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Postmortem Diffusion of Tracheal Lidocaine into Heart Blood Following Intubation for Cardiopulmonary Resuscitation

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ABSTRACT: This study investigated the postmortem diffusion of tracheal lidocaine into the blood after intubation in three individuals whose heart beat was not restored by cardiopulmonary resuscitation. The results are compared with those obtained in animal experiments using rabbits.

The first human subject was a 3.5-month-old female baby who died of sudden infant death syndrome. She was autopsied approximately 20 h after death. A toxicological examination revealed the presence of 0.349 mg/L and 0.102 mg/L of lidocaine in the blood in the left and right ventricles of the heart, respectively. No lidocaine was detected in the cerebrum, liver, or right femoral muscle. The second subject was a 44-year-old man who died of brain swelling due to head injuries, and was autopsied approximately 20 h after death. Lidocaine concentrations in the hili of the left and right lungs were 10.9 mg/kg and 2.65 mg/kg, respectively, and 1.02 mg/L and 0.209 mg/L in the blood in the left and right ventricles of the heart, respectively. The right femoral vein blood contained only a trace amount of lidocaine; no lidocaine was detected in the cerebrum, liver, or right femoral muscle of this subject. The third subject was a 38-year-old man who died of bleeding due to a stab wound to the left thigh, and was autopsied approximately 20 h after death. Lidocaine concentrations were 1.41 mg/kg and 1.37 mg/kg in the hili of the left and right lungs, respectively, and 0.642 mg/L and 0.746 mg/L in the blood in the thoracic aorta and superior vena cava, respectively. No lidocaine was detected in the right femoral vein blood, cerebrum, liver or right femoral muscle.

In the animal experiments, rabbits carcasses were left in the supine position at an ambient temperature following application of 1 mg/kg lidocaine hydrochloride into the trachea just above the bifurcation. Lidocaine concentrations of 0.550–4.03 mg/L and 3.05–7.30 mg/L were detected in the heart blood, one and three days after the lidocaine treatment, respectively; neither the cerebrum nor right femoral muscle contained detectable amounts of lidocaine. The pH values of body fluids and tissues of the human and animal corpses were below 7.0. This study has demonstrated that following intubation, tracheal lidocaine diffuses into surrounding fluids and tissues, and that this is attributable to postmortem acidosis. We suggest that, in subjects who underwent cardiopulmonary resuscitation with intra-tracheal intubation, heart blood and femoral vein blood should be analyzed for lidocaine. In addition, the pattern of distribution of lidocaine in the surrounding tissues may provide some information on the state of victims during cardiopulmonary resuscitation.

KEYWORDS: forensic science, forensic toxicology, lidocaine, postmortem diffusion of lidocaine, endotracheal intubation, cardiopulmonary resuscitation, gas chromatography, animal model, rabbit

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In forensic toxicology, heart blood and urine are the specimens of choice when screening for drugs in non decomposed bodies because these specimens can usually be taken in large enough volumes. Drug concentrations in the blood are often used for evaluating how seriously an individual was under the influence of that drug at the time of death. However, there tends to be some postmortem diffusion to the heart of any drug remaining in the stomach (1). Such basic drugs as tricyclic antidepressants, narcotic analgesics, local anesthetics and antihistamines, that accumulate in the lung and myocardial tissues, lead to erroneously elevated drug concentrations in the heart blood, postmortem (2–5). Thus, whether the postmortem redistribution of a drug has occurred should be judged before the drug concentrations in heart blood are used for the evaluation of the toxic effect of the drug on an individual at the time of death. One of the best ways to establish the extent to which a drug may have diffused into the heart blood is to compare the drug concentrations in the heart blood with those in a peripheral vessel blood or in limb skeletal muscle (1,6). At the Department of Legal Medicine of Kochi Medical School, we have been testing routinely for illicit drugs, and other common basic, neutral and acidic drugs in forensic autopsy cases. In addition, in cases in which patients have undergone hospital treatment prior to death, we review thoroughly the medical records from a toxicological viewpoint.

Here we describe three cases in which a significant quantity of lidocaine, originating from endotracheal intubation for cardiopulmonary resuscitation, was detected in blood in the heart and thoracic large vessels. The intubation was performed postmortem and the cardiopulmonary resuscitation was unsuccessful, with no restoration of the heart beat. The possibility of postmortem diffusion of the tracheal lidocaine into surrounding tissues, especially into heart blood, is discussed, along with findings of animal experiments using rabbits.

