

Morphine Sulfate Extended-Release Liposome Injection

(DepoDur™, Endo® Pharmaceuticals, Inc.)

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Goal. This article is intended to provide the reader with an overview of the pharmacology, pharmacokinetics, adverse effects, drug interactions, storage requirements and safety concerns of morphine sulfate extended-release liposome injection (DepoDur™), herein referred to as liposomal morphine, while also reviewing the published and unpublished clinical evidence for the drug.

Objectives. 1) Identify the FDA-approved indications for the use of liposomal morphine; 2) List the available doses of liposomal morphine; 3) Recognize the published studies that provide evidence for the use of this drug; 4) List proper storage precautions and expiration information; 5) Discuss safety concerns surrounding use of liposomal morphine.

Current pain management strategies in the postoperative setting are not without limitations. Less than optimal analgesia is the result of various factors including the use of “as needed” medication orders when around-the-clock treatment is needed, delay of administration of medications by busy staff, patient reluctance to request medications secondary to stoicism or for fear of addiction, inability to use the oral route given the patient population and complications arising from equipment prone to malfunction.¹

Current advanced approaches to postoperative analgesia include the use of epidural catheters, intravenous patient-controlled analgesia (PCA), continuous peripheral nerve blocks and multimodal analgesia. Each of these approaches has factors that limit its utility and none is without problems. A recent meta-analysis indicated that administration of analgesics via epidural catheters provides greater pain relief than that provided by intravenous PCA or oral pain medication;² however, epidural catheters have limitations that include equipment malfunction, increased labor requirements by nursing staff and others, decreased patient mobility and increased risk of hematoma formation in the presence of anticoagulation. Intravenous PCA and continuous peripheral nerve blocks are also limited by equipment failure and decreased patient mobility. Multimodal analgesia relies on the intermittent administration of several pain medications with differing mechanisms of action to maximize analgesia and minimize side effects. This approach can be labor-intensive and usually requires use of the oral route.¹

The optimal approach to postoperative analgesia would provide uninterrupted pain relief with minimal toxicity, allow for minimal staff time and maximal patient mobility, and would be compatible with administration of anticoagulants.¹

Liposomal morphine, approved by the U.S. Food and Drug

Summary

Indications. Liposomal morphine is indicated for single-dose epidural administration, at the lumbar level, for the treatment of pain after major surgery. It is not intended for intravenous, intrathecal, or intramuscular administration nor administration into the thoracic epidural space or higher. Liposomal morphine is administered before surgery or following clamping of the umbilical cord during cesarean section.

Monitoring Parameters. Patients should be monitored for common adverse effects of opioid use including respiratory depression, hypotension, gastrointestinal obstruction and urinary retention. Respiratory depression may occur more frequently with liposomal morphine use as compared to standard therapy; therefore, patients should be closely monitored for a minimum of 48 hours in a fully equipped and staffed environment with immediate access to narcotic antagonists. In the instance of liposomal morphine administration followed by cancellation of the surgical procedure, patients should be monitored with extreme vigilance, as risk of respiratory depression may be higher.

Dose. The recommended dose for orthopedic surgery of the lower extremity is 15 mg; for lower abdominal or pelvic surgery, 10 mg to 15 mg (some patients may benefit from a 20 mg dose; however, incidence of adverse respiratory events may be higher); for cesarean section, 10 mg.

Geriatrics. As with all opioid use in the elderly, use caution when selecting a dose, as this population may be more sensitive to adverse effects.

Pregnancy. Category C

Breast Feeding. Liposomal morphine is excreted into breast milk. Use caution when administering to a nursing mother.

Renal Insufficiency. No dose adjustment in renal insufficiency as accumulation is not expected since liposomal morphine is intended for single-dose administration.

Hepatic Impairment. No dose adjustment in hepatic impairment as accumulation is not expected since liposomal morphine is intended for single-dose administration.

Cost. Average wholesale price (AWP) for single doses of 10 mg, 15 mg and 20 mg are \$202.03, \$220.96 and \$239.90, respectively.



