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Redistribution of Basic Drugs into Cardiac Blood from Surrounding Tissues during Early-Stages Postmortem

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ABSTRACT: The objective of this study was to elucidate the mechanism(s) responsible for increases in the concentrations of basic drugs in cardiac blood of bodies in a supine position during early-stages postmortem. The concentrations of basic drugs in cardiac blood and other fluids and tissues of three individuals who had used one or more basic drugs were examined. The results were compared with those obtained in experiments using rabbits. In the first case, autopsy of whom was performed approximately 12 h after death, methamphetamine was detected and its concentrations were in the order: lung ⩾ pulmonary venous blood > blood in the left cardiac chambers (left cardiac blood) ⩾ pulmonary arterial blood > blood in the right cardiac chambers (right cardiac blood). In the second case, autopsy of whom was performed approximately 9 h after death, methamphetamine and morphine were detected and their concentrations in the left cardiac blood were roughly twice those in the right cardiac blood. The methamphetamine and morphine concentrations in the lung were 2 to 4 times higher than those in cardiac blood samples. In the third case, autopsy of whom was performed approximately 2.5 days after death, the pulmonary veins and arteries were filled with chicken fat clots. Toxicological examination revealed the presence of four basic drugs: methamphetamine, amitriptyline, nortriptyline and promethazine. Their concentrations in the lung were 5 to 300 times higher than those in cardiac blood, but postmortem increases in the concentrations of these drugs in the cardiac blood were not observed. In the animal experiments, rabbits were given 5 mg/kg methamphetamine intravenously or 20 mg/kg amitriptyline subcutaneously and sacrificed 20 min or 1 h later, respectively. The carcasses were left in a supine position at the ambient temperature for 6 h after or without ligation of the large vessels around the heart. For the groups with ligated vessels, the mean ratios of the drug concentrations in both left and right cardiac blood samples 6 to 0 h postmortem were about 1, whereas in those without ligated vessels, these ratios were about 2 and 1, respectively. The order of the methamphetamine and amitriptyline concentrations in blood and tissue samples were roughly: lungs > myocardium and pulmonary venous blood > cardiac blood, inferior vena caval blood and liver. Our results demonstrate that when bodies are in a supine position, (1) basic drugs in the lungs diffuse rapidly postmortem into the left cardiac chambers via the pulmonary venous blood rather than simply diffusing across concentration gradients, and (2) basic drugs in the myocardium contribute little to the increases in their concentrations in cardiac blood during the early postmortem period.

KEYWORDS: forensic science, forensic toxicology, postmortem redistribution of basic drugs, methamphetamine, morphine, amitriptyline, nortriptyline, promethazine, animal model, rabbit

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In the practice of forensic medicine, there is no doubt that toxicological findings in a corpse contribute greatly to determining the cause and manner of death. As basic and clinical data on the toxicity of many kinds of drugs in relation to their concentrations in blood are available (1,2), drug concentrations in blood obtained postmortem are often used to evaluate how seriously an individual was under the influence of a drug at the time of death. Cardiac blood is the most frequently chosen specimen for determining drug concentrations in nondecomposed bodies because large enough volumes for analysis can usually be obtained at autopsy. However, drug concentrations in cardiac blood tend to be affected by the following factors: (i) postmortem redistribution of drugs from surrounding tissues (3); (ii) postmortem diffusion of drugs from the stomach containing large amounts of drugs (4–6); and (iii) postmortem diffusion of drugs through the trachea associated with agonal aspiration of vomitus (7,8) or medical treatment (9).

Holt and Benstead (10) first reported this phenomenon of postmortem increases in drug concentrations in cardiac blood in human autopsy cases associated with digoxin use and Vorphal and Coe (11) reported similar results. Bailey and Shaw (12) reported that tricyclic antidepressants, narcotic analgesics, local anesthetics and antihistamines accumulated in the myocardium to a significant extent and suggested this might be responsible for the postmortem increases in their concentrations in cardiac blood. The lungs are also thought to contribute to postmortem increases in drug concentrations in cardiac blood (3), as drugs deposited in the lungs may be redistributed by simple diffusion across concentration gradients or via the pulmonary arteries and veins. However, little is known about which mechanism(s) is primarily responsible for increases in drug concentrations in cardiac blood during the early stages postmortem. Elucidation of the mechanism(s) is particularly important to establish how drug concentrations in cardiac blood can be used for toxicological evaluation.

