The role of stimulant designer drug consumption in three fatal cases in South-East Hungary in 2011

Anita Réka Tóth*, Katalin Kovács, Zsófia Árok, Tibor Varga, Éva Kereszty, László Institóris

Abstract: The role of stimulant designer drug consumption has been investigated in three fatal cases. In Case 1 the fatal outcome can be attributed to the come down phase following their application, as the blood and urine concentration of the designer drugs was low. In the second case arrhythmogenic effect of methylone was added to the right ventricular arrhythmogenic dysplasia of the patient and these two factors could lead to death. The suicide case (Case 3) was probably the consequence of the withdrawal effect of MDPV (methylenedioxypyrovalerone). The aim of this issue was to focus on some questions of forensic importance that arose in three autopsy cases where the consumption of amphetamine-like designer drugs could play a role in the fatal outcome.

Key Words: amphetamine-like designer drugs, fatal cases, autopsy, GC-MS analysis.

According to EMCDDA statistics 77 new designer drugs were registered between January 2010 and November 2011 in Europe [1], among which 51 were also seized in Hungary during the same period. Statistics of seized materials, toxicological results of biological samples of suspected drug users and postmortem cases show that stimulant type designer drugs had become the second most frequently used substances after cannabis [2].

Due to this tendency the evaluation of consequences of designer drug consumption has an increasing necessity. However, evaluation of toxicological data is quite difficult in lack of some basic knowledge including but not limited to information about pharmacokinetics, effective and toxic dose ranges, lethal doses, chronic and long term effects [3].

All blood and/or urine samples of suspected drug users in Csongrád County (South-East Hungary, about 420 000 inhabitants) are analyzed with gas chromatograph – mass spectrometer (GC-MS) in Department of Forensic Medicine, University Szeged. Among the 14 stimulant designer drugs (Table 1), in the scope of the analysis the most frequent ones were methylone, 4-methylethcathinone (4-MEC), methylenedioxypyrovalerone (MDPV), 4-fluoromethcathinone (4-FMC), 4-fluoroamphetamine (4-FA), and 3,4-dimethylmethcathinone (3,4-DMMC) in 2011. The aim of the present publication is to investigate the role of stimulant designer drugs in three fatal cases.

MATERIALS AND METHODS

Altogether 571 autopsies were performed at our department in 2011 in accordance with the Medico-Legal Autopsy Rules [4]. In all autopsy cases.
immunoassay pre-screening (Instalert™ Multi-drug one step screen test panel) was performed and in case of suspected illicit, licit and designer drug consumption blood and urine (liver extract in one case) samples were analyzed by GC-MS for the most common illicit drugs, benzodiazepines, and 14 stimulant designer drugs (Table 1).

Sample processing of blood and urine for GC-MS were previously described [4]. The samples prepared for amphetamine determination with GC-MS were also used to measure designer drugs, collecting the adequate SIM ions (under publication). Liver
extract was prepared from 1 g of liver tissue that was cut into small pieces using scissors in 4 ml methanol and put in Ultrasonic bath (ELMA S 15, USA) for 45 minutes. After filtration and evaporation the residue was dissolved in distilled water, pH was adjusted to a value between 2 and 3 with hydrochloric acid. The sample was then evaporated, the residue was re-dissolved in 200 μl distilled water, and the sample was processed as described for blood and urine [5].

RESULTS AND DISCUSSION

Case 1: Driving under impairment?

A 19-year-old man died in a road accident. At a speed of 120 kph his car swept off the road, hit a building, and the victim died at the scene. During autopsy basilar fracture of the skull, bulbo-pontine contusion, blood aspiration, and bilateral serial costal fractures were observed. The results of the toxicological analysis (see Table 2) suggested that he has taken stimulant designer drugs (MDPV, 4-FMC and 3,4-DMMC) and amphetamine 1-2 days before the accident. Designer drugs are frequently used in combination, as described in a study on suspected impaired drivers in Finland when MDPV was generally found together with other stimulant illicit drugs and/or benzodiazepines [6].

