

Lethal monointoxication by overdosage of MDEA

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Abstract

A 19-year-old man died after the intake of ten tablets of Ecstasy containing 3,4-methylenedioxy-*N*-ethylamphetamine (MDEA) as the main active ingredient. According to an eyewitness the symptoms of intoxication were strong sweating, sudden aggressiveness followed by hallucinations, subsequent failure of motoric coordination, severe spasms of arms and back, complete depression of the respiratory system, unconsciousness, and collapse. Resuscitation by an emergency doctor failed. Major autopsy findings were severe vascular congestion of all internal organs, liquid post-mortem blood, numerous subpleural and subepicardial petechial haemorrhages. By GC/MS analysis, MDEA was found in large amounts in serum (12 mg/l in femoral vein, 22 mg/l in heart blood serum), urine (201 mg/l), brain (18 to 28 mg/l) and in other tissue samples. Scalp-hair was highly positive for MDEA (17 ng/mg). Besides MDEA and its metabolites only trace amounts of MDMA could be found in urine and blood; no other drugs were detected. It can be concluded that the cause of death was a monointoxication by overdosage of MDEA. © 1998 Elsevier Science Ireland Ltd.

Keywords: Ecstasy; 3,4-methylenedioxy-*N*-ethylamphetamine; Tissue distribution; Overdose; Hair analysis; Symptoms of intoxication

1. Introduction

Originally the term “Ecstasy” (also called “XTC”, “Extasy” or “Adam”) was used only for the substance 3,4-methylenedioxy-*N*-methylamphetamine (MDMA); currently it is also commonly used for other designer drugs of the methylenedioxyphenylalkylamine type such as 3,4-methylenedioxy-*N*-ethylamphetamine (MDEA, “Eve”) or 3,4-methyl-

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enedioxyamphetamine (MDA). In the last few years Ecstasy has been consumed mainly at techno-parties, where dancers use it as a stimulant to stand the rigors of raves lasting up to several days. Recently, its popularity has greatly increased, and it is assumed that the number of people having used Ecstasy has tripled in the last five years [1]. Consumed in low doses the effects of MDMA, MDA and MDEA are described as follows: heightening of awareness, enhanced perception, increased drive, brighter mood, feeling of a “separation of body and mind”. Adverse effects include nausea, confusion, muscular pain, stiffness, motoric disturbances, concentration problems, occasionally also hallucinations, problems in thinking and speaking, hypertension and raising of body temperature as well as loss of appetite [2].

Ecstasy is considered “harmless” among users. This is a false assumption as proven repeatedly: besides fatal traffic accidents which are caused by changes in perception, and lethal intoxications involving other drugs or alcohol, an increasing number of cases has been reported lately ranging from direct organic lesions to death. In several cases toxic liver necrosis [3–5] as well as hyperthermia, partly associated with rhabdomyolysis, disseminated intravascular coagulation and renal failure were reported [3,6–9]. Further complications described in individual case reports include hyponatraemia [10,11], catatonic stupor [10,12], intracerebral haemorrhage [13], subarachnoid haemorrhage [14,15], intracranial sinus thrombosis [16], or ischaemic cerebral infarction [17].

Pharmacological studies of the action of MDMA on the central nervous system performed on animals and humans revealed a toxic effect on serotonergic neurons [18–20]. It is assumed that related substances have a similar pharmacological mechanism.

Intoxications with MDMA or MDEA cannot be differentiated clinically [21], but can be differentiated easily by toxicological analysis of urine and blood samples. A general-unknown screening of urine, serum and stomach contents using GC/MS has been described by Mauer et al. [22]. The metabolism of methylenedioxyphenylalkylamines has been investigated in humans and rats and mass spectral data are available for the identification of their metabolites found in urine [22–26].

With the following case report a lethal monointoxication by MDEA is presented.

