Fumio Moriya,[1] *Ph.D. and Yoshiaki Hashimoto,*[1] *M.D.*

Determining the State of the Deceased During Cardiopulmonary Resuscitation from Tissue Distribution Patterns of Intubation-Related Lidocaine

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ABSTRACT: The objective of this study was to determine whether the concentrations of lidocaine, used for endotracheal intubation, in body fluids and tissues reflect the state of the circulation of the deceased during cardiopulmonary resuscitation. The tissue distribution of lidocaine was investigated in seven individuals (Cases 1–7) who underwent medical treatment with endotracheal intubation using Xylocaine™ jelly (a 2% lidocaine hydrochloride preparation), before being pronounced dead. Six patients (Cases 1–6) had cardiopulmonary arrest on arrival at hospital.

In Cases 1–4, there was no restoration of heartbeat during cardiopulmonary resuscitation. However, systemic distribution of intubation-related lidocaine was observed and the kidney-to-liver ratios of lidocaine were less than 1. In Cases 5 and 6, the heartbeat resumed temporarily with cardiac massage, and a kidney-to-liver lidocaine ratio greater than 1 was observed. In Case 7, where the patient was comatose upon admission to hospital, the kidney-to-liver ratio of lidocaine was also greater than 1. These phenomena were substantiated in animal experiments.

Our results indicate that the absorption of tracheal lidocaine during the artificial circulation resulting from cardiopulmonary resuscitation results in a kidney to liver ratio of less than 1, whereas absorption during natural circulation gives a ratio greater than 1. The kidney-to-liver ratio of intubation-related lidocaine may give useful information on the state of a patient during cardiopulmonary resuscitation.

KEYWORDS: forensic science, forensic toxicology, lidocaine, tissue distribution of lidocaine, cardiopulmonary resuscitation, endotracheal intubation, absorption during cardiopulmonary resuscitation, gas chromatography, animal model, rabbit

There is no doubt that postmortem testing for drugs contributes greatly to clarification of the circumstances at the time of the accident or to determination of the cause of death. In patients who have undergone emergency medical treatment before being pronounced dead, toxicological findings on the drugs may give useful information on the state of the patient during the treatment. Attempts at cardiopulmonary resuscitation commonly cause various injuries (hyoid fractures, thyroid fractures, rib fractures, etc.) (1,2). Determining the state of the patient during cardiopulmonary resuscitation may greatly contribute to differentiation of these iatrogenic injuries from injuries caused by an environmental incident or from a natural disease process. In Japan, Xylocaine™ jelly, a 2% lidocaine hydrochloride preparation, is often used to facilitate endotracheal intubation for cardiopulmonary resuscitation. In a previous study (3), we reported that a substantial amount of the lidocaine applied to the endotracheal tube was absorbed by the trachea and distributed systemically during the artificial circulation resulting from cardiopulmonary resuscitation, even when there was no restoration of the heartbeat.

In this study, we investigated whether the tissue distribution patterns of lidocaine are characteristic of the state of the circulation, whether natural or artificial, during cardiopulmonary resuscitation.

Materials and Methods

Human Autopsy Cases

We examined the postmortem tissue distribution of lidocaine in seven patients (Cases 1–7) who underwent endotracheal intubation. Six patients (Cases 1–6) had cardiopulmonary arrest on arrival (CPAOA) at hospital and underwent cardiopulmonary resuscitation before being pronounced dead. One patient (Case 7) was comatose upon admission to hospital. No lidocaine preparation other than Xylocaine™ jelly was used for endotracheal intubation; antemortem use of lidocaine preparations in these patients was also excluded. In Cases 1–4 the heartbeat did not resume during cardiopulmonary resuscitation. In Cases 5 and 6 the heartbeat resumed and the patients survived for 3 and 24 h, respectively, following cardiopulmonary resuscitation. The patient of Case 7 survived for 6 h following admission to hospital. Cases 1–7 are summarized in Table 1.

