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SHORT COMMUNICATION

SIGNIFICANCE OF TOXIC INTERACTIONS IN MEDICOLEGAL EVIDENCE. COMPLEX FATAL POISONING WITH DRUGS OF ABUSE IN THE MATERIAL OF THE CHAIR OF FORENSIC MEDICINE, COLLEGIUM MEDICUM, JAGIELLONIAN UNIVERSITY IN KRAKÓW

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Significance of toxic interactions in medicolegal evidence. Complex fatal poisoning with drugs of abuse in the material of the Chair of Forensic Medicine, Collegium Medicum, Jagiellonian University in Kraków. M. KŁYS, B. BYSTROWSKA, B. BUJAK-GIŻYCKA, G. NOWAK. Pol. J. Pharmacol., 2001, 53, 653–658.

The subject of the study was fatal complex poisonings with drugs of abuse in two young men. In the first case, postmortem investigation revealed cardiotoxic death as the result of an interaction between opiates, amphetamine derivatives and oxazepam. In the second case, death followed the administration of amphetamine derivatives and cocaine (xenobiotics known on the illicit drug market as "UFO").

Based on the toxicological postmortem analysis the authors discuss the interpretation of the results in the light of general problems of interactions taking place in toxicokinetic and toxicodynamic phases of intoxication processes.

***Key words**: interactions, opiates, amphetamine derivatives, cocaine, "UFO"*

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INTRODUCTION

Among identified toxic interactions, those occurring between drugs, and drugs and alcohol are of the greatest importance in clinical and forensic toxicology [23]. Nevertheless, in recent years, the extent of complex interactions has been considerably increased. Statistical data on cases of poisoning, both fatal and non-fatal, indicate a tendency towards self-administration of mixtures of licit and illicit drugs, which directly leads to complex poisoning [14, 18, 19]. Interactions resulting from self-administration of different mixtures of drugs of abuse, including derivatives of amphetamine, opiates, cocaine and drugs belonging to various pharmacological groups, have become a subject of investigations. These interactions result in specific consequences, which may culminate in poisoning or even death.

In the present report, the authors discuss two cases of complex fatal poisoning with drugs of abuse where the cause of death has been hypothesized as the consequence of an interaction between xenobiotics detected in postmortem toxicological investigations. In the paper, some possible interaction mechanisms are also discussed.

MATERIALS and METHODS

Postmortem toxicological studies were performed on body fluids and tissue samples collected during autopsies and carried out: at the Chair of Forensic Medicine CMUJ in Kraków for Case A and at the Chair of Forensic Medicine Medical Academy in Gdańsk for Case B. The autopsy speciments were sent to Toxicology Department at the Institute of Forensic Medicine CMUJ in Kraków. The samples remained frozen (–22°C) until the analyses were performed.

To isolate xenobiotics from the biological materials, the samples were subjected to liquid-liquid extraction. The resultant biological extracts were analyzed by means of liquid chromatography/mass spectrometry (LC/MS) with chemical ionization (APCI) option. The investigations followed procedures based on standards employed in toxicological analytical chemistry. In Case A, the procedure for opiates was used [16], whereas in Case B the analysis was based on the procedure developed for amphetamine derivatives and cocaine [17].

CASE PRESENTATION

Case A. Interaction between opiates, amphetamine and benzodiazepine

A 20-year old male drug addict was found dead at home. As indicated by the found syringes and scattered vials and bottles, he had injected himself with a dose of illicit substance(s). A postmortem examination was performed but failed to disclose any morphological or traumatic lesions that might have explained the cause of death. In the course of autopsy body fluids and tissue samples were collected.

The quantitative and qualitative analysis of body fluids and tissue samples of the deceased confirmed the earlier information, revealing the presence of poppy-straw "stew" (concoction) components (morphine, codeine, norcodeine, papaverine, noscapine, narceine), 6-MAM, a metabolite of heroin, as well as amphetamine, ephedrine and oxazepam. The findings support the notion of the late phase of xenobiotic elimination at the time of death, and self-administration of heroine in poppy-straw stew (6-MAM). The addition of other drugs of abuse (amphetamine, ephedrine, oxazepam), intended to potentiate the action of the mixture, also contributed to the final toxic effect, which resulted in death due to a combined effect of the detected xenobiotics.

