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'ADAM' or 'EVE'? — a toxicological conundrum

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Abstract

The 3,4-methylenedioxy ring-substituted amphetamines, including 'ADAM' and 'EVE', are currently popular drugs of abuse. Adverse reactions are reported in the clinical literature but few fatal cases are documented and little toxicological data is available to guide those determining the cause or manner of death in such cases. We report two deaths presenting in a similar manner and with similar clinical features. Various body fluid samples were analysed for amphetamines by gas chromatography/mass spectrometry. In one case, amphetamine alone was detected at levels of 1.54 mg/l and 1.47 mg/l in postmortem blood and admission serum, respectively. The other involved several 3,4-methylenedioxy ring-substituted amphetamines, namely MDA, MDMA and MDEA, at levels of 0.25 mg/l, 0.43 mg/l and 0.3 mg/l, respectively in postmortem femoral blood and 0.24 mg/l, 0.55 mg/l and 0.49 mg/l in admission blood. The interpretation of these toxicological results and some novel legal issues are discussed.

Keywords: Amphetamine; 3,4-Methylenedioxyamphetamines; Fatal poisoning; Culpable homicide

1. Introduction

There are a number of major difficulties encountered in the investigation of deaths associated with 'designer' and 'rave' drugs. There are few, if any, published cases of deaths directly attributed to 'EVE'. The presence of this drug and related

Abbreviations: MDA, methylenedioxyamphetamine; MDMA, methylenedioxymetamphetamine; MDEA, methylenedioxyethamphetamine.

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3,4-methylenedioxy ring-substituted amphetamines may not be detected by routine toxicological analysis. If detected, there is little background pharmacological and pharmacokinetic data available. Thus, interpretation of the findings in these cases may be problematic. We report two deaths following the ingestion of amphetamines at a night-club or 'rave' disco. The two cases presented in a similar manner and had similar clinical features. One was associated with the ingestion of amphetamine alone, the second involved several amphetamines, principally methylenedioxyethamphetamine (MDEA) or 'EVE'.

2. Cases

2.1. Case 1

The deceased was a previously fit and healthy 18 year old female (52 kg, 164 cm) who purchased amphetamine sulphate prior to attending a night-club. She was said to have taken amphetamine sulphate in the past, usually in quantities believed to be approximately 0.5 g of 3% concentration. That evening she apparently inadvertently took approximately 1.5–2 g of 8% purity amphetamine after which she spent the evening dancing, prior to collapsing. Analysis of the residue of the drugs purchased by the deceased confirmed 8% amphetamine sulphate cut predominantly with caffeine. On admission to hospital she was unconscious and fitting with a Glasgow coma scale of 3, irregular rapid respiration, supraventricular tachycardia of 180 b/min and a core temperature of 40°C. Biochemical indices disclosed a hyperkalaemia rising to 7.6 mmol/l. A diagnosis of hypermetabolic state secondary to amphetamine ingestion was made. She was pronounced dead approximately 5.5 h after admission despite intensive treatment.

The autopsy was performed approximately 9 h after death. There were signs of extensive medical intervention. Minor healing bruises were present on the right arm and the shins. There were recent scattered minor bruises and abrasions consistent with a collapse to the ground. No life threatening injuries were present. Petechial haemorrhages were present on the sclera of the left eye and a single petechial haemorrhage on the mucosa of the upper lip. The mouth, oropharynx and nares contained gastric material mixed with blood. There was bruising of the tongue. Numerous petechial haemorrhages were present on the epicardial surface of the heart, the surface of the lungs and the mucosal surface of the oesophagus. There was subendocardial haemorrhage on the septal wall of the left ventricle. Each pleural cavity contained 50–100 ml of blood stained fluid. The lungs exhibited mild pulmonary oedema (right lung: 421 g; left: 396 g). The stomach exhibited patchy gastritis including longitudinal black based erosions and contained approximately 50 ml of 'coffee-ground' material. The brain weighed 1308 g, exhibiting moderate symmetrical uncal and tonsillar herniation and moderate cerebral oedema. The other organ weights and parameters were within normal limits. No natural disease processes were identified macroscopically or microscopically.