Chemicals

Xylocaine™ (2% jelly and 1% injection of lidocaine hydrochloride), Novo heparin™ (sodium heparin: 1000 units/mL), and Nembutal™ (sodium pentobarbital: 50 mg/mL) were purchased from Fujisawa Pharmaceutical Co., Osaka, Japan, Kodama Co., Tokyo, Japan, and Dainippon Pharmaceutical Co., Osaka, Japan, respectively. The other reagents were of analytical grade.

Apparatus

A Shimadzu gas chromatograph (GC-14B, Kyoto, Japan) equipped with a TC-1 capillary column [dimethyl silicone, 15 m by

[1] Associate professor and professor, respectively, Department of Legal Medicine, Kochi Medical School, Kohasu, Oko-cho, Nankoku City, Kochi 783-8505, Japan.

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TABLE 1—*Summary of seven individuals in whom endotracheal intubation with Xylocaine™ jelly (a 2% lidocaine hydrochloride preparation) was performed for medical treatment.*

Case No.	Age (Sex)	State at Time of Admission	Duration of CPR*	Restoration of Heartbeat	Survival Time	Postmortem Interval	Main Pathological Findings (Cause of Death)
1	4 mo (M)	CPAOA†	60 min	No	…	12 h	Petechiae in the conjunctiva of the right eyelid, thymus and epicardium; slight lung emphysema and hemorrhages due to CPR (sudden infant death syndrome)
2	60 yr (F)	CPAOA	20 min	No	…	28 h	Ligature marks encircling the neck; congestion of the face; petechiae in the mucosae of the left and right eyes and the buccal cavity (asphyxia due to self-strangulation)
3	60 yr (F)	CPAOA	20 min	No	…	12 h	Large bruises on the head and back; basal fractures of the skull; subdural hemorrhages; subarachnoid hemorrhages; cerebral contusions; hemorrhages in the brain stem (traumatic shock due to fall from a height)
4	57 yr (M)	CPAOA	60 min	No	…	10 h	Massive subcutaneous hemorrhages in the left lower jaw and ear; laceration of the left vertebral artery; subarachnoid hemorrhage; fractures of the sternum and ribs, and a small rupture of the liver due to CPR (subarachnoid hemorrhage due to traumatic laceration of the left vertebral artery)
5	52 yr (F)	CPAOA	<5 min	Yes	3 h	12 h	Stab wounds in the thorax and liver; partial severing of the portal vein; 2500 mL of blood in the abdominal cavity (bleeding)
6	42 yr (F)	CPAOA	5 min	Yes	1 d	9 h	A stab wound in the left thigh; complete severing, which was anatomosed, of the left femoral artery and vein (hemorrhagic shock)
7	86 yr (F)	Coma	…	…	6 h	20 h	Diffuse petechial hemorrhages in the endocardium of the left ventricle; massive hemorrhages in the iliopsoas muscles (endrin poisoning)

* Cardiopulmonary resuscitation.
† Cardiopulmonary arrest on arrival.

0.53 mm internal diameter, 1.5 μm film thickness (GL Sciences Inc., Tokyo, Japan)], a TC-17 capillary column [50% phenylmethyl silicone, 15 m by 0.53 mm internal diameter, 1 μm film thickness (GL Sciences Inc., Tokyo, Japan)], and a flame thermionic detector (FTD) was employed for the screening and quantification of lidocaine. The temperatures of the injection port and detector were 260°C. The column temperatures were programmed as follows: an initial temperature of 150°C was maintained for 2 min, then increased to 280°C and 260°C for the TC-1 and TC-17 capillary columns, respectively, at a rate of 10°C/min and the final temperatures were maintained for 10 min. The carrier gas was nitrogen, with a flow pressure of 15 kPa.

A gas chromatography/mass spectrometry (GC/MS) system, consisting of a Shimadzu gas chromatograph (GC-9A, Kyoto, Japan) equipped with a 2 m by 0.26 cm internal diameter glass column packed with 2% OV-1 on 60–80 mesh Chromosorb W AW DMCS, and a Shimadzu mass spectrometer (QP 1000 D, Kyoto, Japan) was employed for the confirmation of lidocaine. 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, and the carrier gas was helium, with a flow rate of 40 mL/min.

