Letter to the Editor

Response to “Bupivacaine Liposomal Versus Bupivacaine: Comparative Review”

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To the Editor:

The recent article, “Bupivacaine Liposomal Versus Bupivacaine: Comparative Review,” by Noviasky et al [*Hosp Pharm*. 2014;49(6):539-543] is a valiant effort to review this topic. However, the authors have made a critical oversight in their attempt to interpret analgesic efficacy based solely on pain intensity.

As per Schmidt’s study,¹ analgesic efficacy must be evaluated using not only the pain intensity score, but also other outcome measures such as the post-surgical consumption of rescue medication, subject-reported results from validated outcomes instruments such as the Brief Pain Inventory (BPI), and subject satisfaction with postsurgical analgesia (to name just a few). If one were to study pain intensity scores alone, it would be incorrectly assumed that the analgesic effects of liposomal bupivacaine would last for only 12 to 24 hours. When combined with the other outcome measures, such as the use of postsurgical opioid rescue medications and assessments of patient functionality and satisfaction, it was clear that the analgesic effect lasted throughout the 72-hour study period. Although the pain scores normalized within the first day, they did so because the placebo patients were receiving statistically significantly more narcotic rescue pain medication than the liposomal bupivacaine patients (of course, it would be unethical to study a patient’s pain response without rescue medication being available). Other outcome metrics, such as patient satisfaction and quality of life measures from the BPI, also showed statistically significant advantages to liposomal bupivacaine throughout the entire 72-hour period – not just the first 12 to 24 hours.

Most of the data presented in the Noviasky article comes from studies used in the submission to the US Food and Drug Administration (FDA) for approval of liposomal bupivacaine (*Exparel*; bupivacaine liposome injectable suspension). Subsequent

studies such as the Improve trials for colorectal surgery and the orthopedic data presented at the most recent American Academy for Orthopedic Surgery (AAOS) were completely ignored and unaddressed. In the first Improve trial, Cohen² demonstrated that a liposomal bupivacaine-based multimodal regimen resulted in statistically significantly less opioid consumption, lower hospital costs, and a shorter length of stay than a standard opioid-based analgesic regimen for postsurgical pain in patients undergoing open colectomy compared to his institution’s standard of care (opioid-based patient-controlled analgesia [PCA]). These results have been replicated in several other trials and surgical models (Marcet,³ Candiotti⁴). In fact, a very recent pooled analysis of these similarly designed studies by Cohen et al⁵ showed statistically significant reductions in postsurgical opioid consumption, reductions in hospital median length of stay by 1.4 days, and reductions in mean per-patient hospitalization costs by \$2,455. This decrease by 60% of total narcotic consumption was accompanied by a 67% reduction in opioid-related adverse events. Turning to the orthopedic study at the March 2014 meeting of the AAOS, Barrington and Emerson⁶ compared their last 1,000 total joint arthroplasties (TJA) without liposomal bupivacaine to their first 1,000 TJAs with liposomal bupivacaine; their study demonstrated pain relief for 72 hours compared to bupivacaine HCl, which lasted only 6 to 8 hours, as well as a decreased number of falls (from 10 to 2) and a savings of \$1,246 per patient.

The value of liposomal bupivacaine as an analgesic adjuvant must be considered as a multidimensional concept, including efficacy, safety, and pharmacoeconomics. Because liposomal bupivacaine typically affects the pharmacy budget, pharmacy directors tend to focus on that feature while not observing the hospitalwide savings that may be achieved. As a former

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hospital pharmacy director for many years, I know this only too well. But while working in the group purchasing organization industry, I realized that by integrating quality measures and patient outcomes with pharmacy data, a better, fuller evaluation is realized.⁷ In June 2010, the American Society of Health-System Pharmacists (ASHP) and Society of Hospital Medicine (SHM) reported on survey results⁸ in which directors of pharmacy or members of ASHP's Pharmacy Practice Managers Section reported that only 13% of formulary system decisions made by their Pharmacy and Therapeutics (P&T) Committees in hospitals were influenced by pharmacoeconomic methods, even though 87% of respondents felt that pharmacoeconomic methods should be used. Additionally, more than 9 out of 10 survey respondents reported having pharmacoeconomic analysis available during their most recent P&T Committee discussion, but only 26% rated the available information as extremely helpful and 71% desired additional pharmacoeconomic information.

Hospital pharmacy departments are not financial silos, and perhaps now is the time for hospital pharmacists to again embrace this joint SHM/ASHP statement. Given that liposomal bupivacaine provides pain relief and patient satisfaction over several days while still improving hospital pharmacoeconomics (despite pharmacy budgets being impacted), why aren't we as pharmacists leading the charge to this therapeutic victory?