Toxicological findings obtained in Case A are presented in Table 1 along with ranges of concentrations found in fatal poisoning cases [1, 5, 21, 24, 25].

Case B. Interaction between amphetamine derivatives and cocaine ("UFO")

A 23-year old male was poisoned with drugs of abuse. He spent the final hours before death in a restaurant and was witnessed to manifest limb tremor and trismus, suggestive of epilepsy, subsequently followed by seizures and foaming at the mouth. He was transported to hospital and received at admission as clinically dead, with seizures, respiratory and circulatory failure, dilated and fixed pupils. After a failed resuscitation attempt the patient died.

Upon the performed autopsy sudden death was confirmed. Body fluid and tissue samples were collected. The toxicological analysis demonstrated the presence of amphetamine and its seven derivatives (ephedrine, MDA, MDMA, PMA, PMMA, PMDA;

Table 1. Toxicological findings in autopsy specimens (Case A)

	Concentration [µg/g]				
	Blood	Urine	Brain	Kidney	Liver
Morphine	– [0.2–2.3]	27.95 [14–81]	–	3.06 [14–81]	3.09 [0.4–18]
6-MAM	–	6.46	–	–	–
Codeine	+	11.34	–	0.44	–
Norcodeine	+	+	–	–	+
Thebaine	–	3.58	–	–	–
Papaverine	0.03	0.31	0.28	0.44	0.15
Noskapine	–	0.07	–	–	–
Narceine	0.40	6.63	–	0.45	–
Amphetamine	1.23 [0.5–41]	38.01 [25–700]	– [2.8–3.0]	3.29 [3.2–52]	5.15 [4.3–74]
Ephedrine	– [3.5–21]	49.80 [0–547]	– [7.4–8.9]	1.71 [14–28]	– [10–157]
Oxazepam	0.12 [4.4; 6.1]	2.92 –	0.15 –	0.33 –	0.65 –

Drug concentration ranges found in fatal poisoning cases are given in parentheses [1, 5, 21, 24, 25]

Table 2. Toxicological findings in autopsy specimens (Case B)

	Concentration [µg/g]		
	Blood	Kidney	Liver
Amphetamine (A)	0.04 [0.5–41]	0.89 [3.2–52]	0.92 [4.3–74]
Ephedrine (E)	1.18 [3.5–21]	28.30 [14–28]	16.39 [10–151]
Norephedrine (Ephedrine M)	–	2.70	1.70
Methylenedioxyamphetamine Tenamfetamine (MDA)	0.09 [1.8–26]	5.53 18	1.92 [8–17]
Methylenedioxymethamphetamine Ecstasy (MDMA)	1.69 [0.6–2.8]	18.46 –	17.99 –
Para-methoxyamphetamine (PMA)	1.29 [0.2–4.9]	54.03 –	40.23 [1.4–21]
Para-methoxymethamphetamine (PMMA)	1.88 –	20.85 –	28.29 –
Para-methoxydimethamphetamine (PMDA)	0.09 –	0.15 –	0.67 –
Cocaine	0.26 [0.9–21]	0.96 [0.3–2.7]	– [0.1–20]
Benzoylecgonine	0.27 [0.04–31]	0.59 –	12.57 –

Drug concentration ranges found in fatal poisoning cases are given in parentheses [1, 5, 21, 24, 25]

Tab. 2), as well as cocaine with diverse, but generally low concentration values. The autopsy report indicated that the immediate cause of death was acute circulatory failure with hemorrhagic pulmonary edema, most likely resulting from the poisoning as the effect of a hyperadditive toxic reaction between amphetamine derivatives and cocaine [15]. The xenobiotics demonstrated in the biological material sampled from this patient might constitute components of a preparation known among street drug users as "UFO". Table 2 presents toxicological findings and the range of concentration values found in fatal poisoning cases [1, 5, 21, 24, 25].

