Original Article

Bupivacaine Liposomal Versus Bupivacaine: Comparative Review

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Abstract

Bupivacaine liposomal injection was recently approved by the US Food and Drug Administration (FDA) as a local anesthetic for use in management of postsurgical pain in adults. When compared to placebo, bupivacaine liposomal decreases postoperative pain and opioid use. This review examines the efficacy of bupivacaine liposomal when compared to conventional bupivacaine $\pm$ epinephrine using published and unpublished data provided to the FDA by the manufacturer.

Key Words—bupivacaine, bupivacaine liposomal, formulary, pharmacoeconomics

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Bupivacaine liposomal injection was recently approved by the US Food and Drug Administration (FDA) as a local anesthetic for use in the management of postsurgical pain in adults, and US sales doubled from the second to third quarter of 2012.¹ The objective of this commentary is to compare bupivacaine liposomal with conventional drug, bupivacaine $\pm$ epinephrine, to determine the clinical usefulness of this new formulation. Before addition to hospital formularies and initiation of routine use, clinicians need to consider advantages and disadvantages of bupivacaine liposomal over the conventional product.

Recently published review articles stated that bupivacaine liposomal decreased postsurgical pain over placebo.^{2,3} When compared to bupivacaine, one review noted “positive results”^{2(pp24s-25s)} and the other commented that “more adequately powered trials are needed to establish its superiority over plain bupivacaine.”^{3(p257)} A white paper sponsored by the manufacturer suggests that bupivacaine liposomal reduces opioid-related adverse events that may

lead to decreased patient length of stay.⁴ The manufacturer requested priority review status from the FDA because liposomal bupivacaine “may eliminate or substantially reduce a treatment-limiting drug reaction.”^{5(p127)} However, the FDA reviewer recommended denial of this priority approval request on the grounds that although opioid reduction occurred, this was not shown to be associated with a reduction of adverse effects or other benefits such as clinically relevant reduction in time to discharge or return to normal activities. In this review, we will compare bupivacaine liposomal with standard bupivacaine $\pm$ epinephrine utilizing data provided to the FDA as well as review articles summarizing unpublished and published studies to determine the place of bupivacaine liposomal in therapy.^{5–9}

EFFICACY VERSUS PLACEBO

Three pivotal trials were presented to the FDA for review.⁵ Two of these trials compared bupivacaine liposomal to placebo in patients undergoing bunionectomy and hemorrhoidectomy procedures and

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have been published in peer-reviewed journals.^{7,8} One of the 3 trials compared bupivacaine liposomal to bupivacaine and will be discussed in the next section. Both of the placebo-controlled trials found reduced pain scores and opioid consumption, as well as longer time to first opioid administration and higher patient satisfaction.

The finding of statistically significant differences in pain scores compared to placebo was reassuring. In one hemorrhoidectomy trial, the 72-hour morphine consumption difference was 7 mg (29 mg for bupivacaine liposomal vs 22 mg for placebo).⁵ Another important finding that was discussed in the FDA clinical review was that “although the primary endpoint was the AUC for pain intensity during the first 72 hours postoperatively, the two treatments (bupivacaine liposomal and placebo) differed significantly and clinically only during the first 24 hours”^{5(p92)} The FDA reviewer came to this conclusion based on results from mean pain intensity versus time analysis (Figures 1 and 2).

The lack of clinically meaningful difference in pain control beyond 24 hours and the narrow margin of difference in opioid use over 72 hours compel us to contemplate the margins reported in active controlled trials.

EFFICACY VERSUS ACTIVE CONTROL

One of the 3 pivotal trials compared bupivacaine liposomal to conventional bupivacaine (SIMPLE 312)⁵ and has not been published in a peer-review journal. In SIMPLE 312, 101 patients undergoing hemorrhoidectomy were randomized to bupivacaine liposomal 300 mg and 103 patients to active control (bupivacaine 100 mg plus epinephrine 1:200,000). Most patients were between 18 and 64 years of age (94% and 90%) and more patients were male (53% and 50%) for bupivacaine liposomal and active control groups, respectively.⁵ The results of the primary efficacy endpoint, mean area under the curve (AUC) of the numerical rating scale pain score at rest (NRS-R) at 96 hours, were not significantly different, with 396 ± 213 and 359 ± 194 ($P = .15$) for bupivacaine liposomal and bupivacaine plus epinephrine, respectively. A secondary endpoint of mean integrated NRS-R pain intensity score and supplemental opioid consumption at 84 hours favored bupivacaine plus epinephrine ($P = .03$).⁵ Other secondary measures that were not significantly different between bupivacaine liposomal and bupivacaine plus epinephrine in SIMPLE 312 were proportion of patients avoiding opioid use and patient rating of surgical analgesia.