Animal Experimentation

Twelve male rabbits (2.80 to 3.75 kg) were divided into four groups (Groups I–IV).

Group I—Rabbits were given 1000 units of sodium heparin, intravenously, to prevent blood coagulation during the experiments, and were then anesthetized with intravenous sodium pentobarbital (30 mg/kg). The animals were sacrificed by an intravenous injection of 2 mmol/kg potassium chloride. Fifty microliters of Xylocaine™ jelly per kilogram of body weight (1 mg/kg as lidocaine hydrochloride) was administered into the trachea just above the bifurcation. The rabbit carcasses were given cardiac massage by rhythmical compression of the thoraces (100 to 150 times per minute) in the supine position for 1 h.

Group II—Rabbits were given an intravenous injection of lidocaine hydrochloride (1 mg/kg). Sodium heparin (1000 units) and sodium pentobarbital (30 mg/kg) were administered intravenously 15 min later, and the animals were then sacrificed by an intravenous injection of 2 mmol/kg potassium chloride.

Group III—Rabbits were given ethanol (30%, 10 mL/kg), intraperitoneally, 15 min before an intravenous injection of lidocaine hydrochloride (1 mg/kg). Sodium heparin (1000 units) and sodium pentobarbital (30 mg/kg) were administered intravenously 15 min after lidocaine administration, and the animals were then sacrificed by an intravenous injection of 2 mmol/kg potassium chloride.

Group IV—Rabbits were given imipramine (50 mg/kg), intraperitoneally, 15 min before an intravenous injection of lidocaine hydrochloride (1 mg/kg). Sodium heparin (1000 units) and sodium pentobarbital (30 mg/kg) were administered intravenously 15 min

later, and the animals were then sacrificed by an intravenous injection of 2 mmol/kg potassium chloride.

Blood (0.5 to 1 mL) in the left and right cardiac chambers and tissue samples from the cerebrum, right lobe of the liver, right kidney, and right femoral muscle were procured.

GC Quantification of Lidocaine in Various Fluids and Tissues

Two milliliters of each body fluid (each rabbit blood diluted to ⅕ with distilled water) or 2 g of each tissue homogenate (tissue:distilled water, 1:3) was mixed with carbinoxamine maleate in methanol (100 μL of 12 mg/L internal standard) and carbonate buffer (2 mL, 1 M, pH 9.7). Each mixture was extracted with n-chlorobutane/isoamyl alcohol (98:2, 8 mL), and the organic phase was back-extracted with HCl (1 mL, 0.1 N). The resulting aqueous phase was washed with 2-methylbutane/toluene/isoamyl alcohol (94:5:1, 4 mL) and mixed with carbonate buffer (1 mL). The mixture was re-extracted with 2-methylbutane/toluene/isoamyl alcohol (94:5:1, 4 mL). The organic phase was reduced to approximately 100 μL, and a 1-μL aliquot of the concentrated extract was injected into the GC.

Results

Human Autopsy Cases

The lidocaine concentrations in Cases 1–7 are shown in Table 2. In Cases 1–4, where there was no restoration of heartbeat, as well as in Cases 5–7, where substantial amounts of lidocaine were absorbed by the trachea during natural circulation, small to moderate amounts of lidocaine were detected in all of the specimens examined. The kidney to liver lidocaine ratios were within the ranges 0.1 to 0.8 (mean: 0.5) in Cases 1–4 and 1.3 to 4.6 (mean: 3.3) in Cases 5–7.

Animal Experimentation

Table 3 shows the results of the animal experiments. In Group I, in which the rabbit carcasses were given intratracheal lidocaine and

TABLE 2—*Tissue distributions of intubation-related lidocaine absorbed during artificial circulation created by CPR or natural circulation in seven patients.*