Administration in May 2004, is a new long-acting dosage formulation of morphine sulfate designed for epidural administration. It is indicated for the relief of pain following major surgery and for cesarean section following clamping of the umbilical cord. Liposomal morphine uses the technology of the DepoFoam® drug delivery system, which consists of a matrix of microscopic, sphere-shaped particles that are composed of many nonconcentric internal aqueous chambers containing morphine sulfate. Chambers are separated from each other by synthetic lipid membranes which degrade and/or reorganize and slowly release drug over time. Liposomal morphine offers the benefits of prolonged pain relief (approximately 48 hours) from a single administration without the risks associated with indwelling epidural catheters.³

PHARMACOLOGY/PHARMACOKINETICS

Although the exact mechanism(s) of pharmacological activity are unknown, opioids are thought to interact with saturable binding sites in the central nervous system (CNS) and other tissues and may cause alterations in the rate of release of neurotransmitters. Morphine likely produces analgesia by principally interacting with opioid mu receptors.

Morphine that is released from liposomal morphine is absorbed both neuraxially and systemically. Maximal drug concentration (C_{max}) for standard 5 mg morphine administered epidurally was higher than the C_{max} for 5 mg of liposomal morphine; however, systemic area-under-the-curve (AUC) was comparable to liposomal morphine;³ see Table 1.

Following administration of liposomal morphine, mean concentrations of morphine in lumbar cerebral spinal fluid (CSF) at approximately 3 hours were 100 to 400 times greater than concentrations in plasma. At 24 hours after liposomal morphine administration, CSF concentrations of morphine were similar to the normal range that is associated with pain relief (10.5 ng/mL to 101 ng/mL), suggesting that liposomal morphine can provide effective analgesia for an extended period after only one dose. Clearance of morphine from CSF and plasma occur at similar rates. Spinal metabolism of morphine was not observed.³

Following morphine release from liposomal morphine and systemic absorption, distribution and elimination are the same as other morphine formulations. The volume of distribution of morphine is 1 L/kg to 4 L/kg and it is distributed to the liver, kidneys, skeletal muscle, gastrointestinal tract, lungs, brain and spleen. Plasma protein binding is 20% to 35% and is reversible. Morphine partitions into breast milk and crosses placental membranes. The major route of morphine metabolism is detoxifica-

tion by the liver via conjugation and formation of both active and non-active glucuronides. The majority of glucuronidated morphine metabolites are excreted in the urine, with a small amount excreted in the bile. Ten percent of morphine is excreted in the urine unchanged. Mean plasma clearance of morphine is 20 mL/kg/min to 30 mL/kg/min in adults.³

Bioavailability of morphine from liposomal morphine compared to standard morphine ranged from 100.21% to 81.69%, respectively, in patients receiving 10 mg and 25 mg liposomal morphine dosages. Liposomal morphine demonstrated linear pharmacokinetics. Patients aged 65 years or older exhibited a 13% increase in AUC; pediatric patients have not been studied. Morphine has altered pharmacokinetics in patients with renal and hepatic impairment; however, accumulation of morphine or its metabolites is not expected with liposomal morphine since it is intended for single dose administration.³

CLINICAL TRIALS

To date, two clinical trials^{4,5} involving lower abdominal surgery and elective cesarean section have been published in the biomedical literature.

Other unpublished trials⁶⁻⁹ in hip and knee arthroplasty have been displayed as posters in abstract form at various meetings of professional organizations including the American Society of Regional Anesthesia and the American Society of Anesthesiologists.

Lower abdominal surgery

Gambling et al⁴ conducted a randomized, double-blind study to evaluate the efficacy and safety of 5 mg, 10 mg, 15 mg, 20 mg and 25 mg of liposomal morphine to a standard 5 mg dose of epidural morphine in patients undergoing lower abdominal surgery. Eligible patients included men and women ≥ 18 years of age who were receiving general or intrathecal anesthesia. Patients were excluded if they had American Society of Anesthesiologists (ASA) Physical Status of 4 or Body Mass Index (BMI) ≥ 40 kg/m², had undergone cesarean section, herniotomy, laparoscopy, transurethral prostatectomy, appendectomy, or lower abdominal vascular surgery. Pregnant or lactating females were not eligible.

