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Liposomal Bupivacaine: A New Milky White Drug in the O.R.

By: Michael Kenes, Pharm.D.

Background: Bupivacaine is an amide local anesthetic that binds to intracellular sodium channels on the nerve membrane, preventing the generation and propagation of an action potential.[1] Bupivacaine has an extended duration of action compared with other local anesthetics due to its affinity for nerve tissue, with peripheral nerve blocks of 8 to 12 hours being reported. Because of its high affinity for nerve tissue, the addition of vasoconstrictors has not been shown to increase the duration of anesthesia for bupivacaine compared to other agents. For the treatment of post-operative patients, the American Society of Anesthesiologists recommends utilizing local anesthetics in a multimodal analgesic approach.[2] Even with the extended duration of action of bupivacaine compared to other local anesthetics, its duration is relatively short in the clinical scenario of a post-operative patient. To overcome this clinical issue, liposomal bupivacaine (Exparel®; Pacira Pharmaceuticals) was developed.[3] It contains bupivacaine in a multivesicular liposomal suspension and is administered via infiltration into tissue surrounding the surgical site prior to closure in the operating room. It is currently approved by the Food and Drug Administration (FDA) in October 2011 for use in bunionectomy and hemorrhoidectomy procedures; however several trials are being conducted for other indications. Liposomal bupivacaine is currently approved on the Cleveland Clinic Health System formulary without restriction.

Pharmacokinetics: The half-life of liposomal bupivacaine has been shown to be approximately 24 hours after administration of 106 mg for a bunionectomy and approximately 34 hours after administration of 266 mg for a hemor-

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New Posaconazole Formulations: Hold the Side of Fries

By: Matthew Arango, Pharm.D.

What are the indications for using posaconazole? Posaconazole (Noxafil®; Merck) is a triazole antifungal with a broad spectrum of activity against many yeast and moulds, including *Candida* sp., *Aspergillus* sp., and Zygomycetes. It is often used prophylactically in adult patients at high risk of developing invasive fungal infections (IFIs) (e.g., hematopoietic stem cell transplant recipients with graft-versus-host disease, patients with prolonged neutropenia).[1,2] It can also be used for treatment of IFIs refractory to standard therapy, when resistance to other antifungals is confirmed, or when patients are intolerant to standard therapy.[2,3] At the Cleveland Clinic Main Campus, use of oral posaconazole is restricted to the Department of Infectious Diseases (ID) and to the Bone Marrow Transplant Service. Intravenous (IV) posaconazole is restricted to ID for treatment of IFI only.[3]

How is posaconazole supplied? Posaconazole was initially approved by the Food and Drug Administration (FDA) in 2006 as a 40 mg/mL oral suspension (OS). More recently, two new formulations have received FDA ap-

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rhoidectomy. Approximately 3% of the total bupivacaine dose remains outside of the multivesicular lipid formulation to allow for an initial fast onset. The clinical effect has been reported to last up to 72 hours in regulatory trials, but further review highlights a significant reduction in pain intensity of only 24 hours.

Medication Safety Issues: The Institute for Safe Medical Practices (ISMP) issued a warning regarding the milky white appearance of liposomal bupivacaine and its similarity to propofol emulsion.[4] A visual comparison of both products is provided in Figure 1. Unlike, liposomal bupivacaine, propofol is administered intravenously. If accidentally given intravenously, liposomal bupivacaine has the potential to produce toxic blood concentrations and result in atrioventricular block, ventricular arrhythmias, and cardiac arrest. Thus far, the ISMP reports no mix-up errors between the two agents, but recommends avoidance measures such as proper labeling and separate storage of the medications. Other local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from the liposomal dosage form if administered together locally.[3] Liposomal bupivacaine may be administered after lidocaine with a delay of at least 20 minutes. Additionally, the administration of other bupivacaine formulations following liposomal bupivacaine has not been formally studied; therefore, the manufacturer recommends not administering these products within 96 hours of liposomal bupivacaine infiltration.

The Bottom Line: Liposomal bupivacaine is a novel formulation, which fills a gap in the extended treatment of pain in post-operative patients. It provides a local anesthetic effect at the site of infiltration for up to 72 hours and allows for a practical multimodal analgesic approach. Regarding medication safety, the ISMP has identified a potential issue regarding its similar appearance to propofol and the manufacturer has recommended holding other formulations of bupivacaine for 96 hours after liposomal bupivacaine administration.

