Optimizing Postoperative Pain Management:
Role of Local Anesthetics

ASK THE EXPERTS: USE OF LOCAL ANESTHETICS FOR THE MANAGEMENT OF POSTOPERATIVE PAIN

The management of postoperative pain is the focus of a series of learning opportunities planned by ASHP Advantage. The series began with a Midday Symposium and simultaneous webcast on December 10, 2013, during the 48th ASHP Midyear Clinical Meeting and Exhibition in Orlando, Florida. The learning opportunities are designed to build on each other, focusing on therapeutic options and roles for pharmacists.

As a follow up to the Midyear Meeting, Initiative Chair Julie Golembiewski, Pharm.D., FASHP, and Virginia L. Ghafoor, Pharm.D., presented a live webinar in February that addressed questions submitted during the symposium. Those questions also serve as the basis for two e-newsletters that are part of the educational initiative. The March 2014 issue focused on multimodal analgesia. This issue focuses on the use of local anesthetics, particularly liposome bupivacaine, which is a recently introduced local anesthetic for managing postoperative pain. Other learning opportunities in the series include the following:

- On-demand web-based activity based on the Midyear symposium (2 hours continuing pharmacy education).
- On-demand web-based activity based on the Ask the Experts webinar (1 hour continuing pharmacy education).
- Faculty roundtable discussion available in three parts, each lasting 10 minutes or less, on multimodal analgesia, role of pharmacists in postoperative pain management, and considerations related to the use of local anesthetics.

LOCAL ANESTHETICS FOR POSTOPERATIVE PAIN MANAGEMENT

Local anesthetics are often used as part of a multimodal approach to postoperative pain management. This approach involves the administration of two or more drugs that act by different mechanisms by the same or different routes of administration to provide additive or synergistic effects in relieving postoperative pain and eliminate or minimize adverse effects. Various administration routes and techniques are used for local anesthetics, including intravenous (i.v.) and epidural infusion; subcutaneous, deep tissue injection; intra-articular and periarticular injection; peripheral nerve block; and local instillation at or near the surgical site by single injection or continuous infusion (Figure 1). Various local anesthetics vary in their onset and duration of action. Lidocaine has a rapid onset of action but a short duration of action (1-3 hours), and it is the only local anesthetic that can be given by i.v. infusion. Ropivacaine and bupivacaine HCl have a slower onset of action but a longer duration of action (2-8 hours).

ONLINE ACCESS

For more information and to access other learning opportunities on this topic, go to the initiative portal. This initiative is supported by an educational grant from Pacira Pharmaceuticals, Inc.

www.ashpadvantage.com/postoppain
A meta-analysis was conducted of randomized controlled trials of the use of continuous infiltration of local anesthetics through catheters placed in surgical wounds for postoperative analgesia after various types of non-orthopedic surgery (e.g., cardiothoracic, major abdominal). Compared with placebo, there was no significant reduction in pain at rest or with activity, except in women undergoing obstetric or gynecologic (ob/gyn) surgery, and no significant reduction in opioid analgesic consumption except for the first 24 hours after ob/gyn surgery. The magnitude of these effects was small.

Local infiltration analgesia (LIA) is an increasingly popular technique for managing postoperative pain, particularly following orthopedic surgery. It involves the infiltration of the wound during surgery with a local anesthetic solution, often in combination with adjuvants (e.g., epinephrine, ketorolac). To effectively infiltrate all relevant structures (superficial and deep), the local anesthetic (with or without adjuvant) is diluted to a total volume of 100–200 mL. Epinephrine is a vasoconstrictor that slows systemic absorption and lowers the peak plasma concentration of the local anesthetic. It prolongs the duration of action of
lidocaine and mepivacaine. At high concentrations (e.g., >5 mcg/mL), epinephrine reduces bleeding. Ketorolac has analgesic activity when administered locally or systemically. In an analysis of eight randomized controlled trials and two case series involving the use of LIA for orthopedic surgery, including hip resurfacing arthroplasty, total hip replacement, and total knee arthroplasty, LIA was effective in eight reports and there was no benefit when LIA was added to a multimodal analgesic regimen in two reports. The efficacy of LIA in total hip replacement was questionable.

The potential for local anesthetic systemic toxicity (LAST) characterized by cardiovascular changes (hypertension, tachycardia, and ventricular arrhythmias followed by bradycardia, asystole, decreased contractility, and hypotension) and/or central nervous system excitement (auditory changes, circumoral numbness, metallic taste, and agitation progressing to seizures) is a concern when local anesthetics are administered. Large, deep surgical incisions with muscle and vascular exposure may increase the systemic absorption of local anesthetics. Local anesthetic blood concentrations are influenced by the vascularity of the site of injection and dose, and these concentrations do not necessarily predict concentrations in cardiac or brain tissues, where toxicity occurs. In animal studies, local anesthetic blood concentrations associated with survival after a particular dose were not significantly different from concentrations associated with death. Current recommendations for maximum doses of local anesthetics are based on extrapolations of animal data, clinical experience with the use of various doses and measured blood concentrations, case reports of local anesthetic toxicity, and pharmacokinetic data instead of randomized controlled studies. Because systemic toxicity from the use of local anesthetics is difficult to predict and dose is a risk factor for systemic toxicity, exceeding the maximum recommended dose is not advisable.