In addition to the unpublished pivotal trial with active control, there are several earlier phase II studies of bupivacaine liposomal that have been summarized in a review article by Bergese et al.⁶ This review article contains 7 studies that compare bupivacaine liposomal to bupivacaine $\pm$ epinephrine, including 2 trials not yet published. These 7 studies included 631 patients receiving bupivacaine liposomal and 446 patients receiving bupivacaine $\pm$ epinephrine. The study populations included those undergoing inguinal hernia repair (2 studies; total $N = 174$), total knee arthroplasty (2 studies; total $N = 383$), hemorrhoidectomy (2 studies; total $N = 304$), and breast augmentation (1 study; total $N = 216$).

In the 7 aforementioned studies, there were a total of 17 different bupivacaine liposomal versus bupivacaine $\pm$ epinephrine treatment arms. There was no difference in the proportion of patients avoiding opioid rescue. The secondary measure of time to rescue medication was slightly longer in patients receiving bupivacaine liposomal at 9.3 hours versus 6.4 hours for bupivacaine ($P < .05$), although the clinical significance of this difference is not known.

In 6 of the 17 treatment arms, the liposomal bupivacaine dose exceeded the FDA-approved maximum dose of 266 mg. Of the remaining 11 treatment arms, only 4 treatment arms favored liposomal bupivacaine for 24 hour or 72 hour cumulative pain scores. These 4 treatment arms are found in one phase II hernia repair trial (trial 1) and one phase II hemorrhoidectomy trial.⁶

In the phase II hernia repair trial ($N = 76$), bupivacaine liposomal was compared to bupivacaine 100 mg without epinephrine. The 266 mg and 310 mg treatment arms showed no statistically significant difference in primary endpoint, but a difference was shown in the 199 mg treatment arm. In a separate hernia repair trial ($N = 98$), bupivacaine liposomal 93 mg, 160 mg, and 306 mg was compared to bupivacaine 105 mg plus epinephrine 1:200,000. In this unpublished trial, there was no statistically significant difference in pain control or opioid consumption between treatment groups.⁶

In the phase II hemorrhoidectomy trial, 3 bupivacaine liposomal treatment arms ($n = 25$ each; 66 mg, 199 mg, 266 mg) performed better than 75 mg of bupivacaine plus epinephrine 1:200,000. In this trial, the adjusted geometric mean of opioid total consumption through 24 hours was statistically significant between 266 mg liposomal bupivacaine and 75 mg bupivacaine plus epinephrine (4.2 mg and 8.9 mg, respectively; $P < .05$).⁶ The total postoperative con-

Figure 1. Bupivacaine liposomal mean pain intensity (PI) versus time plot for hemorrhoidectomy study⁵ showing no difference in effect on pain measures compared to placebo after 24 hours.

Figure 2. Mean pain intensity (PI) versus time plot for bunionectomy study⁵ showing no difference in effect on pain measures compared to placebo after 24 hours.

sumption of supplemental opioid pain medication did not differ statistically at any time point, including 12 and 24 hours postoperatively.⁵

Efficacy of both bupivacaine liposomal and bupivacaine appear to have a dose-response relationship with higher doses resulting in increased efficacy.⁶ Many studies using active control bupivacaine used less than maximal dosing: 175 mg without and 225 mg with epinephrine.¹⁰ As described earlier, the SIMPLE 312 trial showed that using a higher bupivacaine plus epinephrine 1:200,000 dose resulted in no statistically significant difference in the primary endpoint.⁵ The insufficient dosing of standard bupivacaine should be considered when evaluating comparative trials.

More recently, the manufacturer supported a meta-analysis of 9 studies using a similar database as Bergese et al.⁹ The analysis reported significant improvement in AUC of NRS at 72 hours (283 vs 329; $P = .039$), median time to first use of opioid medication (10 hours vs 3 hours; $P < .0001$), decreased amount of opioid use (12 mg vs 19 mg; $P < .0001$), and incidence of opioid-related adverse events (20% vs 36%; $P < .0001$) for bupivacaine liposomal and bupivacaine, respectively.⁹

The clinical significance of the findings is questionable. The minimal clinically important difference (MCID) is defined as the minimal change that would be important to the patient. In chronic pain trials, the MCID is a 30% reduction in pain score.¹¹ In Dasta et

al, the statistically significant difference in pain score is less than 15% and does not reach the desired MCID. The second statistically significant result is a 7-hour difference in time to first dose of opioid administration. This will generally result in the patient getting their first dose in the home for surgeries performed in outpatient surgery centers. This may be a disadvantage, because the response to the rescue opioid will be unknown until after discharge. The final statistically significant difference is the reduction in opioid consumption of 7 mg in morphine equivalents over 72 hours. This is approximately 1 to 2 oxycodone 5 mg/acetaminophen tablets over a 72-hour period.

