

Heart Problems Can Occur Early in Anorexia

BY BETSY BATES

LOS ANGELES — Significant cardiac abnormalities were detected in nearly a third of adolescent girls hospitalized for the first time with anorexia nervosa in a San Francisco study, raising questions about whether detailed cardiac work-ups may be warranted early in the course of the disease.

Mortality estimates for anorexia range

from 5% to 20%, with a third of adult deaths due to cardiovascular complications, Dr. Melissa Slivka said at the annual meeting of the Society for Adolescent Medicine.

In adolescents, much less is known about the toll the disease takes on the cardiovascular system and about when changes begin, said Dr. Slivka, a second-year fellow in adolescent medicine at the University of California, San Francisco.

She and her associates enrolled 31 adolescents with a mean age of 15 years whose reported food restricting behavior averaged 8.5 months.

"We chose subjects being hospitalized for the first time to specifically look at cardiovascular abnormalities in subjects with shorter-term restricting histories rather than those with a more chronic illness," she said.

The population was mostly female

(97%) and white or Asian/Pacific Islander (75%). On admission, the patients were at 80% of their ideal body mass index (BMI), based on 50th percentile ideal body weight for age. Their mean length of hospitalization was 16.5 days.

During the first 24 hours of hospitalization, their mean heart rate was 43.5 beats per minute (bpm), with 26 of 31 (84%) patients meeting criteria for sinus bradycardia (less than 50 bpm).

Their mean orthostatic heart rate change when they went from lying down to standing was 29.3 bpm, with 18 of 31 (58%) patients meeting criteria for orthostatic intolerance (an increase of more than 30 bpm).

Resting electrocardiography was performed, with special attention paid to prolonged QTc intervals. The patients' mean QTc was 412 milliseconds, with 5 of 31 (16%) adolescents meeting criteria for prolonged QTc (greater than 440 milliseconds). No other arrhythmias were found, Dr. Slivka reported.

Doppler echocardiography revealed pericardial effusion in 4 of 31 (13%) adolescents and mitral valve prolapse in 2 of 31 (7%). One patient had both findings on echocardiography.

In all, 10 of 31 patients (32%) had at least one significant cardiac finding (prolonged QTc, pericardial effusion, and/or mitral valve prolapse), despite the short duration of their illness.

The adolescents with cardiac findings were at 73% of their ideal BMI, compared with 83% in those without major cardiac issues, a significant difference. No other significant correlational factors were found.

"This study supports [the hypothesis] that cardiac abnormalities occur early in the anorexia nervosa disease course and may warrant consideration and possible work-up even early in the disease and at the time of first hospital admission," she concluded.

Adolescents whose weight is a low percentage of their ideal BMI at diagnosis may warrant special concern, she added.

Dr. Gary Remafedi, professor of pediatrics at the University of Minnesota, Minneapolis, said the study led him to question whether he should incorporate an echocardiogram into his initial work-up of patients with anorexia nervosa.

"I wonder if there were other indicators of the mitral valve prolapse or pericardial effusions ... such as distinctive heart sounds or murmurs suggestive of prolapse," he said.

The issue of whether to order an echocardiogram soon after diagnosis "remains unanswered," Dr. Slivka responded.

"In general, mitral valve prolapse, pericardial effusion, and other valve abnormalities may be audible on physical exam. Pericardial effusion may be noted on ECG. However, in our study patients, these changes were not noted on exam," Dr. Slivka said in an interview.

Neither Dr. Slivka nor her coauthors reported any conflicts of interest with regard to their study. ■



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-xylidine, 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

LIDODERM® is a registered trademark of Hind Health Care, Inc.

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, hyposthesia, 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



LIDODERM® is a Registered Trademark of Hind Health Care, Inc.

Copyright© Endo Pharmaceuticals Inc. 2008

Rev. February, 2008
6524-11 E1

LD-1664 / December 2008



CHADDS FORD, PENNSYLVANIA 19317

© 2009 Endo Pharmaceuticals.

All Rights Reserved

LD-1652R/MARCH 2009

www.lidoderm.com

1-800-462-ENDO