According to the toxicological results in the present case the time of consumption was within 1 day before the accident (no amphetamine and 4-FMC could be detected in the blood, and their concentration in the urine was 13.7 and 13.8 ng/ml, respectively). The blood concentration of 3,4-DMMC (53.2 ng/ml) and that of MDPV (22.2 ng/ml) were also relatively low, and there is no evidence that they cause driving impairment at the blood concentrations measured. Low blood concentrations also raise the possibility that in the fitness to drive was decreased by the "come down" phase following the drugs’ stimulant effect.

Figure 1. Lung (20x Haematoxylin eosin staining) Pulmonary edema with haemorrhage.

Figure 2. Liver (20x Haematoxylin eosin staining) Diffuse microvesicular steatosis.

Figure 3. Heart (4x Haematoxylin eosin staining) Fatty infiltration in right ventricular myocardium.

Figure 4. Heart (40x Haematoxylin eosin staining) Hypercontractile myocardial muscle fibers surrounded by acute focal cardiomalacia.
**Case 2: Natural death related to methylone consumption?**

A 16-year-old boy felt sick at a family party and lost his consciousness. Advanced life support was performed (endotracheal intubation, ventilation, chest compression, i.v. atropine and adrenaline) during transportation to the intensive care unit where the process was continued. He was admitted with Glasgow Coma Scale (GCS) 3. As pneumothorax was suspected thoracic drainage was performed. X-ray showed right-sided subcutaneous emphysema. Family history raised the possibility of pulmonary embolism therefore thrombolysis was performed after which blood was observed in the gastric and tracheal tube. The blood-gas analysis showed a progressive metabolic acidosis. The laboratory results are shown in Table 3. Unsuccessful reanimation was carried out for about one hour. Autopsy revealed a cerebral edema (1400 g), about 40-40 ml serous fluid in the thoracic cavity, right ventricular subepicardial punctuated hemorrhages, uneven distribution of blood in the myocardium (heart weight: 320 g), punctuated bronchial hemorrhages, congestive pulmonary edema (1350 g), punctuated hemorrhages of the gastric mucosa, congested kidneys (330 g), splenomegaly (310 g) and fatty liver (1750 g). Microbiological examination showed the presence of Klebsiella pneumoniae in the respiratory tract. Histology revealed cerebral edema, pulmonary emphysema, bronchial and pulmonary hemorrhages (Fig. 1), diffuse microvesicular steatosis (Fig. 2), fatty infiltration of the right ventricular myocardium with focal fibrosis (Fig. 3), hypercontractile myocardial muscle fibers surrounded by acute focal cardiomyalacia (Fig. 4). Methylone was detected in blood and in the liver extract by GC-MS analysis (Table 4).

According to literature fatal outcome is mostly associated with consumption of amphetamine, methamphetamine or MDMA. The range between the toxic or lethal doses of these amphetamines (Table 5) [7] is wide, whereas in case of methylone it has not yet been established.

Three hundred and sixty four suspected illicit drug users’ urine and/or blood samples were measured in our department in 2011. Out of them, 34 urine samples proved to be positive for methylone and in two of these cases blood samples were available both positive for methylone. However, its concentration was higher in both samples (291 and 628 ng/ml) than in Case 2 (272 ng/ml). This means that the blood concentration value of 272 ng/ml was below the lethal range. Pearson et al. reported three fatal cases where the primary cause of death was methylone consumption. In this study the postmortem methylone concentration varied between 560 and 3300 ng/ml in peripheral blood samples [7]. Although Pearson et al. concluded that a methylone concentration in the peripheral blood as high as 500 ng/ml may cause death in a way that resembles sympathomimetic toxicity, including metabolic acidosis, rhabdomyolysis, acute renal failure, and disseminated intravascular coagulation.

The liver-to-blood concentration ratio of methylone was between 1.19 and 4.66 in five postmortem cases [8, 9], and it was 1.43 in our study. Due to the large deviation it seems unlikely that the blood concentration could be calculated from the concentration in the liver when blood samples are not available.

