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Medicolegal Implications of Drugs and Chemicals Detected in Intracranial Hematomas

REFERENCE: Moriya F, Hashimoto Y. Medicolegal implications of drugs and chemicals detected in intracranial hematomas. J Forensic Sci 1998;43(5):980–984.

ABSTRACT: The purpose of this study was to determine how drug findings in intracranial hematomas should be assessed in forensic autopsy cases. Six cases in which intracranial hematomas containing drugs and chemicals were detected were examined in this study. Of the six cases, five were positive for drugs and chemicals that had been self-administered by the victims prior to injury. Post-traumatic time interval from injury to death was in the range 10 to 65 h. In two individuals who were positive for norephedrine or toluene, the concentrations of these substances were much higher in the intracranial hematomas than in heart blood. In an individual who was positive for phenobarbital, its concentration was only a little higher in the intracranial hematoma than in heart blood. In the remaining two cases, substantial quantities of ethanol were detected in the intracranial hematomas, but little ethanol was detected in heart blood.

In three cases, some drugs were administered at hospital after the injuries. The time interval from the initial drug administration to death was 19 to 60 h. In two individuals given phenytoin and/or lidocaine intravenously, substantial amounts of these drugs were detected in the intracranial hematomas. In an individual given diazepam intravenously, a substantial quantity of diazepam was detected in heart blood, but not in the intracranial hematoma.

Toxicological analysis of intracranial hematomas may be useful not only for determining whether individuals were under the influence of ethanol at the time they were injured, but also for detecting pre-traumatic usage of other drugs and chemicals. However, the medical record should be reviewed thoroughly from a toxicological view point if victims underwent medical treatment prior to death because drugs administered for the purpose of medical treatment can disseminate into preexisting intracranial hematomas, depending on the size of the hematomas.

KEYWORDS: forensic science, forensic toxicology, drugs and chemicals in hematomas, subdural hematomas, epidural hematomas, intracranial hematomas

In victims who survive for several hours or more after injury, it is often difficult to determine whether they were under the influence of some drugs and chemicals at the time of injury because drugs and chemicals with short plasma half-lives may be metabolized completely and excreted prior to death, resulting in no detection of such drugs and chemicals from blood samples obtained at autopsy. Some researchers have reported that, in individuals who suffered from intracranial hemorrhages caused by blunt forces to the head and who survived several hours or more after injury, intracranial hematomas are the specimens of choice for detecting alcohol originating from drinking prior to injury since alcohol in sequestered hematomas disappears more slowly than it does in circulating blood (1–5). Despite growing knowledge of the usefulness of intracranial hematomas in forensic alcohol testing, little information is available about the detection of the other drugs and chemicals in hematomas. In this paper, we discuss how intracranial hematomas can be used for drug testing in forensic cases.

Materials and Methods

Autopsy Cases

Six autopsy cases (Cases 1–6) in which intracranial hematomas containing drugs and chemicals were detected were examined in this study. Of the six cases, three (Cases 1, 4, and 6) were victims of accidental falls and the other three (Cases 2, 3, and 5) were victims of homicidal assaults. Five victims (Cases 2–6) underwent medical treatment for their head injuries, and no enlargement of the hematomas was observed after admission to hospital. Regardless of whether skull fractures were observed, no penetration of the hematomas into the brain was noted. A summary of the patient data for the six cases is shown in Table 1. The body fluids and tissues obtained at autopsy were stored immediately at 4°C; drug analysis was performed within 48 h of autopsy.

Apparatus

The following apparatus was used. (1) A Shimadzu GC-14B (Kyoto, Japan) was 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 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: An 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 gas chromatography/mass spectrometry (GC/MS) system consisted of a Shimadzu GC-9A (Kyoto, Japan) equipped with a 2 m by 0.26 cm inside diameter glass column packed with 2% OV-1 on 60–80 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.

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Received 2 Sept. 1997; and in revised form 6 Jan. 1998; accepted 6 Jan. 1998.

