198

BUPIVACAINE EXTENDED RELEASE LIPOSOME INJECTION (DEPOFOAM® BUPIVACAINE) VS. BUPIVACAINE HCL: A META-ANALYSIS OF MULTIMODAL TRIALS OF DOSES UP TO AND INCLUDING 300 MG

Joseph Dasta[1]; Sonia Ramamoorthy[2]; Gary Patou[3]; Raymond Sinatra[4]

[1]The University of Texas College of Pharmacy, Austin, TX; [2]University of California at San Diego, CA; [3]Pacira Pharmaceuticals, Parsippany, NJ; [4]Yale-New Haven Hospital, New Haven, CT

ABSTRACT

Purpose: DepoFoam bupivacaine (DB) is an investigational formulation of bupivacaine HCl which allows for release over 72 hours. Studies comparing the use of DB at doses up to 300 mg vs bupivacaine HCl at doses up to 150 mg were evaluated for several key endpoints.

Methods: Five active-control, double-blind, randomized, parallel-group trials in >700 patients receiving doses up to and including 300 mg were reviewed. All studies had a multimodal setting (scheduled NSAID and/or acetaminophen plus rescue opioids as needed). Surgical models included hemorrhoidectomy, total knee arthroplasty, and herniorrhapy. Endpoints included the area under the curve (AUC) analysis through 72 hours of the numeric rating scale scores for pain, the median time to first opioid (TTFO), the total amount of morphine equivalents consumed over 72 hours (adjusted geometric mean), and the mean number of opioid-related adverse events (ORAEs) per patient.

Results: Results demonstrated that DB was statistically superior to bupivacaine HCl ($P<0.0001$) for each of the endpoints studied.

	DB (75–300 mg)	Bupivacaine HCl (75–150 mg)	*P* Value
$AUC_{0\text{-}72\ hr}$	315	427	$P<0.0001$
Median TTFO	9.9 hours	2.7 hours	$P<0.0001$
Morphine	7.9 mg	15.8 mg	$P<0.0001$
ORAEs per pt	0.25	0.46	$P<0.0001$

The adverse event profiles of the compounds were comparable; the most common treatment-emergent adverse events reported across the entirety of the DB clinical program were nausea, constipation, and vomiting.

Conclusions: DB appears to offer clinically meaningful advantages over bupivacaine HCl in multimodal trials for postsurgical analgesia.

INTRODUCTION

- Bupivacaine, a local anesthetic/analgesic, has been shown to reduce postsurgical pain when used via infiltration in the surgical setting, but is limited to a duration of 7 hours or less[1]

Figure 1. DepoFoam Multivesicular Liposome Technology

- Opioids are a cornerstone of pain therapy to maintain pain relief following the loss of bupivacaine efficacy
- Opioids are associated with a variety of unwanted and potentially severe adverse events ranging from nausea and vomiting to cognitive impairment and respiratory depression
- These opioid-related adverse events (ORAEs) are costly to treat and can result in a longer hospital stay, further increasing healthcare costs[2]
- Multimodal therapy has evolved, in part, to decrease the adverse events related to opioid therapy
- DepoFoam bupivacaine (DB) uses multivesicular DepoFoam® technology to release bupivacaine for several days, allowing for up to 72 hours of pain control and a reduced reliance on opioids, thus reducing the risk of ORAEs
- DepoFoam is an established product delivery technology that encapsulates drugs without altering their molecular structure and then releases them over a desired period of time (**Figure 1**); the technology is currently used in two commercially available products in the US and ex-US: DepoCyt(e)® and DepoDur®

CLINICAL RELEVANCE

- This pooled analysis examined five trials designed to replicate real-world postsurgical pain management conditions by comparing DB to bupivacaine HCl in a multimodal setting (**Table 1**); numerous Phase 2 and 3 placebo-controlled trials have also been published

Table 1. Multimodal Trials of DepoFoam Bupivacaine Versus Bupivacaine HCl

Surgical Model	Type of Procedure, National Clinical Trial Number*	DB Doses, mg	Bupivacaine HCl Dose, mg
Soft tissue	Hemorrhoidectomy NCT00744848	300	100
Soft tissue	Hemorrhoidectomy NCT00529126	75, 225, 300	75
Soft tissue	Herniorrhaphy NCT00485433	105, 180	105
Soft tissue	Herniorrhaphy NCT01203644	175, 225, 300	100
Orthopedic	Total knee arthroplasty NCT00485693	150, 300	150

DB = DepoFoam bupivacaine.
*All National Clinical Trial (NCT) numbers available at www.clinicaltrials.gov.

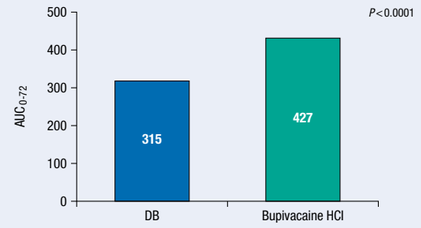
METHODS

- A total of 313 patients received a single administration of DB at doses ranging from 75 to 300 mg at the conclusion of either a total knee arthroplasty, hemorrhoidectomy, or herniorrhaphy. These patients were compared to 409 similar patients who received 75 to 150 mg of bupivacaine HCl
- Patients received scheduled oral acetaminophen (e.g., 1000 mg po TID) and/or non-steroidal anti-inflammatory drugs (e.g., ketorolac 30 mg IV at the end of the procedure), plus rescue opioids as needed
- The following endpoints were investigated
  - Area under the curve (AUC), a measure of pain over time, through 72 hours of numeric rating scale scores for pain
  - Median time to first opioid use (TTFO)
  - Morphine-equivalent opioid consumption over 72 hours (adjusted geometric mean)
  - Mean number of ORAEs per patient during the study period

