Z. Rechtsmedizin · J. Legal Med. 67, 184—189 (1970)

Kasuistik — Casuistry

Lethal Amphetamine Intoxication

A Report of Three Cases

S. Orrenius
Department of Forensic Medicine, Karolinska Institutet, Stockholm
A. C. Maehly
Government Laboratory for Forensic Chemistry, Stockholm

Received January 3, 1970

Summary. Three cases of lethal amphetamine intoxication are reported. The autopsy findings included pulmonary hemorrhage as well as subendocardial and gastric mucosal hemorrhages. The following tissue concentrations of amphetamine were found: 0.05—0.7 mg per 100 ml blood, 1.2—4.5 mg per 100 g liver and 0.4—0.8 mg per 100 g kidney. The pathological and toxicological findings are discussed with respect to previously published cases of metamphetamine poisoning as well as fatal intoxications due to combinations of amphetamine and other drugs.

Key-Words: Central stimulants — Amphetamine — Lethal intoxication.

Zusammenfassung. Pathologisch-anatomische und toxikologische Befunde von drei Fällen von tödlicher Amphetaminvergiftung werden beschrieben. Subpleurale und subendocardielle Blutungen sowie Blutungen im Lungenparenchym wurden beobachtet. Die Konzentrationen des Amphetamins betrugen ca. 0,05—0,7 mg per 100 ml Blut, 1,2—4,5 mg per 100 g Leber, 0,4—0,8 mg per 100 g Niere, und in einem Fall ca. 70 mg per 100 ml Harn. Weder Alkohol noch Arzneimittel konnten nachgewiesen werden.

The intravenous injection of centrally stimulating amines ("Week-amines") can assume epidemic characteristics. This was first reported from Japan (Nagahama, 1968), but has since then been experienced in several other countries among them Sweden (Goldberg, 1968; Inghe, 1969). In this country the abuse of psychoactive drugs, primarily phenmetrazine, amphetamine and metamphetamine, often administered intravenously dissolved in tap water, has been increasing since the 1940-ies and developed into a considerable social and medical problem.

Amphetamine, β-phenylisopropylamine, is a sympathomimetic amine with a multitude of pharmacological effects involving primarily the central nervous and circulatory systems. In high doses it produces a sustained rise in blood pressure and an increased heart rate. Arrythmias, extensive sweating and increase in body temperature are further effects of larger than therapeutic doses of amphetamine. Serious cases progress to convulsions, coma, circulatory collapse and death. Death caused by amphetamine intoxication has been ascribed to cardiovascular collapse, hyperpyrexia or cerebral hemorrhage (Davis *et al.*, 1968).

There are several problems facing the forensic scientists in evaluating the cause of death occurring in connection with the abuse of amphetamine drugs.

Thus, under the influence of these agents the patient is more susceptible to accidents than normally. Moreover, the most common way of administration of these compounds, i.e. by intravenous injections, may *per se* cause complications such as air embolus or the transfer of infectious agents.

A survey of the recent literature has revealed few reported cases of lethal intoxication with centrally stimulating amines in man. The lethal doses of various amphetamines have been determined in a variety of experimental animals and on the basis of these values an approximate lethal dose for human adults of 20 mg per kg body-weight has been estimated (Davis *et al.*, 1968). However, the existence of considerable species and individual differences in metabolism and sensitivity to these drugs make a direct comparison to such figures to be of limited value when trying to establish the cause of death in connection with the abuse of amphetamine drugs in man.

This paper reports three cases of lethal amphetamine intoxication investigated in our departments in 1968.

Methods

Tissue samples including blood, liver and kidney as well as urine, when present, were collected at autopsy and analyzed for the presence of centrally stimulating amines according to methods previously described for body fluids (Bonnichsen *et al.*, 1969; Schubert, 1970). The extraction method for the amphetamines had been changed and perfected in 1968 by Petrovics (1970). However, these methods do not permit to decide whether the amphetamine is present in its racemic form or not.

So far four drugs belonging to the group of centrally stimulating amines have been detected among intravenous abusers in Sweden, i.e., phenmetrazine (as in Preludin®), amphetamine, methylphenidate (as in Ritalina®), and, once in a while, metamphetamine (as in Pervitin®).

When relatively large amounts (tenths of milligrams) of the drugs are present, as often in urine samples, gas chromatography, thin-layer chromatography, and, to a limited extent, even ultraviolet spectrophotometry can be used for identification. The drug concentrations in the blood, however, are often so low that thin-layer chromatography methods are not sensitive enough. When only blood is available, identification can still be achieved by means of mass spectrometric methods (Bonnichsen *et al.*, 1970a).