TABLE 1—*Summary of drug-and-chemical-related cases in which intracranial hematomas were analyzed.*

Case No.	Age (sex)	Admission to Hospital	Time Interval (h)				Intracranial Hematoma (size)	Skull Fracture	Penetration of Intracranial Hematoma into Brain	Cause of Death (Manner of Death)	Drug(s) and/or Chemical Detected
			Injury to Admission	Admission to Death	Injury to Death	Postmortem					
1	82 (F)	No	—	—	Several hours	~30	Subdural (~13 g)	No	No	Death due to cold exposure (accident)	Norephedrine
2	48 (F)	Yes	~12	~45	~57	~8	Subdural (~8 g)	No	No	Brain swelling (homicide)	Phenytoin and phenobarbital
3	21 (M)	Yes	~2	~47	~49	~17	Epidural (~230 g)	Yes	No	Cerebral compression (homicide)	Toluene
4	53 (M)	Yes	~1	~64	~65	~25	Subdural (~15 g)	No	No	Brain swelling (accident)	Phenytoin, lidocaine and ethanol
5	56 (M)	Yes	~1	~9	~10	~23	Subdural (~200 g)	Yes	No	Cerebral compression (homicide)	Ethanol
6	58 (M)	Yes	~8	~25	~33	~4	Subdural (~50 g)	Yes	No	Cerebral contusion (accident)	Diazepam and 2-ACBP

2-ACBP: 2-aminochlorobenzophenone, a hydrolyzed product of benzodiazepines.

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.

Screening for Drugs of Abuse with Triage™ (Biosite Diagnostic Inc., CA)

Urine and/or blood specimens were processed for Triage screening as described previously (6,7).

Screening for Sympathomimetic Amines with the GC and GC/MS

Two milliliters of blood or urine were mixed with 2 mL 0.25 N NaOH. The mixture was extracted with 8 mL n-chlorobutane/diethyl ether (30:20) for 20 min with a mechanical shaker. The upper organic phase was back-extracted with 1 mL 0.1 N HCl for 30 s using a vortex mixer. The lower aqueous phase was washed with 4 mL diethyl ether and mixed with 1 mL 0.25 N NaOH. The mixture was re-extracted with 4 mL diethyl ether for 30 s using the vortex mixer. To the upper organic phase was added a drop of acetic acid, and the mixture was evaporated to dryness. The residue was derivatized with 50 μL ethyl acetate and 50 μL trifluoroacetic anhydride at 70°C for 15 min. The residue was again evaporated to dryness and reconstituted with 50-μL ethyl acetate, and a 1-μL aliquot of the mixture was then injected into the GC and GC/MS.

Screening for Acidic Drugs with the GC and GC/MS

Two milliliters of blood or urine were mixed with 2 mL 0.25 M phosphate buffer (pH 5.5). The mixture was extracted with 8 mL toluene/hexane/isoamyl alcohol (70:28:2) for 20 min using the mechanical shaker. The upper organic phase was back-extracted with 1 mL 0.5 N NaOH for 30 s using the vortex mixer. The lower aqueous phase was washed with 4 mL diethyl ether and mixed with 1 mL 1 N HCl. The mixture was re-extracted with 4 mL diethyl ether for 30 s using the vortex mixer, and the upper organic phase was evaporated to dryness. The residue was reconstituted with 20-μL methanol, and a 1-μL aliquot of the mixture was then injected into the GC and GC/MS.

Screening for Basic Drugs with the GC and GC/MS

Two milliliters of blood or urine were mixed with 2 mL of 1 M carbonate buffer (pH 9.7). The mixture was extracted with 8 mL n-chlorobutane/isoamyl alcohol (98:2) for 20 min with the mechanical shaker. The upper organic phase was back-extracted with 1 mL 0.1 N HCl for 30 s using the vortex mixer. The lower 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 upper organic phase was reduced to approximately 50 μL. A 1-μL aliquot of the concentrated extract was then injected into the GC and GC/MS.

Screening for Benzodiazepines and Neutral Drugs with the GC and GC/MS

Two milliliters of blood or urine were mixed with 2 mL carbonate buffer (pH 9.7). The mixture was extracted with 8 mL n-chlorobutane/isoamyl alcohol (98:2) for 20 min with the mechanical shaker. The upper organic phase was evaporated to dryness. The residue was dissolved in 0.2 mL acetonitrile and partitioned with 0.4 mL n-hexane for 1 min using the vortex mixer. After aspiration of the upper hexane phase, this partition step was repeated, and the residue was again evaporated to dryness and reconstituted with 50-μL methanol. A 1-μL aliquot of the mixture was then injected into the GC and GC/MS.

