

ACUTE METHOXETAMINE AND AMPHETAMINE POISONING WITH FATAL OUTCOME: A CASE REPORT

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Abstract

Methoxetamine (MXE) is a psychoactive substance distributed mostly via the Internet and is not liable to legal regulation in Poland. MXE has a toxicity profile similar to that of ketamine but longer-lasting effects. The paper describes a case of acute poisoning that resulted from recreational use of MXE and amphetamine and ended in death. In mid-July 2012, a 31-year old man was admitted to the clinical toxicology unit in Gdańsk because of poisoning with an unknown psychoactive substance. The patient was transported to the emergency department (ED) at 5:15 a.m. in a very poor general condition, in a deep coma, with acute respiratory failure, hyperthermia ($> 39^{\circ}\text{C}$) and generalized seizures. Laboratory tests showed marked leukocytosis, signs of massive rhabdomyolysis, hepatic failure and beginning of acute renal failure. Despite intensive therapy, the patient died 4 weeks after the poisoning in the course of multi-organ dysfunction syndrome. Chemical and toxicological studies of serum and urine samples collected on the poisoning day at 1:40 p.m. confirmed that amphetamine and MXE had been taken earlier that day. Concentration of amphetamine in the serum ($0.06 \mu\text{g/ml}$) was within the non-toxic range, while MXE ($0.32 \mu\text{g/ml}$) was within the toxic range of concentrations. Amphetamine was also detected in the patient's hair, which suggested a possibility of its use within the last dozen weeks or so. The serious clinical course of intoxication and co-existence of amphetamine and MXE in the patient's blood and urine suggest the possibility of adverse interactions between them.

Key words:

Acute poisoning, Methoxetamine (MXE), Amphetamine, Fatal new drug intoxication, Gas chromatography, Mass spectrometry

INTRODUCTION

Methoxetamine (MXE) is a relatively new psychoactive substance, structurally similar to ketamine and phencyclidine. It is distributed mostly via the Internet and has been available in Poland since 2010. Until now MXE sales have not been legally controlled in Poland [1].

The toxicity profile of the substance is similar to that of ketamine but it has longer-lasting effects [2]. Users of the substance report experience of mild euphoria and hallucinations that resemble those observed while using ketamine. The adverse reactions after taking MXE include: nausea, vomiting, diarrhea, paranoia, anxiety,

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disorientation, confusion, dizziness, loss of sensation and hyperthermia [3].

Case description

The paper describes a case of acute poisoning in a 31-year-old man as a result of recreational use of MXE and amphetamine that took place in July 2012.

At 5:15 a.m. the patient was transported to the ED in a very poor general condition. Due to unclear symptoms of the illness and lack of information from family or friends a broad differential diagnosis was conducted. Just after admission to the ED clinical symptoms of acute respiratory failure, which was confirmed by the arterial blood gasometry, were observed. Additionally, there was hyperthermia with the body core temperature higher than 39°C. Biochemical tests showed leukocytosis with WBC $50 \text{ U} \times 10^3/\text{l}$, an elevated level of creatinine 2.8 mg/dl, and signs of massive rhabdomyolysis with CPK 170 000 U/l.

X-ray examination showed mild inflammatory changes mainly in the left lung. Electrocardiogram (ECG) showed sinus tachycardia about 120–140 beats/min without any other abnormalities.

In the abdominal ultrasonography high echogenicity of renal parenchyma of both kidneys was seen. Computed tomography (CT) scan showed several small foci with increased density in the left cerebellar hemisphere. In the lumbar puncture the increased concentrations of protein and glucose with proper value of cells were observed.

In the neurological consultation deep coma (the 4th grade of the Matthew-Lawson coma scale), temporary and generalized seizures, caused most probably by intoxication with unknown psychoactive substances, were observed. All the mentioned above neurological symptoms disappeared after the next 3 h.

