Intracerebral Hemorrhage Associated with Amphetamine

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Abstract

The authors present a case of the death of a young female drug addict due to intracerebral hemorrhage. Liquid chromatography with mass spectrometry was instrumental in the identification and quantitative determination of amphetamine within an intracerebral hematoma that had persisted for 13 days. In view of the fact that the deceased was young, did not suffer from any detectable diseases, and the narcotic substance was only detected within the hematomas, the case should be classified among rare complications of amphetamine abuse.

Introduction

For many years now, numerous toxicology centers have been conducting studies on the determination of xenobiotics in intracerebral hematomas. The fact that a hematoma is isolated from any contact with other body fluids allows substances ingested both in the course of hematoma formation and sometimes in periods preceding its development to be identified. Many years ago, Hirsch and Adelson (1) were the first investigators to draw attention to the diagnostic value of alcohol level determinations in hematomas. Further reports based on quantitative methods determining the level of alcohol at the moment of hematoma formation allowed the formulation of conclusions helpful in forensic medicolegal opinions (2-6).

Nevertheless, from the historical point of view, the first report describing a cause-effect relationship between the ingestion of xenobiotics and intracerebral hemorrhages was written in 1945 (7), and it focused on amphetamine itself. Studies on determinations of other narcotic agents are less common than investigations of alcohol level because of the costs and complexity of such studies and the fact that their association with the incident of hematoma formation is less frequent. Special attention was focused on cases where the origin of an intracerebral hematoma may be associated with the ingestion of such narcotic agents as derivatives of amphetamine (8-13) or cocaine (14,15). The subject of investigations presented in this report is the case of the death of a female drug addict due to an intracerebral hematoma, where the authors succeeded in detecting amphetamine ingested close to two weeks prior to death.

Case History

The body of a 24-year-old woman was transferred for postmortem examination. The deceased had been hospitalized for two weeks due to an intracerebral hematoma. The medical history indicated that the patient had spent the night before the onset of the disease in a discotheque, where, as she had informed her friend, a substance was added to her drink. In the afternoon hours of the following day, the patient lost consciousness and was brought to the hospital. Upon admission, she was confused, and her blood pressure was 140/80. The patient presented with asymmetric tendon reflexes, intensified on the left side. Amphetamine was detected by an immunological narcotic assay in the urine. Tests for other psychoactive substances such as alcohol, opiates, methamphetamine, THC, and cocaine were negative.

Figure 1. A CT scan of the cerebral hematomas (I and II).
During her stay in the admission room, the patient rapidly deteriorated neurologically, manifesting right-side hemiparesis, spasms, and pupillary dilatation on the left side. The blood pressure increased up to 170/100 and the pulse was 150/min. A CT scan of the head (Figure 1) showed an irregular "double" hematoma situated in the deep structures of the right hemisphere, measuring $60 \times 26 \times 52$ mm and communicating with the ventricles, as well as another smaller part of hematoma, smaller in size ($6$ mm) in the right thalamus. Since that event, the general state of the patient was extremely poor. In view of the fact that cerebral edema with signs of cerebral herniation ruled out surgical treatment, conventional treatment was attempted. On the 13th day of hospitalization, the patient died; she had been previously found to be approximately 8 weeks pregnant. The postmortem examination revealed diffuse encephalomalation, fibrinous, and purulent pneumonia in addition to two compact hematomas situated deep in the right hemisphere.

The results of the analyses of the intracerebral hematomas, blood, and urine are shown in Table I. Figure 2 presents chromatograms and MS spectra of amphetamine in hematoma, which document the analysis.

### Materials and Methods

**Chemicals and reagents**

All chemicals and solvents were of analytical grade. Standards of amphetamine and amphetamine-$d_3$ were obtained from Sigma (St. Louis, MO). Trifluoroacetic acid was from Fluka (Buchs, Switzerland), acetonitrile and ethyl acetate were from Merck (Darmstadt, Germany), and buffer substance TRIS was from Serva (Heidelberg, Germany).

**Materials**

Postmortem specimens, samples of femoral blood, urine, and two intracerebral hematomas (I, 8 g and II, 6 g), were collected at autopsy. The autopsy was performed at the Institute of Forensic Medicine, Collegium Medicum, Jagiellonian University in Kraków within 24 h of death. The samples were kept frozen ($-22^\circ$C) until the analyses were performed.

Along with the materials taken from the deceased, standards of amphetamine and "blank" samples of autopsy blood and urine taken from non-poisoned subjects spiked with this drug were investigated. The latter materials were used to facilitate identification, quantitation, and validation by means of liquid chromatography–mass spectrometry (LC–MS).