RESULTS

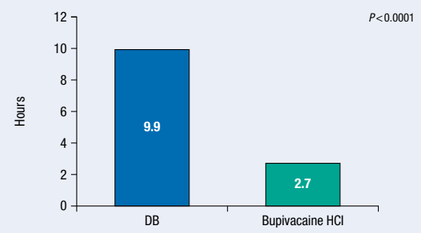
- Across all studies, patients receiving DB experienced less pain over 72 hours compared to patients receiving bupivacaine HCl, as evidenced by an AUC analysis ($AUC_{0\text{-}72}$ 315 vs 427; $P<0.0001$) (**Figure 2**)
- Median TTFO increased by more than 3.5 times for patients receiving DB compared to patients receiving bupivacaine HCl (9.9 hours vs 2.7 hours; $P<0.0001$) (**Figure 3**)
- Patients receiving DB required 50% less opioids than patients receiving bupivacaine HCl (7.9 mg vs 15.8 mg; $P<0.0001$) (**Figure 4**)
- The average number of ORAEs per patient was nearly 2 times higher among patients receiving bupivacaine HCl compared to DB (0.46 vs 0.25; $P<0.0001$) (**Figure 5**)
- Nearly twice as many patients receiving bupivacaine HCl had one or more ORAEs compared to those receiving DB (45.1% vs 24.6%; $P<0.0001$) (**Figure 6**)
- All findings were statistically significant

Figure 2. Area Under the Curve Pain Analysis



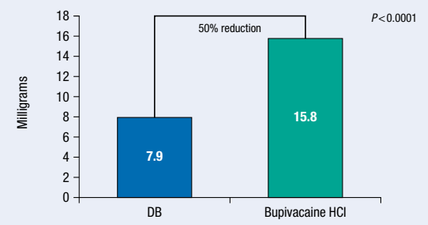
$AUC_{0\text{-}72}$ = area under the curve up to 72 hours; DB = DepoFoam bupivacaine.

Figure 3. Median Time to First Opioid Use



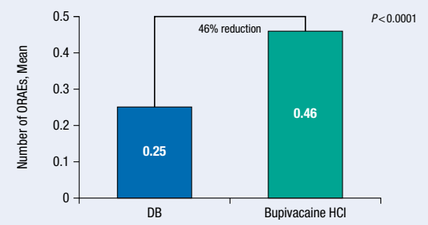
DB = DepoFoam bupivacaine.

Figure 4. Morphine-Equivalent Opioid Use



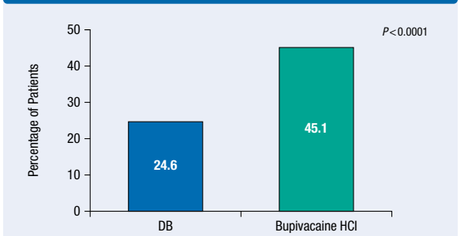
DB = DepoFoam bupivacaine.

Figure 5. Mean Number of ORAEs Per Patient



DB = DepoFoam bupivacaine; ORAEs = opioid-related adverse events.

Figure 6. Percentage of Patients Reporting ≥1 ORAE



DB = DepoFoam bupivacaine; ORAE = opioid-related adverse event.

CONCLUSIONS OF POOLED ANALYSIS

Impact on Pain

- DB provides statistically significantly better pain relief over 72 hours than bupivacaine HCl across a wide range of surgical procedures studied
- At doses up to and including 300 mg, DB appears to offer clinically significant advantages over bupivacaine HCl in the multimodal setting by increasing the analgesia obtained from local administration into the surgical wound, thus delaying the TTFO

Impact on Opioid Use

- Across all surgical models, DB at doses of 300 mg or less administered via wound infiltration resulted in a statistically significant reduction in opioid use and longer TTFO compared with bupivacaine HCl in this multimodal setting:
  - Median TTFO increased by more than three-and-a-half times
  - Half as much opioid burden
- During the 72-hour study period, patients receiving DB experienced statistically significantly less ORAEs compared with patients receiving bupivacaine HCl
- Patients who experience no or few ORAEs are likely to benefit from a more comfortable recovery experience and higher satisfaction[2,3]

Health Economic Implications

- As opioids remain imperative to the art of pain management, the incidence of ORAEs ranges from 20% to 48%[4]; therefore, reduction of their use remains a health economic goal
- ORAEs following surgery have been shown to increase the median hospitalization cost by 7.4% and the median length of stay by 10.3%, again supporting the health economic benefits of reducing opioid usage and subsequent ORAEs[2]
- In this pooled analysis of the use of DB at doses of 300 mg or less in a multimodal setting, patients receiving DB compared to bupivacaine HCl experienced less pain, a reduction in opioid consumption, and a decrease in ORAEs, all of which have beneficial economic implications
- As such, use of DB may have clinical impact on outcomes, hospital costs, and patient satisfaction

REFERENCES

1. Marcaine [package insert]. Hospira, Inc., Lake Forest, IL, 2009.
2. Oderda GM, Said Q, Evans RS, et al. *Ann Pharmacother.* 2007;41:400-407.
3. Oderda GM, Evans RS, Lloyd J, et al. *J Pain Symptom Manage.* 2003;25:276-283.
4. Hutchison RW, Chon EH, Tucker WF, et al. *Hosp Pharm.* 2006;41:659-663.

Supported by funding from Pacira Pharmaceuticals, Inc.