2.2. Case 2

The deceased was a 22 year old male (75 kg, 173 cm) who was fit and well. He was believed to have smoked two joints of marihuana prior to attending a 'rave' disco, during the course of which he apparently consumed a quantity of alcohol and two and a half 'Ecstasy' tablets. No solid drugs were available for analysis in this case. He subsequently began to behave in a bizarre manner, ran out of the night-club and suffered an episode of violent shaking or muscular spasm after which he fell asleep. During the return car journey he was noted to be vomiting, shaking and hyperventilating and was conveyed to hospital. On admission, he was suffering convulsions, hyperventilating (respiratory rate of approximately 60), pulse of 160 b/min and a core temperature of 41.8°C. Investigations disclosed severe metabolic acidosis and deranged clotting factors (APPT > 180 s). A diagnosis of disseminated intravascular coagulation (DIC) was made. EEG was recorded as 'some cerebral activity present, although very abnormal'. Despite intensive treatment he was pronounced dead approximately 17 h after admission.

Autopsy was performed approximately 36 h after death and there was early decomposition shown by marbling of the skin of the shoulders. There were signs of extensive medical intervention and mild jaundice. There was oedema of the face and scattered petechial haemorrhages present on the right conjunctiva and tarsal plate. The mouth contained blood stained fluid. There was bruising of the tongue and focal subgaleal haemorrhages. Petechial haemorrhages were present on the pericardial surfaces with blood staining of the pericardial fluid. There was marked subendocardial haemorrhage affecting the septal wall of the left ventricle and scattered smaller subendocardial haemorrhages elsewhere. There were extensive petechial haemorrhages scattered over the thymus, pleural surfaces, mucosal surface of the oesophagus, serosal surface of the intestines and throughout the mesenteric adipose tissue. The airways contained copious blood stained oedema fluid. There was severe diffuse pulmonary oedema (right lung: 1153 g; left lung: 1065 g) and blood stained pleural effusions of 350–400 ml each. Blood stained fluid was present within the peritoneal cavity. The kidneys were oedematous. The brain weighed 1452 g exhibiting moderate uncal herniation and diffuse cerebral oedema. The other organs were within normal limits. No natural disease was present.

3. Materials and methods

3.1. Extraction methodology for amphetamines

All reagents and chemicals were of analytical grade or higher. The samples were extracted by a previously published method [1]. The liquid sample (1 ml) was added to a test tube containing the extraction solvent (butyl chloride/chloroform 4:1, v/v) and internal standard (phentermine, 50 μl, 5 mg/l). The samples were placed on an orbital shaker for 30 min and then centrifuged. The organic layer was transferred to a clean vial and trifluoroacetic acid anhydride (100 μl) was added. The vials were sealed and incubated at 70°C for 30 min. The solvent was removed under nitrogen at 70°C, ensuring the samples did not reach dryness.

3.2. GC/MS analysis for amphetamines

For case 1, the samples were analysed using a Perkin Elmer 8000 series gas chromatograph attached to a Perkin Elmer ITD (ion trap detector). The chromatographic column was a DB-5 (J & W Scientific, 15 m, 0.32 mm I.D., df = 0.25 μm). The carrier gas was helium. The gas chromatograph oven was programmed from 80°C (held for 1 min) to 200°C (held for 5 min) at 10°C/min. The injector temperature was 250°C. The transfer line from the gas chromatograph was held at 250°C. The instrument was operated in the split/splitless mode with the split valve opening 2 min after injection.

For case 2, the samples were analysed using a Fisons MD800 Quadrapole mass spectrometer attached to a Carlo Erba 8000 series gas chromatograph. The chromatographic column and carrier gas employed were the same as in case 1. The gas chromatograph oven was programmed from 60°C (held for 1 min) to 200°C (held for 10 min) at 10°C/min. The injector temperature was 250°C and the transfer line from the gas chromatograph to the mass spectrometer was held at 250°C. The instrument was operated in the split/splitless mode with the split valve opening 1 min after injection. The mass spectrometer was operated in the full scanning mode, scan between 40 and 400 at 0.9 s with a 0.1 s interscan delay.

