CASE REPORT

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Tissue Distribution of Lidocaine After Fatal Accidental Injection

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ABSTRACT: The accidental death of a 64-year-old heart patient as a result of the injection of an incorrect dose of lidocaine is presented. The attending nurse inadvertently administered an intravenous bolus of 10 mL of 20% lidocaine (2 g). The patient should have received 5 mL of 2% lidocaine (0.1 g). Such iatrogenic overdoses of lidocaine arise from confusion between prepackaged dosage forms. Lidocaine concentrations (mg/L or mg/kg were: blood, 30; brain, 135; heart, 106; kidney, 204; lung, 89; spleen, 115; skeletal muscle, 20; and adipose, 1.3. The results indicate that even during cardiopulmonary resuscitation as much as 38% of the administered dose of lidocaine may be found in poorly perfused tissue such as skeletal muscle and adipose.

KEYWORDS: toxicology, lidocaine, death, tissues (biology), iatrogenic overdose, poisoning, tissue distribution, toxicologic analysis

Lidocaine, a widely used local anesthetic, has also achieved prominence as an antiarrhythmic agent in emergency treatment for ventricular arrhythmias. While its mechanism of action is similar to that of quinidine and procainamide, lidocaine is especially advantageous in emergency situations in that its antiarrhythmic action can be established very rapidly and safely by intravenous (IV) administration. Because of its relatively short plasma half-life and redistribution in the body, lidocaine effects quickly decline when infusion is terminated, thus, allowing moment-to-moment titration of ventricular ectopic activity [*1*].

For rapid antiarrhythmic activity in cases of acute myocardial infarction, lidocaine is usually administered intravenously as a bolus injection of 1 to 2 mg/kg of body weight. The effect of a 50- to 100-mg bolus disappears in 10 to 20 min. The drug is available for IV administration as a 5-mL prefilled syringe or a 5-mL ampul, each containing 20 mg/mL. This is the only preparation of lidocaine indicated for IV bolus injection.

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This communication presents a case of fatal lidocaine poisoning resulting from the inadvertent IV injection of a lidocaine preparation not intended for IV bolus injection. Lidocaine was determined in blood, five visceral organs, and additionally skeletal muscle and adipose tissue. A review of literature indicates this is the most complete distribution study of lidocaine in human tissues.

Case History

A 64-year-old, white male, known to have coronary heart disease with episodes of angina, Parkinsonism, and mild diabetes reported to the emergency room of an area hospital at 10:30 p.m. The patient complained of tight retrosternal chest pain, with noted pallor, diaphoresis, and weakness. Earlier in the day the patient had been raking leaves. One hour before calling the ambulance, the chest pains began and were refractory to nitroglycerin. An electrocardiogram (ECG) read in the emergency room revealed elevation of the ST segment and T wave inversions. He was administered 3 mg of morphine at 11:00 and 11:20 p.m. which relieved his pain. He was admitted to the intensive care unit where he passed an uneventful evening.

A physical examination the next morning revealed the patient to be conscious, alert, coherent, and without chest pain. His heart displayed regular sinus rhythm without gallop, thrill, or murmurs. Blood pressure was 140/80, pulse 88, respiration 20, and temperature 36.77°C (98.2°F). Mitral creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) enzymes were within the normal range. Repeat analysis 6 h after admission demonstrated an elevated CPK but no muscle brain isoenzyme (MB) bands were noted.

At 10:00 a.m., the patient developed a burst of ventricular tachycardia for which 100 mg of lidocaine to be given slowly in IV bolus was ordered. However, the nurse mistakenly injected the patient with 2 g of lidocaine. Immediately following the injection the patient exhibited tonic clonic seizures and proceeded to full cardiopulmonary arrest. A portion of the nursing progress record and subsequent ECG recordings following the mistaken injection are presented in Fig. 1. Resuscitation measures were unsuccessful and the patient was pronounced dead at 11:10 a.m. The Medical Examiner's Office was notified of the death and the body was conveyed there for autopsy.