In this study, we investigated redistribution of basic drugs into cardiac blood from the surrounding tissues during early-stages postmortem by comparing toxicological data from human autopsy cases with those obtained in experiments on rabbits.

Materials and Methods

Human Autopsy Cases

Three autopsy cases (Cases 1 to 3), in whom methamphetamine, morphine, amitriptyline, nortriptyline and/or promethazine were detected and from whom substantial volumes of blood were obtained from the cardiac chambers, were examined in this study. The postmortem interval of Case 3 was approximately 2.5 days, but little sign of putrefaction was observed because the body had

been left at cool temperatures between 0 and 15°C in winter. The data for these three cases are summarized in Table 1. The body fluid and tissue samples obtained at autopsy were stored immediately after collection at 4°C and drug analysis was performed within 48 h of autopsy.

Chemicals

Philopon™ (methamphetamine hydrochloride), amitriptyline hydrochloride and Novo heparin™ (sodium heparin: 1000 μ/mL) were purchased from Dainippon Pharmaceutical Co. (Osaka, Japan), Sigma Chemical Co. (St. Louis, MO) and Kodama Co. (Tokyo, Japan), respectively. All the other reagents used were of analytical grade.

Apparatus

The following apparatuses were used:

- A Shimadzu gas chromatograph (Shimadzu GC-14B, Kyoto, Japan) equipped with a TC-1 capillary column [dimethyl silicone, 15 m by 0.53 mm inside diameter, 1.5 μm film (GL Sciences Inc., Tokyo, Japan)], a TC-17 capillary column [50% phenylmethyl silicone, 15 m by 0.53 mm inside diameter, 1 μm film (GL Sciences Inc., Tokyo, Japan)] and a flame thermionic detector (FTD). The temperatures of the injection ports and detector were 280 and 260°C for the TC-1 and TC-17 capillary columns, respectively. The column temperatures were programmed as follows: an initial temperature of 150°C was maintained for 2 min, then increased to 280 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 at a flow pressure of 15 kPa.
- A gas chromatography/mass spectrometry (GC/MS) system consisting of a Shimadzu gas chromatograph (Shimadzu GC-9A, Kyoto, Japan) equipped with a 2 m by 0.26 cm inside diameter glass column packed with 2% OV-1 on 60 to 80 mesh Chromosorb W AW DMCS or 1.5% OV-1 on 60 to 80 mesh Chromosorb W AW DMCS and a Shimadzu mass spectrometer (Shimadzu QP 1000 D, Kyoto, Japan). The temperatures of the injection ports and columns for the liquid phases of OV-1 and OV-17 were identical to those used for gas chromatography (GC) with the TC-1 and TC-17 capillary columns, respectively, the separator temperature was 280°C, the electron impact ionization energy and accelerating voltage were 70 eV and 3 kV, respectively, and the carrier gas was helium at a flow rate of 40 mL/min.

Animal Experimentation

Male white rabbits (2.70 to 3.42 kg) were given: (1) 5 mg/kg methamphetamine hydrochloride intravenously and sacrificed 20 min later by intravenous injection of 1500 μ sodium heparin and 2 mmol/kg potassium chloride, or (2) 20 mg/kg amitriptyline hydrochloride subcutaneously and sacrificed 1 h later as described above. The sodium heparin preparation was used to prevent blood coagulation during the experiments. Immediately after death, thoracotomy was performed and 0.2-mL of blood samples were drawn from the left and right cardiac chambers by needle puncture. The rabbit carcasses were then left at the ambient temperature in a supine position after (Groups I and III received methamphetamine and amitriptyline, respectively) or without (Groups II and IV received methamphetamine and amitriptyline, respectively) ligation of the large vessels around the heart. Six hours postmortem, 0.2 to 0.4-mL samples of the pulmonary venous blood, blood in the left and right cardiac chambers (left and right cardiac blood, respectively), and inferior vena caval blood and tissue samples from the hilar regions of the left and right lungs, myocardium and right lobe of the liver were procured.