DISCUSSION

While performing a detailed analysis of the interaction, one may observe its complex character, which can thus be discussed from various points of view [20]. A toxic interaction has a different meaning for a research worker, seeking theoretical foundations that would justify the combined effect of xenobiotics, and yet another meaning for an investigator involved in experimental studies. To a clinician specializing in acute poisoning, toxic interactions present a practical aspect, similarly as in forensic toxicology.

Toxic interaction, which occurs during the toxicokinetic phase and encompasses the distribution or biotransformation of a xenobiotic within the body, leads directly to interpretation of such synergy as a phenomenon that is helpful in medicolegal opinion. The content of xenobiotics in body fluids and tissue samples is a result of their translocation within the body, and is determined by a chemical and toxicological procedure, constituting the foundation for medicolegal evidence on the cause of death of poisoning.

The global toxic effect is determined by toxicokinetic mechanisms, and although the values describing drug concentrations in body fluids and tissues have a specific useful significance in an expert opinion, they cannot be simply transposed to a toxic effect which is a consequence of affecting the central nervous system and other organs by xenobiotics. This aspect of the analyzed interaction refers to toxicodynamic consequences that are reflected in the clinical condition of a poisoned patient, which, in turn, is manifested by specific signs. The assessment of the mechanisms leading to death, or, in other words, the subject of medicolegal investigations constitute a supplementary element in medicolegal opinion on the cause of death.

While analyzing the toxicological findings for Case A, one might conclude that the young man injected himself an undetermined dose of poppy-straw stew supplemented with amphetamine, ephedrine and oxazepam to strengthen the mixture. The presence of morphine, other opium components (codeine, noscapine, papaverine, narceine) and 6-MAM, the heroine metabolite, in the urine of the deceased supports the notion of self-administration of a poppy-straw product, e.g. "Polish heroin" [3, 10]. The detection of numerous xenobiotics in the highly concentrated urine of the deceased while the compounds have not been found in the blood indicates the late elimination phase at the time of death. A relatively high contribution can be ascribed here to amphetamine, the blood level of which may be considered toxic [1, 21, 24, 25].

The evaluation of this case employing classic principles of medicolegal opinion, which is based on detection of high levels of xenobiotic(s), predominantly in blood, may raise some doubt [1, 6, 20]. Therefore, there must be other factors that allow for interpreting these results to determine the cause of death. Most likely such factors include the mechanisms governing interactions and occurring in the toxicodynamic phase. The tests do not permit to ascertain whether the injected dose of the mixture of drugs of abuse was lethal.

Nevertheless, when we analyze possible actions of the detected xenobiotics [3, 6, 7, 10, 11], as well as the overdosage signs they trigger, we might expect a pharmacological action with unpredictable toxic effects. For example, it has been suggested that the risk of death following morphine (with its depressing effect on respiration) administration with other opiates is lower than the risk involved in self-administration of a similar dose of morphine alone, since narcotine, a component of the poppy-products, has an antagonistic effect and stimulates respiration [10, 12]. In the toxic effect following self-administration of opiates, it is the respiratory system that plays a critical role. The depressing effect of opioids on the respiratory center may be intensified by high benzodiazepine levels [15]. Yet the strongest additive or even hyperadditive activity of all the detected components involved in poisoning seems to be directed towards circulatory collapse [4, 15]. Opioids release histamine and thus

result in vasodilatation. This effect is directly triggered by papaverine. Also benzodiazepines may evoke blood pressure drop that leads to circulatory collapse. In the case of amphetamine, which elevates blood pressure, circulatory collapse may be triggered by maximal stimulation of cardiac function, cardiac muscle ischemia and arrhythmia leading to secondary blood pressure reduction. In this case, the expected mechanism of death may involve circulatory collapse and concomitant respiratory failure. There is no reason allowing for ruling out such a mechanism of death in Case A.

When we analyze the toxicological findings [1] for Case B as an effect of toxicokinetic processes, we note that MDMA and PMA have the highest quantitative contribution to the global content of all the detected xenobiotics. Toxicological analyses disclosed the presence of norephedrine, a product of both ephedrine and amphetamine metabolism, MDA as a possible metabolite of MDMA, or benzoylecgonine, a metabolite of cocaine. A conclusion may be drown that the drugs were self-administered some undetermined time before death. The analysis failed to detect other amphetamine metabolites (hydroxyl derivatives, phenylacetone).

