Case Study of Fatal Stroke Following Intranasal Lidocaine

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ABSTRACT

A 39-year-old man presented with new onset right hemiparesis and aphasia within an hour of using approximately 120 mL lidocaine 4% topical solution intranasally. Lidocaine had been prescribed over a 3-week period for pain due to multiple debridements of the nasal septum. A total of 650 mL of 4% lidocaine (26 g) had been dispensed to the patient during this time. The patient had a significant history of drug abuse, including snorting crushed tablets. Otherwise he was a healthy man with no chronic diseases or conditions. On arrival, and from previous exams, EKGs were normal without conduction delays. Electrolytes and CBC results were within normal range. The MRI/MRA showed a new thrombus with left middle cerebral artery distribution affecting one-third of the brain mass, including brain stem. Lidocaine likely contributed to cardiovascular embolic development, possibly from a sudden drop in blood pressure and known cardiovascular effects of sodium channel blockade. The patient expired from acute respiratory failure secondary to brain-stem damage. Solutions of topical lidocaine should not be prescribed for use on open wounds or abraded skin as drug absorption will be increased, especially in highly vascularized nasal passages.

Key Words—adverse drug event, cardiovascular, cerebral, local anesthetic, stroke, thromboembolism, toxicity

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INTRODUCTION

Lidocaine, a derivative of the plant alkaloid gramine, was commercialized as a local anesthetic in 1948 under the name of *Xylocaine*. In the 1950s, lidocaine was found to be beneficial for chemical conversion of ventricular dysrhythmia to normal sinus rhythm.

Lidocaine, a narrow therapeutic index drug, was recognized early as potentially toxic.¹ Lidocaine can cause side effects such as seizures, myoclonus, loss of consciousness, asystole, cardiovascular collapse, hypotension, and bradycardia.

If given intravenously, the maximal bolus dose is 300 mg, then a continuous infusion of up to 300 mg per hour is initiated. In one study, a 160 mg lidocaine intravenous injection (2.3 mg/kg in a 70 kg person) produces initial blood levels of 2 to 4 mcg/mL, followed by a decline to a minimal level between 1 to 2 ug/mL at 20 to 40 minutes.² When used percutaneously as a local anesthetic infiltration without added epinephrine, the maximal dose is 300 mg.³

Lidocaine is increasingly being utilized for intranasal administration in migraine, cluster, and icepick headaches⁴ as well as trigeminal neuralgia.⁵

In a small study of 6 healthy men, the mean area under the curve (AUC) values for intranasal and intravenous routes were 421 ± 121 versus $1,616 \pm 30$ ng/mL/h, respectively.⁶

Our patient insufflated at least 4,000 mg, 10 times the maximal recommended dose, into a denuded, highly vascularized nasal passage immediately prior to collapse. We find no specific information about lidocaine absorption and pharmacokinetics through denuded mucous membrane tissue, however absorption likely resembles intravenous administration.

CASE PRESENTATION

A 39-year-old white male arrived at the emergency department following rapid-onset aphasia, right-sided weakness, altered consciousness, and shortness of breath. History was provided by a friend who witnessed the events leading up to the event. The

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differential diagnosis included seizure with Todd's paralysis; meningitis with encephalopathy secondary to recent ear, nose, and throat surgery; and coagulopathies or acute stroke secondary to lidocaine toxicity.

The patient insufflated lidocaine 4% solution approximately 5 hours prior to and immediately before symptom onset. This lidocaine was prescribed for local pain management perioperatively for a series of 3 nasal debridement procedures due to significant septal perforation secondary to repeated drug tablet insufflation. Pharmacist medication reconciliation revealed that 650 mL of 4% lidocaine solution (26 g lidocaine) was dispensed over the prior 3 weeks. The patient was witnessed insufflating approximately 120 mL immediately prior to experiencing stroke-like symptoms. Progression from initial aphasia to obtundation occurred within 30 minutes.

Past medical history was significant only for infectious rhinitis, septal debridement surgery, and polysubstance abuse, including past cocaine and opioid insufflation. The presence of tablet particulate was noted on multiple occasions prior to multiple debridement procedures. Home medications included lidocaine 4% solution, cyclobenzaprine, gabapentin, sulfamethoxazole-trimethoprim, and ibuprofen.