When liver and kidney samples were analyzed, a modification of the technique described for body fluids was employed (Petrovics, 1970). However, it is advisable to remove lipids and other neutral (and acidic) compounds by a preliminary extraction of the tissue at low pH. During all operations, evaporations at high pH values must be avoided.

Tissue samples were also analyzed for the presence of barbiturates (Bonnichsen *et al.*, 1961), salicylates (Maehly and Linturi, 1962), meprobamate (Bonnichsen *et al.*, 1967), methaqualone (Maehly and Bonnichsen, 1966), phenothiazine derivatives and tricyclic amines (Bonnichsen *et al.*, 1970b), benzodiazepine derivatives (Bonnichsen *et al.*, 1970c), and morphine (Petrovics, 1970).

Results

Case Histories

Case I. A 18 year old girl was found dead in a hotel room at a police routine control. The investigation revealed that she had previously been taking centrally stimulating drugs including phenmetrazine, methylphenidate and amphetamine in intravenous injections for various periods of time since two years, although probably not during the last eight or ten months. During the last 24 hours before death she had taken and/or received repeated intravenous injections of amphetamine dissolved in tap water to an estimated total amount of the drug of 750 to 1,500 mg.

Case II. A 49 year old man was found lying dead in the grass close to a public highway. Close to the body the policemen found several small paper bags, some of them still containing a white powder, later identified as amphetamine. The man had twice before tried to commit suicide by taking large doses of barbiturates. Whether he had previously also used centrally stimulating drugs was not revealed by the investigation. Neither was it possible to decide the amount of amphetamine he had taken prior to death.

Case III. A 59 year old man was found unconscious in a bathtub but with his head well above the water line. Before going into the bath he had injected himself intravenously with a solution which was later shown to contain amphetamine. When admitted to a hospital, about eight hours after this injection, he was still unconscious. He was cyanotic with a temperature of 41°, respiratory frequency of 35 per minute, pulse rate of 120 per minute and blood pressure of 80/60 mm Hg. He was sweating heavily. Clinical laboratory findings gave evidence of a state of acidosis which became even more pronounced during the first hours of hospitalisation. He died the following day approximately 30 hours after admittance to the hospital. The investigation further revealed that he had been taking intravenous injections of centrally stimulating drugs regularly during the last six or seven years. Neither in this case, however, was it possible to estimate the amount of amphetamine he had taken prior to being found unconscious in the bathtub.

Autopsy Findings

In all the three cases the lungs were moderately congested and in case I patchy hemorrhage was observed, whereas subpleural hemorrhages were present in case III. In case III there was also subendocardial hemorrhages, while gastric mucosal hemorrhages involved this case as well as case no 1.

The microscopical examination of tissue sections revealed marked congestion in the liver, kidney and spleen. Acute pulmonary hemorrhage was observed in case I. Furthermore, in the latter case as well as in case III focal hepatitis was noted, while liver sections from cases II and III showed fatty degeneration.

Toxicological Findings

The toxicological data are presented in the Table. Blood collected from case III contained only traces of amphetamine, i.e. less than 0.05 mg per 100 g tissue. Urine was not available in cases I and III.

Table. *Amphetamine levels found in the three cases reported. The concentrations are expressed as mg of drug per 100 g of sample*

Drug	Sample	Case I	Case II	Case III
Amphetamine	blood	0.7	0.6	<0.05
Amphetamine	liver	1.2	3.5	4.5
Amphetamine	kidney	0.8	—	0.4
Amphetamine	urine	—[a]	70	—[a]

[a] Not available.

Tissue samples from all three cases were also analyzed for the presence of ethanol and other drugs including barbiturates, salicylates, meprobamate, methaqualone, phenothiazine derivatives and tricyclic amines, benzodiazepine derivatives and morphine, however, with negative results.

Discussion

Although amphetamine intoxications are not uncommon (Espelin and Done, 1968), very few deaths due to an overdose of amphetamines have been reported. Cravey and Baselt (1968) describe a case of fatal metamphetamine poisoning where a 19 year old youngster died a few hours after ingestion of the drug. Marked hyperpyrexia, a severe state of acidosis and shock were noted prior to death. The postmortem findings included hemorrhagic fluid in the bronchi, pericardial sac and stomach. Acute pulmonary hemorrhage was noted as well as marked congestion in the spleen, pancreas, kidney and liver. The blood was found to contain 4.0 mg of metamphetamine per 100 ml, the liver 20.6 mg per 100 g and the kidney 8.7 mg per 100 g tissue. A similar case has also more recently been reported by Smith (1969).

The blood levels of amphetamine observed in the present study were considerably lower. In one case (III) only traces of the drug were found in the blood sample collected at autopsy. Since the total time between the observed intravenous injection of amphetamine and death was almost 40 hours, however, most of the drug was probably excreted during this time period.

