Original Article

Toxicity of topical lidocaine applied to the breasts to reduce discomfort during screening mammography

Colleen K Lambertz, Christopher J Johnson[1], Paul G Montgomery[2], James R Maxwell[3], Stefanie J Fry[4]

Radiation Oncology, [1]Cancer Data Registry of Idaho, Idaho Hospital Association, [2]Medical Oncology, [3]Medical Imaging, St. Luke's Health System, [4]St. Luke's Idaho Cardiology Associates, St. Luke's Mountain States Tumor and Medical Research Institute, United States of America

Abstract

Background: We measured the effect of 30 milliliters (mL) of 4% lidocaine gel on the breasts and chest wall of healthy women covered for 1 h on plasma concentrations of lidocaine and its principal metabolite, monoethylglycinexylidide (MEGX), electrocardiogram (EKG) results, and adverse events.

Materials and Methods: This institutional review board-approved, prospective, open-label study complied with the Health Insurance Portability and Accountability Act (HIPAA). The study evaluated 10 healthy women aged 42–75 years with 30 mL of 4% lidocaine gel on the skin of the breasts and chest wall covered for 1 h. Cardiac and neurological assessments were performed and blood was drawn for lidocaine and MEGX levels at baseline and 1/2, 1, 2, 3, 4, 6, and 8 h after application. EKGs were performed before application and at 3 h. Subjects provided informed written consent. Primary and secondary outcomes were plasma concentrations of lidocaine and MEGX and frequency of adverse events, respectively. Statistical analysis included paired *t*-tests for EKGs and repeated measures regression for vital signs.

Results: No lidocaine was detected in the blood of 9 of 10 subjects. One subject had low plasma concentrations of lidocaine just above the level of detection the first 4 h after application only. No MEGX was detected. Mean decrease in heart rate was likely multifactorial.

Conclusion: Thirty mL of 4% lidocaine gel on the breasts and chest wall covered for 1 h in healthy women resulted in plasma concentrations of lidocaine and MEGX well below therapeutic or toxic levels and no clinically significant adverse events.

Key words: Breast, lidocaine, mammogram, pain, toxicity

Introduction

Fear of pain is a deterrent to screening mammography.[1-7] A clinical trial demonstrated that 30 milliliters (mL) of over-the-counter (OTC) 4% lidocaine gel (TOPICAINE®, ESBA Laboratories, Jupiter, FL) applied to the skin of the breasts and chest wall for 1 h prior to screening mammography provided a significant reduction in discomfort in women who expected substantial discomfort with the procedure.[7] However, reports of serious adverse effects from compounded topical anesthetic products on the skin prior to laser hair removal and fractional photothermolysis generated concern about the use of topical anesthetics prior to all medical procedures, including screening mammography.[8-10]

Potential adverse effects of lidocaine absorption may include cardiac and central nervous system (CNS) effects. The degradation of lidocaine in the liver results in the active metabolites MEGX and glycylxylidide (GX). MEGX and GX exhibit pharmacologic effects as antiarrythmics and anesthetics and may contribute to the toxicities associated with lidocaine. The minimal effective concentration for therapeutic antiarrythmic effects is 1500 nanograms/mL (ng/mL). Lidocaine-associated CNS effects occur particularly with high plasma levels above 5000 ng/mL.[11-13]

In the aforementioned premedication for mammography trial, 30 mL (1200 mg) of TOPICAINE® (a nongreasy 4% lidocaine gel microemulsion of water, ethanol, glycerin, jojoba oil, aloe vera oil, glyceryl monolaureate, benzyl alcohol, carbomer 940, and EDTA[12]) was applied to the skin of the breasts and chest wall and covered for 30–75 min

Address for correspondence: Ms. Colleen K. Lambertz, 100 E. Idaho Street, Boise, ID 83712, USA.
E-mail: lambertc@slhs.org

Access this article online	
Quick Response Code:	Website: www.joacp.org
	DOI: 10.4103/0970-9185.94859