GC Quantification of Methamphetamine, Morphine, Amitriptyline, Nortriptyline and Promethazine

One to two milliliters of each body fluid (each rabbit blood sample was diluted 1:5 with distilled water) or 1 to 2 g each tissue homogenate (tissue:distilled water = 1:3 by weight) was processed for GC quantification of the drugs. The analytical procedure for sympathomimetic amines described previously (13) was used to quantify methamphetamine, using 5 μg *N*-methylbenzylamine or 1.2 μg carbinoxamine maleate as the internal standard. The analytical procedure for basic drugs described previously (13) was used to quantify amitriptyline, nortriptyline and promethazine, using 1.2 μg carbinoxamine maleate as the internal standard. The analytical procedure for opiates described by Spiehler and Brown (14) was performed with 1 or 10 μg levallorphan tartrate as the internal standard.

TABLE 1—*Summary of three individuals in whom postmortem redistribution of basic drugs was investigated.*

Case No.	Age (sex)	Postmortem Interval	Position of Body until Autopsy	Main Pathological Findings (Cause of Death)	Basic Drug(s) Detected in Cardiac Blood
1	64 yr. (♂)	12 h	Supine	Several abrasions of the extremities; old and new injection marks in the right cubital fossa; fluid blood in the heart; lung edema; congestion of other organs (cold exposure)	Methamphetamine
2	42 yr. (♂)	9 h	Supine	Old and new injection marks in the left cubital fossa; petechiae on the conjunctiva of the left eye, laryngeal mucosa, epicardium and mucosae of the renal pelves; fluid blood in the heart; lung edema; congestion of other organs (heroin poisoning)	Methamphetamine and morphine
3	48 yr. (♂)	2.5 days	Supine	Little sign of putrefaction; old and new injection marks in the left cubital fossa; pulmonary veins and arteries filled with chicken fat clots; cardiac blood containing chicken fat clots (poisoning due to multiple drug use)	Methamphetamine, amitriptyline, nortriptyline and promethazine

TABLE 2—*Tissue distributions of basic drugs in three autopsy cases.*

	Concentration (mg/L or mg/kg)							
	Case 1	Case 2			Case 3			
Sample	Methamphetamine	Methamphetamine	Free Morphine	Total Morphine	Methamphetamine	Amitriptyline	Nortriptyline	Promethazine
Blood								
left ventricle	2.99	0.875	0.800	1.17	0.235	0.017	0.018	0.114
right ventricle	1.45	0.551	0.462	0.534	0.236	0.037	0.018	0.104
pulmonary artery	1.65	...	...	...	...	...	...	...
pulmonary vein	3.11	...	...	...	...	...	...	...
thoracic aorta	2.65	...	...	...	...	...	...	...
inferior vena cava	2.22	...	...	...	...	...	...	...
right femoral artery	1.80	...	...	...	...	...	...	...
right femoral vein	1.43	...	...	...	...	...	...	...
Cerebrospinal fluid	1.18	0.610	0.364	0.960	...	...	...	...
Pericardial fluid	1.70	0.750	0.757	1.50	...	...	...	...
Urine	10.1	9.55	0.435	1.68	7.95	0.367	1.21	0.074
Cerebrum (parietal region)	3.90	2.06	0.336	0.340	0.960	0.373	0.529	0.930
Lung (right hilus)	7.48	1.73	1.14	2.27	1.13	4.31	5.52	16.2
Myocardium	...	2.97	0.668	0.848	...	...	...	...
Liver (right lobe)	10.8	8.28	1.44	4.20	1.37	0.371	0.230	0.946
Spleen	7.78	5.28	0.700	0.956	0.980	0.405	0.635	0.964
Right kidney	6.57	6.88	1.79	1.90	0.838	0.539	0.476	1.31
Right femoral muscle	1.77	1.45	0.736	0.992	1.35	0.127	0.622	0.229
Stomach contents	4.52(1.36)	9.76(1.95)	1.20(0.240)	5.22(1.04)	0.820(0.410)	0.117(0.059)	0.077(0.039)	0.092(0.046)

Each figure in parentheses represents the total amount of drug in the stomach (mg).