Case Histories

Case 1

A 3.5-month-old female baby was found lying in a prone position in bed at a day nursery suffering from respiratory arrest. Although she was already in slight rigor mortis when she was admitted to hospital 20 min later, endotracheal intubation was performed to attempt cardiopulmonary resuscitation. Xylocaine™ jelly (Fujisawa Pharmaceutical Co., Osaka, Japan), a 2% lidocaine preparation, was applied to the tube; the amount was undocumented. The heart did not resume beating and the baby was pronounced officially dead 5 min after the resuscitation attempt.

An autopsy was performed approximately 20 h after death. The body height and weight were 62 cm and 6 kg, respectively. Some

injection marks with no hemorrhages, results of medical treatment, were observed in the regions of the groin and ankles. Many petechiae were observed on the thymus. The heart, which exhibited no malformations, weighed 30 g; a small number of epicardial petechiae were observed. The lungs were edematous with a few petechiae; the left lung weighed 43 g and the right 53 g. Other organs showed no remarkable changes other than congestion. The cause of death was diagnosed as sudden infant death syndrome.

Case 2

A 44-year-old man was found lying in a supine position in a parking lot having suffered a cardiac arrest. When he was admitted to hospital 20 min later, cardiopulmonary resuscitation was performed with endotracheal intubation. A few milliliters of Xylocaine jelly was applied to the tube. The heart beat was not restored and the patient was pronounced officially dead 5 min after the resuscitation attempt.

An autopsy was performed approximately 20 h after death. The body height and weight were 160 cm and 43 kg, respectively. Two injection marks with no hemorrhages, results of medical treatment, were observed in the region of the right groin. Massive bruises were observed in the regions of the shoulder blades and the occipital region of the head. Basal fractures of the skull were also observed. The brain, weighing 1,100 g, had a slight subarachnoid hemorrhage and a contusion (2 by 1.5 cm) of the apex of the right frontal lobe. The left cerebral hemisphere was edematous. The heart, weighing 300 g, contained a large amount of liquid blood; a slight hemorrhage was observed in endocardium of the left ventricle. The lungs, with chronic emphysema, were slightly edematous, the left lung weighing 350 g and the right 400 g. The liver weighed 1,500 g; a parenchymal necrosis (1 cm in diameter) was observed in the middle of the right lobe. No remarkable changes were observed in other organs. The cause of death was thought to be brain swelling due to head injuries caused by falling on the back of the head.

Case 3

A 38-year-old man quarreled with his friend during a drinking session and was stabbed with a knife in the left thigh. He was admitted to hospital but dead on arrival. Although cardiopulmonary resuscitation had been performed for about 1 h, the heart beat was never restored and he was pronounced officially dead. Endotracheal intubation with Xylocaine jelly was performed for the cardiopulmonary resuscitation.

An autopsy was performed approximately 20 h after death. The body height and weight were 178 cm and 58 kg, respectively. A stab wound, 5 cm long by 8 cm deep, was observed in the right middle region of the left thigh. The left femoral artery was incompletely cut off. Three injection marks with small hemorrhages, results of medical treatment, were observed in the region of the right groin. Subcutaneous emphysema was observed in the regions of the neck and chest. Fractures of the sternum, left ribs (2nd through 7th) and right ribs (2nd through 6th) that were caused by the cardiopulmonary resuscitation had small hemorrhages. The heart weighed 350 g and contained little blood. The lungs, weighing 400 g each, were in a state of collapse. Other organs showed no remarkable changes other than a low blood content. The cause of death was thought to be bleeding due to the stab wound.

Toxicological Analysis

Screening with Triage™ (Biosite Diagnostic Inc., California, USA), GC and GC/MS

Blood specimens from the heart or superior vena cava were processed for Triage, GC and GC/MS screening, as described previously (7,8).