(application surface area ranges between 224 and 272 cm^2 for most women bra cup size A–H).[14-16] While no systemic adverse effects were reported in the 140 women who received the gel, laboratory data were not evaluated.[7] Owing to the potential for widespread off-label use of 4% lidocaine gel as premedication for screening mammography, we tested the hypothesis that 30 mL of 4% lidocaine gel on the breasts and chest walls of healthy women covered for 1 h does not result in toxic plasma concentrations of lidocaine or its principal metabolite, monoethylglycinexylidide (MEGX), electrocardiogram (EKG) changes, or adverse events.

Materials and Methods

This institutional review board-approved, prospective, open-label study complied with the Health Insurance Portability and Accountability Act. Subjects provided informed written consent. Authors had full control of the data and information submitted for publication, with no conflicts of interest.

Subjects were healthy women age 35 years and older, with intact skin on the breasts and chest wall with no known confounding variables that might alter the rate of lidocaine absorption. Excluded from the study were women who were sensitive or allergic to lidocaine, had liver or kidney dysfunction or preliminary serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, creatinine, or blood urea nitrogen (BUN) out of the normal range for the lab, were pregnant or breast feeding, used lidocaine within 48 h prior to baseline EKG or gel application, used tobacco, exhibited neurological or cardiac signs or symptoms prior to gel application, took antiarrythmic medications,[17] ciprofloxacin, erythromycin products, or oral contraceptives, had Wolffe-Parkinson-White Syndrome (WPW) or congestive heart failure (CHF), had a heart rate (HR) below 60 or above 100 beats per minute (bpm), had systolic blood pressure (SBP) below 95 or above 180 mm Hg, had a PR interval greater than 200 milliseconds (msec), QRS duration greater than 120 msec, QTc greater than 450 msec, or evidence of WPW on EKG, had an automatic implantable cardioverter defibrillator (AICD) or cardiac pacemaker, or had cancer, surgery, trauma, or myocardial infarction in the past 6 months.

Baseline 12-lead EKG, chemistry panel, and serum pregnancy tests (premenopausal women only) were performed. Then, subjects' weight, height, HR, respiratory rate (RR), BP and assessments for drowsiness, euphoria, confusion, disorientation, lightheadedness, visual disturbances, tinnitus, paresthesias, sensations of heat or cold, itching, vomiting, nervousness, tremors, convulsions, palpitations, chest or other new pain, shortness of breath, level of consciousness, and skin changes were recorded prior to gel application and at designated phlebotomy times.

A venous access device (VAD) was inserted. Blood samples for baseline plasma lidocaine and MEGX levels were drawn through the VAD.

Thirty mL of 4% lidocaine gel was then applied to the subjects' breasts and chest wall in a manner identical to the one used prior to screening mammography.[7] The gel was removed with warm water 1 h after application.

Blood samples for lidocaine and MEGX levels were drawn at 1/2, 1 (just after gel removal), 2, 3, 4, 6, and 8 h after gel application. A 12-lead EKG was performed 3 h after application of the gel, at the estimated peak plasma lidocaine/MEGX levels. After the final blood draw and assessment, the VAD was discontinued and subjects were discharged. Follow-up phone calls were made 1 week after gel application to evaluate new or lingering effects from the study.

Lidocaine and MEGX quantitative analyses were performed by gas chromatography with a nitrogen selective detector by NMS Labs (Willow Grove, PA). The level of detection (LOD) for lidocaine and MEGX was 200 ng/mL.

Adverse event was defined as any unfavorable or unintended change in signs or symptoms during the study regardless of presumed relation to the gel and were graded as mild, moderate, severe, or life-threatening. The relationship between adverse events and the gel was assessed as unrelated, possible, or probable.

