Extended-release lipid-foam encapsulated epidural morphine: Clinical efficacy and safety precautions

Rob Hutchison, PharmD

INTRODUCTION

New developments in opioid analgesic delivery systems have centered around extending the release rate. One of the new delivery mechanisms, extended-release lipid-foam encapsulated epidural morphine, DepoDur (Endo Pharmaceuticals, Inc., Chadds Ford, PA), extends the release rate compared to standard 5-mg epidural morphine.[1] Most patients will require supplement opioids during the 48-hour interval after single-injection epidural DepoDur. The sustained-release lipid-foam encapsulated morphine formulation (Figure 1), EREM, is indicated for acute postoperative pain. It is administered as a single one-time dose in the lumbar epidural space for 48 hours' duration. From a theoretical point of view, extending the duration of release, intuitively, would control pain with less opportunity for periods of subtherapeutic levels as compared to intermittent dosing. The extended-release mechanism would also seem to lower the potential for adverse medication reactions compared to potentially excessive amounts of opioids during intermittent therapy. The clinical studies to date do show better pain control, but adverse drug reactions are not lower and may be slightly higher.[2,3] Furthermore, special precautions should be considered when administering extended-release lipid-foam encapsulated epidural morphine.

CLINICAL EFFICACY

The recommended dosing for major orthopedic surgery of lower extremities is 15 mg. For lower abdominal or pelvic surgery the recommended dose is 10 to 15 mg. Some patients may benefit from a 20-mg dose; however, the incidence of respiratory events was dose-related in clinical trials.[1,4]

Pain control

A randomized, multicenter, double-blind parallel-group study evaluated the pain intensity after 10- and 15-mg DepoDur as compared to epidural morphine 5 mg in 75 patients undergoing elective cesarean section.[2] The pain intensity scores were significantly lower in the DepoDur groups.

In another randomized, phase III trial comparing 10- and 15-mg DepoDur (as well as higher doses) with standard epidural morphine 5 mg in patients undergoing lower abdominal surgery, intravenous (IV) fentanyl patient-controlled analgesia (PCA) was available for rescue dosing. In this study, the pain intensity (based on AUC) at rest was significantly lower in the 15-mg DepoDur group ($p < 0.05$) but not the 10-mg DepoDur group.[3]

Supplemental opioids

Although DepoDur has demonstrated better pain control, supplement rescue opioids will be required in most patients during the 48-hour dosing interval. A randomized, multicenter, double-blind parallel-group study evaluated the efficacy of single epidural DepoDur doses of 5 (not a recommended dose), 10, and 15 mg compared to epidural morphine 5 mg in 75 patients undergoing elective cesarean section.[2] Most patients (96 percent) received supplemental analgesics during the 48-hour study period. The opioid use in the 0 to 48 hour period was less in the DepoDur group ($p < 0.05$); the 10-mg DepoDur group required a mean of 25 mg of supplement morphine equivalent (SME) compared to a mean of 47 mg SME in the control morphine group. There were no significant differences among treatment groups in the proportion of patients who received no supplemental analgesics.

Another randomized phase III trial compared 10- and 15-mg DepoDur (as well as higher doses) with standard epidural morphine 5 mg in patients undergoing lower abdominal surgery. IV fentanyl PCA was available for rescue analgesia. In this study, the amount of 48-hour mean rescue IV fentanyl PCA was significantly lower in the 15-mg DepoDur group but not the 10-mg DepoDur group.[3]

Adverse events

A randomized, multicenter, double-blind parallel-group

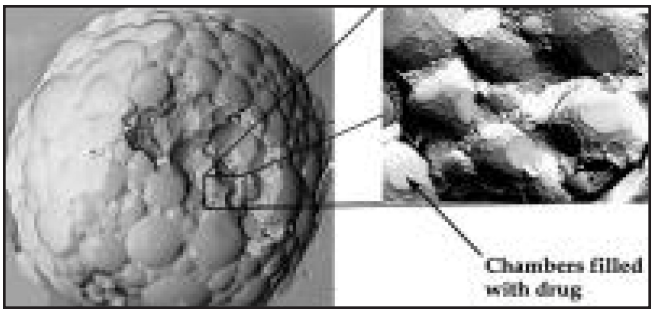

Figure 1. Electron micrograph of DepoFoam particles.

study evaluated the pain intensity after 10- and 15-mg DepoDur compared to epidural morphine 5 mg in 75 patients undergoing elective cesarean section.[2] See Table 1 for adverse reaction rates.