The following apparatus was used: 1) a Shimadzu GC-14B (Kyoto, Japan) equipped with a TC-1 capillary column [dimethyl silicone, 15 m by 0.53 mm ID, 1-mm film thickness (GL Sciences Inc., Tokyo, Japan)], a TC-17 capillary column [50% phenylmethyl silicone, 15 m by 0.53 mm ID, 1-mm film thickness (GL Sciences Inc., Tokyo, Japan)] and a flame thermoionic detector (FTD). The temperature of the injection port and detector was 280°C for the TC-1 capillary column and 260°C for the TC-17 capillary column. The column temperatures were programmed as follows: The initial temperature of 150°C was maintained for 2 min, then increased to 280°C for the TC-1 capillary column and to 260°C for the TC-17 capillary column at a rate of 10°C/min. The final temperatures were maintained for 10 min. The carrier gas was nitrogen, with a flow pressure of 15 kPa; 2) a GC/MS system, consisting of a Shimadzu GC-9A (Kyoto, Japan) equipped with a 2 m by 0.26 cm ID glass column packed with 2% OV-1 on 60–80 mesh Chromosorb W AW DMCS, and a Shimadzu QP 1000 D (Kyoto, Japan). The temperatures of the injection port and column were identical to those for the GC with the TC-1 capillary column. The temperature of the separator was 280°C. The electron impact ionization energy and accelerating voltage were 70 eV and 3 kV, respectively. The carrier gas was helium, with a flow rate of 40 mL/min. The Triage screening was negative for all illicit drugs that could be detected by the device. The GC and GC/MS analyses revealed the presence of lidocaine in the blood specimens.

GC Quantification of Lidocaine in Body Fluids and Tissues

The body fluids and tissues obtained at autopsy were stored immediately at 4°C; quantification of lidocaine was performed within 48 h of the autopsy. A portion of each tissue was homogenized in three portions of distilled water, 2 mL of each body fluid, or 2 g of each tissue homogenate was mixed with 100 μL of 12 mg/L carbinoxamine maleate in methanol (internal standard) and 2 mL 1 M carbonate buffer (pH 9.7). Each mixture was extracted with 8 mL n-chlorobutane/isoamyl alcohol (98:2) for 20 min with a mechanical shaker and centrifuged at 2,500 rpm for 5 min. The organic phase was back-extracted with 1 mL of 0.1 N HCl for 30 s using a vortex mixer and centrifuged at 2,500 rpm for 5 min. The resulting aqueous phase was washed with 4 mL 2-methylbutane/toluene/isoamyl alcohol (94:5:1) and mixed with 1 mL carbonate buffer. The mixture was re-extracted with 4 mL 2-methylbutane/toluene/isoamyl alcohol (94:5:1), and the organic phase was reduced to approximately 100 μL at 70°C. A 1-μL aliquot of the concentrated extract was injected into the GC. The sensitivity of the GC quantification for lidocaine in body fluids and tissues was about 0.005 mg/L and 0.020 mg/kg, respectively.

Animal Experimentation

Ten male rabbits (2.03–2.45 kg) were sacrificed by means of ether anesthesia. Fifty microliters of 2% Xylocaine jelly per kilogram of body weight (1 mg/kg as lidocaine hydrochloride) was administered to the trachea just above the bifurcation, and the rabbit carcasses were left in the supine position at an ambient

temperature. The heart blood, cerebrum, hili of the lungs, myocardium, liver, and right femoral muscle were procured one day (Group A; $n = 5$) and 3 days (Group B; $n = 5$) after lidocaine treatment. Lidocaine analysis was performed by the GC as described above.

Results

Table 1 shows the results of lidocaine quantification in Cases 1, 2 and 3. In Case 1, higher concentrations of lidocaine than 0.1 mg/L were detected in the blood in the left ventricle of the heart (left heart blood), in the right ventricle of the heart (right heart blood) and in the thoracic inferior vena cava, and in the pericardial sac fluid. The lidocaine concentration in the left heart blood was 3.4 times higher than that in the right heart blood. No lidocaine was detected in the cerebrum, liver or right femoral muscle. No ethanol was detected in the blood specimens.

In Case 2, very high concentrations of lidocaine, 10.9 mg/kg and 2.65 mg/kg, were detected in the hili of the left and right lungs, respectively. Lidocaine concentrations in the blood specimens were in the order: Left heart blood>right heart blood>thoracic inferior vena cava blood>right iliac vein blood>right femoral vein blood. The lidocaine concentration in the left heart blood, 1.02 mg/L, was 4.9 times higher than that in the right heart blood; only a trace amount of lidocaine was detected in femoral vein blood. No lidocaine was detected in the cerebrum, liver, kidney, or femoral muscle. The pH values of the body fluids and tissues were in the range 5.8–6.5. The ethanol concentrations in the right heart blood and femoral vein blood were 0.223 g/dL and 0.248 g/dL, respectively.