Statistical Analysis

The Student's *t*-test was used to compare drug concentrations in cardiac blood of each animal group 6 h postmortem with those at the time of death. Differences at $p < 0.05$ were considered to be significant.

Results

Human Autopsy Cases

The tissue distributions of the basic drugs detected in Cases 1 to 3 and ratios of the drug concentrations in the left cardiac blood and lung to those in the right cardiac blood are shown in Tables 2 and 3, respectively.

In Case 1, the presence of methamphetamine was confirmed by GC/MS and the order of its concentrations in the lung, cardiac blood and pulmonary vessels was: lung ⩾ pulmonary venous blood > left cardiac blood ⩾ pulmonary arterial blood > right cardiac blood. The methamphetamine concentrations in the left cardiac blood and lung were 2.06 and 5.16 times, respectively, higher than that in the right cardiac blood and its concentrations in the right cardiac and femoral venous blood were almost the same, whereas its concentration in the left cardiac blood was 1.76 times higher than that in the pericardial fluid.

In Case 2, the presence of methamphetamine and morphine was confirmed by GC/MS and the methamphetamine concentration in the left cardiac blood was 1.59 times higher than that in the right cardiac blood. The free and total morphine concentrations in the left cardiac blood were 1.73 and 2.19 times, respectively, higher than those in the right cardiac blood. The proportions of free morphine (as percentages of the total) in the right and left cardiac blood, myocardium and lung were 86.6, 68.4, 78.8 and 50.5%, respectively. The methamphetamine and morphine concentrations

TABLE 3—*Ratios of the concentrations of basic drugs in the left cardiac blood and lung to those in the right cardiac blood of three autopsy cases.*

Case No.	Drug(s) Detected	Left Cardiac Blood/Right Cardiac Blood	Lung/Right Cardiac Blood
1	Methamphetamine	2.06	5.16
2	Methamphetamine	1.59	3.14
	Free morphine	1.73	2.47
	Total morphine	2.19	4.25
3	Methamphetamine	1.00	4.79
	Amitriptyline	0.46	116
	Nortriptyline	1.00	307
	Promethazine	1.10	156

in the lung were 2.47 to 4.25 times higher than those in the right cardiac blood. The methamphetamine and free morphine concentrations were higher in the left cardiac blood than in the pericardial fluid and the total morphine concentration in the left cardiac blood, although lower than that in the pericardial fluid, was higher than that in the myocardium.

In Case 3, the presence of methamphetamine, amitriptyline, nortriptyline and promethazine was confirmed by GC/MS and all their concentrations in the left cardiac blood, except that of amitriptyline, were almost the same as those in the right cardiac blood. The methamphetamine concentration in the lung was 4.79 times higher than that in the right cardiac blood and the concentrations of the other three drugs in the lung were over 100 times their levels in the right cardiac blood.

In all three cases, the total amounts of drugs in the stomach were not particularly large.

TABLE 4—*Ratios of the methamphetamine concentrations in cardiac blood 6 to 0 h after death of rabbits given 5 mg/kg methamphetamine hydrochloride intravenously and left in a supine position at the ambient temperature after (Group I) or without (Group II) ligation of the large vessels around the heart.*

Experimental Group	Cardiac Blood	6 to 0 h Postmortem Concentration Ratio
Group I ($n = 4$)	Left chambers	1.13 ± 0.42
	Right chambers	1.07 ± 0.04
Group II ($n = 4$)	Left chambers	1.62 ± 0.47
	Right chambers	1.13 ± 0.57