Five hundred forty-one patients were randomized to receive a single dose of liposomal morphine or standard morphine 30 minutes prior to surgery and all patients were allowed access to fentanyl via a PCA pump. Key endpoints included total fentanyl usage at 48 hours, pain intensity at 48 hours and patient satisfaction of pain medication.

The investigators observed a dose-related reduction in need

TABLE 1. PHARMACOKINETICS OF LIPOSOMAL MORPHINE AND STANDARD MORPHINE SULFATE³

Parameter	Liposomal morphine 5 mg (n=10)		Standard morphine sulfate 5 mg (n=9)	
	Mean	SD	Mean	SD
C_{max} (ng/mL)	7.1	3.4	23.8	12.8
t_{max} (hr)*	1.0	(0.3-4.0)	0.3	(0.3-2.0)
AUC (ng·hr/mL)	38.8	10.4	42.8	8.4
$t_{1/2}$ (hr)	3.8	1.0	2.2	0.5

*Median (range); SD=standard deviation

TABLE 2. MEAN TOTAL FENTANYL USAGE (\pm SD) AT 48 HRS AS REPORTED BY GAMBLING ET AL⁴

Liposomal morphine			
5 mg	10 mg	20 mg	25 mg
1218 \pm 894 mcg	995 \pm 987 mcg	972 \pm 982 mcg	683 \pm 620 mcg
-	p=0.0446	p=0.0221	p<0.0001

SD= standard deviation

for fentanyl through 48 hours for patients receiving liposomal morphine (estimated slope by linear regression analysis was -22.2; p=0.0002). The 10 mg, 20 mg and 25 mg liposomal morphine groups had mean total fentanyl usage of 995 \pm 987 mcg (p=0.0446), 972 \pm 982 mcg (p=0.0221), and 683 \pm 620 mcg (p<0.0001), respectively at 48 hours as compared with a total fentanyl usage of 1218 \pm 894 mcg in patients receiving the 5 mg liposomal morphine. See Table 2. Thirteen percent of liposomal morphine-treated patients required no IV fentanyl at 48 hours as compared to 2% of the standard morphine-treated patients (p<0.01). Patients receiving liposomal morphine 15 mg, 20 mg and 25 mg reported significantly lower pain intensity scores and more satisfaction with their pain relief when compared to patients receiving standard morphine.

The adverse events experienced in patients enrolled were typical of those observed with opioid use. No significant differences were reported between the liposomal morphine and standard morphine groups other than the incidence of pruritis (39% versus 55% in the 5 mg standard morphine group and 15 mg liposomal morphine groups, respectively, p<0.05) and urinary retention (3% in the 5 mg standard morphine group and 13% in the 15 mg liposomal morphine groups, p<0.05). See Table 3 for a summary of adverse events.

Twelve percent of liposomal morphine-treated patients received an opioid antagonist as compared to 4.5% of the patients treated with standard morphine. Naloxone use for respiratory

depression was administered in 1.5% of the 5 mg standard morphine group, 0% of the 5 mg and 10 mg liposomal morphine groups, 1.1% in the 15 mg liposomal morphine group, 2.4% and 4.5% in the 20 mg and 25 mg liposomal morphine groups, respectively. See Table 4.

Interpretation of rates of respiratory depression in this study should be performed with caution as respiratory depression was not specifically defined in the protocol, rather left to the discretion of the investigator at each site. Further study of the rate of respiratory depression with liposomal morphine is needed as this study was not sufficiently powered to assess safety. One of the deaths that occurred during this study was considered possibly related to study drug. The authors recommend that if a surgical procedure is cancelled, the patient should be monitored for a minimum of 48 hours in an intensive care setting with access to a continuous infusion of naloxone.