There are several considerations regarding this meta-analysis that need to be addressed. Data from bupivacaine liposomal versus two *placebo-controlled* trials were included in an analysis that shows lower cumulative pain score at 72 hours for bupivacaine liposomal versus *active control*. The second consideration is that, per the author's statement, this analyses was conducted using the same patient database as reported by Bergese et al. However, when discussed by Bergese et al, in only a few limited circumstances did the same data favor bupivacaine liposomal. The incorporation of the placebo-controlled trials appears to have altered interpretation of the data. Until all the studies are available as full text, it will be difficult to re-examine the findings of this meta-analysis.⁹

TOLERABILITY

The commonly observed adverse effects associated with bupivacaine liposomal reported by the manufacturer include tachycardia (3.9%), pruritus (3.1%-5.2%), constipation (2.1%), nausea (40.2%), vomiting (27.8%), dizziness (6.2%), headache (3.8%), somnolence (up to 5.2%), and fever (2.1%).¹² In the SIMPLE 312 trial, bupivacaine with epinephrine adverse effects with an incidence of $\geq 5\%$ were headache, nausea, constipation, and vomiting. In the bupivacaine liposomal group, nausea, constipation, vomiting, flatulence, abdominal pain, pyrexia, pruritis, and urinary retention occurred with an incidence $\geq 5\%$.⁵

Clinician satisfaction with wound healing, wound status (postsurgical edema, erythema, induration), and wound scarring was evaluated in an analysis of 10 studies.¹³ In the 8 trials that included data that allowed for wound healing assessment, there was no difference between bupivacaine liposomal and bupivacaine $\pm$ epinephrine. As far as wound status, 4 studies found no difference between groups. In the other studies, 3 outcomes (erythema, edema, and induration) in 2 trials favored bupivacaine and 2

outcomes (edema and induration) in 2 trials favored bupivacaine liposomal. Wound scarring was assessed in 5 studies, and no statistically significant difference was found between bupivacaine liposomal and bupivacaine. The incidence of local adverse events was similar between groups, ranging from 9% to 20% with bupivacaine liposomal compared to 8% to 19% with bupivacaine.

MEDICATION SAFETY ISSUES

When bupivacaine liposomal is administered concurrently with lidocaine, an increase in systemic bupivacaine exposure occurs due to disturbance of the liposomal delivery system. Lidocaine systemic exposure is also increased. In animal studies, when lidocaine was followed 5 minutes later with bupivacaine liposomal, the lidocaine and bupivacaine maximal concentrations (C_{max}) and AUC were increased by 1,640% and 48% and 67% to 1,000% and 50% to 95%, respectively.¹⁴

This is a practical logistic concern, as lidocaine and bupivacaine are mixed in clinical practice in order to get immediate onset of lidocaine with duration of bupivacaine activity.¹⁵ Due to significant systemic exposure when mixed, consideration should be given to increasing attention to this interaction in the package insert. It is currently listed as an Administration Precaution and in the Drug Interactions section of the prescribing information.¹²

Another patient safety concern is the milky-white appearance of bupivacaine liposomal that is similar to another common operating room injectable, propofol. Once pulled into syringes, there is no visual distinction between the 2 products creating the high potential for inappropriate intravenous administration of bupivacaine liposomal and resultant bupivacaine toxicity.¹⁶ A bulletin from the National Alert Network recommends rigorous procedures for the storage, labeling, and utilization of bupivacaine liposomal to prevent accidental intravascular administration.¹⁶

ECONOMICS

The economic impact of a drug must take into consideration both the acquisition cost of the agent and its impact on patient outcome. In this case, the acquisition cost of bupivacaine liposomal is approximately 100 times the cost of generic bupivacaine. The manufacturer estimates a potential 39 million surgeries per year based on Thompsons Research.¹⁷ This would result in an \$11 billion increase in drug acquisition cost. For an investment of this magnitude, compelling patient outcome differences need to

be quantified and duplicated in well-conducted trials. Unfortunately, a limitation of current blinded and active-controlled studies evaluating bupivacaine liposomal is that length of stay and indirect costs have not as yet been assessed.