Pathology Findings

The body was 170 cm (67 in.) and weighed 84 kg (185 lb). The anterior abdominal wall fat was 4 cm thick. An endotracheal tube was taped in place. Three recent IV puncture marks were noted in the middle of the right intraclavicular area. The left antecubital fossa displayed a recent puncture site. An intracatheter with syringe attached was present over the right antecubital fossa. The pericardial sac contained 25 to 30 mL of clear yellow fluid. The pericardial surfaces were smooth, glistening, and transparent. The 395-g heart displayed an old subendocardial myocardial infarction measuring 6 by 3 cm occupying the central portions of the free wall of the left ventricle and extending into the papillary muscles of the mitral valve. There was no evidence of new myocardial infarctions. The coronary arteries were extensively calcified and narrowed. The right coronary artery contained a fresh grey thrombus approximately 3 cm from its origin, and completely occluding the vessel for a distance of 1 cm. The cardiac valves were unremarkable. Examination of other organs including the brain was unremarkable.

Toxicology Findings

Lidocaine was extracted from blood and tissue homogenates at pH 9.5 (carbonate buffer) with hexane/isoamyl alcohol (98/2), which was back extracted in 0.5*N* sulfuric acid. The

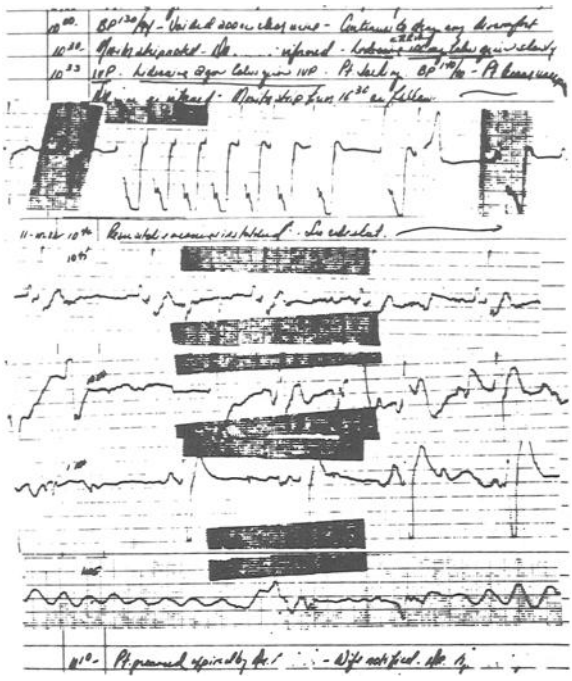

FIG. 1—*Portion of patients' chart: error in lidocaine administration noted (10:30 a.m.). Electrocardiograph tracings demonstrate cardiotoxicity of lidocaine and cardiopulmonary collapse.*

separated acid solution was then made basic, pH 9.5, with solid carbonate buffer and extracted with fresh hexane/isoamyl alcohol (98/2). The organic layer was separated and dried with anhydrous sodium sulfate and evaporated to dryness under nitrogen at room temperature. Qualitative analysis of lidocaine in the resultant extracts was by thin-layer chromatography (TLC) [*2,3*], temperature programmed gas liquid chromatography (TPGLC) [*4*], and ultraviolet spectrophotometry (UV). Lidocaine was indicated by iodoplatinate positive spots of R_f 0.76 and 0.71 in TLC development system of Davidow et al [*2*] and Clarkes' T1 [*3*], respectively. Spots presumed to be lidocaine were eluted from the TLC plates by the method of Freimuth [*5*] and examined by UV. Lidocaine gave a maximum at 262 nm in 0.1*N* sulfuric acid. Analysis of extracts by TPGLC indicated lidocaine with retention indices of 1865 and 2170 on SE-30 and OV-17 liquid phases, respectively.

Quantitative analyses of specimens for lidocaine were by GLC using a nitrogen detector. Blood and tissue homogenates were extracted as described above except that cyclizine (internal standard, 25 mg/mL) was added to the initial hexane/isoamyl alcohol extracting solvent. Analysis was performed in a 1.8-m by 4-mm inside diameter glass column packed with 3% OV-17 on Chromsorb WHP 80–100 mesh (Alltech Associates) connected to a nitrogen detector. The temperatures were: injection port, 255°C; column 215°C; and detector, 300°C. Gas flows or pressures or both were: nitrogen carrier gas, 30 mL/min; air, 179 kPa (26 psig); and hydrogen, 83 kPa (12 psig). The detector bead adjustment was 2.26 A. Under these conditions the retention times of lidocaine and cyclizine were 2.7 and 4.4 min, respectively.

