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CASE REPORT

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One fatal and seven non-fatal cases of 4-methylthioamphetamine (4-MTA) intoxication: clinico-pathological findings

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Abstract We present a case history involving one fatal and seven survived cases of intoxication with 4-methylthioamphetamine (4-MTA), also called *para*-methylthioamphetamine (*p*-MTA) or methylthioamphetamine (MTA), a relatively new amphetamine analogue. Two of the seven survivors required a 24-h-period of observation in hospital. This report proves once again that the new amphetamine designer drugs are not without danger, as is thought by many young people. In addition, individually different subjective reactions are described. Finally, the medico-legal implications of new, as yet unregistered drugs are discussed.

Keywords Drug abuse · 4-MTA · 4-Methylthioamphetamine · Amphetamines · Intoxication

Introduction

The substance 4-methylthioamphetamine (4-MTA), also called *para*-methylthioamphetamine (*p*-MTA), methylthioamphetamine (MTA) or "flatliner" [1], is a relatively new phenylethylamine-based compound. It was first synthesised and investigated by Huang et al. [2] in the rat animal model in which MTA was proven to be non-neurotoxic at low doses, but was found to induce typical serotonergic behaviour at high doses. MTA was in fact developed as a potent and "purer" serotonin-releasing agent for use in experimental research [2]. This serotonin-releasing property was compared with that of other amphetamine derivatives and a study in rats indicated, for example, that MTA had a delayed reaction compared to MBDB [3] (also known as Methyl-J and Eden [4]). The main site of toxicity with MDMA is believed to be within the serotonergic pathways in the central nervous system and explains the influence of MDMA on affective behaviour and thermoregulation, for example [5]. Studies in the rat indicated that another amphetamine derivative, methamphetamine, was able to induce apoptosis of the thymic and splenic lymphocytes [6]. Recently, the cardiotoxic effect of methamphetamine has been studied in isolated adult rat cardiomyocytes [7]. Others have investigated the liver toxicity caused by single or repeated intraperitoneal doses of MDMA in the rat [8]. However, many mechanisms of toxicity caused by amphetamine and its derivatives still remain to be elucidated.

MTA, just as MBDB [4], can be sold as an "ecstasy" pill and the use of MTA as an illegal "designer" drug was first reported in the Netherlands [9]. MTA is structurally closely related to *para*-methoxyamphetamine (PMA), another ring-substituted amphetamine (Fig. 1) and some cases of fatal poisoning involving PMA have recently been reported [10, 11]. To our knowledge, only one fatal

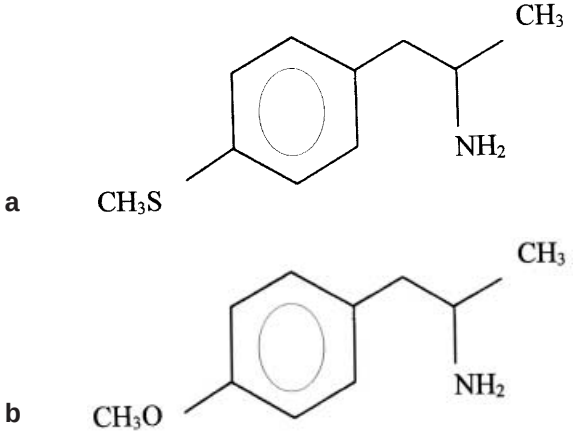

Fig. 1 **a** Chemical structures of 4-MTA (4-methylthioamphetamine) and **b** PMA (*para*-methoxyamphetamine)

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case of MTA intoxication [1] and very few cases of poisoning have been published [12, 13].

History and case reports

One morning, the emergency services were called to a residence where they found one person unconscious and six other people in a state of intoxication. The six young people were admitted to hospital and two required a 24-h-period of observation. Further police investigation revealed that another male person (case 8) was also involved, but had left the house before the emergency services arrived.

Case 1 (M.)

A 27-year-old drug dealer was found in a state of cardiorespiratory arrest at about 9.00 a.m. The emergency team attempted intensive reanimation which failed. On post-mortem examination, the body weighed 55 kg and was 171 cm in length, the rectal temperature at 1.05 p.m. was 35 °C and the ambient temperature 17 °C. During the external examination, fresh ecchymoses on both legs and a few small fresh excoriations on both forearms and the left ankle were noticed. These superficial skin lesions were consistent with slight to moderate blunt trauma (e.g. fall or blow).