4. Results

4.1. Amphetamines

The results of analyses for amphetamine in case 1 and amphetamines in case 2 are shown in Tables 1 and 2, respectively.

4.2. Additional toxicology

In both cases, blood samples were analysed for ethanol, salicylates, paracetamol, acid/neutral drugs, non-steroidal anti-inflammatory drugs, benzodiazepines, opiates, LSD and buprenorphine; vitreous humour for ethanol; stomach contents for paracetamol, acid/neutral drugs and basic drugs and liver for basic drugs. The admission samples for case 2 were also analysed for cannabinoids. The liver sample in case 1 contained lignocaine (0.002 mg/kg), atropine (0.21 mg/kg), diazepam (0.05 mg/kg), desmethyl-diazepam (0.06 mg/kg), midazolam (2.3 mg/kg) and propranolol

Table 1
Concentration of amphetamine in fluid samples in case 1

Sample	Amphetamine (mg l)
Ante mortem samples	
Admission serum	1.47
ICU serum	1.19
Postmortem samples	
Femoral blood	1.54
Cardiac blood	1.80

Table 2
Concentration of amphetamines in fluid samples in case 2

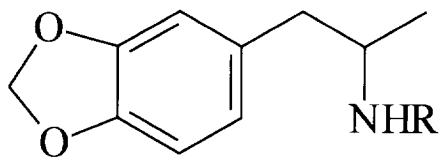
Sample	Amphetamine (mg/l)	MDA (mg/l)	MDMA (mg/l)	MDEA (mg/l)
Ante mortem samples				
Admission blood	neg.	0.24	0.55	0.49
Gastric aspirate	neg.	0.11	2.09	0.25
Admission urine	neg.	1.75	14.3	68.0
Postmortem samples				
Femoral blood	neg.	0.25	0.43	0.30

(0.38 mg/kg) and in case 2 lignocaine (1.72 mg/kg). The drugs present in the liver in both cases are consistent with medical intervention. LSD was detected by radioimmunoassay in the postmortem blood sample of case 2, but it was not possible to confirm its presence in the admission blood and urine samples due to insufficient sample. All other analyses gave negative results.

5. Discussion

Illicit manufacture of amphetamines produces street drugs containing variable concentrations of different amphetamines as well as other impurities, intermediate products and adulterants. A number of 3,4-methylenedioxy ring-substituted amphetamines are available on the streets. Their structures are illustrated in Fig. 1.

There are few, if any, recognised clinical uses for amphetamine and its related compounds, including MDA, MDMA and MDEA. Methylenedioxyamphetamine (MDA) is referred to as 'The Love Drug' by some sources [2]. Methylenedioxymetamphetamine (MDMA) is known as 'Ecstasy', 'XTC' or 'ADAM'. Methylenedioxyethamphetamine (MDEA) has the street name 'EVE'.



R = H methylenedioxyamphetamine (MDA)
R = CH_3 methylenedioxymetamphetamine (MDMA)
R = CH_2CH_3 methylenedioxyethamphetamine (MDE)

Fig. 1. Structures of some 3,4-methylenedioxy ring-substituted amphetamines.

Table 3
Summary of available toxicological information on amphetamine and its analogues

Drug	Dose (mg)	Therapeutic blood level (mg l)	Toxic blood level (mg/l)	Fatal blood level (mg l)	Min. lethal dose (mg)	Duration of action (h)
Amphetamine [3]	20–100	<0.1 (up to 3 in addicts)	0.2–3 (8.6 average)	0.5–41	200	4–6
MDA [3,4]	80–160	n.a.	n.a.	2.3–26	500	8–12
MDMA [2,4,5]	80–300	n.a.	n.a.	0.11–1.26	n.a.	4–6
MDEA [4]	100–200	n.a.	n.a.	n.a.	n.a.	3–5

n.a., Data not available.