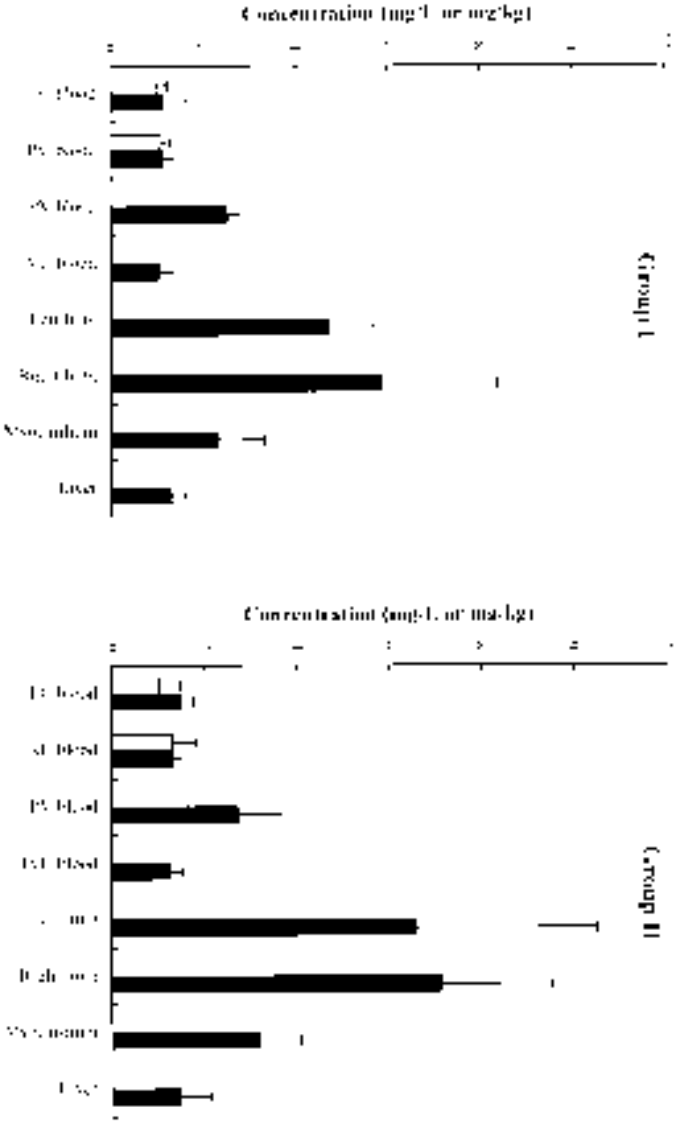

FIG. 1—*Methamphetamine concentrations in cardiac blood samples obtained at the time of death (□) and in various blood and tissue samples obtained 6 h postmortem (■). Rabbits were sacrificed 20 min after intravenous administration of 5 mg/kg methamphetamine hydrochloride and left in a supine position at the ambient temperature after (Group I) or without (Group II) ligation of the large vessels around the heart. Each column represents the mean + SD of four animals. LC blood = left cardiac blood, RC blood = right cardiac blood, PV blood = pulmonary venous blood and IVC blood = inferior vena caval blood.*

Animal Experimentation

(1) Methamphetamine Administration—The methamphetamine concentrations of Groups I ($n = 4$) and II ($n = 4$) are shown in Fig. 1. The order of the methamphetamine concentrations in the blood and tissues of both groups was roughly: lungs > pulmonary venous blood and myocardium > cardiac blood, inferior vena caval blood and liver. For Group I, the mean ratios of the methamphetamine concentrations in the left and right cardiac blood samples 6 to 0 h postmortem were about 1, whereas for Group II, they were about 1.5 and 1, respectively (Table 4).

(2) Amitriptyline Administration—The amitriptyline and nortriptyline concentrations of Groups III ($n = 4$) and IV ($n = 4$) are shown in Figs. 2 and 3, respectively. The order of the amitriptyline concentrations in the blood and tissues of both groups was roughly: lungs ⩾ pulmonary venous blood and myocardium ⩾ cardiac blood, inferior vena caval blood and liver. For Group III, the mean ratios of the amitriptyline concentrations 6 to 0 h postmortem for both the left and right cardiac blood samples were about 1, whereas the Group IV ratios were about 2 and 1, respectively (Table 5). Substantial amounts of nortriptyline were detected in the lungs, pulmonary venous blood and myocardia of both these groups, but none was detected in any of the blood samples obtained from the hearts or inferior vena cavae of Group III. Tiny amounts of nortriptyline were detected in the left cardiac blood samples obtained from Group IV 6 h after death, but none was detected in those obtained at the time of sacrifice.