During internal inspection 2 days postmortem, obvious signs of intensive cardiopulmonary resuscitation were found, including some rib fractures. Numerous Tardieu spots were observed on the pericardium, thymus and both pleurae. Both lungs weighed 970 g and obvious emphysema, severe congestion and moderate oedema were found. The heart weighed 255 g and showed no conspicuous anomalies. The stomach contained only a small amount of bloody mucus and the mucosa showed a few pin-point ulcerations. The brain weighed 1,320 g and apart from slight oedema and congestion of the white matter, nothing unusual was found. The remaining organs showed no obvious macroscopic anomalies, except for congestion.

On histological examination, pronounced pulmonary congestion, haemorrhagic oedema, a slight intra-alveolar infiltration with a few polymorphonuclear cells and some leucocyte sludging in the septal veins were found. Groups of alveolar macrophages were seen, although staining with Prussian blue was negative. Obvious eosinophilic infiltration was found in some lymph nodules although not seen in the lungs. The Purkinje cells in the cerebellar vermis were pyknotic and somewhat reduced in number. In the nucleus lentiformis, a few venulae were surrounded by a lymphocytic infiltration and macrophages containing haemosiderin. The hippocampus showed no marked hypoxemic lesions. No obvious pre-existing disease was identified.

Toxicological screening revealed MDMA in the urine, MTA in the blood, urine and liver and tetrahydrocannabinoic acid in the urine. These results were confirmed by GC/MS (liver/urine) and HPLC/DAD (blood) analysis. Blood, urine and liver analysis showed MTA concentrations of 8.38 μg/ml, 100 μg/ml and 30 μg/g, respectively. The MDMA level in the urine was 1.2 μg/ml. The amount of MDMA in the blood was below the limit of quantitation (< 0.1 μg/ml). The urine pH was 5.6. The size of the stomach content sample was insufficient for toxicological analysis. No other psycho-active drugs were found. In addition, analysis of two small plastic bags (containing green-brownish herbs) found in the victim's pockets, demonstrated cannabinol (marijuana).

Questioning of the surviving persons revealed that M. had been walking around the whole night, but around 8.00 a.m. he started sweating and thrashing around on the floor. M. started shaking intensely and his behaviour became increasingly more strange. This went on for quite some time, for at least 1 h. Somewhat later, one of them noted that M.'s heartbeat was fading and oedema was appearing on his mouth. They then tried to resuscitate him, but even before the emergency services arrived, M. felt cold to the touch. One of the survivors declared that M. had taken at least six pills: first, two pills at the same time and then each of the other four pills at intervals of about 2 h. In addition, M. had smoked five or six joints. The girlfriend of the deceased (case 7) admitted that M. was dealing in "ecstasy" pills, marijuana and speed and drove to the Netherlands for his supplies. M. was heavily addicted to "smart pills" and easily took six of them in the course of a single evening followed by a shaking period that usually subsided after a few minutes. On the morning in question, M. started shaking but this time it did not stop after a few minutes. He had told her about ingesting 15 pills at one time in the previous year. In the dealer's car, a note printed in Dutch describing some characteristics of MTA (called "MTA-1" in the note) was retrieved.

Case 2 (D.W.)

This 18-year-old man, found lying in a chair, apathetic and staring vacantly into space, was conveyed to hospital for observation. Upon being discharged 24 h later, he stated to the police officer that he had been using drugs since the age of 14, mainly cannabis, and sometimes "a pill". On the night in question, all those present in the house had smoked joints and swallowed pills. He could not remember exactly when, but he himself had taken two pills at the same time. He described how he had taken leave of his senses thereafter, had had a "threefold" vision and hallucinations and was unable to control all his acts (e.g. he could not stop his chin from shivering). He felt that his heart rate had clearly increased and one moment he was sweating, while a few moments later he would turn icy cold.

Case 3 (B.)

The emergency services found this 22-year-old female unsteady on her feet, although a certain amount of conversation was possible. She had arrived home at about midnight, when she smoked some joints together with her friends and then took one pill. From that point on, she could remember very little, although she knew she had slept a lot. She regularly smoked joints at the weekends, but it was the first time that she had taken such a pill.

Case 4 (W.)

This 15-year-old female looked extremely tired but was able to confirm that everyone had smoked joints and, shortly thereafter, M. had handed out "smart" pills. She was admitted to hospital, although observation was not required and she was interrogated about 12 h later. She herself took one pill at about 0.15 a.m. and 20 min later, she "experienced a very pleasant feeling". In order to enhance the sensation, she smoked a joint. She was awake during the whole night and, like the others, she drank no alcohol.

This subject was also able to give some information about the number of pills the different individuals had swallowed (Table 1). W. claimed that she herself took a pill and smoked a joint "now and then", but only at weekends.