Moreover, the high extravascular concentration of amphetamine leads to low drug levels in the blood. Beckett and Rowland (1965) found, after injection of 30 mg (+) amphetamine into a volunteer, amphetamine levels of 17 μg per 100 ml after 0.5 minute and 12 μg per 100 ml after 2.5 minutes. Furthermore, in a recent investigation Änggård *et al.* (1970) measured plasma levels after the intravenous injection of a large dose of amphetamine sulphate (160 or 200 mg) into amphetamine dependent subjects. The mean value of the peak plasma level was found to be 42 μg per 100 ml plasma.

Goodman and Gilman (1965) describe severe reactions occurring after the intake of 30 mg amphetamine and death has been reported with rapid intravenous injection of 120 mg. Conversely, regular users of metamphetamine have injected 500 to 1,000 mg without serious morbidity (Goodman and Gilman, 1965; Kramer *et al.*, 1967). Thus, a lethal dose in a nonuser may be an average psychoactive dose for a regular user. The mechanism of this tolerance is not yet understood.

Differences in tolerance may explain the lower tissue concentrations of amphetamine in cases I and II of the present study as compared to the metamphetamine levels found by Cravey and Baselt (1968) and by Smith (1969). The 18 year old girl (case I) had probably not taken psychoactive drugs during the last eight or ten months until she started again one or two days before death, whereas in case II, the 49 year old man, there was no evidence that he had taken such drugs previously.

Deaths have also been reported after the combined intake of centrally stimulating amines and other drugs. Thus, Hardmeier and Schmidlin-Mèszàròs (1965) have described a fatal poisoning of a small girl with the antiallergic drug Plimasin®,

which contains tripelennamine as well as methylphenidate with the latter as the minor — and probably less toxic — component. Furthermore, Jelliffe *et al.* (1969) have reported the death of a 19 year old boy on a weight-reduction regimen of thyroid preparations, digitalis, metamphetamine and diuretics, where death was probably due to the combined drug action causing myocardial irritability, cardiac arrythmias and hypokalemia.

Animal experiments have demonstrated that monoamine oxidase inhibitors potentiate the toxicity of amphetamine (Valzelli *et al.*, 1968). Death after combined dexamphetamine and phenelzine poisoning has also been reported (Alban Lloyd and Walker, 1965). They describe the case of a 30 year old woman, who had been treated for five weeks with phenelzine (3×15 mg daily). A few hours after she had taken 20 mg of dexamphetamine sulphate, she died from an intracerebral hemorrhage following a hypertensive crisis — most probably due to the amphetamine-induced release of noradrenaline accumulated in the peripheral sympathetic nerve endings.

Subpleural and subendocardial hemorrhages as well as parenchymal pulmonary hemorrhage and gastrointestinal mucosal hemorrhage are common postmortem findings in fatal amphetamine poisoning as revealed by the present report as well as by previously published papers (Zalis *et al.*, 1966; Cravey and Baselt, 1968). Zalis *et al.* (1966) have suggested that the pathologic changes occur as a result of the profound hypermetabolic state with the associated hyperpyrexia.

In only one of the present cases (III) was the patient observed clinically. The symptoms recorded agree well with those published in other reports (Zalis *et al.*, 1966; Cravey and Baselt, 1968), which indicate that marked hyperpyrexia and shock are usually noted prior to death from amphetamines. After treatment of mice with amphetamine, Hardinge and Peterson (1964) found that those whose temperatures rose above 42.4° died while those whose temperatures remained below 41.7° usually survived. This and other studies (Askew, 1962; Clark *et al.*, 1967) demonstrate that hyperthermia is an important factor in amphetamine toxicity.

References

Alban Lloyd, J. T., Walker, D. R. H.: Death after combined dexamphetamine and phenelzine. Brit. med. J. **2**, 168 (1965).

Änggård, E., Gunne, L.-M., Jönsson, L.-E., Niklasson, F.: Pharmacokinetic and clinical studies on psychotic amphetamine dependent subjects. Personal communication (1969).

Askew, B. M.: Hyperpyrexia as a contributory factor in the toxicity of amphetamine to aggregated mice. Brit. J. Pharmacol. **19**, 245 (1962).

Beckett, A. H., Rowland, M.: Urinary excretion kinetics of amphetamine in man. J. Pharm. Pharmacol. **17**, 628 (1965).

Beckett, A. H., Salmon, J. A., Mitchard, M.: The relation between blood levels and urinary excretion of amphetamine under controlled acidic and under fluctuating urinary pH values using (^{14}C)-amphetamine. J. Pharm. Pharmacol. **21**, 251 (1969).