Discussion

It is well documented that basic drugs such as tricyclic antidepressants, narcotic analgesics, local anesthetics and antihistamines that accumulate in the myocardium and lungs in large amounts can easily be redistributed into the cardiac blood, resulting in enormously elevated drug levels in the latter (3). In the state of hypoxia after death, rapid depletion of adenosine triphosphate and adeno-

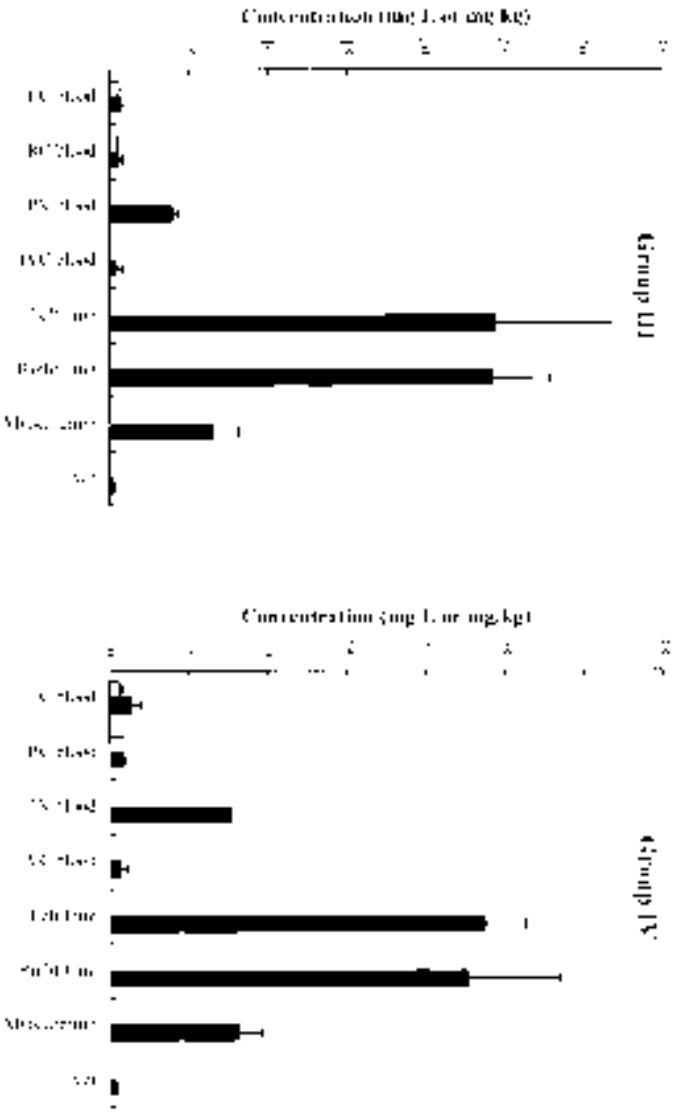

FIG. 2—*Amitriptyline concentrations in cardiac blood samples obtained at the time of death (□) and in various blood and tissue samples obtained 6 h postmortem (■). Rabbits were sacrificed 1 h after subcutaneous administration of 20 mg/kg amitriptyline hydrochloride and left in a supine position at the ambient temperature after (Group III) or without (Group IV) ligation of the large vessels around the heart. Each column represents the mean + SD of four animals. LC blood = left cardiac blood, RC blood = right cardiac blood, PV blood = pulmonary venous blood and IVC blood = inferior vena caval blood.*