Screening for Opiates with the GC and GC/MS

One milliliter of blood and/or urine specimens was processed as described previously (8).

GC Quantification of Norephedrine, Phenobarbital, Phenytoin, Lidocaine, and Diazepam

Each hematoma specimen was homogenized in an equal amount of distilled water; a portion of each brain specimen homogenized in distilled water (3 parts water to 1 part specimen). Two milliliters of body fluids and 2 g of tissue homogenates were processed for GC quantification of the drugs.

The analytical procedure for sympathomimetic amines was performed for quantification of norephedrine using methamphetamine

hydrochloride in methanol (100 μL, 20 mg/L) as an internal standard. The analytical procedure for acidic drugs was performed for quantification of phenobarbital and phenytoin using sodium secobarbital in methanol (100 μL, 100 mg/L) as an internal standard. The analytical procedure for basic drugs was done for quantification of lidocaine using carbinoxamine maleate in methanol (100 μL, 12 mg/L) as an internal standard. Finally the analytical procedure for benzodiazepines and neutral drugs was done for quantification of diazepam using 2-aminobenzophenone in methanol (100 μL, 20 mg/L) as an internal standard. Quantification of conjugated metabolites of diazepam, mostly oxazepam glucuronide, was performed as follows: 1 mL of each body fluid or 1 g of each tissue homogenate was mixed with 100 μL of 20 mg/L 2-aminobenzophenone in methanol (internal standard) and 1 mL of concentrated HCl. The mixture was heated at 100°C for 30 min to obtain 2-aminochlorobenzophenone, a hydrolyzed product of oxazepam. After being cooled on ice, the mixture was neutralized with 5N NaOH and extracted with 8 mL diethyl ether. The upper organic phase was evaporated to dryness. This step was then followed by the partition technique described above in the analytical procedure for benzodiazepines and neutral drugs.

GC Quantification of Ethanol and Toluene

Quantification of ethanol was performed by head space gas chromatography as described previously (9). The concentration of toluene was determined by the same method as the analytical procedure for ethanol.

Results

As shown in Table 2, five cases (Cases 1–5) were positive for drugs and chemicals that were self-administered by the victims prior to injury. In the Case 1 patient, who survived for several hours after injury, norephedrine was detected, and its level was about two times higher in the subdural hematoma than in heart blood. In the Case 2 patient, who survived for approximately 57 h, phenobarbital was detected, and its level was only a little higher in the subdural hematoma than in heart blood. In the Case 3 patient, who survived for approximately 49 h, toluene was detected, and its level was about nine times higher in the epidural hematoma than in heart blood. In the patients of Cases 4 and 5, who survived for approximately 65 h and 10 h, respectively, ethanol was detected in the subdural hematomas at concentrations of 0.049 g/100 g and 0.033 g/100 g, respectively, but only small amounts were detected in heart blood. In Case 4, ethanol concentration in venous blood drawn at the time of admission to hospital was as high as 0.375 g/dL.

As shown in Table 3, three cases (Cases 2, 4, and 6) were positive for drugs administered during medical treatment for injuries. In Case 2, a phenytoin (250 mg) preparation was intravenously drip-infused 42 h and 23 h prior to death; phenytoin level was about 1.7 times higher in the heart blood than in the subdural hematoma. In Case 4, phenytoin and lidocaine were used for medical treatment. Although detailed clinical information about drug administration could not be obtained, the patient had been treated with phenytoin from shortly after admission to the hospital until death. Phenytoin level in heart blood was about 3.7 times higher than it was in the hematoma. Lidocaine level, however, was a little lower in the heart blood than in the hematoma. In Case 6, a diazepam (10 mg) preparation was intravenously administered 19 h and 11 h prior to death. Diazepam was detected at a concentration of 0.138 μg/mL in the heart blood but not in the hematoma.