Elective cesarean section

Carvalho et al⁵ conducted a randomized, double blind study to evaluate the safety and efficacy of liposomal morphine 5 mg, 10 mg, or 15 mg compared to 5 mg of standard morphine in 75 patients undergoing elective cesarean section. Women >18 years of age receiving intrathecal anesthesia with bupivacaine and fentanyl, and who had an ASA Physical Status of 1 or 2 were eligible for inclusion. Patients were excluded if their BMI was \geq 40 kg/m² at the beginning of pregnancy, if they gained more than 20 kg during pregnancy or had a history of any condition that would

TABLE 3. PERCENTAGE OF PATIENTS WITH OPIOID RELATED ADVERSE EVENTS AS REPORTED BY GAMBLING ET AL⁴

Adverse effect	Standard morphine	Liposomal morphine				
		5 mg	10 mg	15 mg	20 mg	25 mg
Nausea	67%	58%	75%	65%	68%	66%
Hypotension	21%	16%	25%	24%	24%	23%
Vomiting	26%	28%	25%	24%	25%	23%
Pruritis*	39%	42%	56%	55%	61%	57%
Urinary retention*	3%	4%	6%	13%	11%	14%
Hypoxia	3%	2%	4%	2%	8%	6%
Bradycardia	0%	1%	4%	6%	1%	3%
Somnolence	3%	1%	2%	2%	1%	2%
Hypoventilation	3%	1%	2%	0%	1%	1%

*p<0.05; all other comparisons were nonsignificant

TABLE 4. PERCENTAGE OF PATIENTS WHO RECEIVED OPIOID ANTAGONIST FOR RESPIRATORY DEPRESSION AS REPORTED BY GAMBLING ET AL⁴

Standard morphine	Liposomal morphine				
5 mg	5 mg	10 mg	15 mg	20 mg	25 mg
1.5%	0%	0%	1.1%	2.4%	4.5%
Data did not reach statistical significance					

impact surgery or postoperative care. Patients were ineligible if they received a dural puncture from an epidural needle, a local anesthetic via an epidural catheter, general anesthesia, or if they experienced excessive bleeding during surgery.

Supplemental pain medication was available to all patients in the form of oral and intravenous opioids including intermittent bolus IV morphine and IV morphine via a PCA pump. Key end-points included total usage of supplemental opioid medication, pain intensity using a 100-mm Visual Analog Scale (VAS) and a categorical (CAT) scale, patient satisfaction with pain medication, and overall functional ability.

The mean total supplemental opioid use (\pm standard deviation) in morphine milligram equivalents at 48 hours ranged from 25 mg \pm 21 mg (10 mg liposomal morphine group) to 35 mg \pm 24 mg (5 mg liposomal morphine group), versus 47 mg \pm 34 mg (standard 5 mg morphine sulfate group). Statistical significance was not reached in the 5 mg liposomal morphine group. Ten percent of patients in the 10 mg and 15 mg liposomal morphine groups required IV opioids compared to 44% of patients in the standard 5 mg morphine group during the 24 hour to 48 hour postdose interval ($p=0.029$ for both groups).

No statistically significant differences were observed regarding the proportion of patients who received no supplemental opioids; however, there was a trend toward fewer liposomal morphine-treated patients requiring supplemental pain medication. See Table 5.

Mean pain intensity at rest and with activity as measured by VAS was lower in the liposomal morphine 10 mg and 15 mg groups as compared to the standard 5 mg morphine group ($p=0.0031$ and $p=0.0029$, respectively, at rest and $p=0.0051$ and $p<0.0003$, respectively, with activity). Patients in the 10 mg and 15 mg liposomal morphine groups had better overall functional ability scores as compared to the standard morphine group ($p<0.05$) with the exception of the value for sitting in the 15 mg

group at the 48 hour mark. Twenty-two percent of the standard morphine group ranked their pain control as “very good” as compared to 32%, 53% and 74% of patients in the 5 mg, 10 mg and 15 mg liposomal groups, respectively.