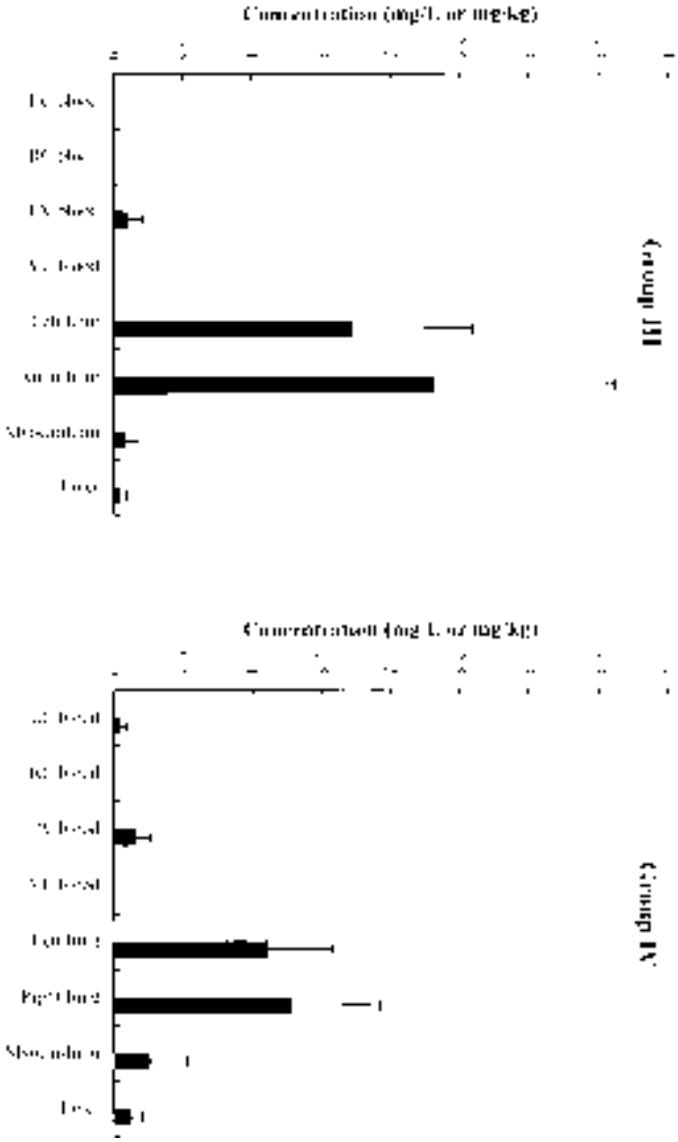

FIG. 3—*Nortriptyline concentrations in cardiac blood samples obtained at the time of death (□) and in various blood and tissue samples obtained 6 h postmortem (■). Rabbits were sacrificed 1 h after subcutaneous administration of 20 mg/kg amitriptyline hydrochloride and left in a supine position at the ambient temperature after (Group III) or without (Group IV) ligation of the large vessels around the heart. Each column represents the mean + SD of four animals. LC blood = left cardiac blood, RC blood = right cardiac blood, PV blood = pulmonary venous blood and IVC blood = inferior vena caval blood.*

sine triphosphatase occurs, resulting in functional failure of the sodium/potassium pumps, damage to the plasma membranes and mitochondria and the intra- and extra-cellular pH values decline due to lactate accumulation (16). We confirmed that the pH values of body fluids and tissues of human autopsy cases decrease rapidly postmortem to below 7 (9,17). The above conditions may facilitate the leakage of intra-cellular drugs into the extra-cellular spaces. Drugs distributed in the myocardium can diffuse directly into cardiac blood across a concentration gradient and the left cardiac blood surrounded by a thick myocardium rich in an absolute amount of a drug may be affected to a greater extent than the right cardiac blood surrounded by a thinner myocardium. Drugs sequestered in the pulmonary tissues can be redistributed into cardiac blood by simple diffusion across a concentration gradient or via pulmonary blood vessels and when a body is in a supine position, the left cardiac chambers may be affected more than the right cardiac chambers because the former are located anatomically below the latter. However, it is not known which mechanism predominates during the early stages postmortem.