Discussion

If individuals survive several hours or more at hospital after injury, it is often difficult for forensic toxicologists analyzing blood

TABLE 2—*Tissue concentrations of drugs and chemicals self-administered by victims prior to head injuries.*

Case No.	Drug or Chemical Detected	Concentration (μg/mL or μg/g)					
		Blood Obtained at the Time of Admission to Hospital	Heart Blood	Hematoma	Brain	Cerebrospinal Fluid	Urine
1	Norephedrine	—	0.132	0.283	0.222	0.581	38.7
2	Phenobarbital	NA	5.01	5.31	NE	4.17	4.77
3	Toluene	NA	0.33	3.08	16.5	NA	ND
4	Ethanol	0.375	trace	0.049	ND	NA	NA
5	Ethanol	NA	ND	0.033	ND	NA	NA

Unit of ethanol concentration: g/dL or g/100 g.
Abbreviations used: NA = not available; NE = not examined; and ND = not detectable.

TABLE 3—*Tissue concentrations of drugs administered at hospital after head injuries.*

Case No.	Drug(s) Detected	Duration of Drug Exposure (h)	Pattern of Drug Administration	Concentration (μg/mL or μg/g)				
				Heart Blood	Hematoma	Brain	Cerebrospinal Fluid	Urine
2	Phenytoin	~42	Phenytoin (250 mg) was drip-infused 42 and 23 h before death.	1.93	1.15	NE	0.728	1.58
4	Phenytoin	~60	Unknown	5.46	1.48	6.76	NA	NA
	Lidocaine	Unknown	Unknown	0.029	0.034	0.070	NA	NA
6	Diazepam	~19	Diazepam (10 mg) was intravenously administered 19 and 11 h before death.	0.138	ND	NE	ND	0.681*

* The concentration of 2-ACBP, presumably originated mostly from conjugated oxazepam; neither diazepam nor nordiazepam was detected. No 2-ACBP was detected in the other specimens.

samples taken at autopsy to determine how seriously individuals had been intoxicated with alcohol and/or drugs at the time they were injured. However, autopsy specimens sometimes provide the only source of data upon which an opinion can be formulated as to what extent the decedent was under the influence of drugs and/or ethanol since an adequate amount of blood for analyzing them is not routinely drawn at hospital. Provided a victim survives several hours or more, ethanol and drugs, which are rapidly metabolized and excreted from the body, would not be detected from postmortem blood, even if they had existed in blood at the time of injury. In such cases, no opinion as to whether the victim had been under the influence of ethanol and/or drugs can be offered on the basis of autopsy blood specimen with no traces of ethanol or drugs. However, the foregoing dilemma may be ameliorated to some extent if the individual suffered from traumatically formed, anatomically sequestered hematomas such as subdural and epidural hematomas since ethanol and drugs may disappear more gradually in these intracranial hematomas than in circulating blood. Some researchers have demonstrated the usefulness of intracranial hematomas for detecting ethanol (1–5). In 1973, Hirsch and Adelson (1) first reported the importance of measuring ethanol levels in subdural hematomas. Similar observations were reported by Freireich et al. (2) and Nanikawa et al. (3). Eisele et al. (4) reported that estimation of blood ethanol levels at the time of injury from intracranial hematomas is complicated by the following unpredictable factors: (1) postinjury metabolism of ethanol is variable; (2) diffusion rates of ethanol from an intracranial hematoma into surrounding tissues may depend largely on size and region of the hematoma; and (3) in individuals who were still in the absorption phase of ethanol when they were injured, blood ethanol levels determined at the hospital shortly after injury would be higher than those attained at the time of injury, affecting ethanol levels in slowly formed intracranial hematomas. Despite these problems, Buchsbaum et al. (5) reported the usefulness of ethanol testing subdural hematomas in their study involving 75 cases, concluding that this technique provides forensically pertinent information, particularly when used in the right setting (e.g., relatively long or unknown post-traumatic time interval). In cases of delayed subdural hemorrhages, which are formed several hours or more after head injuries, ethanol testing of the subdural hematomas may give negative results even when extended ethanol consumption occurred prior to injury (10). Thus, forensic scientists should be aware that negative ethanol results in subdural hematomas do not always prove that victims were not under the influence of ethanol at the time of injury. However, from a different perspective, the subdural ethanol test may give useful information about when subdural hemorrhages occurred. Despite growing knowledge of the usefulness of intracranial hematomas for ethanol testing, there are few comprehensive reports on the medicolegal significance of detecting drugs in sequestered hematomas. Moreover, there is scant literature on how drugs used for the purpose of medical treatment affect postmortem drug testing in intracranial hematomas that were formed prior to drug administration.