In Case 3, 1.41 and 1.37 mg/kg of lidocaine were detected in the hili of the left and right lungs, respectively. The blood lidocaine concentrations were in the order: Superior vena cava blood>thoracic aorta blood>thoracic inferior vena cava blood>right iliac vein blood. No lidocaine was detected in right femoral vein blood, cerebrum, liver, right kidney or right femoral muscle. The pH values of the body fluids and tissues were in the range 5.0–6.7. The concentrations of ethanol in thoracic aorta blood and right iliac vein blood were 0.256 and 0.288 g/dL, respectively.

As shown in Table 2, small to large amounts of lidocaine were detected in the hili of the lungs and heart blood of all rabbit carcasses in Group A. All but one of the myocardia contained detectable amounts of lidocaine. No lidocaine was detected in the cerebrum, liver or right femoral muscle.

In Group B, large amounts of lidocaine were detected in the hili of the lungs and heart blood of all rabbit carcasses with some intersubject variations. All of the myocardia contained lidocaine, but its concentrations were much lower than those in the heart blood. Of the five rabbit carcasses, two showed slightly elevated concentrations of lidocaine in the liver. No lidocaine was detected in the cerebrum and right femoral muscle. The mean pH values of the heart blood and tissues were in the range 5.9–6.8 and 5.7–6.7 in Groups A and B, respectively.

TABLE 1—*Lidocaine concentrations in various fluids and tissues of patients who underwent unsuccessful cardiopulmonary resuscitation with endotracheal intubation.**

Specimen	Lidocaine concentration (mg/L or mg/kg)		
	Case 1	Case 2	Case 3
Blood			
Left ventricle	0.349 (–)	1.02 (6.2)	–
Right ventricle	0.102 (–)	0.209 (6.1)	–
Thoracic aorta	–	–	0.642 (6.4)
Superior vena cava	–	–	0.746 (6.4)
Thoracic inferior vena cava	0.195 (–)	0.163 (6.1)	0.133 (5.0)
Right iliac vein	–	0.074 (6.2)	0.057 (6.4)
Right femoral vein	–	0.015 (6.3)	ND (6.4)
Pericardial sac fluid	0.193 (–)	0.097 (6.2)	0.171 (–)
Cerebrospinal fluid	ND (–)	–	–
Cerebrum (parietal region)	ND (–)	ND (6.5)	ND (6.7)
Lung			
Left hilus	–	10.9 (5.9)	1.37 (6.5)
Right hilus	–	2.65 (6.1)	1.41 (5.7)
Liver (right lobe)	ND (–)	ND (5.8)	ND (4.6)
Right kidney	–	ND (6.4)	ND (5.7)
Right femoral muscle	ND (–)	ND (5.9)	ND (6.0)

*Xylocaine™ jelly containing 2% lidocaine hydrochloride was used for endotracheal intubation.

ND = Not detectable at lower detection limits of 0.005 mg/L for fluids and 0.020 mg/kg for tissues.

Each figure in parentheses represents the pH value.

Discussion

It is well documented that drug concentrations in heart blood are elevated erroneously for a short postmortem period due to drug diffusion from stomachs that contain a large amount of unabsorbed drug, or from the lung and myocardial tissues in which there is an accumulation of a drug (1–5). Pounder et al. (1) demonstrated that, in human corpses instilled with 50 mg amitriptyline and 5 g paracetamol in an acidic or alkaline solution, drug diffusion occurred in many of the thoracicoabdominal fluids and tissues examined 48 h after drug instillation with large intersubject variation. In these experiments, severe diffusion of those drugs was detected in the left lung base, left lobe of the liver, spleen and pericardial sac fluid. Jones and Pounder (9) reported a multiple drug overdose case in which: 1) great accumulation of imipramine, desipramine, diphenhydramine and codeine in the lungs was observed; 2) blood concentrations of those drugs were in the order: Pulmonary vein blood>>pulmonary artery blood>thoracic aorta blood>inferior vena cava blood>femoral vein blood; and 3) little site dependence in blood concentrations of acetaminophen and ethanol with high water solubility was observed.