The general autopsy findings at lethal doses of ‘classical’ amphetamines are cerebral edema, pulmonary edema and hemorrhage, at lower doses cardiomyopathy, acute myocardial infarction, endocarditis, coronary sclerosis, pulmonary fibrosis, stroke, various infections and rhabdomyolysis [10-

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**Table 4. Toxicological results of Case 2**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Alcohol (g/L)</th>
<th>Methylene (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>0.11</td>
<td>272 ng/mL</td>
</tr>
<tr>
<td>Liver</td>
<td>-</td>
<td>387 mg/g</td>
</tr>
</tbody>
</table>

**Table 5. Therapeutic, toxic, and lethal concentrations of amphetamine, methamphetamine, and MDMA in plasma**

<table>
<thead>
<tr>
<th>Substances</th>
<th>Effective (ng/ml)</th>
<th>Toxic (ng/ml)</th>
<th>Lethal (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine</td>
<td>20-150</td>
<td>200</td>
<td>500</td>
</tr>
<tr>
<td>Metamphetamine</td>
<td>10-50</td>
<td>200-1000</td>
<td>4000</td>
</tr>
<tr>
<td>MDMA</td>
<td>0-350</td>
<td>500</td>
<td>1260</td>
</tr>
</tbody>
</table>

**Table 6. Toxicological results of Case 3**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Alcohol (g/L)</th>
<th>Amphetamine (ng/ml)</th>
<th>Codeine (ng/ml)</th>
<th>MDPV (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>-</td>
<td>25</td>
<td>16.6</td>
<td>-</td>
</tr>
<tr>
<td>Urine</td>
<td>0.20</td>
<td>2942</td>
<td>222</td>
<td>44</td>
</tr>
</tbody>
</table>
Besides cerebral edema, pulmonary edema and hemorrhage, in this case microvesicular hepatic steatosis, fatty infiltration of the right ventricular myocardium and focal hyper-contractile myocardial necrosis were also observed. As microvesicular hepatic steatosis can be caused by toxic agents, e.g. alcohol, licit or illicit drugs, the role of regular designer drug consumption cannot be excluded despite the lack of drug use in the past history. The hyper-contractile myocardial necrosis has already been described in the case of amphetamine-like compound’ intake (rhabdomyolysis syndrome) [14].

Although in Case 2, the application of pressor agents during reanimation could also lead to myocardial damage. There was no cylinder formation in the kidneys but, due to the short survival, it doesn’t exclude the presence of rhabdomyolysis syndrome. Unfortunately, we have no information about the body temperature before death.

The metabolic acidosis can be caused by methylene through releasing lactate-dehydrogenase from the cells [8, 15]. The metabolic acidosis and fatty infiltration in the right ventricular myocardium raises the possibility of the ventricular arrhythmogenic dysplasia which, in case of stimulant drug consumption, can lead to sudden cardiac death.

**Case 3: A suicide – jump down from the 9th floor**

A 22-year-old man jumped down from 9th floor of a student hostel. According to the scene investigation the window could be opened only to 21 cm; suicide note was not found. During autopsy multiple open skull fractures, multifocal cerebral contusion, bilateral serial costal fractures, vertebral fracture, upper-arm and sternum fracture, pulmonary contusion, blood aspiration, cardiac contusion, spleen and liver rupture were found. In blood samples amphetamine and codeine, while in urine samples amphetamine, codeine and MDPV were detected by GC-MS analysis (Table 6).

According to the past history the victim was an illicit drug abuser who was treated at the local Drug Addiction Department. GC-MS analysis of his blood showed a concentration of 25 ng/ml amphetamine while amphetamine concentration of 2942 ng/ml and MDPV concentration of 44 ng/ml in the urine represent a typical elimination stage after stimulant consumption. It is unclear whether he used MDPV (or in combination with other designer drugs) first and amphetamine later (maybe to substitute MDPV) or an amphetamine-designer mixture was used. The most probable cause of suicide was a hallucinatory delirium caused by MDPV deprivation [16], but the possible role of other amphetamine-like designer(s) in the ‘come down’ phase cannot be excluded.

At present little knowledge is available about deaths and impairments associated with designer drug abuse therefore it is difficult to determine the cause of death in these situations. In Case 1 and 3 the role of the ‘come down’ phase and deprivation may have led to the fatal outcome, while in Case 2 the arrhythmogenic effect of methylene contributed to the death.

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**References**

11. H. Inoue, N. Ikeda, K. Kudo, et al. Methamphetamine-related sudden death with a concentration which was of a 'toxic level'. Legal Med. 2006; 8 150-155