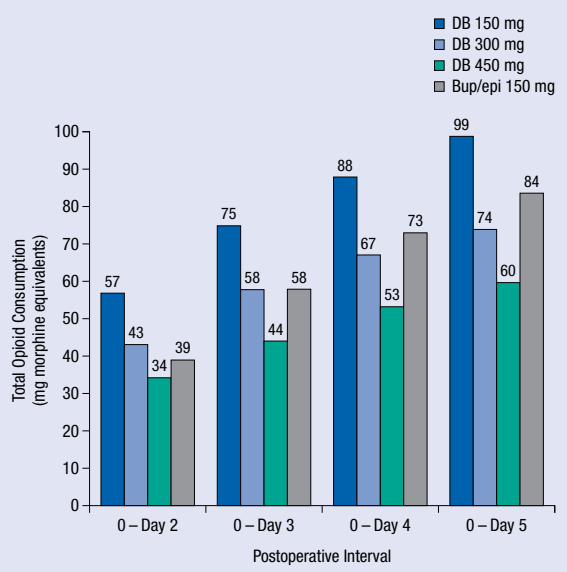
Figure 4. Pain Intensity With Activity



*$P<0.05$ versus Bup/epi 150 mg.
Abbreviations: Bup/epi=bupivacaine HCl with epinephrine; DB=DepoBupivacaine.

- DB 450 mg significantly reduced opioid rescue medication use (cumulative mg morphine equivalents) versus Bup/epi 150 mg throughout the observation period (Figure 5).
- In addition, 8% of subjects in the DB 450-mg group avoided opioid use versus 0% for all other treatment groups.
- The occurrence of postoperative nausea and vomiting (PONV) in the Bup/epi group was 70% compared with 40% in the 450-mg DB group.

Figure 5. Use of Opioid Rescue Medication



Abbreviations: Bup/epi=bupivacaine HCl with epinephrine; DB=DepoBupivacaine.

Safety

- DB administration was associated with wound-healing scores equivalent to Bup/epi over the first 5 days following surgery.
- DB was not associated with any infections.
- DB was not associated with clinical signs of cardiac or central nervous system (CNS) AEs.

CONCLUSIONS

- A single administration of DB 450 mg intraoperatively statistically significantly reduced pain in patients undergoing unilateral TKA.
- DB effectively controlled moderate to severe pain over 96 hours, with better relief achieved with higher doses.
- A dose-dependent effect was noted in both analgesia and reduction in opioid rescue.
- DB 450 mg significantly decreased opioid use in subjects undergoing TKA and was also associated with a lower rate of PONV.
- There were no differences in the safety profile of DB compared with Bup/epi.
- No cardiac or CNS toxicity was seen.
- No interference with wound healing or increase in infection rates was noted.
- DB may provide a safe and effective longer-acting opioid-sparing alternative to currently available local analgesics.

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