The adverse events were typical of those observed with opioid use. No significant differences in the incidence of adverse effects were observed between all treatment groups. Fifteen percent of patients treated with liposomal morphine and 22% of patients treated with standard morphine received supplemental oxygen due to decreased oxygen saturation. Two patients receiving liposomal morphine and one patient receiving standard morphine required an opioid antagonist. One of the patients in the liposomal group received an opioid antagonist for pruritus and the other for a respiratory rate of 8 breaths per minute and oxygen saturation on air of 91%-96%. The patient receiving standard morphine received an opioid antagonist for pruritus.

Hip arthroplasty

Crews et al⁶ conducted a double blind, placebo-controlled, multicenter study to determine the efficacy and safety of single doses of epidurally administered liposomal morphine versus placebo in patients undergoing hip arthroplasty. Men and women aged 18 years to 75 years were eligible to enroll. Pregnant and lactating women were excluded as well as patients with ASA Physical Status of 4, weight of less than 45 kg, or current or history of complicated hip fracture.

One hundred and twenty patients were randomized and received either placebo or one of three doses of liposomal morphine (10 mg, 20 mg or 30 mg) 30 minutes prior to surgery along with anesthesia. Postoperatively, all patients were allowed to receive IV fentanyl via a PCA pump. Key end points included total fentanyl used for 48 hours post dose, patient pain intensity using VAS and CAT scales, and patient satisfaction with pain medication at 24 hours and 48 hours post dose.

Of patients receiving liposomal morphine (10 mg, 20 mg

TABLE 5. PERCENTAGE OF PATIENTS RECEIVING NO POSTDOSE SUPPLEMENTAL OPIOID BY TREATMENT GROUP AS REPORTED BY CARVALHO ET AL⁵

Time interval (hours)	Standard morphine sulfate 5 mg	Liposomal morphine			
		5 mg (n=19)	10 mg (n=19)	15 mg (n=19)	All (n=57)
0-48	0%	5%	0%	11%	5%
0-24	0%	11%	21%	21%	18%
24-48	0%	11%	5%	21%	12%

Data did not reach statistical significance.

and 30 mg), 20%, 40.6% and 42.3%, respectively, had not required any fentanyl through 24 hours post surgery as compared to 3.7% of the placebo-treated patients ($p=0.001$). At 48 hours, patients receiving liposomal morphine 10 mg, 20 mg and 30 mg had exhibited a similar trend: 5.7%, 15.6%, and 26.9%, respectively versus 3.7% of placebo treated patients ($p=0.042$). Total fentanyl doses from 0 to 48 hours post study drug administration were 2,433.7 mcg, 1,321.2 mcg, 905.2 mcg and 652.1 mcg for the placebo, liposomal morphine 10 mg, 20 mg and 30 mg groups, respectively ($p<0.001$). Patients receiving liposomal morphine generally reported mean pain in the mild range compared to placebo-treated patients who, from 3 hours to 18 hours post dose, reported higher median pain scores in the moderate range ($p<0.001$ for treatment effect at each point in time). Most patients in the liposomal morphine arm of the study rated the study medication as "very good" or "excellent" (55% to 79%) compared to the placebo-treated group (37%). Adverse events included nausea, pruritis, vomiting, hypoxia, hypoventilation, constipation and somnolence.

In a similar study conducted by Viscusi et al,⁷ one hundred ninety-four patients undergoing hip arthroplasty received either placebo or liposomal morphine 15 mg, 20 mg or 25 mg prior to surgery. Men and women aged >18 years receiving general or intrathecal anesthesia and had an ASA Physical Status of 1 to 3 were eligible. Pregnant or lactating women were excluded as well as patients with a BMI ≥ 40 .