2. Case report

A 19-year-old man consumed ten tablets of Ecstasy in his apartment at irregular intervals from approximately 9 p.m. to 5 a.m. According to the statement of an eyewitness, his girlfriend, who also took three of these tablets with “hammer” and “sickle” imprinted, the tablets were “extremely strong”. After consumption of the eighth tablet the psychostimulating effect of the drug decreased rapidly. In order to overcome this he consumed two more Ecstasy tablets.

Some minutes later he began sweating profusely, trembling and experiencing severe spasms of the back. He was unable to walk without support. Then he suddenly became aggressive and started shouting and talking to people who were not present. His girlfriend helped him to bed, but he fell out. He found breathing increasingly difficult. His head was flexed backward with neck and back being completely stiff. At that time

he was unable to speak; his face was distorted, his arms flexed and cramped. An emergency doctor was called. Shortly afterwards the young man suddenly started retching and salivating, with whitish foam flowing from his mouth, before he became unconscious. The young woman and another young man living in the flat tried to resuscitate him by exerting pressure on his chest. Mouth-to-mouth resuscitation was not carried out. When the emergency doctor arrived shortly afterwards, the young man was unconscious, without respiration and pulse and showed wide, fixed pupils. In spite of resuscitation measures (repeated electric defibrillation; drugs: atropine 5 mg, suprarenin 10 mg) over a 35-min period no cardiac action could be achieved.

3. Autopsy results

The autopsy was performed 29 h after death was determined. The major internal findings were as follows: severe vascular congestion of all internal organs; liquid post-mortem blood; numerous subpleural and subepicardial petechial haemorrhages; focal emphysema of the lung; bronchial content watery, foamy, and somewhat mucid; no traces of tablets visible in the content of the stomach.

3.1. Histology

Pulmonary oedema with pronounced vascular congestion and severe vascular congestion of the internal organs were found. Neither inflammatory changes of the liver nor pathological changes of the myocardium could be observed.

4. Materials and methods for toxicological analyses

4.1. General-unknown analysis

General-unknown screening of serum, urine and gastric contents for drugs and poisons was performed by GC/MS using neutral and alkaline liquid–liquid extraction (ethyl acetate: diethylether, 1:1, v/v) and acidic urine-hydrolysis followed by basic liquid–liquid extraction (ethyl acetate: dichloromethane: 2-propanol; 3:1:1; v/v/v) as described by Maurer et al. [26,27]. For the analysis, 2 ml urine, 1 ml serum and 1 ml gastric content were used. Urine was hydrolysed (acidification with hydrochloric acid and 30-min reflux) and the extract acetylated (100 μ l acetic anhydride/70 μ l pyridine, 60°C for 30 min). After solvent evaporation, the extracts of urine, serum and gastric content were redissolved in 50 μ l, 100 μ l and 1 ml ethyl acetate, respectively. GC/MS conditions using a Hewlett-Packard GC/MS System (GC 5890 and MSD 5970) were as follows: 1- μ l splitless injection, capillary column: DB5-ms 30 m $\times$ 0.25 mm i.d., 0.25 μ m film thickness (J&W Scientific), injector: 270°C, capillary interface: 280°C, temperature gradient: 3 min constant at 100°C, 30°C/min to 310°C, 8 min at 310°C; scan: 50–550 amu, 1 scan/s. The mass-spectra library of Pflieger et. al. was used for the

identification of drugs and metabolites by their electron-impact mass spectrum [26] (see Fig. 1).

Furthermore, an immunological screening for opiates, cocaine-metabolites, amphetamines, cannabinoides, LSD, benzodiazepines, barbiturates and methadone was performed with either fluorescence-polarization-immunoassay or radio-immunoassay. Urine was analyzed with an automated HPLC system (Bio-Rad, München/Germany). Blood and urine were also analyzed for ethanol with head space GC and with an alcohol-dehydrogenase method.