Patients with advanced age or underlying cardiac, neurologic, renal, hepatic, pulmonary, or metabolic disease appear to be at increased risk for LAST. Local anesthetic dose reduction and heightened vigilance may be warranted for these patient populations.

LIPOSOME BUPIVACAINE

A liposome injectable suspension form of bupivacaine that uses the DepoFoam® drug delivery system to provide a more rapid onset and prolonged duration of analgesia for up to 72 hours compared with conventional bupivacaine HCl injection recently was introduced for managing postoperative pain. The liposome product, Exparel, is infiltrated as a single dose into soft tissues at the surgical site where initial release of bupivacaine HCl occurs, followed by slow release of bupivacaine from the liposomes. The single injection is a potential advantage of liposome bupivacaine over shorter-acting local anesthetics administered by continuous wound infiltration via a catheter and elastomeric device filled with a 2–5 day supply of local anesthetic. The liposome bupivacaine product is supplied as a 13.3-mg/mL suspension that may be administered undiluted or diluted up to 0.89 mg/mL with preservative-free sterile saline (no other diluent should be used).

In a retrospective analysis of robotic-assisted and laparoscopic urologic surgeries performed by a single surgeon, the mean morphine equivalent dose (i.e., postoperative opioid analgesic consumption) in 54 consecutive patients who received a continuous
ropivacaine infusion by wound catheter and the next 54 consecutive patients who received liposome bupivacaine by wound infiltration was 65.9 mg and 23.8 mg, respectively, a difference that is significant (p < 0.0001). Compared with the ropivacaine group, the group receiving liposome bupivacaine had a longer mean time to first rescue opioid use (186 minutes vs. 63.9 minutes, p = 0.0043). There was no significant difference between the two groups in length of stay (1.8 days for ropivacaine vs. 1.6 days for bupivacaine; p = 0.64).

In a phase 2, randomized, double-blind, dose-ranging study, liposome bupivacaine 133 mg, 266 mg, 399 mg, and 532 mg were compared with bupivacaine HCl 150 mg plus epinephrine given via local infiltration into superficial and deep surgical wound tissues in 138 patients undergoing total knee arthroplasty (TKA). Liposome bupivacaine 532 mg provided better analgesia than bupivacaine HCl plus epinephrine (p = 0.045). There was no significant difference in analgesic efficacy between the other liposome bupivacaine doses and bupivacaine HCl plus epinephrine. It should be noted that the 532-mg liposome bupivacaine dose used in this dose-ranging study exceeds the maximum recommended dose (266 mg).

In an analysis of the pooled results from 10 phase 2 and 3 randomized, double-blind clinical trials comparing liposome bupivacaine with placebo or bupivacaine HCl by wound infiltration in patients undergoing various types of surgery, including orthopedic surgery, a total of 823 patients received various doses of liposome bupivacaine. There were 17 treatment arms comparing liposome bupivacaine with bupivacaine HCl. Cumulative pain scores favored liposome bupivacaine through the first 24 hours after surgery in 16 of 17 treatment arms and for 72 hours after surgery in five of 17 treatment arms. The median time to postoperative rescue use of opioid analgesics was significantly longer with liposome bupivacaine (9.3 hours) than bupivacaine HCl (6.4 hours; p = 0.013) and placebo (3.6 hours; p < 0.0001). Greater likelihood of avoidance of opioid rescue medication, lower total postoperative consumption of opioid rescue medication, and greater patient or care provider satisfaction with postoperative analgesia were associated with liposome bupivacaine than bupivacaine HCl in some but not all studies. Thus, the favorable effects of liposome bupivacaine on pain scores may or may not result in improvement in other patient outcomes.

Liposome bupivacaine used as part of multimodal analgesia (with scheduled nonsteroidal anti-inflammatory drugs [NSAIDs] and acetaminophen for 72 hours after surgery) was compared with i.v. opioids by patient-controlled analgesia (PCA) in small open-label phase 4 clinical trials of patients undergoing ileostomy reversal or laparoscopic colectomy. The therapies were used sequentially, with i.v. opioids by PCA used by the first cohort followed by multimodal analgesia in a second cohort. All patients in both cohorts were offered rescue opioid analgesics. The total postoperative opioid consumption and hospital length of stay were significantly lower with multimodal analgesia than i.v. opioids by PCA. In patients undergoing ileostomy reversal, hospital costs were significantly lower with multimodal analgesia ($6484) than i.v. opioids by PCA ($9282, p = 0.01). In patients undergoing laparoscopic colectomy there was no significant difference between treatment groups in hospital costs. These findings support the use of a multimodal analgesia regimen with liposome bupivacaine and scheduled acetaminophen and NSAID (opioid rescue only) instead of i.v. opioids by PCA only (no non-opioid...
analgesics), although it was not possible to attribute the observed advantages to any one component of the multimodal analgesia regimen.

