

Triple Therapy Reduces Restenosis After PCI

BY MITCHEL L. ZOLER

NEW ORLEANS — Adding cilostazol to a standard, dual-antiplatelet regimen following the placement of either drug-eluting or bare-metal stents led to less restenosis, late loss, and need for revascularization in a meta-analysis of eight small, randomized trials.

The addition of cilostazol—an inexpensive drug available as a generic for-

mulation—to the standard regimen of aspirin and clopidogrel following percutaneous coronary intervention (PCI) may be “particularly beneficial in patients who are at high risk of restenosis.” Adding cilostazol “should undergo further evaluation in large, definitive, randomized controlled trials,” Dr. Umesh U. Tamhane and his associates reported in a poster at the annual scientific sessions of the American Heart Association.

Cilostazol is primarily used for treating patients who have peripheral artery disease, noted Dr. Tamhane, a cardiologist at the University of Michigan in Ann Arbor. It recently has been investigated as a treatment for PCI patients because of indications that it can reduce neointimal hyperplasia and smooth muscle-cell proliferation following stent placement, Dr. Tamhane said in an interview.

Adding cilostazol may also be a way to

further inhibit platelet aggregation and the risk of thrombosis, another important goal of medical therapy following PCI. Adding a cilostazol regimen of 100 mg b.i.d. to standard dosages of aspirin and clopidogrel in patients who underwent PCI following an acute myocardial infarction led to significantly greater platelet inhibition, compared with both dual-antiplatelet therapy with standard dosages and dual-antiplatelet therapy with a doubled clopidogrel dosage, in a randomized study with 90 patients, reported researchers from South Korea in a second poster presented at the meeting.

Currently, the data supporting cilostazol-based triple therapy are “not robust enough to support routine use, but a case can be made for [using it on] patients who are considered extremely high risk for restenosis,” said Dr. Hitinder S. Gurm, director of carotid interventions in cardiovascular medicine at the University of Michigan in Ann Arbor and a coauthor of the meta-analysis presented by Dr. Tamhane.

“I have used triple therapy [aspirin, clopidogrel, and cilostazol] in a handful

Triple therapy including cilostazol was associated with significant reductions in binary restenosis, late loss, and need for target lesion revascularization during follow-up.

of patients who were undergoing PCI for restenotic lesions, the patients who usually have the highest risk for restenosis,” Dr. Gurm said in an interview. The meta-analysis by Dr. Tamhane, Dr. Gurm, and their associates used a literature search in October 2008 that identified eight randomized, controlled studies reported during 2005-2008 that compared triple therapy with aspirin and clopidogrel. Three studies involved bare-metal stents, and five used drug-eluting stents. The studies together included about 2,600 patients.

The meta-analysis showed that triple therapy including cilostazol was associated with significant reductions in binary restenosis, late loss, and need for target lesion revascularization during follow-up. Most of the studies had consistent results in favor of triple therapy for all of these end points.

The South Korean study of MI patients who underwent PCI involved 90 evaluable patients, 30 of whom were randomized to 75 mg clopidogrel and 200 mg aspirin daily following PCI. Another 30 patients were treated with 200 mg aspirin and 150 mg clopidogrel daily. The third group received 75 mg clopidogrel and 200 mg aspirin as well as 100 mg cilostazol b.i.d.

The regimen that included cilostazol led to significantly better reductions in platelet aggregation than did the other two regimens tested, reported Dr. Young-Hoon Jeong and his associates from Gyeongsang National University Hospital in Jinju, South Korea. ■



LIDODERM® (Lidocaine Patch 5%)

Rx only

Brief Summary (For full Prescribing Information refer to package insert.)

INDICATIONS AND USAGE

LIDODERM is indicated for relief of pain associated with post-herpetic neuralgia. It should be applied only to **intact skin**.

CONTRAINDICATIONS

LIDODERM is contraindicated in patients with a known history of sensitivity to local anesthetics of the amide type, or to any other component of the product.

WARNINGS

Accidental Exposure in Children

Even a used LIDODERM patch contains a large amount of lidocaine (at least 665 mg). The potential exists for a small child or a pet to suffer serious adverse effects from chewing or ingesting a new or used LIDODERM patch, although the risk with this formulation has not been evaluated. It is important for patients to **store and dispose of LIDODERM out of the reach of children, pets, and others.** (See HANDLING AND DISPOSAL)

Excessive Dosing

Excessive dosing by applying LIDODERM to larger areas or for longer than the recommended wearing time could result in increased absorption of lidocaine and high blood concentrations, leading to serious adverse effects (see ADVERSE REACTIONS, Systemic Reactions). Lidocaine toxicity could be expected at lidocaine blood concentrations above 5 µg/mL. The blood concentration of lidocaine is determined by the rate of systemic absorption and elimination. Longer duration of application, application of more than the recommended number of patches, smaller patients, or impaired elimination may all contribute to increasing the blood concentration of lidocaine. With recommended dosing of LIDODERM, the average peak blood concentration is about 0.13 µg/mL, but concentrations higher than 0.25 µg/mL have been observed in some individuals.

PRECAUTIONS

General

Hepatic Disease: Patients with severe hepatic disease are at greater risk of developing toxic blood concentrations of lidocaine, because of their inability to metabolize lidocaine normally.

Allergic Reactions: Patients allergic to para aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine. However, LIDODERM should be used with caution in patients with a history of drug sensitivities, especially if the etiologic agent is uncertain.