Case 5 (W.W.)

The story of this 19-year-old man was consistent with the others. He stated that he had taken only one pill, followed by three joints, and had played music the whole night through.

Case 6 (D.J.)

Although this 22-year-old man was heavily intoxicated, he agreed to make a statement. Since his answers frequently went beyond the question and he behaved very strangely (e.g. hitting his head against the table, almost falling off his chair), the police officers decided to send him to hospital for observation. He was discharged 24 h later, when he was capable of being interrogated. His mind

Table 1 Summary of the data found in the surviving persons

Case	Number[a]	Blood sampling time	Urine sampling time	Urine pH	MTA level in blood (μg/ml)	MTA level in urine (μg/ml)
2. D.W.	≥ 2	12.44	12.20	6.6	0.63	10
3. B.	1	16.52	16.57	8.1	1.08	4
4. W.	1	12.41	15.23	7.3	2.08	8
5. W.W.	1 or 1.5	12.33	12.23	6.4	1.93	4
6. D.J.	3, 5 or 6	12.43	15.22	5.8	1.26	40
7. V.	≥ 2	12.36	12.31	5.5	0.43	32

[a] Possible number of ingested pills according to the statements

was a blank except for a few fragments, but he believed that he had taken two pills at an interval of half an hour. He explained that when he took one pill, nothing happened, but following the second, he felt good and was unable to sit still. Somewhat later he took a third pill, and from then on everything was fuzzy. He recalled having difficulty in urinating but he did not remember being in hospital. According to his girlfriend (case 3) it was the first time he had taken such a pill.

Case 7 (V.)

This 19-year-old woman, the girlfriend of the deceased (case 1), was also interrogated the evening following the occurrence. She had been using drugs since the age of 10 and was addicted to marijuana and stimulating drugs (including speed and "MTA-1"). The two pills she swallowed made her feel sick and she vomited several times. She fell asleep for a few short periods.

Case 8 (G.)

This 20-year-old man arrived at the house at about 1.00–1.30 a.m. and left at about 7.30 a.m. He confirmed that everybody was "in a whirl" when he arrived. For the first time in his life he took one pill at about 1.45 a.m. and somewhat later fell asleep. By the time he went home, the effects of the pill had worn off. When he was interrogated more than 36 h after taking the pill, he was behaving totally normally, so no blood or urine sampling was ordered by the coroner.

Blood and urine samples were obtained from all the other survivors (cases 2–7) and all were positive for tetrahydrocannabinoic acid. The MTA levels found in the blood and urine samples and the estimated number of pills ingested are presented in Table 1. The MDMA levels were < 0.1 μg/ml.

The police searched the residence where the event took place, as well as the cars, pockets, purses, etc. of all the persons involved. A few pills were found in the residence. The yellow pills, weighing 345 mg, contained 28% or 97 mg MTA. In addition, a small amount of an unknown product, possibly 1-(4-methylthiophenyl)propene or 1-(4-methylthiophenyl)-2-propene, was found. This compound was present in the pills in less than 0.5% of the MTA peak area in the chromatogram and could not be quantified due to the absence of a reference standard.

Materials and methods

Analytical procedures

The 4-MTA reference material was supplied by the Wetenschappelijk Instituut Louis Pasteur in Brussels, Belgium. The reagents and chemicals were of analytical grade. The drug standards and the internal standards were obtained from commercial suppliers (Sigma, Radian).

Biological samples

Routine systematic toxicological analyses were performed on the samples to investigate for illegal drugs, medical drugs, alcohol, volatile substances and other poisons. Immunoassay screening (ADx) was performed to test for amphetamines, cannabinoids, opiate groups, methadone and cocaine metabolite in urine and barbiturates, salicylates, tricyclic antidepressants and benzodiazepines in blood. Radio-immunoassay (RIA) was used to screen for LSD in urine and benzodiazepines in blood. Colour spot tests on urine and gastric content were used to detect salicylates, acetaminophen, phenothiazines and imipramines. Post-mortem blood was analysed for the presence of carboxyhaemoglobin and cyanide. Urine was screened for the presence of acidic, neutral and basic drugs by thin-layer chromatography. Gas chromatography/mass spectrometry (GC/MS ion trap) was used to screen urine samples for the presence of basic drugs. Blood was screened by high-performance liquid chromatography with photodiode-array detection (HPLC/DAD). Analysis for the presence of alcohol and other volatile substances in blood and urine was performed by head-space gas chromatography with a flame ionisation detector (GC/FID). The UV spectrum of 4-MTA obtained by HPLC/DAD was characterised by a strong absorption at 253 nm and 4-MTA was confirmed by GC/MS monitoring ions at m/z 44, 138, 165 and 182.