The EKG PR interval, QRS duration, and QTc interval (all in msec) were compared between the baseline and subsequent EKG using paired t-tests. Variation of HR (bpm), RR (respirations per minute, rpm), SBP (mmHg), and diastolic blood pressure (mmHg) over time was assessed using generalized linear mixed models with time modeled as a fixed effect and study subject modeled as a random effect. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

Results

Thirteen subjects enrolled; three did not meet the preliminary EKG or laboratory criteria and were withdrawn prior to gel application. Ten subjects completed the study. The demographics are shown in Table 1.

No lidocaine was detected at any measurement time in nine of the ten subjects. One subject had detectable

plasma lidocaine concentrations during four of the eight measurement times (in ng/mL): 240 at 1 h, 310 at 2 h, 240 at 3 h, and 230 at 4 h, and nondetectable levels for the other measurement times. No MEGX was detected in any of the ten subjects.

Percentages of subjects exhibiting adverse events at each of the eight time measurements are shown in Table 2. No moderate, severe, or life-threatening adverse events occurred. No significant differences in EKG measures from baseline to 3 h were noted. Mean HR and RR differed significantly from baseline, following "U"-shaped functions with time (P,.0011 and P,.0291, respectively) [Table 3].

Table 1: Demographics

Demographic variable	Minimum	Maximum	Mean	Std Dev
Age	42.0	75.0	53.9	9.8
Weight (kg)	56.9	121.6	86.6	19.6
Height (cm)	152.4	172.7	162.9	7.1
Body mass index	23.0	43.3	32.5	6.5
Surface area (cm^2)	214.0	317.0	269.5	32.1
Bra cup size	Frequency			
A or B	4			
C	3			
D or DD	3			

kg = Kilograms; cm = Centimeters

Discussion

Application of 30 mL of 4% lidocaine gel to the skin of the breasts and chest wall covered for 1 h resulted in undetectable plasma concentrations of lidocaine in 9 of 10 subjects and reached concentrations just above the 200 ng/mL LOD at four intervals in one subject. The highest lidocaine level was 310 ng/mL. This result was consistent with mean serum levels found in studies performed on similar products and, importantly, well below the antiarrhythmic level of 1500 ng/mL or the toxic level of 5000 ng/mL.[18-22] No MEGX was detected.

Skin contact with the gel and plastic wrap resulted in mild erythema in the gel area in 70% of subjects, an anticipated side effect described in the product literature. Erythema resolved spontaneously in all subjects 2–3 h after gel removal as expected. The mild metallic taste reported by one subject at 1 h was possibly related to the gel's pungent odor permeating up from the anterior chest, as it resolved minutes after the gel

Table 2: Adverse events

Signs/symptoms	Baseline %	½ h %	1 h %	2 h %	3 h%	4 h %	6 h %	8 h %
Tinnitus								
None	90	90	90	90	90	100	100	100
Mild unrelated	10	10	10	10	10	0	0	0
Tremors								
None	90	90	90	90	90	90	90	90
Mild unrelated	10	10	10	10	10	10	10	10
Other Pain (Scale 0–10)								
0	80	90	90	90	90	90	90	90
1–3 (Mild unrelated)	20	10	10	10	10	10	10	10
4–10	0	0	0	0	0	0	0	0
Skin erythema: [1]								
None	90	50	30	60	90	90	90	90
Mild related	0	40	70	30	0	0	0	0
Mild unrelated	10	10	0	10	10	10	10	10
Other signs/ symptoms:								
Possibly related:								
Metallic taste	0	0	10	0	0	0	0	0
Unrelated:								
Ankle pain	10	0	0	0	0	0	0	0
Faintness/ lab draw	10	0	0	0	0	0	0	0
Mild IV tenderness	0	10	0	10	20	10	10	10
Mild body/ head ache	20	10	10	10	10	10	10	10

[1]Location of skin erythema was the gel area for all subjects. One subject had pre-existing mild erythema on upper sternal area at baseline (unrelated) and throughout 8 h. The condition worsened slightly at 60 min only, and then all skin returned to baseline