In the other phase III trial previously described, which compared 10- and 15-mg DepoDur (as well as higher doses) with standard epidural morphine 5 mg in patients undergoing lower abdominal surgery, pruritus and urinary retention were significantly higher in the DepoDur group.[3]

PRECAUTIONS

There are several inherent precautions required with sustained-release lipid-foam encapsulated morphine.

Protection from freezing

DepoFoam consists of lipid-based particles containing discrete water-filled chambers dispersed through the lipid matrix. Freezing DepoDur may destroy the slow-release mechanism.

Refrigeration storage

DepoDur is stored in a refrigerated temperature range of 2° to 8° C (36° to 46° F), but may be held at 15° to 30°C (59° to 86°F) for up to seven days in the intact, unopened vial.

Physicochemical interaction

It is important that DepoDur not be administered within 15 minutes of a local anesthetic such as lidocaine. Concomitant administration results in an increase in the rate of system morphine delivery.

Administration

The vial should be gently inverted and not vigorously shaken. An inline filter should not be used.

Awareness

One of the postoperative concerns is identification of a patient who has received sustained-release lipid-foam encapsulated morphine. As compared to standard epidural therapy, DepoDur requires no infusion device to enhance awareness after administration. Therefore, a special monitoring protocol should be established to ensure that members of the staff are aware that the patient has been given a medication with ongoing effects for 48 hours. In several case reports, fentanyl transdermal patches, which also have an extended release, have been overlooked and/or created associated adverse events owing to lack of awareness.[5]

Proper monitoring

Patients getting DepoDur may be inadvertently regarded by staff as needing less monitoring than patients with indwelling epidural catheters and IV PCA infusions.[6] Studies in patients who have sleep apnea are needed before DepoDur can be administered in this group of patients.

SUMMARY

DepoDur is a unique delivery system that has a Food and Drug Administration–approved recommended dose of 15 mg for orthopedic lower extremity surgery and a 10- to 15-mg dose for lower abdominal or pelvic surgery. Some patients may benefit from a 20-mg dose, but the incidence of serious adverse respiratory events has been dose related in clinical trials. For cesarean section, the recommended dose is 10 mg. Most patients will require supplemental analgesics during the 48 hours post surgical

Table 1. Adverse reaction rates in DepoDur versus morphine[2]

	Morphine 5 mg	DepoDur 10 mg	DepoDur 15 mg
Pruritus	28%	33%	67%
Nausea	39%	50%	50%
Vomiting	22%	11%	33%
Constipation	6%	17%	6%

procedure as well as routine monitoring similar to present continuous epidural monitoring procedures. The unique delivery system requires additional safety and storage precautions. The clinical studies to date do not show DepoDur administration to have any lower adverse reaction profile compared to standard epidural morphine.[2,3]

Rob Hutchison is a clinical pharmacy specialist in pain management at Presbyterian Hospital of Dallas and assistant professor at Texas Tech University Health Sciences Center School of Pharmacy, in Dallas, Texas. Contact author: robhutchison@texashealth.org.

REFERENCES

1. DepoDur (morphine sulfate extended-release liposome injection) package insert. Endo Pharmaceuticals, Inc. May 2004.
2. Carvalho B, Riley E, Cohen S, et al.: Single-dose, sustained-release epidural morphine in the management of postoperative pain after elective cesarean delivery: Results of a multicenter randomized study. *Anesth Analg.* 2005; 100: 1150-1158.
3. Gambling D, Hughes T, Martin G: A comparison of DepoDur(r), a novel, single-dose extended-release epidural morphine, with standard epidural morphine for pain relief after lower abdominal surgery. *Anesth Analg.* 2005; 100: 1065-1074.
4. Cada D, Levien T, Baker D: Morphine sulfate extended-release liposomal injection. *Hospital Pharmacy.* 2004; 39(9): 871-879.
5. Institute for Safe Medicine Practices Newsletter. July 1, 2004.
6. Institute for Safe Medicine Practices Medication Safety Alert. 10(3); February 10, 2005.