The results of the lidocaine analyses are presented in Table 1. Morphine from the emergency room injections was detected in bile and urine. No other toxicants were detected in the specimens.

TABLE 1—*Distribution of lidocaine following a 2-g IV bolus injection and 25 min of unsuccessful cardiopulmonary resuscitation.*

Specimens	Weight, kg	Lidocaine		
		mg/kg or Mg/L	Total, mg	Tissue/Blood Ratio
	RAPIDLY EQUILIBRATING TISSUE			
Blood	5[a]	30	150	...
Brain	1.50	135	203	4.5
Heart	0.395	106	42	3.5
Kidney	0.460	204	94	6.8
Lung	1.07	87	93	2.9
Spleen	0.390	115	45	3.8
Total			627	
	SLOWLY EQUILIBRATING TISSUE			
Skeletal muscle	36.0[a]*n*	20	720	0.67
Adipose tissue	24.0[a]	1.3	31	0.04
Total			751	
Total recovered lidocaine			1378	

[a]Total weight estimated from Butler [*6*].

Discussion

Prefilled syringes of lidocaine are available in two dosage forms; a 5-mL, 20-mg/mL (100-mg dose) to be administered as an IV bolus, and a 10-mL, 200-mg/mL (2000-mg dose) to be added to a continuous IV infusion bottle. The similarities of the packages and ease at which the 2-g injectable needle may be added to an intravenous line are evident in Fig. 2. While, the packages may be misidentified by medical personnel, particularly under the mental stress of treating a patient with life threatening cardiac arrhythmia, the 2-g syringe and vial are both clearly labeled in red "Caution: Must Be Diluted Not For Direct Injection." Iatrogenic lidocaine overdoses as a result of confusion over the package syringes are not uncommon; life threatening toxic reactions with variable sequelae [*7,8*] including death [*9,10*] have been reported previously. Following discussions with other hospital staff physicians, Finkelstein and Kreeft [*7*] concluded, "the true incidence of this phenomenon (iatrogenic lidocaine overdose) may be higher than suspected."

The major toxic actions of lidocaine involve the central nervous system. Early symptoms consist of dizziness, drowsiness, euphoria, dysarthria, and visual disturbances. These may proceed to more severe reactions including; disorientation, hearing loss, respiratory depression, convulsions, and coma. Cardiotoxic effects of lidocaine overdose include: depression of myocardial contractility and worsening of conduction delay in the bundle branches which may precipitate complete infranodal heart block. These cardiotoxic effects may be observed with usual therapeutic doses, as well as in overdose situations. They most frequently occur in patients with preexisting compromise of the cardiovascular system [*11*].

Lidocaine is metabolized chiefly in the liver by dealkylation to monoethylglycinexylidide (MEGX) and glycinexylidide (GX). Both metabolites produce antiarrhythmic effects (83 and 10% as active as lidocaine, respectively); however, only MEGX is considered to contribute significantly to the toxic effects of lidocaine [*12*]. Following IV injection lidocaine is rapidly cleared from blood. Lidocaine follows a typical biphasic elimination curve (second-order kinetics), with an initial rapid alpha phase followed by a slower beta phase with a plasma half-life of approximately 100 min. Therapeutic plasma concentrations for antiarrhythmic control are considered 2 to 5 mg/L [*13*]. Concentrations greater than 5 mg/L may be associated with toxicity. Patients with liver failure have reduced lidocaine clearance and those with congestive heart failure exhibit both reduced clearance and a reduction in the apparent vol-