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RESPONSE TO THE LETTER TO THE EDITOR

John Noviaskey, PharmD, BCPS; Deirdre P. Pierce, PharmD, BCPS, CGP; Karen Whalen, BS Pharm, BCPS; Roy Guharoy, PharmD, MBA, FASHP; and Kenneth Hildreth, MD

We would like to offer the following in response to Dr. Kessler's comments regarding our review article comparing bupivacaine liposomal to standard bupivacaine.

We agree with Dr. Kessler that a pain intensity scale is not the only outcome that should be utilized when comparing analgesics. Our article reported the mean area under the curve of the numerical rating scale pain score-at rest (NRS-R) and the secondary endpoint of mean integrated NRS-R pain intensity score and supplemental opioid consumption for SIMPLE 312¹ (a randomized, blinded, comparison of bupivacaine liposomal to standard bupivacaine). What we did not include were the multiple secondary outcomes that did not favor bupivacaine liposomal (referred to as SKY0402) and these should satisfy Dr. Kessler's concerns. To summarize, lack of superiority of SKY0402 over bupivacaine was demonstrated by no difference in the following assessments at 12, 24, 36, 48, 60, 72, 84, and 96 hours: total postoperative consumption of supplemental opioid pain medication, integrated rank assessment using the NRS-R scores, and total postoperative opioid usage. Measures that also showed no difference between bupivacaine liposomal and bupivacaine were proportion of subjects receiving no supplemental opioid pain medication postoperatively, time to first postoperative use of opioid medications,

postoperative administration of antiemetic medication, time to first bowel movement, pain with first bowel movement (NRS-BM), average daily pain with bowel movement (NRS-BM), quality of life questionnaire (EQ-5D), time to first occurrence of postoperative nausea and vomiting, discharge readiness, subject's overall satisfaction with postoperative analgesia, blinded care provider's satisfaction with postoperative analgesia, and time to return to work or normal daily activities. In addition, a randomized, blinded, dose-ranging study by Bramlett² showed that bupivacaine liposomal was not better than standard bupivacaine in the primary outcome of numerical rating scale pain score-active (NRS-A). In addition, there was no difference in secondary outcomes of total consumption of rescue opioids after surgery and time to resumption of work or normal daily activities. The secondary outcome of NRS-R was significantly lower in the high-dose bupivacaine liposomal group compared to standard bupivacaine. However, this high dose (532 mg) is double the maximal dose listed in bupivacaine liposomal package insert³ (266 mg).

Dr. Kessler is correct in that we did not include more recent studies such as Improve trial⁴ and unpublished orthopedic data presented at a conference. These company-sponsored studies that are conducted by consultants do not prove that bupivacaine liposomal is superior to the current standard bupivacaine. What they do show is that patients receiving bupivacaine liposomal plus anti-inflammatory agents plus acetaminophen plus opioids have marginal outcome improvement over those patients who only receive opioids. If unblinded comparisons are included, consider the study performed by Bagsby et al.⁵ Periarticular ropivacaine, epinephrine, morphine was compared to bupivacaine/epinephrine sequentially combined with bupivacaine liposomal in total knee arthroplasty. There was no difference in mean postoperative morphine equivalents, mean antiemetic doses, or mean naloxone doses. There was no difference in numerical pain scores during the first 24 hours or post discharge. There was a difference in numerical pain scores from post 24 hours until discharge, but this favored the comparator (ropivacaine, epinephrine, morphine) and not the liposomal bupivacaine group.

Our intent was to provide a comparison of bupivacaine liposomal to standard bupivacaine using the best evidence available. In our opinion, best evidence does not include nonblinded retrospective comparisons, such as those mentioned by Dr. Kessler, when blinded, randomized evidence is available.^{1,2}

The decision that clinicians make in daily practice regarding which agent to use does not include the choice of bupivacaine liposomal versus placebo or bupivacaine liposomal plus opioids plus anti-inflammatory agents versus opioids with some acetaminophen. Their decision will be between bupivacaine liposomal and conventional bupivacaine. In regard to efficacy, there is no difference between liposomal bupivacaine and standard bupivacaine. Additionally, in regard to pharmacoeconomics, we do not believe the conclusion made in Dr. Kessler's comments, as it is based on nonblinded, nonrandomized, retrospective comparison data.

We agree that hospital pharmacy departments should not view themselves as financial silos. However, it is our duty to serve as stewards of the limited health resources that we have to serve our patients. Our responsibility includes evidence-based evaluation of current and proposed treatments. We should only embrace those therapies that demonstrate an improvement in outcomes over current standards. Bupivacaine liposomal does not match that description.

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