Bonnichsen, R., Dimberg, R., Maehly, A. C., Åqvist, S.: Läkemedel och trafik. Meddelande Nr 16, Inst. för Maltdrycksforskning, Stockholm (1967).

— Geertinger, P., Maehly, A. C.: Toxicological data on Phenothiazine Drugs in Autopsy cases. Z. Rechtsmedizin — J. Legal Med., **67**, 158 (1970b).

— Maehly, A. C., Åqvist, S.: Arzneimittel und Fahrtüchtigkeit. II. Mitteilung: Zentralstimulierende Amine und aromatische Kohlenwasserstoffe. Blutalkohol **6**, 245 (1969).

— — — Arzneimittel und Fahrtüchtigkeit. III. Benzodiazepinderivate. Blutalkohol, **7**, 1 (1970c).

Bonnichsen, R., Maehly, A. C., Frank, A.: Barbiturate analysis: Method and statistical survey J. forensic Sci. **6**, 411 (1961)
— — Mårde, Y., Ryhage, R., Schubert, B.: Determination and identification of sympathomimetic amines in blood samples from drivers by a combination of gas chromatography and mass spectrometry. Z. Rechtsmedizin — J. Legal Med. **67**, 19 (1970[a]).
Clark, W. C., Blackman, H. J., Preston, J. E.: Certain factors in aggregated mice d-amphetamine toxicity. Arch. int. Pharmacodyn. **170**, 350 (1967).
Cravey, R. H., Baselt, R. C.: Metamphetamine poisoning. For. Sci. Soc. J. **8**, 118 (1968).
Davis, J. M., Bartlett, E., Terminì, B. A.: Overdosage of psychotropic drugs, a review. II. Antidepressants and other psychotropic agents. Dis. nerv. Syst. **29**, 246 (1968).
Espelin, D. E., Done, A. K.: Amphetamine poisoning. Effectiveness of chlorpromazine. New Engl. J. Med. **278**, 1361 (1968).
Goldberg, L.: Drug abuse in Sweden. I. Bull. Narcot. **20**, No 1, 1 (1968). II. Bull. Narcot. **20**, No 2, 9 (1968).
Goodman, L. S., Gilman, A.: The pharmacological basis of therapeutics, 3rd ed. New York: MacMillan Co. 1965.
Hardinge, M. G., Peterson, D. J.: The effect of forced excercise on body temperature and amphetamine toxicity. J. Pharmacol. exp. Ther. **145**, 47 (1964).
Hardmeier, E., Schmidlin-Mèszàros, J.: Tödliche Vergiftung eines Kleinkindes mit dem Antiallergicum Plimasin®. Arch. Toxikol. **21**, 131 (1965).
Inghe, G.: The present state of abuse and addiction to stimulant drugs in Sweden. In: Abuse of central stimulants (F. Sjöqvist and M. Tottie, editors). Stockholm: Almquist & Wiksell 1969.
Jelliffe, R. W., Hill, D., Tatter, D., Lewis, E. Jr.: Death from weigth-control pills. A case report with objective postmortem confirmation. J. Amer. med. Ass. **208**, 1843 (1969).
Kramer, J. C., Fischman, V. S., Littlefield, D. C.: Amphetamine abuse. J. Amer. Med. Ass. **201**, 305 (1967).
Machly, A. C., Bonnichsen, R.: Fünf tödliche Vergiftungen mit Methaqualon (2-Methyl-2-o-tolyl-4(3H)-chinazolinon) in Schweden. Dtsch. Z. ges. gerichtl. Med. **57**, 446 (1966).
— Linturi, M. K.: Detection of drugs other than barbiturates in the routine method for barbiturate analysis. Acta chem. scand. **16**, 283 (1962).
Nagahama, M.: A review of drug abuse and counter measures in Japan since World War II. Bull. Narcot. **20**, no 3, 19 (1968).
Petrovics, J.: To be published (1970).
Schubert, B.: Detection and identification of methylphenidate in human urine and blood samples. Acta chem. scand., in press **24**, 433 (1970).
Smith, D. E.: Personal communication (1969).
Valzelli, L., Dolfini, E., Tansella, M., Garattini, S.: Activity of centrally acting drugs on amphetamine metabolism. J. Pharm. Pharmacol. **20**, 595 (1968).
Zalis, E. G., Lundberg, G. D., Knutzon, R. A.: Pathologic changes in experimental amphetamine poisoning. Abstracts. IVth Intern. Meet. Forens. Med., Copenhagen, 1966, p. 170.

Dr. Sten Orrenius
Rättsmedicinska Institutionen
Karolinska Institutet
Dr. Andreas C. Maehly
Statens Rättskemiska Laboratorium
S-10401 Stockholm 60, Sweden