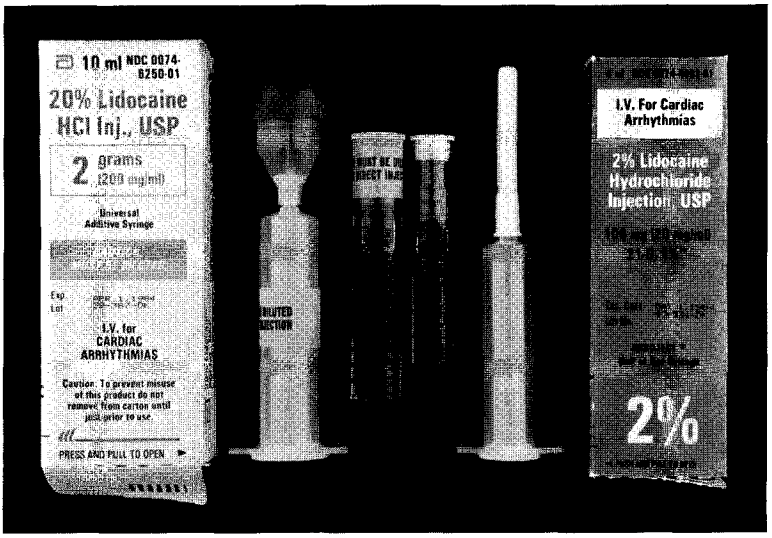

FIG. 2—*Prefilled syringe dosage forms of lidocaine: note the warning labels of the 2-g dosage form and the plastic extension of the syringe which encircles the neck of an intravenous infusion bottle* (left); *5-ml, 0.1-g prefilled syringe for intravenous bolus injection* (right).

ume of distribution; hence, a reduction in lidocaine dosage is necessary to prevent toxic plasma concentrations in these patients [*14*].

Baselt [*15*] lists postmortem blood concentrations of 6 to 33 mg/L in five adults (including one case from Ref *8*) dying suddenly after receiving accidental IV injections of 250 to 1000 mg of lidocaine. The postmortem blood lidocaine concentration of 30 mg/L in the present case is six times greater than plasma concentrations associated with toxicity, and is consistent with the observations of others in sudden death from lidocaine. The high concentrations of lidocaine found in brain, heart, kidney, lung, and spleen reflect the rapid movement of lidocaine into tissues during the alpha distribution phase following administration.

Benowitz et al [*16*] studied lidocaine pharmacokinetics in the unanesthetized restrained rhesus monkey and man after bolus injection and steady infusion. They measured in the monkey systemic and regional blood flows, tissue masses, and lidocaine concentrations in blood, plasma, plasma ultracentrifugate, and tissues. Combining the physiological and pharmacokinetic data, they developed a perfusion model for man that is predictive of lidocaine concentrations in various tissues at various times. The model indicates that immediately after IV bolus injection, much of the dose is taken up by brain, heart, lungs, and other rapidly perfused tissue. The redistribution of lidocaine into skeletal muscle and adipose accounts for the relatively long beta elimination phase. The model predicted that within 15 min after IV bolus injection, 32% of dose would be found in skeletal muscle tissue. Also, within the same time, almost 30% of the dose would be eliminated by hepatic biotransformation. This work indicated that the percentage of an IV dose of lidocaine found in any given tissue during the alpha distribution phase is greatly dependent on the perfusion (blood flow rate) of the tissue.

Because lidocaine is often used in patients with cardiac disease, the effects of cardiac failure on the distribution of the drug is of clinical and forensic science concern. Any disease or trauma associated with tissue hypoperfusion, sympathetic nervous stimulation, and redistribution of blood flow would be expected to alter the distribution and resultant tissue concentrations of lidocaine. Benowitz et al [*17*] used data obtained from the monkey during

hemorrhage to construct a perfusion model that would predict the effects of cardiac failure in man on lidocaine distribution. Computer simulations predicted higher concentrations of the drug in blood during cardiac failure because of decreased flow to and uptake by tissues. Preservation of blood flow to the heart and brain, in the presence of higher concentrations of blood lidocaine would lead to greater accumulation of the drug in these organs soon after injection. Therefore, adverse central nervous system and cardiac effects are more likely to occur in situations of cardiac failure. These predictions are consistent with clinical observations in man [*11,14,18*].