Mean postoperative fentanyl used at 48 hours for the liposomal morphine-treated groups was 510.2 mcg versus 2,091.4 mcg for placebo. The mean total fentanyl usage was reduced in groups receiving liposomal morphine compared to the placebo group ($p<0.0001$). A 75% reduction in usage of fentanyl was observed for all liposomal morphine-treated patients at 48 hours as compared to the patients receiving placebo. Patients receiving liposomal morphine 15 mg had required a mean of 663 mcg of fentanyl at 48 hours; the 20 mg and 25 mg groups had received 485.4 mcg and 370.6 mcg, respectively, at 48 hours. Patients receiving liposomal morphine consistently reported less pain than the placebo group. Patients in the liposomal morphine groups rated their pain control significantly better than the placebo group at both 24 and 48 hours ($p<0.0001$ and $p\leq 0.0025$, respectively). Most adverse events experienced in patients enrolled were typical of those observed with opioid use and were mild to moderate in intensity. However, patients receiving liposomal morphine had a 4% incidence of respiratory depression. Almost all cases of respiratory depression occurred within 16 hours of administration of liposomal morphine (excluding the 25 mg group).

An open-label study by Viscusi et al⁸ evaluated single doses of liposomal morphine 10 mg, 20 mg and 30 mg versus a standard 5 mg morphine epidural dose in 37 patients undergoing total hip arthroplasty with concurrent spinal anesthesia. Men and women ages 18 years to 65 years who were free of significant cardiovascular, hepatic, renal, respiratory, hematologic, endocrine or neurologic disease were included. Patients must have been classified as ASA Physical Status of 1 to 3 and were within 35% normal body mass.

Patients were given standard morphine or liposomal morphine just prior to spinal anesthesia and within 30 minutes of surgery. All patients were allowed to receive IV fentanyl via a PCA pump following the surgery. Study endpoints included total amount of fentanyl used post study drug administration, time between dose of study drug and first use of fentanyl, and postoperative pain intensity measured via VAS and CAT scales.

Study groups receiving liposomal morphine 10 mg, 20 mg and 30 mg doses had more patients who did not require supplemental fentanyl (25%, 67%, and 50%, respectively) as compared to the group receiving standard 5 mg morphine (8%) at 24 hours ($p=0.0105$). Statistically significant lower times to first post surgery fentanyl dose were observed in the morphine group as compared to the liposomal morphine groups ($p<0.001$). Fewer patients in the standard morphine-treated group rated their pain intensity as "excellent" as compared to the patients in the liposomal morphine-treated groups at 48 hours (15.4% and 46.2%, respectively).

Knee arthroplasty

Drass et al⁹ conducted a randomized, double-blind study to determine the efficacy and safety of liposomal morphine 20 mg and 30 mg doses compared to IV morphine given via a PCA pump in 168 patients undergoing knee arthroplasty. Inclusion criteria included men and women >18 years of age and ASA Physical Status of 1 to 3. Exclusion criteria included BMI ≥ 40 , pregnant or lactating women, clinically significant disease that could impact the surgery or recovery, previous knee arthroplasty secondary to Paget's disease or cancer metastases of the bone.

Patients were administered either 20 mg or 30 mg of liposomal morphine or a sham placebo epidural injection 30 minutes prior to surgery and the induction of regional or general anesthesia. Following surgery, patients in the liposomal morphine groups were allowed to receive bolus IV hydromorphone until no pain was reported, followed by a PCA pump containing saline. Patients who received the placebo epidural injection were administered an IV morphine bolus followed by morphine via a PCA pump (1 mg every 6 minutes, maximum of 10 mg/hour) at the first request for pain relief. Patients in the placebo group whose pain was not adequately controlled received an IV saline bolus followed by an increase in dose of morphine PCA.

Patients treated with liposomal morphine 20 mg and 30 mg had a significant reduction in mean total opioid usage through 48 hours post dose as compared to the group receiving morphine PCA ($p\leq 0.0001$ at each time point). The liposomal morphine 20 mg and 30 mg groups had a total opioid usage of 44.0 mg and 38.9 mg, respectively, compared to 132.2 mg for the morphine PCA group within the 0 to 48 hour interval ($p\leq 0.0001$). Both treatment groups receiving liposomal morphine had a greater reduction in time-weighted pain intensity scores as compared to the placebo group during time intervals 4 hours to 8 hours, 4 hours to 12 hours, 4 hours to 24 hours and 4 hours to 30 hours ($p<0.05$). The liposomal morphine-treated groups exhibited the adverse effects of pyrexia and pruritus more frequently compared with the morphine PCA-treated group ($p=0.018$ and $p<0.001$, respectively).