Anecdotal reports from individual orthopedic surgeons suggest that the use of liposome bupivacaine instead of conventional analgesic therapies (e.g., bupivacaine HCl) is associated with reduced postoperative nausea and vomiting, which can interfere with physical therapy and increase the risk for venous thromboembolism.\textsuperscript{15} Anecdotal reports also suggest a reduced risk for falling due to elimination of the need for peripheral nerve blocks and reduced opioid analgesic use with the use of liposome bupivacaine. As noted by the faculty, further studies are needed to determine if early recovery and hospital discharge may be facilitated by liposome bupivacaine, particularly when an Enhanced Recovery After Surgery (ERAS) protocol is in place.\textsuperscript{16,17}

The potential for LAST from liposome bupivacaine use and interactions between liposome bupivacaine and other medications have been investigated. Plasma bupivacaine concentrations have been detected 96 hours after local infiltration of liposome bupivacaine.\textsuperscript{12} The manufacturer advises against administration of other formulations of bupivacaine within 96 hours following administration of liposome bupivacaine.\textsuperscript{9} Concomitant administration of liposome bupivacaine and bupivacaine HCl increases overall exposure to bupivacaine, thereby increasing the risk of systemic toxicity.\textsuperscript{18} Although not recommended, if coadministration of liposome bupivacaine and bupivacaine HCl at the same site occurs, the dose ratio should be 2:1 or higher to avoid excessive release of free bupivacaine (i.e., the bupivacaine HCl dose should not exceed 50\% of the liposome bupivacaine dose). Excessive release of free bupivacaine occurs when a liposome bupivacaine to bupivacaine HCl dose ratio of 1:12 or less is used.

Lidocaine, ropivacaine, and mepivacaine cause the rapid release of bupivacaine if administered within 10 minutes before liposome bupivacaine.\textsuperscript{18} This effect is avoided if the drugs are given 20 minutes or 40 minutes before liposome bupivacaine.

The manufacturer advises against admixing liposome bupivacaine with any other drugs (including bupivacaine HCl) in the same syringe because of the risk of physicochemical incompatibility and rapid release of free bupivacaine.\textsuperscript{9} According to published and unpublished compatibility studies, interactions between liposome bupivacaine co-administered with opioid analgesics, NSAIDs, epinephrine, antibiotics (e.g., gentamicin, bacitracin, cefazolin), and corticosteroids (e.g., triamcinolone acetonide, methylprednisolone acetate) are not clinically significant.\textsuperscript{18} The faculty cautioned that the studies looked at physical compatibility with liposome bupivacaine only, not efficacy or safety of these agents administered with liposome bupivacaine into the surgical wound.

Liposome bupivacaine should not be diluted with water or other hypotonic agents because it could result in disruption of the liposomal particles.\textsuperscript{9}

**NEW PRODUCT IN DEVELOPMENT**

A new long-acting bupivacaine product, Posidur, is in development for the management of postoperative pain. It uses the Saber\textsuperscript{©} drug delivery system, with the drug dispersed or dissolved in an injectable biodegradable
sucrose acetate isobutyrate solvent, and provides up to 72 hours of postoperative analgesia. The drug is also administered at the surgical site prior to wound closure. Fifteen clinical trials have been conducted using the product in subjects undergoing various surgical procedures. Results of a phase 2b randomized, double-blind, parallel-group, placebo-controlled, dose-finding study in patients undergoing elective open inguinal hernia repair suggest that the drug is safe and effective for managing postoperative pain. On February 12, 2014, the Food and Drug Administration requested additional safety data before approval of the product can be considered.

**IMPORTANCE OF MEDICATION-USE EVALUATION**

Making formulary decisions about a long-acting bupivacaine product may be difficult because of the limited available clinical data. Institution-specific characteristics, including the patient mix, types of surgery performed, and surgeon techniques and preferences, should be taken into consideration in making formulary decisions about these products.

The medication-use evaluation (MUE) process can be instrumental in making formulary decisions and improving the use of local anesthetics for postoperative pain management. A variety of process and outcome measures can be used. The appropriateness of the local anesthetic administration route and technique based on indications for use, evidence-based clinical guidelines for dosing, adherence to institutional pain management protocols, and safety considerations should be evaluated. Possible outcome measures include pain intensity, opioid analgesic requirements, incidence of adverse effects, and length of stay. Patient satisfaction with how well health system staff help them manage their pain using Hospital Consumer Assessment of Healthcare Providers (HCAHPS) scores also should be taken into consideration. Cost may be a component of MUE efforts because of the potential for reduced or increased overall costs when all resources and desirable patient outcomes are considered.

Data gathered through the MUE process can be helpful in determining the current state and how best to use liposome bupivacaine and other local anesthetic modalities (e.g., continuous wound infiltration, i.v. lidocaine infusion, peripheral nerve block, or epidural analgesia) to improve patient outcomes. Patterns should be assessed so that trends can be identified and action can be taken to provide education and modify individual regimens if warranted. The results of MUE studies should be shared with appropriate individuals and departments in the institution to promote quality improvement.

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