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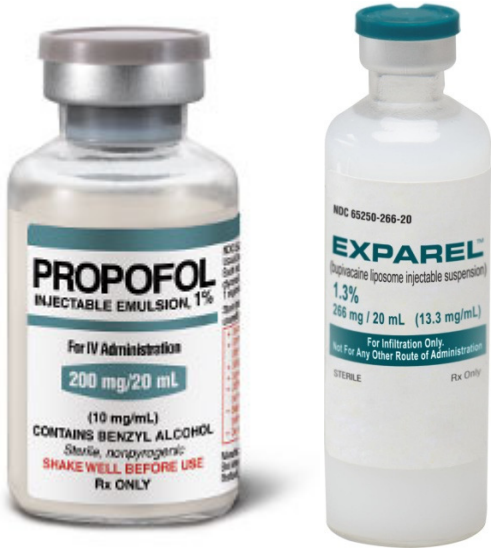
2. The American Society of Anesthesiologists (ASA) Committee on Standards and Practice Parameters. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American society of anesthesiologists task force on acute pain management. Anesthesiology 2012;116:248-73.
3. Exparel [package insert]. Pacira Pharmaceuticals, Inc: San Diego, CA. October 2011.
4. National Alert Network (NAN). Potential for wrong route error with Exparel. *NAN Alert.* March 20, 2012.

Figure 1: Visual Comparison of Propofol versus Exparel®



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proval: a 100 mg delayed-release (DR) tablet in 2013 and a 300 mg (18 mg/mL) IV vial in 2014.[2]

What is a usual dose of posaconazole? Table 1 contains FDA-approved indications and doses for posaconazole. However, alternative dosing regimens have been suggested for other indications.[3] Posaconazole DR tablets and IV solution are not FDA-approved for treatment of IFIs due to limited data, though some experts have recommended using higher doses for treatment than those recommended for prophylaxis.[4] It is recommended to consult with an ID specialist if the DR tablet or IV form is to be used for treatment.

Are there any special considerations for administering IV posaconazole? Similar to the IV formulation of voriconazole, IV posaconazole contains a cyclodextrin vehicle. The package insert recommends avoiding use of IV posaconazole in patients with eGFR < 50 mL/min.[2] For patients with renal insufficiency the risks and benefits of IV posaconazole therapy should be evaluated on an individual basis. It is recommended to administer each dose of IV posaconazole over 90 minutes through a central line with a 0.22 micron filter. Posaconazole IV may be administered through a peripheral line for a single infusion while central access is being obtained, but should then be administered over 30 minutes to minimize time in contact with peripheral veins. Clinicians should monitor for infusion site reactions as peripheral administration of IV posaconazole is associated with a 60% incidence of phlebitis.[2]

How does the DR tablet differ pharmacokinetically from the oral suspension? Posaconazole DR tablets are better absorbed and show less inter- and intra-patient variability. Pharmacokinetic studies have shown that higher posaconazole maximum concentrations and areas-under-the-curve can be achieved with the DR tablet compared to the OS.[4,5] The package insert still recommends administering posaconazole DR tablets with food, but unlike the OS a high-fat meal is not required.[2] No clinically significant effects on posaconazole absorption were observed when proton pump inhibitors (PPIs), H_2-receptor antagonists (H2RAs), or metoclopramide were administered with posaconazole DR tablets. Due to the delayed-release mechanism, posaconazole DR tablets should not be crushed and cannot be administered via a feeding tube.[2]

What strategies can be recommended to improve absorption of posaconazole OS? Patients should take posaconazole OS with a full meal, ideally one with high fat content (~50 g fat). Patients who cannot tolerate a full meal should receive posaconazole OS with a nutritional supplement drink or an acidic carbonated beverage. Patients should not receive a PPI, H2RA, or metoclopramide concomitantly with posaconazole OS. If concomitant use cannot be avoided, the patient should be monitored closely for signs of an IFI and switched to the DR tablet or IV posaconazole when possible.[2] Monitoring of posaconazole levels may be considered for patients felt to be at risk of poor absorption, but there is currently no established therapeutic range and patients should still be monitored closely for development of an IFI.[1]

Table 1: FDA-approved Indications and Doses of Posaconazole Formulations[2,3]

	Oral Suspension	DR Tablets or IV
Prophylaxis	200 mg Q8H*	300 mg Q12H x 1 day, then 300 mg daily*
Treatment of OPC	100 mg Q12H x 1 day, then 100 mg daily x 13 days	*Not FDA-approved for treatment of IFIs*
Treatment of refractory OPC	400 mg Q12H†	*Not FDA-approved for treatment of IFIs*

DR=Delayed-release FDA=Food and Drug Administration IFIs=Invasive fungal infections IV=Intravenous
OPC=Oropharyngeal candidiasis
*Duration is based on recovery from neutropenia or immunosuppression
†Duration of therapy is based on patient's underlying disease and clinical response

What's the bottom line? Posaconazole OS requires administration with a high-fat meal for best absorption. Posaconazole DR tablets do not require a high-fat meal and are not affected by acid suppressants. For IV administration of posaconazole a central line is required and the risk of accumulation of the cyclodextrin vehicle must be considered in patients with renal impairment.