4.2. Quantitation of MDEA in body fluids and tissue samples

Body fluids and tissue samples (heart blood and femoral venous blood serum, urine, gastric contents, bile, liver, kidney, cerebellum and cerebrum) were analyzed specifically for amphetamine derivatives by GC/MS using deuterated standards (amphetamine-D5, methamphetamine-D5, MDMA-D5, MDA-D5, MDEA-D5; Radian/Promochem, Wesel/Germany). Tissue samples were homogenized using an Ultra-Turrax homogenizer. Fifty μl of a methanolic solution of the five deuterated standards (2 ng/ μl each) were added to a total of 1 ml of homogenized material diluted with phosphate buffer (0.1 M NaH_2PO_4 , pH 6.0).

For calibration, methanolic mixtures of 25 to 1000 ng of the amphetamine derivatives were spiked with 50 ng of deuterated amphetamine derivatives each, derivatized by incubating with trifluoroacetic anhydride (30 min, 60°C) [28] and analyzed by GC/MS in selected ion monitoring mode (see Table 1). Linear calibration curves were obtained in this concentration range. Samples were diluted with a phosphate buffer (see Table 2) prior to the addition of deuterated standards, to obtain analyte-to-standard ratios which were in the linear range of the calibration curves.

Solid-phase-extraction (SPE) was performed using mixed-mode solid-phase extraction columns (Chromabond Drug 200 mg, Macherey-Nagel, Düren/Germany) [29,30]. Columns were preconditioned by rinsing with methanol and phosphate buffer (pH 6), the sample was slowly applied onto the column and rinsed subsequently with 2 ml water, 1 ml 0.1 M acetic acid and 2 ml methanol. After drying the column elution was performed by adding 1.5 ml of dichloromethane/2-propanol/25% ammonia solution (80:20:2; v/v/v). The solvent was evaporated, the residue was trifluoroacetylated and was reconstituted in 100 μl ethyl acetate. One microlitre was analyzed by splitless-injection with a GC/MS system (MD800, CE Instruments). Chromatographic separation was performed with a DB-5 ms capillary column (see above) with a modified temperature gradient (2 min at 60°C; 30°C/min to 310°C; 7 min at 310°C, injector 250°C, interface 250°C). The masses monitored are shown in Table 1.

Hair-analysis for amphetamine derivatives was performed using a modified method described by Skopp et al. [31]. Hair was cut distal from the scalp (0.2–3.0 cm). This hair segment was washed with methanol and water (five times each). The dried hair sample was powdered with a nitrogen-cooled ball-mill. The hair sample was weighed (22 mg) and 2 ng of the deuterated standard-mixture (see above) were added per milligramm of hair sample. Extraction of the powdered hair-sample was performed by incubation with 2 ml 0.6 M hydrochloric acid for 1.5 h in an ultrasonicator bath at 40°C (Bandelin,