In this study, we selected three cases with relatively small amounts of drugs in the stomach in order to exclude, or at least minimize, postmortem diffusion of drugs from the stomach. Drugs

TABLE 5—*Ratios of the amitriptyline concentrations in cardiac blood 6 to 0 h after death of rabbits administered with 20 mg/kg amitriptyline hydrochloride subcutaneously and left in a supine position at the ambient temperature after (Group III) or without (Group IV) ligation of the large vessels around the heart.*

Experimental Group	Cardiac Blood	6 to 0 h Postmortem Concentration Ratio
Group III ($n = 4$)	Left chambers	1.18 ± 0.15
	Right chambers	1.24 ± 0.17
Group IV ($n = 4$)	Left chambers	2.09 ± 0.64*
	Right chambers	0.99 ± 0.18

* Significant difference (Student's t-test, $p < 0.05$) between the amitriptyline concentrations 6 h postmortem and those at the time of death.

deposited in the liver, although they diffuse into neighboring blood and tissues, are thought not to affect their concentrations in cardiac blood significantly during the early postmortem period (15). Thus,in Cases 1 and 2, whose postmortem intervals were relatively short, redistribution of drugs in the liver into cardiac blood can be excluded, even though the hepatic drug concentrations were higher than the pulmonary drug concentrations. However in Case 1, the inferior vena caval blood might have been affected to some extent by methamphetamine in the liver. The viscosity of postmortem blood samples should also be taken into consideration, as it affects drug concentrations in blood and can be determined indirectly from the hematocrit. In each case, the hematocrits of the left and right cardiac blood obtained were almost the same, indicating that this factor can be discounted. The blood samples in the pulmonary vessels and cardiac chambers of Cases 1 and 2 were completely liquid and the drug concentrations were higher in the left than the right cardiac blood. However, the pulmonary vessels of Case 3 were filled with chicken fat clots and only slight differences between the left and right cardiac blood concentrations of three of the drugs, but not amitriptyline, were observed. Although the amitriptyline concentrations in the left cardiac blood were about half that in the right cardiac blood, both values were too low to establish whether postmortem redistribution had occurred. In addition to the findings discussed above, the relative concentrations of methamphetamine and morphine in the pulmonary vessel blood, left cardiac blood, pericardial fluid and/or myocardia of Cases 1 and 2 suggest strongly that these drugs in the lungs primarily reached the left cardiac chambers via the pulmonary venous blood during the early postmortem period. However, it was still not clear from these findings to what extent a drug accumulating in the myocardium affects its concentration in cardiac blood postmortem.

In an attempt to establish this, we conducted experiments on rabbits using methamphetamine and amitriptyline as model drugs. In spite of the high concentrations of these drugs in the lungs, pulmonary venous blood and myocardia of rabbits with ligated large vessels around the heart, only slight increases in their concentrations in both the left and right cardiac blood were observed 6 h after death. In rabbit carcasses left without ligation of these vessels for 6 h, the methamphetamine concentrations in the left, but not the right, cardiac blood showed a tendency to be elevated and the amitriptyline concentrations were elevated significantly in the left ($p < 0.05$), but not the right, cardiac blood, and the results for nortriptyline were parallel to those.

These results led us to draw the following conclusions: First, drugs deposited in the myocardium in large amounts contribute little to increases in their concentrations in cardiac blood during the early postmortem period, and second, drugs in the lungs are redistributed rapidly into the pulmonary venous blood and then into the left cardiac chambers if the blood remains liquid after death. As the lungs have the richest supply of blood vessels in the body, drugs can be sequestered in the pulmonary tissues at high concentrations antemortem and diffuse postmortem from these tissues into the thin-walled pulmonary veins more rapidly than into thick-walled pulmonary arteries.

We recommend that drug concentrations in left cardiac blood should not be used for toxicological evaluation, even if the postmortem interval is short. Right cardiac blood, however, may be the specimen of choice, as well as peripheral blood samples, for the evaluation of drug concentrations during early postmortem stages. Furthermore, it should be borne in mind that postmortem redistribution of drugs from solid organs into blood may also be facilitated by mechanical factors, such as the movement of blood through the vascular system due not only to postmortem rigidity (18), but also to postural changes during postmortem inspection and carriage of the body.

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