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Simeprevir and Sofosbuvir: New Oral Treatments for Hepatitis C

By: Abira Corrigan, Pharm.D. Candidate

Introduction: Treatment of hepatitis C has long involved complex drug regimens with significant side effects for the patient. Recently the Food and Drug Administration (FDA) approved two new oral medications, simeprevir (Olysio®; Janssen Products LP) and sofosbuvir (Sovaldi®; Gilead Sciences, Inc.), for the treatment of hepatitis C. These two medications may make treatment easier and better tolerated for the nearly 3.2 million people in the United States diagnosed with hepatitis C.[1] Additionally, they offer new approaches to therapy where there are currently limited available options.

Clinical Trials: In clinical trials, simeprevir has demonstrated improved sustained virologic response (SVR) rates in patients with genotype 1 that failed to respond to therapy with peg-interferon/ribavirin, while sofosbuvir has been associated with an improved SVR in previously untreated patients with genotypes 2 and 3 and has the benefit of being part of an all oral therapy regimen.[2,3] When administered with ribavirin alone, sofosbuvir has been shown to be effective in treating hepatitis C, offering a potential new treatment approach when peg-interferon combination therapy is not an option.[4]

Comparison of New Agents: With simeprevir and sofosbuvir's recent availability, it is important to be knowledgeable about these medications to help care for patients and be able to answer various questions about these new therapies. A summary of key information about simeprevir and sofosbuvir is provided in Table 1. The content of this table highlights important differences and similarities between the two medications including FDA-approved indications, dosing and administration, mechanism of action, side effects, monitoring, available dosage forms, pregnancy risk-category, and suggested wholesale cost .

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3. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon S et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013;368 (20):1878-87.
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6. Simeprevir (Olysio®) package insert. Jansen Therapeutics, Division of Jansen Products, LP, Titusville, NJ 08560. 2013 Nov.
7. Sofosbuvir (Sovaldi®) package insert. Gilead Sciences, Inc. Foster City, CA 94404. 2013 Dec.

Table 1: Comparison of Simeprevir and Sofosbuvir[5,6,7]

	Simeprevir (Olysio®)	Sofosbuvir (Sovaldi®)
FDA-Approved Indication	Treatment of genotype 1 chronic hepatitis C as a component of a combination antiviral treatment regimen	Treatment of genotype 1, 2, 3, or 4 chronic hepatitis C including patients with hepatocellular carcinoma and those with HCV/HIV-1 co-infection
Dosage/ Administration	150 mg once daily with food Must be given in combination with peg-interferon alfa and ribavirin Treatment duration is specific to indication and therapy response	400 mg daily with or without food May be given with ribavirin and peg-interferon alfa or ribavirin alone Treatment regimen and duration based on HCV genotype and clinical scenario
Mechanism of Action	Direct-acting antiviral treatment for HCV, specifically targeted antiviral therapy for HCV	Direct-acting antiviral agent against HCV
Side effects	Most common SEs in patients receiving combination therapy with peg-interferon and ribavirin were: rash (including photosensitivity), pruritus, and nausea	Most common SEs observed in patients receiving combination therapy with peg-interferon alfa/ribavirin were fatigue, headache, nausea, insomnia, and anemia Most common SEs in patients receiving combination therapy with ribavirin were: fatigue and headache
Pregnancy-Risk Category	X	B/X*
Monitoring	Bilirubin, liver enzymes, and uric acid at baseline and when clinically indicated Serum HCV-RNA at baseline, weeks 4, 12, and 24, at end of treatment, and when clinically indicated Prior to therapy and monthly pregnancy tests up to 6 months following discontinuation for women of child-bearing age	Bilirubin, liver enzymes, and serum creatinine at baseline and when clinically indicated Serum HCV-RNA at baseline, during treatment, end of treatment, and when clinically indicated Prior to therapy and monthly pregnancy tests up to 6 months following discontinuation for women of child-bearing age
Dosage Forms/Cost	150 mg capsule SWP: $948/capsule†	400 mg tablet SWP: $1200/tablet†

FDA=Food and Drug Administration HCV/HIV=Hepatitis C Virus/Human Immunodeficiency Virus SEs=Side Effects
SWP=Suggested Wholesale Price
*If given in combination with ribavirin or peginterferon alfa/ribavirin
†Prices from AmeriSourceBergen wholesaler website