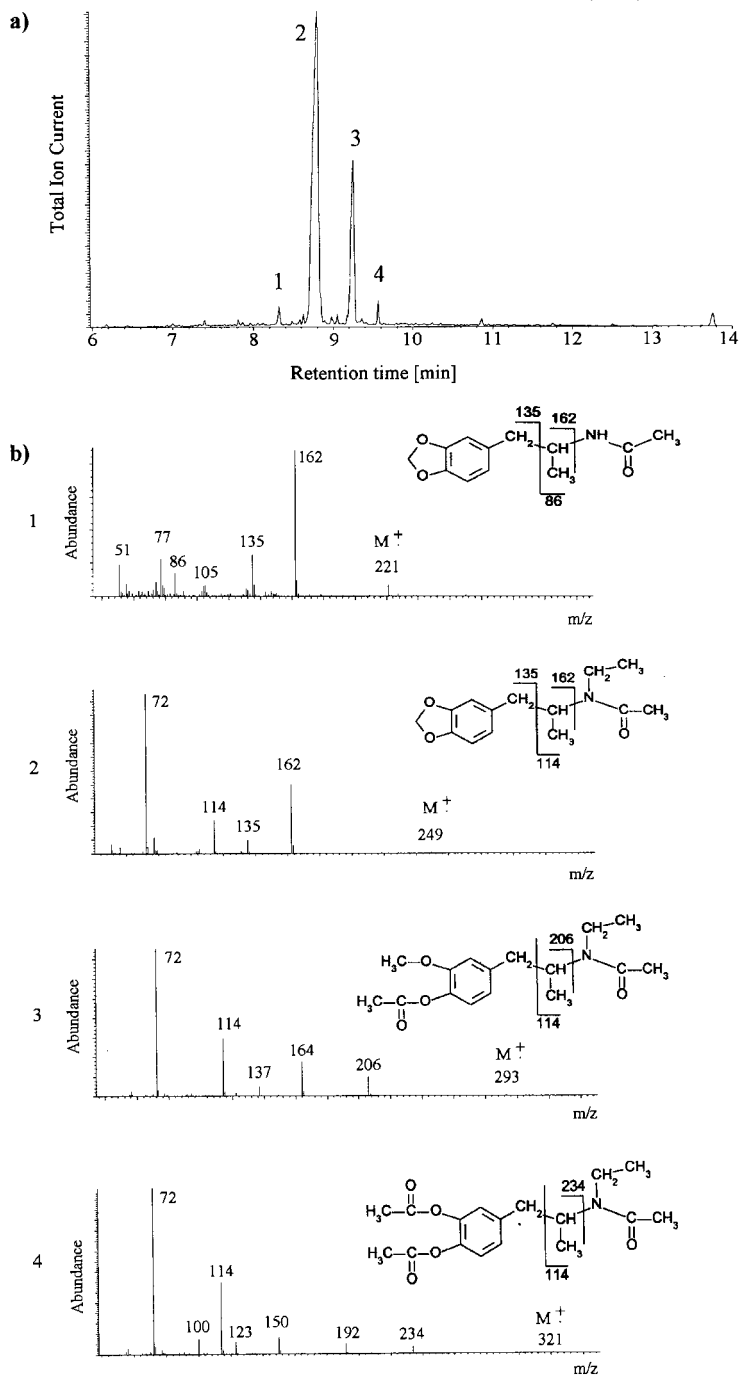


Fig. 1. (a) Chromatogram of the urine extract after acidic hydrolysis and acetylation acquired by GC/MS in full scan-mode; (b) mass-spectra of the major components of the acetylated urine extract [chromatographic peaks numbered with 1 to 4, see (a)].

Table 1
m/z-values for the GC/MS-analysis of the nondeuterated and deuterated amphetamine derivatives

Trifluoroacetylated derivative of	<i>m/z</i> -values (nondeuterated/ deuterated)	Retention time (min)
Amphetamine/ amphetamine-D5	118/122 <u>140/144</u>	6.7
Methamphetamine/ methamphetamine-D5	110/113 118/120 <u>154/158</u>	7.5
MDA/MDA-D5	162/167 <u>275/280</u>	9.0
MDMA/MDMA-D5	110/113 154/158 <u>289/294</u>	9.8
MDEA/MDEA-D5	168/173 <u>303/308</u>	10.1

Underlined *m/z*-values were used for quantitation, all other *m/z*-values were used as qualifiers.

Berlin/Germany). After centrifugation the supernatant was adjusted to pH 6 by addition of 2 ml 0.6 M NaOH and 2 ml phosphate buffer and then extracted by solid-phase extraction (see above).

Qualitative and quantitative analysis of an Ecstasy tablet found at the victims apartment was performed by GC/MS, using external standard calibration with acetylated MDEA (acetylation and GC/MS analysis with a MSD 5970 see above). Mass spectra were acquired in full-scan mode, extracted ion-chromatograms of acetylated MDEA (*m/z*-values 72, 135 and 162) were used for quantitation.

