

Lidocaine Toxicity Misinterpreted as a Stroke

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For more than 50 years lidocaine has been used to treat ventricular arrhythmias. Neurologic dysfunction, manifested as a stroke, occurred acutely in an 87-year-old woman after she had been administered repeated doses of lidocaine, a lidocaine infusion, then an intravenous amiodarone infusion for ventricular tachycardia. This was ultimately diagnosed as lidocaine toxicity with a serum lidocaine level of 7.9 mg/L (1.5 - 6.0 mg/L). We discuss lidocaine toxicity and risk factors leading to its development, which include particularly hepatic dysfunction, cardiac dysfunction, advanced age and other drug administration. [West J Emerg Med. 2009;10(4):292-294.]

INTRODUCTION

Sudden cardiac death, most commonly caused by ventricular tachycardia or fibrillation, affects over half a million people in the United States each year.¹ Intravenous lidocaine has been administered for the treatment of ventricular arrhythmias for over 50 years and is still commonly used to treat these arrhythmias, although it is no longer considered first line therapy.² Newer antiarrhythmics are replacing lidocaine for many indications and are sometimes concomitantly administered with potential drug interactions. If prescribers are aware of the presentation of lidocaine toxicity and its precipitants they can better avoid complications. We describe a patient in whom a lidocaine bolus and drip successfully abolished ventricular arrhythmias who was then administered concurrent amiodarone. This precipitated severe neurologic deterioration suggesting stroke. We will review the dosing, metabolism, and other factors that contribute to decreased metabolism of lidocaine with severe neurologic toxicity.

CASE REPORT

Near midday an 87-year-old woman activated 911 complaining of shortness of breath. The patient's past history was significant for myocardial infarction. A recent echocardiogram showed left ventricular hypokinesis consistent with an ischemic cardiomyopathy with an ejection fraction of 20 to 25%. Previous magnetic resonance imaging showed a 9x11x16 mm meningioma, without metastasis, edema or hydrocephalus. Her medications included verapamil,

timolol, and diazepam.

The initial assessment by paramedics at 1320 described an alert and appropriate patient with pupils equal, round and reactive; the breathing was not labored, lungs were clear, and finger stick glucose was 139. The rhythm was ventricular tachycardia. Paramedics gave 50mg lidocaine intravenous (IV) push, with resolution of the tachycardia to a narrow complex sinus rhythm at a rate of 80 beats per minute. The rhythm was stable for one to two minutes, then recurred. They administered a second dose of lidocaine 50mg IV push, resulting in resolution of the tachycardia to a sinus rate of 78 beats per minute. The patient reported a decrease in shortness of breath and some mild dizziness. Paramedic personnel initiated a lidocaine drip at 2mg/minute for transport to the emergency department (ED).

In the primary ED, 28 minutes later, the patient had a ventricular rate of 152 beats per minute. She received a third 50mg dose of lidocaine IV. Her electrocardiogram (EKG) revealed normal sinus rhythm with left ventricular hypertrophy and an anteroseptal infarct of indeterminate age. At 1413 the physician increased the lidocaine drip to 4mg/minute, and administered aspirin 325mg by mouth. Shortly thereafter, the patient received a loading dose of amiodarone 150mg IV, followed by an amiodarone drip at 1mg/minute. She then came via EMS to our hospital.

En route emergency medical service personnel noted the patient to be in normal sinus rhythm with ventricular ectopy. The lidocaine drip remained at 4mg/minute and the amiodarone drip at 1mg/minute. The IV pump delivering

amiodarone failed 20 minutes into the transfer and the medication discontinued. During transfer the report notes that the patient complained of “being sleepy” but was alert and appropriate. Six minutes prior to arrival the patient’s mental status changed abruptly. She became non-verbal, her eyes remained open with a fixed gaze, but she was able to flex her hands on command.

Upon arrival to our ED the patient’s vitals signs were: heart rate 76 beats/min, respiratory rate 22 per minute, blood pressure 135/65, tympanic temperature 96.4°F, and oxygen saturation 92% on 15-liter flow nonrebreather mask. Her weight was 49 kilograms. Her airway was patent. The EKG monitor showed normal sinus rhythm. The patient was unresponsive to painful stimuli with pupils 4mm and nonreactive with intact gag reflex. Plantar reflexes were neutral. Given the patient’s abrupt change in mental status, brainstem stroke was considered and we consulted neurology. We ordered an expedited computerized tomographic scan (CT) of the head 19 minutes after arrival. Two minutes later she received 0.4mg naloxone intravenously and the lidocaine drip was discontinued. The patient’s National Institute of Health (NIH) stroke score was 24, indicating severe neurologic impairment.

Initial imaging studies included a chest x-ray with the only abnormality being an enlarged cardiac silhouette. CT scan of the head revealed mild microvascular ischemic changes. An 11 mm partially calcified right falxine mass was consistent with a stable meningioma. CT angiography examination in the ED 51 minutes after arrival demonstrated no evidence of vaso-occlusive change affecting the cervical or intracranial arterial vessels. Laboratory values drawn 19 minutes after arrival at our facility were as follows: Sodium 135 mmol/L, potassium 3.7 mmol/L, chloride 103 mmol/L, bicarbonate 19 mmol/L, creatinine 0.7 mg/dL, blood urea nitrogen 19 mg/dL, glucose 164 mg/dL, Mg 1.6 mg/dL, phosphorus 4.8 mg/dL, ionized calcium 1.10 mmol/L (reference 1.17-1.33 mmol/L). Cardiac enzymes, creatinine kinase (CK), CKMB and Troponin-T were normal. The initial arterial blood gas obtained on room air showed a pH of 7.28; the pCO₂ was 44 mmHg, pO₂ 63 mmHg, and oxygen saturation 87%. The serum lidocaine level drawn 51 minutes after arrival, 30 minutes after the lidocaine drip was discontinued, resulted 7.9 mg/L with a reference range in our laboratory of 1.5-6.0 mg/L.