Non-intact Skin: Application to broken or inflamed skin, although not tested, may result in higher blood concentrations of lidocaine from increased absorption. LIDODERM is only recommended for use on intact skin.

Eye Exposure: The contact of LIDODERM with eyes, although not studied, should be avoided based on the findings of severe eye irritation with the use of similar products in animals. If eye contact occurs, immediately wash out the eye with water or saline and protect the eye until sensation returns.

Drug Interactions

Antiarrhythmic Drugs: LIDODERM should be used with caution in patients receiving Class I antiarrhythmic drugs (such as tocainide and mexiletine) since the toxic effects are additive and potentially synergistic.

Local Anesthetics: When LIDODERM is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: A minor metabolite, 2, 6-xylylidine, has been found to be carcinogenic in rats. The blood concentration of this metabolite is negligible following application of LIDODERM.

Mutagenesis: Lidocaine HCl is not mutagenic in Salmonella/mammalian microsome test nor clastogenic in chromosome aberration assay with human lymphocytes and mouse micronucleus test.

Impairment of Fertility: The effect of LIDODERM on fertility has not been studied.

Pregnancy

Teratogenic Effects: Pregnancy Category B. LIDODERM (lidocaine patch 5%) has not been studied in pregnancy. Reproduction studies with lidocaine have been performed in rats at doses up to 30 mg/kg subcutaneously and have revealed no evidence of harm to the fetus due to lidocaine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, LIDODERM should be used during pregnancy only if clearly needed.

Labor and Delivery

LIDODERM has not been studied in labor and delivery. Lidocaine is not contraindicated in labor and delivery. Should LIDODERM be used concomitantly with other products containing lidocaine, total doses contributed by all formulations must be considered.

Nursing Mothers

LIDODERM has not been studied in nursing mothers. Lidocaine is excreted in human milk, and the milk: plasma ratio of lidocaine is 0.4. Caution should be exercised when LIDODERM is administered to a nursing woman.

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Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Application Site Reactions

During or immediately after treatment with LIDODERM (lidocaine patch 5%), the skin at the site of application may develop blisters, bruising, burning sensation, depigmentation, dermatitis, discoloration, edema, erythema, exfoliation, irritation, papules, petechia, pruritus, vesicles, or may be the locus of abnormal sensation. These reactions are generally mild and transient, resolving spontaneously within a few minutes to hours.

Allergic Reactions

Allergic and anaphylactoid reactions associated with lidocaine, although rare, can occur. They are characterized by angioedema, bronchospasm, dermatitis, dyspnea, hypersensitivity, laryngospasm, pruritus, shock, and urticaria. If they occur, they should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

Other Adverse Events

Due to the nature and limitation of spontaneous reports in postmarketing surveillance, causality has not been established for additional reported adverse events including:

Asthenia, confusion, disorientation, dizziness, headache, hyperesthesia, hypoesthesia, lightheadedness, metallic taste, nausea, nervousness, pain exacerbated, paresthesia, somnolence, taste alteration, vomiting, visual disturbances such as blurred vision, flushing, tinnitus, and tremor.

Systemic (Dose-Related) Reactions

Systemic adverse reactions following appropriate use of LIDODERM are unlikely, due to the small dose absorbed (see CLINICAL PHARMACOLOGY, Pharmacokinetics). Systemic adverse effects of lidocaine are similar in nature to those observed with other amide local anesthetic agents, including CNS excitation and/or depression (light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold, or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression, and arrest). Excitatory CNS reactions may be brief or not occur at all, in which case the first manifestation may be drowsiness merging into unconsciousness. Cardiovascular manifestations may include bradycardia, hypotension, and cardiovascular collapse leading to arrest.

OVERDOSAGE

Lidocaine overdose from cutaneous absorption is rare, but could occur. If there is any suspicion of lidocaine overdose (see ADVERSE REACTIONS, Systemic Reactions), drug blood concentration should be checked. The management of overdose includes close monitoring, supportive care, and symptomatic treatment. Dialysis is of negligible value in the treatment of acute overdose with lidocaine.

In the absence of massive topical overdose or oral ingestion, evaluation of symptoms of toxicity should include consideration of other etiologies for the clinical effects, or overdosage from other sources of lidocaine or other local anesthetics.

The oral LD₅₀ of lidocaine HCl is 459 (346-773) mg/kg (as the salt) in non-fasted female rats and 214 (159-324) mg/kg (as the salt) in fasted female rats, which are equivalent to roughly 4000 mg and 2000 mg, respectively, in a 60 to 70 kg man based on the equivalent surface area dosage conversion factors between species.

DOSAGE AND ADMINISTRATION

Apply LIDODERM to intact skin to cover the most painful area. Apply up to three patches, only once for up to 12 hours within a 24-hour period. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. (See HANDLING AND DISPOSAL) Clothing may be worn over the area of application. Smaller areas of treatment are recommended in a debilitated patient, or a patient with impaired elimination.

If irritation or a burning sensation occurs during application, remove the patch (es) and do not reapply until the irritation subsides.

When LIDODERM is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered.

HANDLING AND DISPOSAL

Hands should be washed after the handling of LIDODERM, and eye contact with LIDODERM should be avoided. Do not store patch outside the sealed envelope. Apply immediately after removal from the protective envelope. Fold used patches so that the adhesive side sticks to itself and safely discard used patches or pieces of cut patches where children and pets cannot get to them. LIDODERM should be kept out of the reach of children.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature].

Manufactured by:
Endo Pharmaceuticals Inc.
Chadds Ford, Pennsylvania 19317



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