Table 2
Concentrations of the amphetamine-derivatives in the autopsy specimens

Autopsy specimen	MDEA-concentration (dilution factors) ^a	MDA-concentration	MDMA-concentration
Femoral vein serum	12 mg/l (1:20)	0.32 mg/l	0.016 mg/l
Heart serum	22 mg/l (1:20)	0.34 mg/l	0.02 mg/l
Urine	201 mg/l (1:200)	7.1 mg/l (1:50)	0.135 mg/l
Gastric content	52 mg/kg (1:100)	1.5 mg/kg (1:25)	n.d. ^b
Liver	30 mg/kg (1:100)	n.d.	n.d.
Kidney	15 mg/kg (1:100)	n.d.	n.d.
Bile	19 mg/kg (1:100)	0.44 mg/kg (1:10)	n.d.
Cerebrum	28 mg/kg (1:50)	0.65 mg/kg (1:10)	n.d.
Cerebellum	18 mg/kg (1:50)	0.51 mg/kg (1:10)	n.d.
Hair	17 ng/mg	0.3 ng/mg	n.d.

^a The dilution factors of sample with phosphate buffer prior to quantitative analysis using deuterated internal standards are listed in parentheses.

^b n.d. not detected.

5. Results of the toxicological analyses

MDEA could be detected in large amounts in all autopsy specimens and in the hair-sample using GC/MS. In the acetylated extract of the hydrolysed urine sample acetylated MDEA was the largest signal detected besides hydrolysed and acetylated MDEA-metabolites (3,4-methylenedioxyamphetamine (MDA); 4-hydroxy-3-methoxy-*N*-ethylamphetamine (HME); 3,4-dihydroxy-*N*-ethylamphetamine (DHE) [22,26,32]. The total ion-chromatogram of the acetylated extract of hydrolysed urine and the mass spectra of the major components identified by mass-spectra library search are shown in Fig. 1 [26,32]. In addition to MDEA and its metabolites low concentrations of MDMA could be detected in urine and serum through specific GC/MS analysis for amphetamine derivatives. The concentrations of MDEA, MDA and MDMA in the autopsy specimens, which were determined through GC/MS analysis using deuterated standards, solid-phase extraction and trifluoroacetylation, are listed in Table 2. Amphetamine and methamphetamine could not be detected in any sample.

Atropine which was given by the emergency doctor was detected in serum through GC/MS and HPLC analysis, but no atropine was found in urine. Immunological screening tests were positive for amphetamines and negative for all other tested drugs. The analysis for ethanol was negative. No other exogeneous substances could be detected in any sample.

The active contents of the tablets (imprinted: hammer and sickle) were MDEA and trace amounts of MDMA besides pharmacologically inactive ingredients. The MDEA content was approximately 130 mg/tablet.

6. Discussion

In contrast to the numerous reports and reports on MDMA there are relatively few published reports on MDEA intoxications. Tehan et al. [33] presented the case of a patient with hyperthermia, rigor, rhabdomyolysis and disseminated intravascular coagulation after ingestion of MDEA. Woods and Henry [34] also reported on MDEA-induced hyperthermia, while Gouzoulis et al. [35] described a case of toxic psychosis. Thus far deaths following the ingestion of MDEA have rarely been published (see Table 3).

Hyperthermia, which was frequently reported with Ecstasy intoxications (both MDMA and MDEA), could be responsible for the histologically detectable organic lesions and also for the death of the consumers – at least in some cases. Milroy et al. [5] drew parallels between the pathological organic changes in seven Ecstasy related deaths and the findings following heatstroke (centrilobular necrosis of the liver, contraction band necrosis and individual myocyte necrosis of the myocardium). These findings were compared with those of Kew et al. [36], who regularly found liver necrosis on examining deaths by heatstroke in black goldmine workers who worked under high temperatures and humidity. As the authors justly stated, these working conditions are not dissimilar to the external conditions in a disco. Another comparison with histologically detectable changes of the liver in caucasian recruits, who died of heatstroke, showed however, that in these cases liver changes were less common [37].