Following termination of the lidocaine drip the patient’s mental status gradually and steadily improved. By 60 minutes after termination of the drip her NIH stroke scale score was three, indicative of minimal impairment. During the ensuing hospitalization no more abnormalities of mental status or other neurologic complaints were encountered.

DISCUSSION

Lidocaine is a class Ib anti-arrhythmic drug used

intravenously for ventricular dysrhythmias and subcutaneously for local anesthesia. The 2005 (most recent) guidelines of the American Heart Association suggest that it is a second line drug after amiodarone for ventricular arrhythmia. Amiodarone is now the primary recommendation for medical cardioversion because it is believed that aqueous amiodarone is more effective than lidocaine in the treatment of shock-resistant ventricular tachycardia. An alternative treatment is intravenously administered lidocaine.²

The two major categories of the adverse effects of lidocaine are neurologic and cardiac, with the former being more common. Lidocaine’s mechanism of action is depression of neuronal excitability by blockage of voltage-dependent sodium channels in the cell membrane. This produces the therapeutic effects of myocardial stabilization and local anesthesia and causes lidocaine’s toxicity.³ Neurologic manifestations include paresthesias, confusion, dizziness, and respiratory depression, which can progress to psychosis, loss of consciousness and seizure. Cardiac manifestations of lidocaine toxicity are many, including dysrhythmia, sinus bradycardia, and QRS widening.⁴ There have also been reports of sino-atrial node suppression by lidocaine particularly in conjunction with other sodium channel blockers such as phenytoin. Toxicity may be associated with cardiovascular collapse and complete loss of blood pressure, even in younger patients.⁴ The atrioventricular node can be adversely affected by inadvertent overdose. Severe bradycardia and asystole have been described in patients with myocardial infarction and in patients with high grade atrioventricular block.⁵

Initial doses of lidocaine range from 0.5 up to 1.5 mg/kg. One may repeat 0.5 to 0.75 mg/kg every five to 10 minutes to a maximum total dose of 3 mg/kg. In the patient with normal hepatic function, maintenance infusion of 1 to 4 mg/min should be initiated.² This administration is necessary due to lidocaine’s biphasic elimination with an initial half-life of approximately seven to 30 minutes (due to plasma protein binding and redistribution into adipose and muscle tissue) and a terminal half-life of approximately 1.5 to two hours which is prolonged with alterations in liver function. The parent compound is rapidly metabolized in the liver by dealkylation to active metabolites, monoethylglycine xylidide (more toxic than the parent compound) and glycine xylidide which have extended half-lives of two and 10 hours.⁴ This may account for prolonged neurologic symptoms. Less than 10% is excreted in the urine, so a history of renal failure or dialysis do not alter ED dosing.

At the time our patient’s mental status was recognized to be a manifestation of lidocaine toxicity and when the lidocaine drip stopped, the patient had received a total of 811 mg of lidocaine in three hours and 20 minutes, a total dose of approximately 13 mg/kg over two half-lives of the drug. Similar impairments have been reported with larger doses of lidocaine over shorter periods.⁵

Pfeifer et al.⁶ looked at 750 recipients of intravenous lidocaine. The mean age of these patients was 65 years, and almost 75% of these patients had received the drug for a cardiovascular disorder. Adverse reactions were described in 47 patients; 31 were central nervous system disturbances, and eight had cardiovascular complications. Significant adverse reactions were more frequent in patients with acute myocardial infarction and congestive heart failure. Toxicity was increasingly frequent in patients with decreased body weight and with increasing age but not with serum albumin or blood urea nitrogen. This study was performed before the widespread use of amiodarone.

Other studies have sought to understand the interaction of lidocaine and amiodarone both *in vitro* and *in vivo*. In laboratory experiments lidocaine metabolism was slowed with the inhibition of cytochrome P-4503A4 by amiodarone and its metabolite. In six test patients the mean lidocaine clearance was decreased by nearly 20 percent when the drugs were co-administered.⁷ This interaction would be especially relevant when lidocaine accumulates in patients with congestive heart failure or hepatic dysfunction.

Our patient appears to fit all the major determinants of lidocaine toxicity found in these studies. She was a thin elderly woman with previous myocardial infarction, documented poor ventricular function, and secondarily decreased hepatic clearance. Amiodarone was co-administered, which decreased the systemic clearance of lidocaine, leaving this patient extremely vulnerable to overdose.

CONCLUSION

Although amiodarone has replaced lidocaine as the medication of choice for stable wide complex tachycardia, lidocaine is still widely used. Physicians should be familiar with the neurologic and cardiac toxic effects. Risk factors for lidocaine toxicity include previous evidence of myocardial infarction, congestive heart failure, decreased body weight, increased age, and other conditions that affect hepatic clearance (Table). Co-administration of amiodarone and lidocaine decreases the clearance of lidocaine and may increase the risk of toxicity.

Table. Factors increasing the likelihood of lidocaine toxicity

- Older age
- Decreased body weight
- Acute myocardial infarction
- Congestive heart failure
- Decreased hepatic function
- Concomitant use of drugs decreasing P-450 activity (including amiodarone)

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