For the quantitation of 4-MTA in blood, 1 ml of water was added to 1 ml of a sample or a spiked blood standard and then 100 μl of 3% sodium hydroxide (w/v) was added, along with 20 μl of diphenylamine as an internal standard and 6 ml of diethylether. After mixing and centrifugation (10 min, 1,121 *g*), the organic phase was separated and transferred to a new 10 ml glass screw-top tube. The ether was then mixed with 0.025 M HCl, the ether was discarded and the ether remaining in the aqueous phase was evaporated using nitrogen at room temperature. The extract was submitted for HPLC/DAD analysis. The correlation coefficient of the calibration curve was 0.9996, recovery for 4-MTA 82% (Cordonnier and Coopman, personal communication).

Illicit preparation

The yellow powder was finely pulverised. The quantitation of MTA was performed with HPLC/DAD (Varian) monitored at 254 nm: 10 mg amounts of the powder were dissolved in 1 ml of methanol, then diluted with the mobile phase acetonitrile-buffer containing an external standard (diphenylamine 20 μg/ml) and then separated by chromatography on a Lichrocart cartridge column (125 × 4 mm i.d., 4 μm) filled with Superspher 10 RP-18 packing [14]. Standards (10–100 μg/ml) containing a constant amount of the same external standard were prepared in the mobile phase. The concentration was calculated by comparing the peak area of the drug to the external standard versus the standard calibration curve (r = 0.9998).

Identification of the contaminant was achieved by a GC/MS Saturn III ion trap (Varian). All GC/MS analyses were performed using a 0.25 mm i.d. × 30 m fused silica capillary column coated with 0.25 μm of 5% phenyl/95% methyl-silicone. The injector was set at 250 °C. The GC oven programme consisted of 70 °C for

2 min, 70–290 °C at 12 °C/min maintained for 5 min. Helium was used as the carrier gas, with an inlet pressure of 275 kPa. Mass spectra were obtained at 70 eV. Ethyl acetate was used as the solvent instead of methanol in order to exclude the possibility of the formation of methylated analytical artefacts inside the injection port of the gas chromatograph.

The contaminant was identified as possibly 1-(4-methylthiophenyl)propene or 1-(4-methylthiophenyl)-2-propene.

Discussion

We report seven more or less serious and one fatal intoxication involving a relatively new amphetamine analogue, 4-methylthioamphetamine, also called *para*-methylthioamphetamine. To our knowledge, there are only rare reports in the literature of such intoxications [1, 12, 13] and the analytical profile of 4-MTA was recently described [9]. As the event took place near the border with the Netherlands, the source of the product could probably be traced to that country.

As MTA is a new "designer drug", there is no consensus concerning the toxic or lethal blood concentrations. In our fatal case, the 4-MTA blood level established (8.38 μg/ml) was higher than in the previously reported case which had peri- and post-mortem MTA levels of 4.2 μg/ml and 4.6 μg/ml, respectively [1]. Compared to other amphetamine-related compounds, the author assumed that MTA blood levels exceeding 4 μg/ml can potentially result in death, or at least constitute a serious health risk [1]. However, guidelines indicate that blood MTA levels of 0.2–0.6 μg/ml result in moderate toxicity, levels higher than 0.6 μg/ml cause dangerous toxicity and levels exceeding 1.5 μg/ml can lead to death [12]. We believe that in our fatal case, there will be no argument that the detected MTA concentration in subclavian blood (8.38 μg/ml) was capable of causing death. However, assuming we can believe the statements of his girlfriend, the man claimed to have taken 15 MTA pills at once a few months prior to his death and survived without medical intervention.

Compared to MTA, blood PMA levels greater than 0.5 μg/ml are likely to be associated with toxic effects [11]. As for MDMA, there is also no consensus about the lethal blood level but in general, a blood MDMA concentration higher than 1.0 μg/ml can be potentially lethal, whereas levels lower than 0.6 μg/ml are capable of inducing intoxication [15]. However, there is a considerable range in reported fatal blood MDMA levels [16, 17, 18]. Furthermore, some toxic effects could also be related to contaminants [19].

A number of studies have been carried out on the content of clandestine tablets containing amphetamines, analogues and various possible impurities [e.g. 20, 21, 22, 23]. Various analytical techniques have been proposed as a means of identifying the drugs incorporated in tablets or powder and capillary electrophoresis has been established as a rapid method for qualitative and quantitative determination [24]. In the pills taken by our cases only a small amount of an unknown product – possibly 1-(4-methylthiophenyl)propene or 1-(4-methylthiophenyl)-2-propene – was found. This product was recently also identified by Kirkbride et al. [25]. This may indicate that the illicit 4-methylthioamphetamine might be derived from this compound, since a shipment of 1-(4-methylthiophenyl)-2-propene was recently seized in Europe [9].