**Extraction**

Hematomas were homogenized using a homogenizer stick (MPW-302, Mech. Prec. Warszawa, Poland) at 10,000 $\times$ g for 5 min, and samples (2 g) of each hematoma were subjected to liquid–liquid extraction parallel to samples (2 g) of postmortem blood and urine. Amphetamine-$d_3$ at 0.5 $\mu$g/g was used as the internal standard. At first, samples (2 g) were mixed with 2 mL TRIS buffer (hydroxymethyl-aminomethane) pH 9.0 and put in an ultrasonic bath for 15 min. Afterwards, the samples were mixed with 3 mL acetonitrile for precipitation, then vortex mixed and centrifuged. The supernatant was mixed with 10 mL of ethyl acetate, and the solutions were separated on silicone-treated filter paper (Whatman 1PS). The organic phase was collected and evaporated to dryness at 40$^\circ$C under a stream of nitrogen. The residue was reconstituted in 100 $\mu$L of HPLC mobile phase, and 10 $\mu$L of the reconstituted extracts was injected into the LC–MS system.

**Calibration curves and quantitation**

Calibration curves were constructed after the analysis of drug-free blood and urine (blank samples) containing known amounts of amphetamine. To prepare these standards, blood and urine samples were spiked with the studied compound to the following concentrations: 0.05, 0.1, 0.5, and 1.0 $\mu$g/g. Amphetamine-$d_3$ was used as the internal standard. The samples were extracted according to the procedure described. Calibration curves were constructed by plotting the peak-area ratios amphetamine/
internal standard. Recoveries were calculated for blood and urine.

As a result of the validation procedure for blood and urine amphetamine determinations, the authors arrived at parameters presented in Table II.

**Analytical method**

**LC-MS.** A Finnigan MAT LC (San Jose, CA) equipped with a model TSP 4000 pump and a model TSP AS 3000 autosampler with a 20-μL injection loop were used in gradient mode. The chromatographic separation was performed with a LiChroCART column (125 × 3 mm i.d., 5-μm particle size) filled with Puro-therapeutic agents were found only in light-weight hematomas (8–50 g). The results point to a possibility of the drugs passing from the blood to the hematoma even after it had developed. On the other hand, one must also consider the possibility of drug disappearance, especially from light-weight hematomas. According to these authors, the longest time of hematoma persistence, or the time interval between the injury and death, was 65 h.

The case of death described in this report represents the second direction of investigations. Based of the current level of knowledge, amphetamine detected within the hematoma supports the contention of the possible origin of intracerebral hemorrhage that occurred 13 days before death.

Diffuse encephalomalacia, and blood flow disturbances in the area of the hematoma can be due to the persistence of amphetamine in the hematoma, which might have isolated them from environment and therefore made it difficult for amphetamine molecules to penetrate into circulation.

In the presented case, cerebral hemorrhage occurred 3 h after admission, with the patient previously presenting symptoms that may be now interpreted as signs of ischemia involving certain areas of the central nervous system and resulting from a cerebral vasospasm, most likely in consequence of amphetamine activity. Cerebral hemorrhage following amphetamine or cocaine ingestion is most often observed in drug addicts. Investigators involved in studying this subject point to the fact that drug addicts who abuse such substances as derivatives of amphetamine or cocaine often complain of severe headaches, which could be in many cases prodromal symptoms heralding intracerebral hemorrhage (9). Although cases have been described where a cerebral stroke occurred when the drug was taken for the first time (16), hemorrhaging occurs

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**Discussion**

Although studies of drugs and narcotics in intracerebral hematomas have been the subject of only a few reports, they are well-documented. In the experimental material presented in such reports one may distinguish two directions: probing into the validity of toxicological determinations in patients with hematomas as a proof of the presence of a xenobiotic at the time of and prior to the injury and analyzing the formation of hematomas in consequence of narcotics ingestion.

The conclusions formulated by Moriya and Hashimoto (2) in their extensive investigations support the usefulness of toxicological tests leading to the determination of the presence of a xenobiotic at the time the injury was inflicted, as well as confirming possible narcotic ingestion in the preceding period. In six cases of epidural and subdural hematomas, the authors managed to determine the presence of such xenobiotics as norephedrine, phenobarbital, and toluene, and in some of those cases, alcohol. All these substances had been ingested prior to the injury. The analyses also revealed the presence of medications administered to those patients in the course of their hospitalization (phenytoin, lidocaine, and diazepam), but these therapeutic agents were found only in light-weight hematomas (8–50 g). The results point to a possibility of the drugs passing from the blood to the hematoma even after it had developed. On the other hand, one must also consider the possibility of drug disappearance, especially from light-weight hematomas. According to these authors, the longest time of hematoma persistence, or the time interval between the injury and death, was 65 h.