MARKETING

In cooperation with the manufacturer, Frost and Sullivan produced a white paper focused on the use of liposomal bupivacaine and its potential benefits regarding reduction in postoperative outcomes and costs, suggesting that the drug is able to indirectly decrease cost and length of stay from opioid adverse event avoidance.⁴ However, these outcome findings are based on decreased opioid use compared to placebo, a finding not replicated in active-control trials as described earlier. The white paper also uses informal survey information to support its findings and cites liposomal bupivacaine as a more cost-effective alternative than elastomeric pump drug delivery when no head to head data are available.

CONCLUSION

Bupivacaine liposomal is being marketed as a novel anesthetic agent for treatment of postsurgical pain in adults. Clinical outcomes in active comparator trials have not been improved as evidenced by no statistical difference in AUC pain scores and proportion of patients avoiding use of opioid rescue medication. In trials showing a difference in opioid consumption, some versus placebo, the mean difference was 7 mg morphine equivalents. Clinical significance of this difference has not been demonstrated.

Finally, the use of a new product is justifiable when it fulfills an unmet need or the increased cost is offset by improved outcomes over current standard. However, based on the available data, bupivacaine liposomal does not meet such a need.

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REFERENCES

1. Pacira Pharmaceuticals Inc. News release. November 1, 2012. <http://investor.pacira.com/phoenix.zhtml?c=220759&p=irol-newsArticle&ID=1752686&highlight=>. Accessed January 2, 2013.
2. Candiotti K. Liposomal bupivacaine: An innovative nonopioid local analgesic for the management of postsurgical pain. *Pharmacotherapy*. 2012;32:19S-26S.
3. Chahar P, Cummings KC. Liposomal bupivacaine: A review of a new bupivacaine formulation. *J Pain Res*. 2012;5:257-264.
4. New opportunities for hospitals to improve economic efficiency and patient outcomes: The case of Exparel, a long-acting non-opioid local analgesic. A Frost & Sullivan White Paper. 2012. <http://www.frost.com/prod/servlet/cpo/252218999>. Accessed April 2, 2014.
5. Simone A. Center for Drug Evaluation and Research Clinical Review, NDA 022-496. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022496Orig1s000MedR.pdf. Accessed April 2, 2014.
6. Bergese SD, Ramamoorthy S, Patou G, et al. Efficacy profile of liposome bupivacaine, a novel formulation of bupivacaine for postsurgical analgesia. *J Pain Res*. 2012;5:107-116.
7. Gorfine SR, Onel E, Patou G, Krivokapic ZV. Bupivacaine extended-release liposome injection for prolonged postsurgical analgesia in patients undergoing hemorrhoidectomy: A multicenter, randomized, double-blind, placebo-controlled trial. *Dis Colon Rectum*. 2011;54:1552-1559.
8. Golf M, Daniels SE, Onel E. A phase 3, randomized, placebo-controlled trial of DepoFoam bupivacaine (extended-release bupivacaine local analgesic) in bunionectomy. *Adv Ther*. 2011;28:776-788.
9. Dasta J, Ramamoorthy S, Patou G, Sinatra R. Bupivacaine liposomal injectable suspension compared with bupivacaine HCL for the reduction of opioid burden in the postsurgical setting. *Curr Med Res Opin*. 2012;28:1609-1615.
10. *Maracaine* [package insert]. Lake Forest, IL: Hospira, Inc; October 2011.
11. Younger J, McCue R, Mackey S. Pain outcomes: A brief review of instruments and techniques. *Curr Pain Headache Rep*. 2009;13(1):39-43.
12. *Exparel* [package insert]. San Diego, CA: Pacira Pharmaceuticals, Inc; June 2012.
13. Baxter R, Bramlett K, Onel E, Daniels S. Impact of local administration of liposome bupivacaine for postsurgical analgesia on wound healing: A review of data from ten prospective, controlled clinical studies. *Clin Ther*. 2013;35:312-320.
14. Richard BM, Rickert DE, Doolittle D, et al. Pharmacokinetic compatibility study of lidocaine with EXPAREL in Yucatan miniature pigs. *ISRN Pharm*. 2011;2011:582351. doi: 10.5402/2011/582351.
15. Diaz-Palacios GA, Eslava-Schmalbach JH. Perirectal block for out-patient anorectal surgery: A new technique. *Bio-medica*. 2011;31:196-199.
16. Potential for wrong route errors with *Exparel* (bupivacaine liposome injectable suspension). National Alert Network. March 2012. <http://www.ismp.org/NAN/files/NAN-20120318.pdf>. Accessed April 3, 2014.
17. *Exparel*. <http://www.pacira.com/products/exparel.php>. Accessed April 3, 2014. ■