In forensic medicine, individuals are encountered who have received cardiopulmonary resuscitation with endotracheal intubation before being pronounced dead. For smooth intubation, Xylocaine jelly is often applied to a tube. In the present cases, in which endotracheal intubation with Xylocaine jelly was performed after the cessation of both the blood circulation and the heart beat had occurred and were not restored by cardiopulmonary resuscitation, moderate to large amounts of lidocaine were detected in the blood in the cardiac chambers and thoracic large vessels. Antemortem use of lidocaine preparations were denied to the victims by family members or friends. Thus, the only origin of the detected lidocaine was thought to be the tracheal lidocaine that remained following intubation. Although an accelerating effect of cardiopulmonary resuscitation on lidocaine diffusion from the trachea might have occurred, the lack of lidocaine in the cerebrum, liver and femoral muscle in all three cases indicates that the detected lidocaine in the hili of the lungs and blood specimens was a result of postmortem diffusion. The experiments using rabbit carcasses described in our study substantiated the view that severe diffusion of tracheal lidocaine into surrounding tissues could occur, resulting in higher concentrations in heart blood, and that the brain and femoral muscles are protected from postmortem diffusion of tracheal lidocaine.

TABLE 2—*Lidocaine concentrations in heart blood and tissues of rabbit carcasses given 1 mg/kg lidocaine hydrochloride, intratracheally, and left at an ambient temperature.*

Specimen	Lidocaine concentration (mg/L or mg/kg)			
	Group A (n = 5)		Group B (n = 5)	
	Mean (Range)	pH range	Mean (Range)	pH range
Heart blood	2.00 (0.550–4.03)	6.3–6.5	5.66 (3.05–7.30)	6.2–6.4
Cerebrum	ND	6.6–6.9	ND	6.6–6.8
Myocardium	0.230 (ND–0.450*)	6.2–6.5	0.770 (0.310–1.42)	6.1–6.5
Lung				
Left hilus	13.1 (0.180–55.5)	6.3–6.5	6.65 (1.34–12.0)	6.3–6.6
Right hilus	2.43 (0.410–8.37)	6.3–6.5	38.1 (7.25–52.5)	6.3–6.6
Liver (middle lobe)	ND	5.9–6.2	0.164 (ND-0.530†)	5.9–6.0
Right femoral muscle	ND	5.3–6.2	ND	5.7–6.1

Rabbit carcasses in Groups A and B were left in the supine position for one and three days, respectively.
ND = Not detectable at lower detection limits of 0.005 mg/L for blood and 0.020 mg/kg for tissues.
*Of the five carcasses, one was negative for lidocaine.
†Of the five carcasses, two were positive for lidocaine.

Moreover, the animal experiments clarified that lidocaine had less affinity to the myocardium. Unfortunately, the myocardia of the human corpses were not analyzed for lidocaine.

As expected, the pH values of body fluids and tissues of the human and animal corpses were below 7.0. Lidocaine, as do many other basic drugs, forms a salt to increase its water solubility under acidic conditions. Thus, most of the tracheal lidocaine in corpses may diffuse into heart blood simply according to a concentration gradient. However, the large differences in lidocaine concentrations between the left and right heart blood in Cases 1 and 2, and much lower concentrations of lidocaine in the pericardial sac fluid than in the left heart blood in these cases can not be explained purely by simple diffusion of tracheal lidocaine. One possible explanation for these phenomena is that, initially, a much larger amount of tracheal lidocaine diffuses into the pulmonary artery and vein around the hili. Redistribution of lidocaine from the pulmonary vein blood into the left heart blood then occurs more rapidly than that of the lidocaine in the pulmonary artery blood into the right heart blood, due to their anatomical location in a supine position. The concentration of lidocaine in the left heart blood in Case 2, 1.02 mg/L, was as high as a subtherapeutic concentration for arrhythmia (10), even though the postmortem interval was only about 20 h. As demonstrated in the animal experiments, a longer postmortem interval would permit a much more severe diffusion of tracheal lidocaine, to produce heart blood concentrations near, or even higher than the therapeutic concentrations.

To our knowledge, this is the first report of severe postmortem diffusion of lidocaine from the trachea. Although little attention has paid to postmortem diffusion of tracheal lidocaine, it should be taken into account in patients who undergo cardiopulmonary resuscitation with endotracheal intubation. In these cases, both heart blood and femoral vein blood should be analyzed in order to judge whether detected lidocaine is a result of antemortem absorption, postmortem diffusion from the trachea, or both. In addition, the pattern of distribution of lidocaine in the tissues may provide some information on the state of the victims during cardiopulmonary resuscitation.

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