Table 3: Vital signs

Vital sign: mean (std)	Baseline	½ h	1 h	2 h	3 h	4 h	6 h	8 h	Time effect *P* value
Heart rate (bpm)	74.4	71.8	71.8	69.8	71.0	68.0	73.8	74.6	0.0011
	(8.0)	(10.1)	(8.7)	(7.4)	(6.3)	(5.3)	(6.6)	(5.5)	
Respiratory rate (rpm)	15.4	15.3	15.4	15.4	15.2	15.0	16.0	16.0	0.0291
	(1.3)	(1.0)	(1.0)	(1.0)	(1.0)	(1.1)	(1.3)	(1.4)	
Systolic blood pressure (mmHg)	117.6	116.6	117.6	114.8	118.1	123.0	118.7	116.4	0.6402
	(10.5)	(9.6)	(9.8)	(8.1)	(8.5)	(11.2)	(7.1)	(10.9)	
Diastolic blood pressure (mmHg)	73.5	73.4	72.6	71.8	74.0	78.0	73.0	73.7	0.5181
	(8.4)	(8.9)	(7.1)	(7.3)	(6.9)	(7.7)	(7.7)	(6.6)	

bpm = Beats per minute; mm Hg = Millimeters of mercury

was removed and well before the peak plasma concentration of lidocaine.

The mean HR decreased from baseline after gel application (6.4 bpm at 4 h; *P* .0011). This change was possibly related to the gel, but more likely to changes in activity and anxiety levels. The subjects' activity changed from driving to the clinic and ambulating several hundred feet in anticipation of a needle stick just prior to baseline assessment, to resting in a quiet room for extended periods prior to the subsequent assessments. This decrease in activity likely had a slowing effect on the HR during this period of time.

Conversely, the RR increased by 0.6 rpm at 6 h (*P* .0291), which was opposite the potential effect of lidocaine, and 4 h past expected peak levels when lidocaine was undetectable. Thus, a relationship to lidocaine absorption was unlikely. Importantly, the mean HR and RR remained within normal limits for an adult and there were no changes in blood pressure.

The doses of the gel and duration of application were limited to recommendations from the product literature and were the same for all 10 subjects regardless of BMI, bra cup size, or body surface area. It is unknown what plasma concentrations or adverse events would be achieved with larger doses or longer application times, but greater exposure to lidocaine is unnecessary for reducing the discomfort of screening mammography.[7]

This study established baseline information about the absorption and toxicity of lidocaine gel when applied to the breasts of women without factors that may change metabolism of the drug. A full placebo-controlled safety study measuring absorption and adverse events after this topical application of lidocaine gel in the general population of women undergoing screening mammography is recommended.

Women defer screening mammography due to fear of discomfort. A randomized trial revealed that premedication with 30 mL of 4% lidocaine gel on the breasts and chest wall for 1 h significantly reduces discomfort with screening mammography in women who expect greater discomfort. [7] In healthy women, this application of 4% lidocaine gel resulted in minimal plasma concentrations well below therapeutic or toxic levels and no clinically significant adverse events.

Acknowledgment

St. Luke's Mountain States Tumor and Medical Research Institute. St. Luke's Mountain States Tumor Institute. St. Luke's Health System Auxiliary