Because of an acute non-obstructive, hypodynamic respiratory failure mechanical ventilation lasting 28 days was applied. Due to acute renal insufficiency with anuria intensive supportive treatment including intensive diuresis

with alkalization, Continuous Veno-Venous Hemodialysis with citrate anticoagulation (CVVHD CaCi) were carried out. Single Pass Albumin Dialysis (SPAD) was done because of hepatic failure. Procedure of CVVHD CaCi was applied during whole hospitalization and was interrupted 3 times for SPAD (lasting 6 h for each procedure). The history taken from the family a few hours after admission revealed that during a social meeting directly preceding the hospitalization the man took at least two kinds of psychoactive substances, including an amphetamine derivative, 2-CB (1 “stamp” saturated with 100–120 µg) and a ketamine derivative, MXE which was sniffed by the patient. Both substances were also taken by other participants of the meeting. According to the patient’s sister, all narcotics had been bought via the Internet. Additionally, the patient might have sniffed amphetamine. They also reported that he had smoked hashish on the same day too. At 6:58 a.m. on the same day, a urine sample was taken from the patient to conduct laboratory tests for such psychoactive substances as cocaine, amphetamine, barbiturates, opiates, THC, morphine and ecstasy. The result of the examination, performed by means of the InstAlert immunochromatographic test, was negative for each of the above groups. On the following day the patient was transferred to the clinical toxicology unit in Gdańsk with a suspicion of poisoning with an unknown psychoactive substance. Laboratory tests showed elevated leukocytosis, signs of massive rhabdomyolysis as well as renal and hepatic failure (Table 1).

Despite intensive therapy, including mechanical ventilation, continuous renal replacement therapy and single pass albumin dialysis the patient died 28 days after the poisoning in the course of multiple organ dysfunction syndrome (MODS). The forensic autopsy performed at the department of forensic medicine (DFM) showed: generalized edema (so-called anasarca) and presence of effusion in the pleural cavities (1650 ml in total) and in the peritoneal cavity (2 l); pulmonary edema and confluent

Table 1. Results of laboratory tests during hospitalization

Parameter	Treatment day							
	1	2	3	4	7	14	21	28
WBC (U×10 ³ /l)	50.0	23.00	18.0	10.0	22.0	34.0	16.0	17.0
Creatinine (mg/dl)	2.8	3.56	2.7	1.4	3.2	3.2	2.8	3.0
Urea (mg/dl)	55.8	85.00	50.0	45.0	120.0	106.0	100.0	100.0
ASPAT (U/l)	n.d.	3 160.00	2 592.0	2 623.0	851.0	373.0	298.0	140.0
ALAT (U/l)	n.d.	1 097.00	1 778.0	2 848.0	781.0	476.0	293.0	203.0
PT (%)	n.d.	53.00	61.0	78.0	83.0	86.0	81.0	86.0
CPK (U/l)	17 000.0	22 0531.00	129 800.0	83 300.0	38 087.0	12 058.0	6 466.0	3 233.0

WBC – white blood cells; ASPAT – aspartate transaminase; ALAT – alanine aminotransferase; PT – prothrombin time; CPK – creatine phosphokinase.

n.d. – not determined.

bronchopneumonia; cerebral edema without morphological signs of increased intracranial pressure brain, small foci of pallor in the cortex and basal nuclei of the cerebral hemispheres and focal hemorrhages showing signs of extravasation in the left hemisphere temporal lobe. Additionally, the examination showed parenchymatous lesions in the kidneys – acute tubular necrosis (ATM).

METHODOLOGY

On the admission day at 1:40 p.m., the patient's serum and urine were collected *in vivo* and secured at the clinical toxicology unit. During the postmortem examination performed at DFM, ca. 200 mg of hair (ca. 3–4 cm long) was taken from the chest to determine possible long-term *in vivo* exposure to the use of psychoactive substances. The biological material collected post mortem was not analyzed because of the interval between the poisoning and time of death (28 days).

The tests were performed using chemical reagents of analytical purity (over 99.9%), analyzing blanks and control samples at the same time. The test for ethyl alcohol was performed using the reference method of headspace analysis coupled with gas chromatography flame ionization detection (HS-GC/FID) (“TriPlus” analyzer and

“Focus GC” gas chromatograph from ThermoFinnigan). The immunochemical urinalysis was performed by means of the plate tests, TOX/See Drug Screen Test, from BIO-RAD, to detect: amphetamine and its analogs (positive result for calibration substance at a concentration over 1.0 µg/ml for amphetamine), methamphetamine and its analogs (over 1.0 µg/ml for methamphetamine), benzodiazepines (over 0.3 µg/ml for oxazepam), barbiturates (over 0.3 µg/ml for secobarbital), cocaine and its metabolites (over 0.3 µg/ml for benzoylecgonine), cannabinoids (over 0.05 µg/ml for 11-nor- Δ^9 -THC-9-COOH), opiates (over 0.3 µg/ml for morphine), tricyclic antidepressants (over 0.1 µg/ml for nortriptyline). Enzyme-linked immunosorbent assays of the serum were performed by means of ELISA kits from Neogen to detect amphetamine and its analogs (positive result for calibration substance at concentration over 0.05 µg/ml for amphetamine) and benzodiazepines (over 0.05 µg/ml for oxazepam).