The amphetamine derivatives detected in the course of toxicological studies include synthetic compounds with the α-phenylethylamine structure and CNS-stimulating action (amphetamine). Some of these compounds are hallucinogens (MDA, MDMA, PMA) [2, 8, 9, 13, 20, 22]. In addition, the investigation also revealed the presence of natural CNS-stimulating agents, such as ephedrine and cocaine.

While analyzing the mechanisms leading to death in the case under consideration, the investigators have indicated a possible toxic interaction that might have occurred prior to death as an effect of a combined, additive action of amphetamine derivatives and cocaine, what might have directly affected the final toxic effect.

Possible signs of poisoning with particular amphetamine derivatives and cocaine are well known [1, 4, 15]. Various sources point to the similarity of toxic mechanisms for the above substances. Based on available data it may be surmised that a mixture of these xenobiotics may trigger sudden blood pressure fluctuations, respiratory disturbances and hallucinations. As available sources indicate, when administered at high doses, amphetamine derivatives and cocaine elevate the blood pressure through cardiac muscle hypoxia and arrhythmia (a cardiotoxic effect), which may lead to circulatory collapse [4, 15]. An overdose of cocaine also results in respiratory center depression and seizures.

In the case under analysis, the signs of overdosing described in great detail by witnesses, are in accordance with the present knowledge. The forensic medicine expert accepted acute circulatory failure as the mechanism leading to death, which is a logical consequence of such a course of acute poisoning.

Postmortem examinations allowed to put forward a hypothesis on the cause of death, namely it was assumed to be a consequence of the interactions between the components of a toxic preparation. We cannot rule out that this might have been a preparation known in drug subculture as "UFO". In view of the toxicological findings, it seems likely that the preparation has the following components: A, E, MDMA, MDA (?), PMA and PMMA (Tab. 2). A compound with a possible PMDA structure may be an impurity inherent in amphetamine derivatives. MDA may constitute an independent component of the preparation, but it may also be a product of MDMA degradation.

In addition, toxicological findings do not provide any evidence that cocaine was introduced into the body as a component of the "UFO" tablet. It is a well-known fact that the composition of street drugs is not based on standards and thus may be variable and depend on the components currently available to the producer. To date no "UFO" tablets have been available for chemical analysis and thus their composition must remain in the realm of supposition.

The issue of combined effects of xenobiotics occupies a prominent position both in research and in casuistry of fatal poisoning. Conclusions from such observations are widely used in medicolegal expertise. In many instances they provide a foundation on which the opinion is constructed.

Although postmortem toxicological studies that provide information on the status of tissues of the deceased at the time of death allow us to draw conclusions on the course of premortal (intravital) processes, yet the opinion concerning the cause of death which is constructed on the basis of these investigations is hypothetical in character. Therefore, considering death as a consequence of particular toxic interactions leads to a specific opinion, which may be translated into legal consequences. The latter are of significance especially in cases when

a third-party contribution must be taken into consideration.