References

1. Schillinger JA, Mosbaek C, Austin D, Jack L Jr, Heumann M, Moore J, *et al.* Health care reform in Oregon: The impact of the Oregon Health Plan on utilization of mammography. Am J Prev Med 2000;18:11-17.
2. Keefe FJ, Hauck ER, Egert J, Rimer B, Kornguth PJ. Mammography pain and discomfort: A cognitive-behavioral perspective. Pain 1994;56:247-60.
3. Rutter D, Calnan M, Vaile MS, Field S, Wade KA. Discomfort and pain during mammography: Description, prediction, and prevention. BMJ 1992;305:443-5.
4. Kornguth PJ, Keefe FJ, Conaway MR. Pain during mammography: Characteristics and relationship to demographic and medical variables. Pain 1996;66:187-94.
5. Nielsen BB, Miaskowski C, Dibble SL, Beber B, Altman N, McCoy CB. Pain and discomfort associated with film-screen mammography. J Natl Cancer Inst 1991;83:1754-6.
6. Mendelblatt J, Kanetsky PA. Effectiveness of interventions to enhance physician screening for breast cancer. J Fam Pract 1995;40:162-71.
7. Lambertz CK, Johnson CJ, Montgomery PG, Maxwell JR. Premedication to reduce discomfort during screening mammography. Radiology 2008;248:765-72.
8. U. S. Food and Drug Administration Center for Drug Evaluation and Research. FDA public health advisory: Life-threatening side effects with the use of skin products containing numbing ingredients for cosmetic procedures. Feb 9 2007. Available from: http://www.fda.gov/Cder/drug/advisory/topical_anesthetics.htm. [Last accessed on 2011 Aug 23].
9. U.S. Food and Drug Administration Center for Drug Evaluation and

Research. FDA public health advisory: Potential hazards of skin products containing numbing ingredients for relieving pain from mammography and other medical tests and conditions. January 16 2009. Available from: http://www.fda.gov/cder/drug/advisory/topical_anesthetics2009.htm. [Last accessed on 2011 Aug 23].
10. Marra D, Yip D, Fincher E, Moy R. Systemic toxicity from topically applied lidocaine in conjunction with fractional photothermolysis. Arch Dermatol 2006;142:104-6.
11. Brunton LL, Lazo JS, Parker KL, editors. Goodman and Gilman's the pharmacological basis of therapeutics. 11th ed. New York: McGraw-Hill; 2006.
12. TOPICAINE® Package insert. ESBA Laboratories Inc. Jupiter, FL, USA. Available from: http://www.topicaine.com/medical_information.htm. [Last accessed on 2011 Aug 23].
13. Micromedex® *Healthcare Series* [intranet database].Version 5.1. Greenwood Village, Colo: Thomson Healthcare. [Last accessed on 2011 Aug 23].
14. Hidvegi N, Nduka C, Myers S, Dziewulski P. Estimation of breast burn size. Plast Reconstr Surg 2004;113:1591-7.
15. Mosteller R. Simplified calculation of body-surface area. N Engl J Med 1987;317:1098.
16. Brosh-Nissimov T, Ingbir M, Weintal I, Fried M, Porat R. Central nervous system toxicity following topical skin application of lidocaine. Eur J Clin Pharmacol 2004;60:683-4.
17. Antiarrhythmic Drugs 2009. American Heart Association, Inc. Available from: http://www.americanheart.org/presenter.jhtml?identifier = 153. [Last accessed on 2011 Aug 23].
18. PLIAGLIS™ package insert. GALDERMA LABORATORIES, L.P., Fort Worth, TX. 2007.
19. EMLA® package insert. AstraZeneca LP, Wilmington, DE.
20. Nestor M. Safety of occluded 4% liposomal lidocaine cream. J Drugs Dermatol 2006;5:618-20.
21. Gammaitoni AR, Alvarez NA, Galer BS. Pharmacokinetics and safety of continuously applied lidocaine patches 5%. Am J Health-Syst Pharm 2002;59:2215-20.
22. Campbell BJ, Rowbotham M, Davies PS, Jacob III P. Systemic absorption of topical lidocaine in normal volunteers, patients with post-herpetic neuralgia, and patients with acute herpes zoster. J Pharm Sci 2002;91:1343-50.

How to cite this article: Lambertz CK, Johnson CJ, Montgomery PG, Maxwell JR, Fry SJ. Toxicity of topical lidocaine applied to the breasts to reduce discomfort during screening mammography. J Anaesthesiol Clin Pharmacol 2012;28:200-4.

Source of Support: Nil, **Conflict of Interest:** None declared.