ADVERSE EFFECTS

The most common adverse effects (>10%) that occurred in open-label and controlled clinical studies included those typical of opioid medications: nausea, pruritus, vomiting, hypotension, urinary retention, and decreased oxygen saturation. Respiratory depression occurred in 0.7%, 5.1% and 5.8% of the liposomal morphine 10 mg, 15 mg and 20 mg groups, respectively compared to 1% in the standard 5 mg morphine group and 1.8% in the morphine PCA group. The incidence of respiratory depression in liposomal morphine-treated patients of all ages was 4.3% when indicated doses were used, and 6.8% in those patients that received greater than indicated dosages. Respiratory depression occurred in 8.3% of patients 65 years and older when considering all liposomal morphine dosages studied. Narcotic antagonists were required in 4% of all patients receiving liposomal morphine. When respiratory depression occurred in patients receiving recommended liposomal morphine doses, the onset was within 16 hours post dose. Overall adverse event rates were not altered by differences in age, sex, race, BMI, ASA Physical Status or type of anesthesia. A higher rate of serious adverse events was seen in ASA Physical Class 3 patients compared to the overall population.³

DRUG INTERACTIONS

As with standard morphine and all opioid medications, the concurrent use of other CNS depressants can increase the risks of respiratory depression, hypotension, extreme sedation and coma. Patients receiving CNS depressants including tranquilizers, hypnotics, sedatives, droperidol, phenothiazines, general anesthetics and alcohol should be monitored closely. Monoamine oxidase inhibitors have been known to potentiate morphine's action. Monoamine oxidase inhibitors should be discontinued at least 14 days prior to liposomal morphine administration. When neuromuscular blocking agents are administered concomitantly with liposomal morphine, recovery of spontaneous pulmonary ventilation may be delayed.³

Maximal drug concentration of morphine may be elevated when liposomal morphine is administered within less than 15 minutes of a 3-mL epidural test dose of lidocaine 1.5%/epinephrine 1:200,000. No difference in C_{max} occurred when liposomal morphine was administered 15 minutes before or after anesthetic test dose; therefore it is recommended to administer liposomal morphine at least 15 minutes after anesthetic test doses to avoid altered morphine release from liposomal morphine. Flushing the catheter with 1 mL of preservative-free normal saline following the anesthetic test dose is recommended. Administration of liposomal morphine in relation to other epidural anesthetics has not been studied *in vivo*. *In vitro* studies have suggested a similar interaction is likely with other amide local anesthetics. Ester local anesthetics have not been studied with liposomal morphine *in vivo* nor *in vitro*. No other pharmacokinetic drug-drug interactions have been studied. Liposomal morphine should not be mixed with any other medications. No other medications should be administered into the epidural space for a minimum of 48 hours following liposomal morphine. In-line filters should not be used when administering liposomal morphine.³

STORAGE

For routine storage, liposomal morphine must be kept refrigerated at 2° to 8° C. The product may be held at room temperature (15° C to 30° C) in the original, intact, unopened vials for a maximum of 7 days. Liposomal morphine should never be frozen; discard product if freezing has occurred. The vial containing drug requires gentle inversion to resuspend particles just prior to use; avoid shaking or agitation. Liposomal morphine must be used within 4 hours of withdrawal from the vial, discard any remainder product.³ Storage information is summarized in Table 6.