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**Table II. Validation Data**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Retention Time (min)</th>
<th>Limits of Detection (LOD)* (μg/g)</th>
<th>Limits of Quantitation (LOQ) (μg/g)</th>
<th>Limits of Linearity (LOL) (μg/g)</th>
<th>Linearity</th>
<th>Recovery† (%)</th>
<th>Precision‡ (%) R.S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>9.61</td>
<td>0.025</td>
<td>0.05</td>
<td>0.05–1.0</td>
<td>y = 0.0044x – 0.31</td>
<td>0.9948</td>
<td>91</td>
</tr>
<tr>
<td>Urine</td>
<td>9.61</td>
<td>0.025</td>
<td>0.05</td>
<td>0.05–1.0</td>
<td>y = 0.0115x – 0.02</td>
<td>0.9937</td>
<td>85</td>
</tr>
</tbody>
</table>

* Defined as 3x a signal-to-noise ratio of 3. Twice the LOD was taken to be the limit of quantitation.
† Defined as the percentage peak area of corresponding amounts of non-extracted drugs injected into the LC-MS system.
‡ Calculated in three series (day-to-day) at the following concentration 0.5 (μg/g) for amphetamine.
several hours after the ingestion of a narcotic substance in the majority of cases (8,11).

Nevertheless, in the analyzed case it is more likely that intracerebral hemorrhaging resulted from a prolonged action of amphetamine. As the records confirmed it, the patient worked as a prostitute and had a long-term history of drug abuse. Neither clinical nor postmortem examinations revealed any cerebral vascular lesions (an aneurysm or malformations); hypertension and head injury were ruled out by autopsy. Thus, in the investigated case, it could have been accepted that the intracerebral hemorrhage was a consequence of amphetamine ingestion.

Among the pharmacological properties of amphetamine is its strong sympathicomimetic activity, manifested by angiospasms of peripheral blood vessels and accelerated heart rate. This effect is responsible for the rare complication in the form of intracerebral hemorrhages. According to some authors, a rupture of a cerebral vessel is a consequence of a rapid increase of blood pressure, whereas others believe it to result from a segmental vasospasm (14). The latter effect is assumed to be responsible for both hemorrhagic and ischemic cerebral stroke. In some cases aneurysms or vein malformations are found, leading to the assumption that hemorrhages after the intake of amphetamine occur in subjects with previous vascular changes (9).

Hematomas developing as a consequence of amphetamine activity are most commonly situated in the white matter and less frequently in the subcortical nuclei (8–13,17,18). Similar complications, also occurring as the result of sympathicomimetic activity, develop in consequence of another narcotic substance ingestion, such as cocaine and methamphetamine (19), as well as following the administration of some drugs, such as ephedrine and phencyclidine (2,14,15). These substances are responsible for a large proportion of intracerebral hemorrhages occurring in young people. It has been also noted that in some urban populations in the United States, almost 50% of all cerebral stroke cases in individuals below 45 years of age are directly associated with the ingestion of the above mentioned substances (11,14).

The detection of a xenobiotic in the hematoma after such a long survival time is probably extremely rare. The authors did not manage to find a case of detecting amphetamine in intracerebral hematoma in a treated patient after hemorrhage in available literature. Moriya and Hashimoto (19) described detection of methamphetamine in a hematoma of a dead person; however, the time between formation of the hematoma and death was unknown.

Although determinations of the xenobiotic content in intracerebral hematomas are of a great importance in forensic medical opinions, one has to be aware of the complexity of this issue. Xenobiotic levels in the environment of a hematoma depend on many factors.

The first is the interval between xenobiotic ingestion and the development of a hematoma (2). Secondly, there is the problem of a xenobiotic release from the hematoma while the patient is still alive, as well as the penetration of the hematoma by various molecules, including drugs administered in the course of therapy (2).

The matter is further complicated by the fact that hematomas develop over time, and as time passes, the volume of a hematoma may increase at a varying rate, determined by the degree of vascular damage, the location of the lesion, and the degree of progressing intracerebral hypertension (6). Thus, it is likely that the concentration of a xenobiotic within the hematoma may be higher than the peripheral blood level, especially in the case of medications with a short half-life. This phenomenon may be particularly predominant in patients in whom hematomas developed slowly and whose survival was relatively long (2). In such cases the detection of a xenobiotic in the hematomas gains a special significance, allowing a more comprehensive forensic-medical evaluation that often has a definitive character.

Conclusions

A positive result for amphetamine in an intracerebral hematoma persisting for 13 days confirms the usability of the procedure in explaining the circumstances surrounding the injury resulting in an epidural or subdural hematoma formation.

In view of the fact that some cases of intracerebral hemorrhage may be also triggered by the ingestion of amphetamines or other narcotic substances, it might be postulated that such a test should be performed in cerebral hematomas of unclear etiology, especially in young drug addicts.

References


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