Extended-Release Epidural Morphine (DepoDur™)

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EPIDURAL MORPHINE HAS been administered by single and intermittent bolus doses, continuous infusion, and patient-controlled analgesia (PCA) for the management of postoperative pain for many years. All of these methods have proven to be safe and effective in controlling pain,[1,2] but each also has its limitations. A single epidural injection of conventional morphine (Astramorph; AstraZeneca LP, Wilmington, DE) produces pain relief for as long as 24 hours, which may not be long enough for some patients after major surgery.[3] Although continuous epidural infusion and patient-controlled epidural analgesia (PCEA) techniques provide prolonged relief, they require an indwelling catheter, which can impede mobility and carries the risk of intraspinal infection.[4] In addition, guidelines for insertion and removal of indwelling epidural catheters must be carefully followed in patients receiving prophylactic anticoagulant therapy to prevent the occurrence of an epidural hematoma.[5,6] However, the US Food and Drug Administration (FDA) has recently approved a unique formulation of epidural morphine called extended-release epidural morphine (EREM) (DepoDur; Endo Pharmaceuticals, Chadds Ford, PA) that may provide a better choice for pain control after some surgical procedures. A single epidural bolus of EREM is capable of providing pain relief for as long as 48 hours, which represents an exciting new postoperative pain management option for many patients undergoing major surgery.

Characteristics and Pharmacology Overview

EREM is distinguished from conventional epidural morphine (Astramorph, Duramorph) by its unique delivery system called DepoFoam™, which consists of multiple microscopic, liposomal (fat-based) particles. The liposomes contain aqueous chambers that encapsulate preservative-free morphine.[3] After injection into the epidural space, the liposomes slowly release morphine over a period of 48 hours by erosion or reorganization of the lipid membranes.[7,8]

After epidural injection, EREM is absorbed both neuraxially and systemically.[8] The primary site of analgesic action is at the μ opioid receptor sites in the spinal cord. This, in addition to the fact that a comparatively low dose of morphine is administered for neuraxial analgesia (eg, 1-time 10-mg dose of EREM) than for parenteral analgesia (eg, 10 mg of intravenous [IV] or intramuscular [IM] morphine every 4 hours), is thought to result in minimal systemic concentration of the drug.[8] Further research and clinical use is needed to determine the significance of this with EREM; however, the primary advantage noted in studies of other epidural opioids is

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a reduction in the severity of systemic opioid-induced adverse effects, such as nausea and sedation.[4] A benefit of EREM is that it produces analgesia without the motor or sensory deficits that can occur when local anesthetics are combined with opioids and administered in the lumbar region for epidural analgesia.[8]

EREM is metabolized by the liver and excreted by the kidneys, similar to other opioids. Because EREM is administered by a single bolus dose, morphine metabolites (morphine-3-glucuronide and morphine-6-glucuronide) should not accumulate, even in patients with impaired hepatic or renal function.[8] The exact onset of the drug is unclear and will likely be better defined with more clinical use. In addition to extended drug release, the DepoFoam™ delivery system avoids excessive peak concentrations and the adverse effects that can occur with them.[3]

Dosage and Administration

The recommended dose of EREM is 10 mg for cesarean delivery, 10 to 15 mg for lower abdominal or pelvic surgery, and 15 mg for major orthopedic surgery of lower extremities.[8] EREM is given before surgery or after the umbilical cord is clamped during cesarean delivery. It is intended for single-bolus dosing into the lumbar epidural space only; thoracic and higher administration has not been adequately studied and is not recommended.[8] The drug also should not be administered via the intrathecal (spinal), IV, or IM routes of administration and should not be given by continuous infusion. EREM should be administered by an anesthesiologist or certified registered nurse anesthetist via an epidural needle or an epidural catheter that is removed shortly after the drug is given. Test doses of lidocaine and epinephrine to verify catheter placement may increase the release rate of EREM, so the drug should not be given for 15 minutes after a test dose.[8] Epidural local anesthetics should not be given with EREM because this can produce a physiochemical interaction and reduce the extended-release mechanism.[3] EREM has not been studied in infants and children.

Breakthrough pain (an increase in pain above the level of ongoing pain) occurs with most patients.[3,9,10] Therefore, supplemental doses of nonopioid or opioid should be made available to patients.

As with any other opioid used to treat postoperative pain, EREM should be administered as part of a multimodal analgesic plan.[11] Nonopioid analgesics, such as acetaminophen and a nonsteroidal antiinflammatory drug (NSAID), if not contraindicated, will improve pain control and perhaps reduce the amount of supplemental opioid required.[11] Further research is needed to determine if the routine addition of nonopioids to the treatment plan will allow administration of a reduced EREM dose; however, it seems that this would be likely. The benefit of this approach is that a lower EREM dose could lead to a reduction in opioid-induced adverse effects.[11]

Effectiveness of EREM in Surgical Patients

The following research articles show that EREM at doses of 10 to 15 mg provides effective analgesia for surgical patients undergoing lower abdominal or lower extremity surgery. The time to first request for additional analgesics varies widely with reported median times of approximately 3 to 21 hours.[9,10] The most common adverse effects are nausea and pruritus, and all adverse effects are most common during the first 24 hours after EREM injection.[3,9,10]

A placebo-controlled, double-blind, multicenter study evaluated EREM use in 200 patients after total hip arthroplasty.[10] Patients were randomized to receive 15 mg, 20 mg, or 25 mg of EREM, or an epidural injection of saline before the induction of general or spinal anesthesia, approximately 30 minutes before surgery. Upon first request for analgesia, all patients were given a 25-μg clinician-administered dose