All the persons involved in this report took pills probably having the same content. In addition, in some of our surviving cases, an obvious inconsistency between the MTA levels detected and the described clinical symptoms can be noted. For example, case 4 had an MTA blood level of 2.08 μg/ml and showed relatively less obvious symptoms than cases 2 and 6, with MTA blood levels of 0.63 and 1.26 μg/ml, respectively. In contrast to cases 2 and 6, case 4 did not require a 24- h-period of observation in hospital. Furthermore, case 7 showed the lowest MTA blood level. She took at least 2 pills, but had vomited a lot. In addition, although she admitted being addicted to marijuana and stimulating drugs, including speed and "MTA-1", it seems somewhat bizarre that she became so sick after taking the pills. Thus, the obvious differences in individual responses to MTA must be taken into consideration. This fact is substantiated by the report of de Boer et al., who reported a patient who suffered from amnesia and other problems during a 2-week-period following the ingestion of a single pill [13]. However, the possibility cannot be excluded that adverse reactions may occur due to contaminants. In addition, all of them had smoked marijuana followed by the intake of MTA so we cannot exclude the possibility that the MTA effect was enhanced by the simultaneous intake of cannabinoids.

Pharmacological and toxicological information for MTA in the literature are scarce, but it is clearly not a safe product. Moreover, although it is too speculative to draw a correlation between the ingested amount declared by the persons involved and the corresponding blood and urine concentrations, we believe that individually different rates of metabolism and/or excretion of the product cannot be excluded. For amphetamine and d-methamphetamine, the urinary excretion is pH-dependent and it has previously been established that acidification increases the level retrieved [26]. In our cases, the persons with the lowest urinary pH, cases 6 and 7 for example, showed the highest urinary MTA levels.

Since MTA is a relatively new amphetamine derivative and the number of reported poisonings is limited, the pathology findings and the mechanism of death due to this product have not yet been fully evaluated. The side-effects of MTA are probably comparable with those reported after MDMA intake, being mainly related to the sympathicomimetic and neurotoxic effect of "ecstasy", but multi-organ failure including acute hepatic decompensation and/or renal failure (due to rhabdomyolysis) should also be considered [27]. Some of the frequently reported sympathicomimetic effects include tachycardia, tremors, palpitations, diaphoresis, paraesthesias, trismus and bruxism [28] and the symptoms described for M. by his friends were similar. The different experiences of the survivors, such as agitation (see cases 1 and 6) or insomnia (see cases 3, 7 and 8), have previously also been reported after MDMA intake [29].

The mechanism of death in this case remains uncertain. The pathology of seven deaths associated with MDMA

and MDEA abuse has been described and involves centrilobular liver cell necrosis, catecholamine-induced myocardial damage and injuries caused by hyperthermia [19]. Fineschi et al. described a fatal case following MDMA and MDEA intake that presented a morphological picture consistent with hyperthermia and disseminated intravascular coagulation (DIC) [30]. In our case, the rectal temperature of 35 °C measured at the scene 4 h after death, makes hyperthermia unlikely. In addition, the fact that the brain weighed 1,320 g is not consistent with hyperpyrexia. Moreover, none of the above-mentioned microscopical findings were established, and neither were there any particular arguments for multi-organ failure. "Ecstasy" ingestion and sudden cardiac death has previously been reported, although the deceased in this particular case had a history of Wolff-Parkinson-White (WPW) syndrome [17]. In view of our autopsy findings a fatal cardiac arrhythmia should be considered as a possible mechanism of death. However, fatal epileptic insults cannot be excluded. The mechanism could perhaps be compared with epilepsy-related cardiac shock due to activation of the autonomic nervous system [31]. Finally, only a few microscopical signs consistent with chronic drug abuse were noted: eosinophilic infiltration in the lymph nodes and a somewhat decreased number of Purkinje cells in the brain, as well as atypical perivascular lymphocyte infiltration and siderophages in the nucleus lentiformis.

As 4-methylthioamphetamine is a fairly recent "designer drug", the medico-legal implications of these cases of intoxication are of considerable importance. Indeed, at the time this incident occurred, MTA was not included on the list of forbidden drugs. As MTA at present is still not a registered illegal drug, it is very difficult to prosecute dealers. In our case, incidentally, the dealer himself died.

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