Upon arrival to the emergency department, the patient's eyes were open and moving. Pupils were 2.5 mm and reactive. He was not responsive to commands. His right arm was flaccid. There were some purposeful movements of the left arm. Breath sounds were clear to auscultation. Respiratory rate was 35 breaths per minute. Cardiovascular examination showed a pulse of 105 bpm; no murmurs, rubs, or gallops were noted. Electrocardiogram (ECG) showed sinus rhythm with heart rate of 86 bpm. Blood pressure was 106/80 mm Hg. Two days earlier, blood pressure had been measured at 155/104 mm Hg. The patient was intubated in order to protect his airway and admitted to the intensive care unit. Extremities revealed no edema, and there were weak pulses in the lower and upper extremities.

Magnetic resonance imaging (MRI) revealed a massive left-sided middle cerebral artery stroke, likely embolic. Computed tomographic angiography (CTA) showed a notable clot in the aortic arch with thrombus seen up to the left internal carotid artery with an abrupt occlusion at the mid-portion of the left cerebral artery. It was estimated that about one-third of the patient's brain was affected by the stroke. The radiologist suggested that the new clot in the aorta was likely the source of the embolism. Due to the emergency situation and proven clot, venous

duplex was not performed. Although the patient was admitted within 3 hours of trauma, tissue plasminogen activator was not indicated in this case.

Transthoracic echocardiogram (TEE) indicated a left ventricular ejection fraction of 55%, no significant valvular abnormalities, and a suggestion of a small patent foramen ovale (PFO). We cannot determine if a clinically significant clot from a PFO was formed leading to massive middle cerebral arterial occlusion.

Laboratory studies noted an anion gap of 19, glucose of 212 mg/dL, and white blood cell count of 24.2×10^6 cells/mL. Serum potassium and magnesium levels were within normal limits. Basic metabolic panel and complete blood count on admission were otherwise unremarkable. Troponin T was less than 0.02 ng/mL and fibrinogen was 510 mg/dL. Venous blood gases and urinalysis were normal. Serum lidocaine was obtained 3 hours post intranasal bolus of at least 4 g. It was 1.2 µg/mL. Serum drug screen was negative for all substances except lidocaine.

All potential etiologies were ruled out, except for toxicity due to lidocaine. Aggressive medical stabilization was attempted, however the patient died within 48 hours due to respiratory depression associated with brainstem involvement.

Scoring of the case via the method of Naranjo et al yielded a score of 6, indicating a probable adverse reaction.⁷

DISCUSSION

Our patient's preexisting stroke risk was minimal. Apart from recent nasal debridements, there were no recent surgeries. The patient did not receive topical thrombin or other coagulants during the procedures. He had no known coagulopathies, infections, or preexisting cardiac conditions contributing to the adverse event. We feel that atrial stunning due to chemical effects of lidocaine on contractility resulted in a milieu for thrombosis.

Chemical cardioversion temporarily increases the risk of stroke through decreased mechanical atrial function and stasis of the blood. One study of anticoagulated patients given electrical mechanical conversion with or without a Class I antiarrhythmic, procainamide, showed transient left atrial stunning.⁸ Another study showed cardioversion causes left atrium contractility impairment.⁹ In a study of 357 patients who underwent cardioversion, 3 had thromboembolic events (0.8%). None of these 3 patients had a history of thromboembolism or recurrent atrial fibrillation.¹⁰

Serum levels obtained in our patient several hours after self-administration of prescribed lidocaine 4% solution show that lidocaine was systemically absorbed and likely reached concentrations high enough to potentiate cardiovascular effects. We suspect both intranasal and oral absorption was involved; certainly there are reports of massive oral ingestion leading to mortality.¹¹

We find no case reports of embolic stroke due to lidocaine in Embase, Ovid, or PubMed (1946 to 2015). We do find rare cases of aortic thromboembolism found within hours of cocaine insufflation or smoking free-base cocaine, an amino ester with cardiac effects similar to lidocaine.^{12,13}

Physicians should carefully evaluate the risk versus benefit before prescribing topical anesthetics post procedurally. Predisposing risk factors such as history of intranasal drug abuse, cardiac history, or known coagulation disorders may contribute to toxicity where drug application is extensive and over denuded mucosa. Where known abuse of “caine” drugs is part of the history, the potential for lidocaine misuse should be strongly considered. Caution is essential when prescribing anesthetics to persons with prior drug abuse.

The prescription must include the specific area intended for drug application, the exact volume of drug to be used with each dose, and a maximal daily limit. Total dispensed quantities and refills should be limited. Dosing frequency, including a daily maximum dose, should accompany every order. Our patient's prescription was written to be used “as directed,” with 5 refills and no maximum daily dose. A total of 650 mL was dispensed within a 3-week period preceding death.

Although there is an overall general impression that topical lidocaine is extremely safe, the drug needs to be applied to surfaces that are intact per manufacturer recommendation. Any other application is contraindicated.

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