In Case 1, the norephedrine concentration was about two times higher in the subdural hematoma than in heart blood, although the victim survived only several hours after having suffered head injuries. In Case 2 with a post-traumatic time interval of approximately 57 h, substantial amounts of phenobarbital were detected both in the subdural hematoma and in heart blood. In Case 3 with a post-traumatic time interval of approximately 49 h, the concentration of toluene was about nine times higher in the epidural hematoma than in heart blood. All of these three substances detected in Cases 1–3 had been self-administered by the victims prior to injury. The plasma half-lives of norephedrine, phenobarbital and toluene have been reported to be about 4 h, 50–150 h, and about 7.5 h, respectively (11). Thus, the present results indicate that toxicological analysis of intracranial hematomas is valuable for detecting pre-traumatic usage of substances with relatively short plasma half-lives (less than several hours). In Case 3, since the victim was diagnosed to be brain dead about 37 h prior to cardiac arrest, disappearance of toluene from the epidural hematoma and brain may have been more extensively hindered than in the other two cases, due to the limited supply of blood to the brain (12). The usefulness of subdural hematomas for the detection of ethanol present at the time of injury was confirmed in Cases 4 and 5.

In Cases 2, 4, and 6, drugs (phenytoin, lidocaine and diazepam) originating from therapeutic treatment after injury were detected. In these three cases, no increase in the subdural hematomas was observed after admission to the hospital, and there was no evidence of pre-traumatic use of these drugs. In Cases 2 and 4, the hematomas containing post-traumatic phenytoin and/or lidocaine were approximately 8 g and 15 g, respectively. In Case 6, in which diazepam was detected in heart blood but not in the subdural hematoma, the hematoma was nearly 50 g. In Cases 2, 4, and 6, the postmortem interval was much shorter than the duration of antemortem exposure to the therapeutic drugs. Thus, phenytoin and lidocaine that were detected in the subdural hematomas in Cases 2 and 4 may have simply diffused from circulating blood, cerebrospinal fluid and/or the brain during medical treatment, indicating that drugs administered therapeutically could easily be distributed into even preexisting subdural hematomas, depending largely on the size of the hematomas. Undoubtedly, the concentration ratios of post-traumatically administered drugs in intracranial hematomas relative to those in postmortem blood remaining in the blood vessels are strongly affected not only by the size of the hematomas but also by factors such as the duration of drug administration and time interval from last administration of drugs to death. However, further investigation is necessary to determine the extent of postmortem diffusion of these drugs into subdural hematomas from surrounding tissues. Additionally, after being distributed into preexisting subdural hematomas, a therapeutic drug such as lidocaine with a short plasma half-life of 1 to 2 h (11) may sometimes remain at higher concentrations in the hematomas than in circulating blood. This phenomenon may become marked when a slow formation of subdural hematomas is still occurring at the time of drug administration and if patients survive for several more hours. In such examples a drug can be detected in the hematomas but not in postmortem vascular blood. Thus, an incorrect interpretation that the drug detected in the hematomas was self-administered by victims prior to injury may arise.

Although the number of cases in our present study is small, some conclusion can be drawn: (1) Intracranial hematomas are specimens of choice, especially for detecting drugs with short plasma half-lives in individuals who survive several hours or more after head injuries. (2) Therapeutic drugs administered after injury can easily be distributed into preexisting subdural hematomas when the hematomas are small. Toxicological analysis of intracranial hematomas may be useful not only to determine whether a victim was under the influence of ethanol, but also to detect pre-traumatic use of drugs. However, medical records should be reviewed thoroughly from a toxicological viewpoint if victims underwent medical treatment prior to death.

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