REFERENCES

1. Baselt R.C., Cravey R.H.: Disposition of Toxic Drugs and Chemicals in Man. 4th edn., Chemical Toxicology Institute, California, 1995.
2. Błachut D.: Phenylethylamine – a new admixture of amphetamine sulphate (Polish). Probl. Krym., 2000, 230, 24–30.
3. Bogusz M.J., Maier R.D., Erkens M., Driessen S.: Determination of morphine and its 3- and 6-glucuronides, codeine, codeine-glucuronide and 6-monoacetylmorphine in body fluids by liquid chromatography atmospheric pressure chemical ionization mass spectrometry. J. Chromatogr. B, 1997, 703, 115–127.
4. Brody T.M., Larner J., Minneman K.P.: Human Pharmacology Molecular to Clinical. Mosby-Year Book, Inc., St. Louis, MO, USA, 1998.
5. Druid H., Holmgren P.: A compilation of fatal and control concentrations of drugs in postmortem femoral blood. J. Forensic Sci., 1997, 42, 79–87.
6. Druid H., Holmgren P.: Fatal injections of heroin. Interpretation of toxicological findings in multiple specimens. Int. J. Legal Med., 1998, 112, 62–66.
7. Felby S., Christensen H., Lund A.: Morphine concentration in blood and organs in cases of fatal poisoning. Forensic Sci., 1974, 3, 77–81.
8. Felgate H.E., Felgate P.D., James R.A., Sims D.N., Vozzo D.C.: Recent paramethoxyamphetamine death. J. Anal. Toxicol., 1998, 22, 169–172.
9. Fineschi V., Masti A.: Fatal poisoning by MDMA (ecstasy) and MDEA: a case raport. Int. J. Legal Med., 1996,108, 272–275.
10. Goldenberger B.A., Cone E.J., Grant T.M., Caplan Y.H., Levine B.S., Smialek J.E.: Disposition of heroin and its metabolites in heroin-related death. J. Anal. Toxicol., 1994, 18, 22–28.
11. Hayes L.W., Krassel W.G., Mueggler P.A.: Concentration of morphine and codeine in serum and urine after ingestion of poppy seeds. Clin. Chem. 1987, 33, 806.
12. Henneberg M., Skrzydlewska E.: Poisonings with Plants and Fungi (Polish). PZWL, Warszawa, 1984.
13. James R.A., Dinan A.: Hyperpyrexia associated with fatal paramethoxyamphetamine (PMA) abuse. Med. Sci. Law, 1998, 38, 83–85.
14. Kała M.: Dependence-inducing substances in the practice of the Institute of Forensic Research in Kraków (Polish). Przegl. Lek.,1997, 54, 430–437.
15. Katzung B.G.: Basic & Clinical Pharmacology. Appleton & Lange, Norwalk, CT, USA, 1995.
16. Kłys M., Bujak-Giżycka B.: Usefulness of liquid chromatography with mass detection (LC/MS) in toxicological expertise (Polish). Arch. Med. Sąd. Krym., 2000, 50, 115–121.
17. Kłys M., Jankowski Z., Bystrowska B., Bujak-Giżycka B., Nowak G.: A significance of toxic interaction in medicolegal evidence. Complex fatal poisoning with amphetamine derivatives and cocaine ("UFO"?) (Polish). Arch. Med. Sąd. Krym., 2001, 51, 133–143.
18. Kłys M., Klementowicz W., Bujak-Giżycka B., Kołodziej J., Trela F.: Medicolegal certification of fatal cases after drug-abuse in the light of modern toxicological analysis (Polish). Przegl. Lek., 2000, 57, 572–576.
19. Kłys M., Rutkiewicz A., Szkolnicka B., Bujak-Giżycka B.: Fatal and non-fatal poisonings with drugs in a medico-legal aspect in the material of the Institute of Forensic Medicine and Toxicological Clinic, Collegium Medicum, Jagiellonian University in the years 1987–1998. Acta Pol. Toxicol., 2000, 8, 101–111.
20. Milroy C.M., Clark J.C., Forrest A.R.: Pathology of deaths associated with "ecstasy" and "eve" misuse. J. Clin. Pathol., 1996, 49, 149–153.
21. Moffat A.C., Jackson J.V., Moss M.S., Woddop B.: Clarke's Isolation and Identification of Drugs in Pharmaceuticals, Body Fluids, and Postmortem Materials. 2nd edn., Pharmaceutical Press, London, 1986.
22. Rohring T.P., Prouty R.W.: Tissue distribution of methylenodioxymethamphetamine. J. Anal. Toxicol., 1992, 16, 52–53.
23. Seńczuk W.: Toxicology (Polish). PZWL, 1995.
24. Stead A.H., Moffat A.C.: A collection of therapeutic, toxic and fatal blood drug concentrations in man. Hum. Toxicol., 1983, 3, 437–464.
25. Uges D.R.A.: Therapeutic and toxic drug concentrations. The Bulletin of the International Association of Forensic Toxicologists, 1996, 26/1, Suppl.

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