

Homocysteine-Lowering Therapy: Doubts Persist

BY BRUCE JANCIN

Denver Bureau

VIENNA — Homocysteine lowering with B vitamins and folate didn't reduce mortality or cardiovascular events in the large randomized Western Norway B-vitamin Intervention Trial (WENBIT), Dr. Marta Ebbing reported at the annual congress of the European Society of Cardiology.

WENBIT wasn't the first negative trial of homocysteine lowering as secondary car-

diovascular prevention therapy. Completed randomized trials involving nearly 20,000 patients have shown no overall significant benefit, noted Dr. Ebbing of Haukeland University Hospital, Bergen, Norway.

"At this time, vitamin B supplementation is not justified as secondary prevention for coronary artery disease," she concluded. "Homocysteine is a risk marker, but maybe not a causal factor."

WENBIT involved 3,090 patients with established coronary heart disease, most-

ly stable angina and two- or three-vessel disease. They were randomized in a two-by-two factorial design to daily treatment with 0.8 mg of folic acid, 40 mg of B₆, plus 0.4 mg of B₁₂; folic acid and B₁₂; B₆ only; or placebo. The mean baseline homocysteine level was 10.8 micromol/L. It fell by 28% in the groups receiving folate. There is no mandatory fortification of foods with folate in Norway.

During a median 38 months there was a 13.7% incidence of the combined end

point of all-cause mortality, unstable angina, or nonfatal stroke or MI, with no significant difference among the four treatment arms.

Discussant Dr. Salim Yusuf argued that's too early to close the book on homocysteine lowering as preventive therapy. Despite the lack of evidence of an impact on ischemic heart disease events in the nearly 20,000 randomized trial participants to date, there is a modest trend toward fewer strokes, with an average 14% relative risk reduction. WENBIT echoed this trend: there were 9 nonfatal strokes in patients assigned to folic acid plus vitamins B₆ and B₁₂, compared with 15 or 16 in each of the other study arms.

The stroke benefit in the studies reported thus far isn't statistically significant, but the studies were underpowered to show such an effect, with the exception of the second Heart Outcomes Prevention Evaluation (HOPE-2), chaired by Dr. Yusuf.

"There was a nominally significant reduction in strokes with homocysteine lowering in HOPE-2, the only study with a significant number of stroke patients followed up longer than 3 years. When we wrote the paper we believed it was due to play of chance because we had looked at many end points, but perhaps we were wrong," added Dr. Yusuf, director of the Population Health Research Institute and professor of cardiology at McMaster University, Hamilton, Ont.

Homocysteine lowering may have divergent effects in the coronary vascular and cerebrovascular trees. Due to be completed within the next 1-2 years are two major ongoing randomized trials: the Australian VITamins TO Prevent Stroke (VITATOPS) study, featuring 8,000 patients with recent stroke or transient ischemic attack, and the Oxford University-based Study of the Effectiveness of Additional Reductions In Cholesterol and Homocysteine (SEARCH) trial in more than 12,000 patients with various forms of occlusive vascular disease.

"We will have another 20,000 patients' worth of new data, but the key difference is it will be twice as much follow-up. ... It would be wise to wait for the results before we pronounce judgment. Like the WENBIT investigators, I would say at the moment there is no reason to lower homocysteine. But it is too early to write off the hypothesis," he said.

WENBIT was funded by Norwegian nonprofit organizations. ■

LIDODERM® (Lidocaine Patch 5%)

Brief Summary (For full Prescribing Information and Patient 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-xylydine, 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.

Rx only

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CHADDS FORD, PENNSYLVANIA 19317

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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 for:

Endo Pharmaceuticals Inc.
Chadds Ford, Pennsylvania 19317

Manufactured by:

Teikoku Seiyaku Co., Ltd.
Sanbonmatsu, Kagawa 769 2695
Japan

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Vitamin B supplementation is not yet justified for use in secondary prevention.