	Lidocaine Concentration (mg/L or mg/kg)						
	Absorption During Artificial Circulation of CPR				Absorption During Natural Circulation		
Specimen	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Blood							
left cardiac chambers	0.569	0.575	1.55	0.167	0.231	0.220	0.178
right cardiac chambers	0.373	0.576	0.699	0.178	0.117	0.121	0.214
inferior vena cava	0.225	0.238	0.491	0.095	0.078	0.088	0.218
right femoral vein	0.171	0.032	…	0.030	0.036	…	0.200
Cerebrospinal fluid	0.268	0.406	0.191	…	0.136	0.339	0.079
Pericardial fluid	0.449	0.406	0.489	0.065	0.164	0.240	0.280
Cerebrum (parietal region)	…	0.094	0.044	0.015	0.157	0.393	0.198
Lung							
left hilus	…	0.628	9.33	0.195	0.281	0.413	0.405
Right hilus	…	4.67	2.60	0.182	0.354	0.461	0.330
Liver (right lobe)	0.213	0.089	0.183	0.053	0.036	0.064	0.076
Right kidney	0.167	0.057	0.020	0.029	0.047	0.295	0.310
Right femoral muscle	0.340	0.046	…	0.026	0.036	0.179	0.212
Kidney/liver	0.8	0.6	0.1	0.5	1.3	4.6	4.1

TABLE 3—*Lidocaine concentrations in blood and tissues of rabbit carcasses administered 1 mg/kg lidocaine hydrochloride intratracheally, and given cardiac massage for 1 h (Group I), and rabbits sacrificed 15 min after an intravenous injection of 1 mg/kg lidocaine hydrochloride (Groups II–IV).*

	Mean (Range) of Lidocaine Concentration (mg/L or mg/kg)			
Specimen	Group I ($n = 3$)	Group II ($n = 3$)	Group III* ($n = 3$)	Group IV† ($n = 3$)
Blood				
left cardiac chambers	11.2 (10.4–16.5)	0.232 (0.197–0.272)	0.207 (0.184–0.246)	0.195 (0.175–0.226)
right cardiac chambers	2.89 (1.36–3.79)	0.260 (0.216–0.313)	0.297 (0.249–0.330)	0.259 (0.246–0.286)
Cerebrum	0.229 (0.105–0.358)	1.04 (0.837–1.31)	1.11 (0.999–1.18)	0.989 (0.801–1.17)
Liver (right lobe)	0.426 (0.054–0.627)	0.148 (0.124–0.193)	0.204 (0.157–0.252)	0.154 (0.145–0.160)
Right kidney	0.136 (ND–0.232‡)	4.02 (2.16–6.57)	2.77 (1.98–3.55)	1.71 (1.12–2.19)
Right femoral muscle	0.223 (ND–0.385‡)	0.510 (0.398–0.712)	0.758 (0.561–0.894)	0.669 (0.438–0.949)
Mean kidney/liver (range)	0.2 (0.0-0.4)	28.8 (17.3–51.7)	13.7 (11.0–17.5)	11.1 (7.1–13.7)

* Rabbits were given 3 g/kg ethanol, intraperitoneally, 15 min before lidocaine administration.
† Rabbits were given 50 mg/kg imipramine hydrochloride, intraperitoneally, 15 min before lidocaine administration.
‡ Of the three carcasses, two were positive for lidocaine.

cardiac massage, systemic distribution of tracheal lidocaine was observed and the kidney to liver lidocaine ratios were within the range 0.0 to 0.4 (mean: 0.2). In Groups II–IV, in which the rabbits were given an intravenous injection of lidocaine, singly or following ethanol or imipramine treatment, the tissue distributions of lidocaine were very similar to one another. The kidney-to-liver lidocaine ratios were within the ranges 17.3 to 51.7 (mean: 28.8) in Group II, 11.0 to 17.5 (mean: 13.7) in Group III, and 7.1 to 13.7 (mean: 11.1) in Group IV.

Discussion

Lidocaine used for endotracheal intubation readily diffuses from the trachea into the lungs, especially into blood in the thin-walled pulmonary veins (4) and drugs accumulating in the pulmonary venous blood can easily be redistributed into blood in the left cardiac chambers within several hours after death (5). Postmortem diffusion of lidocaine remaining in the trachea may result in an increase in its concentration in the cardiac blood to subtherapeutic levels (4). Plasma lidocaine concentrations of 2 to 5 mg/L are considered desirable for antiarrhythmic control. Signs of lidocaine toxicity, which include confusion, dizziness, apprehension, delirium, paresthesia, hypotension, central nervous system depression, and convulsion, may appear at plasma lidocaine concentrations exceeding 8 mg/L (6). However, a careful toxicological examination should not lead to the misjudgment that lidocaine detected in cardiac blood is a result of antemortem lidocaine absorption, because the postmortem diffusion of tracheal lidocaine does not result in an increase in its level in peripheral blood, the brain, and femoral muscle (4).