Table 3
Comparison of published intoxications involving Ecstasy

Authors	Age (sex)	MDEA-concentration in blood	Other compounds	Circumstances of the case
Dowling et al. [41]	21 (m)	2.0 mg/l	Propoxyphen 0.26 mg/l Norpropoxyphen 1.0 mg/l	Found unconscious after the ingestion of three Ecstasy tablets
Dowling et al. [41]	25 (m)	0.95 mg/l	Butalbital 0.8 mg/l	Traffic accident
Cox and Williams [21]	22 (m)	0.3 mg/l	MDMA 0.43 mg/l MDA 0.25 mg/l	Collapsed after attending a rave disco
Milroy et al. [5]	24 (m)	0.187 mg/l	Amphetamine 0.453 mg/l	Collapsed dead in disco
Forrest et al. [42]	21 (m)	3.5 mg/l	MDMA 2.1 mg/l MDA 8.5 mg/l Amphetamine 0.256 mg/l	Found dead in his bed
Own case	19 (m)	12 mg/l (femoral vein serum) 22 mg/l (cardiac serum)	0.320 mg/l MDA 0.016 mg/l MDMA (femoral vein serum) 0.340 mg/l MDA 0.020 mg/l MDMA (cardiac serum)	Died at home after the ingestion of ten MDEA-tablets

In contrast to many case reports published so far, in which Ecstasy was taken in the course of a party or a disco visit and where the physical exertion is an additional factor for a rise in body temperature, the case presented here does not show any external reasons for hyperthermia. The eyewitness stated, however, that shortly after her boyfriend had taken the tenth tablet he suddenly started sweating combined with trembling and muscular spasms; these symptoms were frequently described with MDMA- and MDEA-intoxications as well as with hyperthermia of other genesis [38]. In fact the emergency doctor did not find a markedly increased body temperature. Unfortunately the rectal temperature was not measured during the investigations following the determination of death either. The histologically detectable organic changes of the heart and the liver [5,39] could not be found in our case: the liver only showed severe acute sinusoidal congestion, whereas the heart was without any pathological findings.

The lungs, however, not only showed oedema with pronounced vascular congestion, but also focal signs of an acute emphysema and numerous subpleural haemorrhages, as they may occur in suffocation. According to the statement of the eyewitness, the young man was lying on his back with his head flexed backward for a prolonged period of time and also lost consciousness in this position. He was not moved into a lateral recumbent position and no mouth-to-mouth resuscitation was carried out. It is therefore possible

that respiration was mechanically obstructed in the agonal phase, as the tongue blocked the pharynx when he lost consciousness and the protective reflexes no longer worked.

In contrast to all published case-reports (see Table 3), where MDEA was detected in combination with other amphetamine derivatives or other drugs in the autopsy specimens, in the case reported here, MDEA was the predominant amphetamine derivative found in body liquids and tissues, as well as in the Ecstasy tablets. MDMA was only present in trace amounts in the body liquids and in the tablets. MDA, which was detected in low concentrations (<3% of the concentration of MDEA) in serum and urine, is an active first-pass metabolite of MDEA. In urine the major metabolites of MDEA could be found, while MDEA was the predominant compound. This reflects the prolonged intake of several Ecstasy tablets – presumably ten tablets (1.3 g MDEA) over a time-period of 8 h as reported by an eyewitness. Quantitation of MDEA in tissue-samples shows, that MDEA concentrations in the cardiac blood and the brain are higher than the concentrations in the femoral venous blood, which is in accordance with data found for MDMA intoxications [40]. The analysis of the deceased's hair, which was highly positive for MDEA, showed that he must have consumed MDEA repeatedly in the weeks before his death. Due to the low concentrations of MDA and MDMA and due to the absence of other drugs or other toxic substances, it can be concluded that this case was a monointoxication by overdosage of MDEA.

7. Notation

MDA, 3,4-methylenedioxyamphetamine

MDMA, 3,4-methylenedioxy-*N*-methyl amphetamine

MDEA, 3,4-methylenedioxy-*N*-ethylamphetamine

GC/MS, gas chromatography–mass spectrometry

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