To broaden the possibility of detecting psychoactive substances in the biological material, tests based on liquid-liquid extraction, derivatization and gas chromatography combined with mass spectrometry (GC/MS) were performed. Samples of 1.8 ml of serum and 1 ml of urine were simultaneously collected for the tests, internal standard was added (isotope-labeled amphetamine-D11),

and the supernatants obtained after the extraction were evaporated until dry in a mild nitrogen stream at 40°C. The volume of 50 µl of ethyl acetate was added to the dry residue. Serum and urine extracts were analyzed by means of gas chromatography combined with mass spectrometry (GC/MS-SCAN), using DSQ Trace gas chromatograph from ThermoFinnigan operating under the following conditions: Zebron ZB-5 Guardian capillary column from Phenomenex (length: 30 m, inner diameter: 0.25 mm, film thickness: 0.25 µm), programmable oven temperature: 50–285°C; carrier gas: helium; ion analysis in the mass scan mode: 35–380 m/z.

The results of the chromatographic analysis were compared with the mass spectral library NIST/EPA/NIH of 2008, listing most pharmacologically active and toxic substances. Particular emphasis was placed on the detection of pharmacologically active substances mentioned in the medical history such as: amphetamine, MXE (methoxetamine), 2-CB (4-bromo-2,5-dimethoxyphenylethylamine), metamizole and paracetamol.

To confirm the presence of amphetamine and methoxetamine in the above-named extracts, 50 µl of trifluoroacetic anhydride was added. After that, derivatization lasting 20 min at 55°C was performed. At the end of the process, everything was re-evaporated until dry in the above conditions, and then the dry residues were dissolved in ethyl acetate. At the same time, 124 mg of the hair sample collected from the chest during the autopsy were dried, taken and prepared pursuant to the procedure described by Kintz et al. [4].

Thus prepared extracts were injected into the GC/MS-SIM unit. The analysis used the technique of gas chromatography combined with mass spectrometry (GC/MS) using Trace GC gas chromatograph and Trace DSQ detector from ThermoFinnigan, capillary column Zebron ZB-5 Guardian (30 m × 0.25 mm × 0.25 µm), oven temperature programmed from 50–250°C, carrier gas – helium, in the mode of selected ion monitoring (SIM). At the same time,

model solutions of the following substances were analyzed: amphetamine, methamphetamine, 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxymethamphetamine (MDMA), 3,4-methylenedioxyethyloamphetamine (MDEA) and MXE (methoxetamine).

RESULTS

The chemical and toxicological examination of serum and urine collected *in vivo* on the poisoning day at 1:40 p.m. did not detect any ethanol. The immunochemical urinalysis was positive for substances from the benzodiazepine group and amphetamine and its analogs.

The serum ELISA screening assay was positive for benzodiazepines and negative for amphetamine or its analogs.

As during hospitalization the patient had been treated with benzodiazepines (diazepam, midazolam), the qualitative and quantitative determination of the substances from this group using instrumental methods was abandoned. In GC/MS-SIM chromatographic analysis, amphetamine and MXE were detected and determined in the biological material taken from the patient (Table 2).

Table 2. Results of GC/MS-SIM chromatographic analysis of biological material collected from the patient*

Biological material	Concentration	
	amphetamine	methoxetamine
Serum	0.06 µg/ml	0.32 µg/ml
Urine	0.27 µg/ml	4.36 µg/ml
Hair	0.19 µg/g	not found

* Collected on the poisoning day at 1:40 p.m. (serum, urine) and during the autopsy (hair).