In Cases 1–4, systemic distribution of the intubation-related lidocaine was observed, despite no restoration of the heart beat during cardiopulmonary resuscitation. Prolonged cardiac massage for 20 to 60 min may have resulted in artificial circulation during which substantial amounts of lidocaine were absorbed by the trachea. Thus, in patients who were CPAOA at hospital and officially pronounced dead after prolonged cardiopulmonary resuscitation, it is difficult to determine whether the heart beat temporarily resumed during resuscitation due to the concentrations of intubation-related lidocaine in the body fluids and tissues, because the tissue distribution patterns of lidocaine are very similar in both patients with no restoration and temporary restoration of the heartbeat. However, there was a clear difference in the kidney to liver lidocaine ratios between patients with and without restoration of the heartbeat during cardiopulmonary resuscitation: absorption of lidocaine by the trachea during the artificial circulation of cardiopulmonary resuscitation gave a kidney-to-liver lidocaine ratio of less than 1, whereas absorption during natural circulation gave a ratio greater than 1.

To substantiate this phenomenon, we performed experiments using rabbits. Group I was designed as a model of unsuccessful cardiopulmonary resuscitation, Group II as the control for the tissue distribution of lidocaine during natural circulation, Group III as a model of alcohol intoxication, and Group IV as a model of imipramine intoxication. Severe poisoning by alcohol and tricyclic antidepressants are often seen in the emergency room (7,8). The doses of ethanol and imipramine in our experiments were moderately to severely toxic for the animals (9). A dose of 1 mg/kg lidocaine hydrochloride was chosen to approximate the dose of Xylocaine™ jelly which is usually applied at an amount of 2 to 3 mL (approximately 1 mg/kg lidocaine hydrochloride for a patient weighing 50 kg) for endotracheal intubation. Rabbit carcasses which were given cardiac massage following intratracheal administration of Xylocaine™ jelly showed a kidney to liver lidocaine ratio of less than 1. In contrast, rabbits given an intravenous injection of lidocaine hydrochloride showed a kidney to liver lidocaine ratio of greater than 1, irrespective of the presence of ethanol or imipramine. Ethanol and imipramine may not significantly inhibit lidocaine metabolism by the liver enzymes. Thus, the kidney-to-liver lidocaine ratio seems to be useful for determining the different patterns of absorption.

The different patterns of antemortem and postmortem distribution of lidocaine in the liver and kidney may simply reflect the metabolic state of lidocaine in the liver. In individuals who suffer cardiopulmonary arrest, liver function will deteriorate markedly leading to a kidney-to-liver lidocaine ratio of less than 1 if the heartbeat does not resume. In contrast, lidocaine is extensively metabolized in the liver of living persons and animals (10). Thus, the accumulation of parenterally administered lidocaine is likely to be greater in the kidney than in the liver, even though the liver function has deteriorated to some extent. Additionally, the detection of lidocaine metabolites in individuals who are not successfully resuscitated after endotracheal intubation with Xylocaine™ jelly may also be helpful in judging whether the accumulation of lidocaine in the tissues is a result of its absorption antemortem or postmortem.

In conclusion, although the number of cases is limited, it is suggested strongly that the kidney-to-liver lidocaine ratio is helpful for judging whether tracheal lidocaine has been absorbed antemortem or postmortem in individuals who have undergone cardiopulmonary resuscitation. The pattern of the tissue distribution of intubation-related lidocaine may give useful information on the state of the victim during cardiopulmonary resuscitation.

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Additional information and reprint requests:
Fumio Moriya, Ph.D.
Department of Legal Medicine
Kochi Medical School
Kohasu, Oko-cho
Nankoku City, Kochi 783-8505
Japan