TABLE 6. STORAGE INFORMATION³

- C-II medication; requires locked storage
- Refrigeration for routine storage at 2° to 8° C
- Room temperature at 15° C to 30° C in the original, intact, unopened vials for a maximum of 7 days
- Must use product within 4 hours of withdrawal from the vial
- Do not freeze; discard if freezing has occurred

MEDICATION SAFETY

The Institute for Safe Medication Practices (ISMP) in their February 10, 2005 issue of MedSafetyAlert! Acute Care newsletter identified medication safety issues surrounding liposomal morphine.⁸ Concerns were raised related to clear identification of patients who have received liposomal morphine. Lack of an effective mechanism to identify these patients can lead to overprescribing of narcotics, and concomitant administration of other central nervous system depressants resulting in higher rates of respiratory depression and other avoidable adverse reactions. Proper identification of patients would also be important in relation to physical drug-drug interactions that may occur if other medications are administered into the epidural space with 48 hours of liposomal morphine. The Institute for Safe Medication Practices raised the concern that there may be a potential for nursing staff to inappropriately regard patients receiving liposomal morphine as requiring less monitoring than patients receiving standard morphine via indwelling epidural catheters.

Potential solutions to reduce errors were suggested by ISMP. Suggestions included creation of a preprinted order form indicating the date and time of liposomal morphine administration and monitoring parameters, removal of the epidural catheter to prevent other medications from being delivered epidurally, use of labels on charts, patients' doors, and above beds to indicate that the drug has been given, creation of alerts in computerized physician order entry systems and limiting prescribing of narcotics to anesthesia staff during the first 48 hours following administration of liposomal morphine.

COST, DOSE AND HOW SUPPLIED

Liposomal morphine is available in preservative-free 10 mg/1mL, 15 mg/1.5mL, and 20 mg/2mL single use, amber vials packaged in cartons of five. Average wholesale price (AWP) for single doses of 10 mg, 15 mg, and 20 mg are \$202.03, \$220.96 and \$239.90, respectively.³

CONCLUSION

Liposomal morphine is an epidurally administered, long-acting formulation of morphine sulfate that presents a unique approach to postoperative analgesia. Major benefits of this product include approximately 48 hours of uninterrupted analgesia from single-dose administration without the use of indwelling catheters, compatibility with anticoagulation and the potential for increased patient mobility. Several safety concerns have arisen concerning this product that include uncertainty regarding identification of patients who have received liposomal morphine. Lack of a mechanism to clearly identify these patients can lead to life-threatening and avoidable adverse drug reactions. Additionally, the risk of respiratory depression may be higher with liposomal morphine as compared to standard morphine administered epidurally. Further clinical trials that are powered to assess safety are needed to fully elucidate this issue. Hospital Pharmacy and Therapeutics committees that consider liposomal morphine for formulary inclusion may be inclined to restrict its use to a specific department (i.e. anesthesia), institute guidelines for proper use, create preprinted order forms with required monitoring parameters, provide educational programming for staff, and conduct drug utilization reviews to detect any potential problems. ●

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QUIZ ANSWER FORM *circle one answer per question*

- | | | |
|------------|-------------|-----------|
| 1) a b c d | 7) a b | 13) a b |
| 2) a b c d | 8) a b | 14) a b |
| 3) a b | 9) a b | 15) a b |
| 4) a b c d | 10) a b c d | 16) a b c |
| 5) a b c d | 11) a b c d | 17) a b |
| 6) a b c d | 12) a b | 18) _____ |

Name _____ Designation (RPh, CPhT, etc.) _____

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July/August 2005
Morphine Sulfate Extended-Release Liposome Injection
ACPE Universal Program Number: 175-000-05-050-H01
(No longer valid for CE credit after July 1, 2008)
Release Date: July 1, 2005

KREMER DRUG COMPANY MISSES TWO GOLD FISH

125 years

B. J. Kremer, Fond du Lac, reports the loss of his two prize acrobatic gold fish during a recent raid on his store by a flock of high school students. Following a wager that gold fish were not delectable food, two students proceed to prove that they were. They won their dollar and then took a dish of ice cream for a chaser.

Mr. Kremer is looking for a pair of acrobatic gold fish. Who can supply him?

The Wisconsin Pharmaceutical Journal, December 1920