DISCUSSION

Methoxetamine (MXE) is a psychoactive substance, structurally similar to ketamine and phencyclidine (Figure 1). Its sales are not currently regulated by law in European

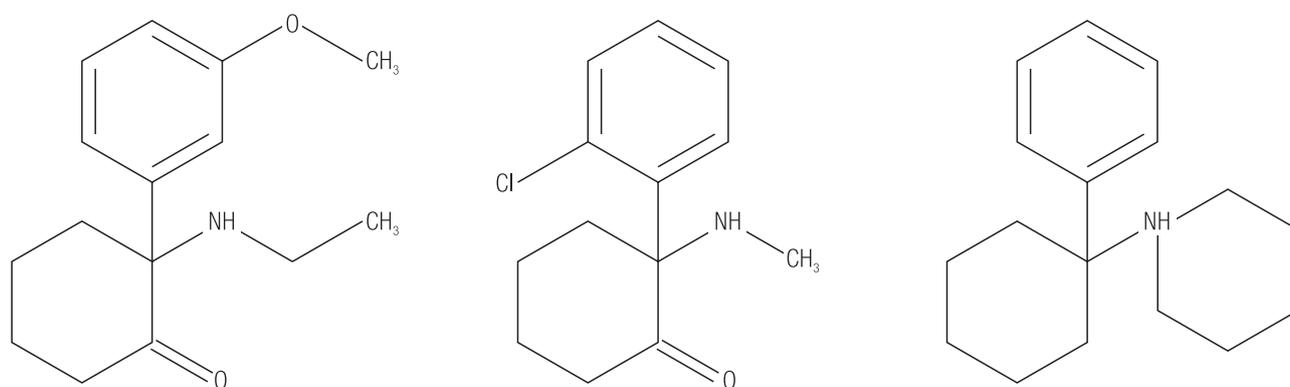


Fig. 1. Formulas of (a) MXE, (b) ketamine and (c) phencyclidine

countries. There are no objective studies on its mechanism of action, toxicity or pharmacological properties. It is presumed that the mechanism of action of MXE is similar to that of ketamine through its effects on the NMDA receptors (N-methyl-D-aspartate) and inhibition of dopamine reuptake [5].

The change of N-methyl group into N-ethyl group in MXE molecule has extended its duration of action, whereas the change of 2-chloro group into 3-methoxy group in the aromatic ring has reduced its anesthetic and analgesic effects [2].

It is worth emphasizing that the anti-depressant effects of MXE raise hopes for developing new antidepressant drugs [6].

Recent studies have revealed that MXE is not a safer alternative to ketamine. They have also pointed the need for toxicity studies in humans [7,8].

Methoxetamine is most commonly taken in the dose of 5–90 mg as a powder inhaled through the nose, administered sublingually, intravenously or intramuscularly. The effects of MXE begin to appear within 10–20 min from taking it and last for 1–3 h. Methoxetamine users report that after taking the drug they experience mild euphoria and hallucinations similar to those observed after taking ketamine. Unpleasant and adverse effects include: tachycardia, nystagmus, nausea, vomiting, diarrhea, paranoid reactions, anxiety, disorientation, confusion, dizziness,

loss of sensation and numbness. No other adverse effects associated with the use of ketamine (e.g. hypertension, laryngeal and pulmonary edema) have been observed in MXE users.

The treatment of methoxetamine poisoning is symptomatic, the procedures resembling those applied in ketamine or phencyclidine poisoning [3,9].

The cases of acute poisoning with methoxetamine described so far were sometimes associated with hyperthermia, but it might have been brought on by other substances taken at the same time [2].

The serum and whole blood concentrations of methoxetamine described in the literature ranged 0.09–0.45 $\mu\text{g/ml}$ in young people (aged 17–42) with acute poisoning symptoms [10,11]. Similar concentrations in the whole blood (0.13–0.49 $\mu\text{g/ml}$) were detected in Swedes suspected of minor narcotic offenses, whereas the person with the highest concentration (0.49 $\mu\text{g/ml}$) exhibited disorders of consciousness. In the described case of MXE lethal poisoning in Sweden, its level in femoral blood was 8.6 $\mu\text{g/g}$, and other psychoactive substances (venlafaxine, O-desmethylvenlafaxine, tetrahydrocannabinol, AM-694, AM-2201, JWH-018) were also detected [12].