The rate of blood flow to and the percentage of cardiac output received by a given tissue is altered in states of circulatory insufficiency. Therefore in such cases the rate of presentation of lidocaine to tissues such as spleen, kidney, and liver is slowed resulting in an increased alpha phase half-life. Uptake of lidocaine by less rapidly equilibrating tissue, such as adipose and skeletal muscle tissue, is markedly delayed. For example, the cardiac failure model of Benowitz et al predicted that maximum uptake of skeletal muscle would occur at 30 rather than 15 min in man [*17*]. Also the rate of hepatic biotransformation and plasma clearance of lidocaine are related to cardiac output [*19*]. Therefore, a decrease in hepatic blood flow would be expected to decrease biotransformation resulting in increased blood concentrations of lidocaine. Following high infusion rates of lidocaine in normal subjects, Lalka et al [*20*] reported reduced nonlinear plasma clearance of lidocaine. This observation may be due to an effect of lidocaine or its metabolites of hepatic blood flow, or to possible saturation of metabolizing enzymes. While lidocaine exhibits second-order kinetics (dose-independent elimination rate) following IV bolus injections of therapeutic doses [*21*], saturation kinetics (dose-dependent elimination rate) may occur following IV bolus injections of massive doses such as 2 g administered in the presented case.

In our case, the patient lapsed into cardiopulmonary collapse within minutes after the 2-g injection and received cardiopulmonary resuscitation (CPR) for about 25 to 30 min. Chow et al [*22*] studied the effect of external CPR on lidocaine distribution and elimination in anesthetized mongrel dogs. During the 60-min study period, lidocaine concentrations in blood and tissues were significantly elevated and plasma clearance was greatly reduced in CPR dogs compared to controls. They attributed alterations in lidocaine disposition to tremendous reductions in cardiac output and blood flow during CPR. Additionally, the extraction ratio (ER)[4] for lidocaine across skeletal muscle was determined. In CPR dogs, a positive muscle ER was noted over the entire time course of the study, indicating a net uptake of lidocaine by muscle tissue and that distribution equilibrium was not achieved. The presence of 20 mg/kg of lidocaine in the muscle from our case, indicates that although muscle may be poorly perfused during CPR a significant percentage of the administered dose may be expected to be sequestered in that tissue. The calculated total of 720 mg of lidocaine in skeletal muscle after 25 to 30 min of CPR was 36% of the administered dose (Table 1). The cardiac failure model of Benowitz et al predicts that our patient would have approximately 22% of the dose in muscle at 30 min [*17*]. The differences between our observed value and that predicted by Benowitz et al may be due to numerous factors. The decrease in blood flow to the liver during CPR would decrease the percent of dose available for biotransformation, thereby increasing the concentration of drug available in the blood supply to muscle. Also the partition ratio (PR)[5] of an organic base in muscle would be expected to increase as acido-

[4]Extraction ratio (ER) = rate of drug uptake/rate of drug delivery

$$ER = (Q\,Ca\text{-}Q\,Cv/Q\,Ca) = (Ca\text{-}Cv/Ca)$$

where

Ca = arterial drug concentration,
Cv = venous drug concentration, and
Q = blood flow.

[5]Partition ratio (PR) = concentration of drug in tissue/concentration of drug in blood supply.

sis developed in tissue during CPR. Therefore, the increase in available blood lidocaine and an increased PR may account for the muscle lidocaine in our case.

As presented in Table 1, the analysis of the blood and seven available tissues accounted for 1.378 g of lidocaine, or 69% of the administered dose. Unfortunately, liver was not submitted to the laboratory. However, assuming the liver lidocaine concentrations were similar to the other internal organs, this could account for an additional 200 to 300 mg of lidocaine. Also, if lidocaine biotransformation was reduced to only 30% normal rates, an additional 200 mg of drug would still have been eliminated during the time of CPR. Making these assumptions about liver concentrations and biotransformation, we can account for 94%[6] the dose of lidocaine administered in our case.

This case demonstrates that for estimation of the amount of dose administered in fatal lidocaine poisoning, skeletal muscle is an important specimen to analyze even following CPR. Additionally, skeletal muscle may be considered for analysis when death is related to any drug whose pharmacologic activity is related to a significant redistribution between visceral organs and skeletal muscle or adipose tissue.

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[6] 1.378 g recovered + 0.3-g liver + 0.2-g biotransformed × 100/2-g administered dose = 94%

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