It should be noted that the possibility of reliable determination of MXE in biological material should not cause much difficulty in toxicological diagnostics since qualitative and quantitative analysis is possible both by means

of liquid chromatography with ultraviolet diode array detection (HPLC-UV-DAD) as well as by means of gas chromatography with chemical ionization mass spectrometry (GC-EI/CI-MS) [13].

Amphetamine and its derivatives are characterized by stimulation of the central nervous system. In small doses (5–10 mg) they can improve concentration and capacity for physical effort, while in higher doses they reduce appetite, raise body temperature and arterial blood pressure, cause insomnia, nervousness, anxiety, increased excitability, euphoria, trembling, headaches and dizziness, dryness in the mouth, perspiration, tachycardia, feeling of accelerated heartbeat and difficulties with micturition. People under the influence of amphetamine present an increased motor and mental activity, without feeling sleepy or tired. The pupils are dilated; fainting and vomiting can sometimes be observed.

Amphetamine is rapidly absorbed and transported by the circulatory system. It appears in the urine within 20 min and approx. 20–30% of the dose is excreted with the urine in an unchanged form. The elimination rate largely depends on the urine pH level and sharply increases with its acidification. After taking large doses, amphetamine can be present in the urine even for a few days. The effects of amphetamine continue for 3–6 h after taking it, and this is approximately the time during which amphetamine can be detected in blood.

Psychological dependence caused by amphetamine leads to rapid development of tolerance to the effects on the side of the central nervous system, making the user gradually increase doses (100–500 mg), which has a toxic effect on the cardiovascular system. For instance, after oral consumption of 2.5–15 mg of amphetamine, the maximum plasma level of 0.03–0.17 µg/ml was recorded in 2 h. The half-life of amphetamine is 8–12 h. The non-toxic concentration of amphetamine in the serum is usually below 0.1 µg/ml, while 0.2–3 µg/ml are considered as toxic concentrations [14]. In people occasionally using

amphetamine, the serum concentration does not usually exceed 0.2 µg/ml, while in people addicted to amphetamine higher concentrations, up to even 3 µg/ml, can be observed. Amphetamine concentrations detected in hair are usually between 0.02 and 6.5 µg/g (on average 0.84 µg/g of hair) [15].

The detection time (detection window) of blood amphetamine does not usually exceed a few up to a dozen or so hours after taking it (depending mostly on the dose taken and urine pH). The detection window of amphetamine in the urine is 2–3 days, while substances may pass to the urine with a time-lag of up to several hours. The longest detection time of amphetamine is in hair – up to a few months, depending on its length.

As regards MXE, there is no exact pharmacological data on its detection time in the system. If this time was similar to that of ketamine, the biological half-life in the system would not exceed 2–3 h. It should be noted that the results of blood assays usually permit a qualitative and quantitative interpretation, while those for urine and hair provide mostly qualitative information on a possible previous use of a substance.

The patient was brought to the ED in July 2012 at 5:15 a.m., and the serum and urine samples were collected more than 8 h later, at 1:40 p.m. The determined higher concentrations of amphetamine and MXE in the urine in comparison with the blood suggest that these substances were in the elimination phase at the time of biological material collection.

In the urine sample taken from the patient at 6:58 a.m. (shortly after admission to the ED) no amphetamine or derivative compounds were detected probably because by that time these substances had not been metabolized yet. This explanation is also confirmed by the information gathered in the medical history that the patient had taken amphetamine, MXE and other drugs during the party.

The patient was also reported to smoke marijuana and take an amphetamine derivative in the form of 2-CB,

which was not, however, confirmed in the laboratory tests. The amphetamine detected in the hair sample proves that it had been previously taken over a longer period of time (a dozen or so weeks), and that the patient used to take this kind of drug.

CONCLUSIONS

Amphetamine concentration, 0.06 µg/ml, in the serum was within the non-toxic range, while 0.32 µg/ml of methoxetamine was within the range of toxic concentrations noted in the cases of acute poisoning. However, maximum blood concentrations of these narcotics could have been much higher because the analyzed samples were taken over 8 h after admission to the ED.

According to the authors' opinion, such serious side effects connected with poisoning with amphetamine and MXE could be associated with high blood concentration of MXE alone and some kind of patient's susceptibility to this narcotic or adverse and life threatening interaction between MXE and amphetamine.

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