Pharmacokinetic, protein binding and volume of distribution data is available on amphetamine [3] but similar data is not available for the 3,4-methylenedioxy ring-substituted amphetamines. Amphetamine and amphetamine analogues are sympathomimetic agents having peripheral and central alpha and beta adrenergic effects, resulting in strong stimulant cardiovascular, central nervous and anorectic activity. Acute toxicity is apparently related to the exacerbation of the pharmacological effects. The mechanism of action of amphetamine is believed to be related to a close structural resemblance to the neurotransmitters dopamine and noradrenaline. Methylenedioxyamphetamine (MDA) has hallucinogenic properties and is equipotent in its alpha adrenergic effects as amphetamine. MDMA is said not to have significant sympathomimetic or hallucinogenic effects at low doses but high doses may result in dysphoria and amphetamine-like cardiovascular affects. Animal studies indicate a different mechanism of action between MDA and MDMA and a lack of cross reactivity.

A summary of available toxicological information on amphetamine and its analogues is shown in Table 3.

Acute overdoses of amphetamine analogues have a similar clinical presentation. Deaths are related to cardiovascular, cerebrovascular and hyperthermic effects. Several authors [6–9] have remarked on the increased risk of adverse reactions when combined with strenuous physical activity such as dancing. Acute ingestions of amphetamine or MDA have been associated with hyperpyrexia, rhabdomyolisis, myoglobinuria and disseminated intravascular coagulation (DIC). Case 2 demonstrates that ingestion of MDEA and MDMA may also present in this way.

The lethal dose varies with age, route of administration and previous exposure to the drugs. Fatalities are not apparently directly linked to the size of the dose ingested, as illustrated in our cases. Interpretation of toxicological data in case reports of deaths associated with these agents may be difficult because of the presence of several drugs [10] or the attribution of death to causes other than the amphetamines detected [11]. Case 1 demonstrates that pure amphetamine deaths may be associated with postmortem blood amphetamine levels which are considerably lower than previously published fatal concentrations. It is possible that the

previously published ranges may not have taken into account the potential effects of postmortem redistribution and consequently the values may be artefactually elevated. This may cause problems in the interpretation of the cause and manner of such deaths, particularly where interpretation is based solely on comparison of postmortem blood drug levels with the published data.

Recent case law in England [12] grouped MDA, MDMA and MDEA as a single category of Class A controlled drug under the common name 'Ecstasy' for the purposes of sentencing those convicted of offences listed in Part 1 of Schedule 2 to the Misuse of Drugs Act 1971, as modified by the Misuse of Drugs Act (Modification) Order (SI 1977 No 1243). This judgement also set sentencing criteria for offences based on the assumption that each 'Ecstasy' tablet contains about 100 mg of active constituent.

The local sale of amphetamine on the streets in 1993 involved the use of £10 bags, known as a 'deal' and widely believed to contain 1 g. In reality it usually consisted of 1/3–1/2 g of 3% purity amphetamine (10–15 mg) cut predominantly with caffeine or sodium bicarbonate. In case 1, the deceased apparently purchased a 'sub-dealers purchase' of approximately 7 g for £45 in the belief that it was of the same strength as the 'deal' she had bought in the past. The 'sub-dealers purchase' is normally cut by the addition of an equal amount of sodium bicarbonate prior to division into 'deals' and street sale. The deceased was said to consume approximately one third of the amount purchased (1.5–2 g of 8% purity amphetamine, corresponding to approximately 120–160 mg of amphetamine). The dose ingested was, therefore, approximately 10 times the dose intended. The death resulted in a prosecution in Scotland for culpable homicide against the individual who sold the 'sub-dealers purchase' to the deceased. This was one of the first such prosecutions under the Criminal Procedure (Scotland) Act 1975. The accused was acquitted on the basis that there was no case to answer as the chain of causation had been broken by the action of the deceased in taking the drug. The High Court subsequently held that the trial judge had been wrong and that the causal link was not broken by the deceased's voluntary act of taking the drug [13].

In case 2, no solid drugs were available for analysis. Anecdotal evidence suggested that he had smoked two joints, consumed a quantity of alcohol and taken two and a half 'Ecstasy' tablets. Analytical results of autopsy samples do not corroborate the alleged consumption of alcohol or cannabis. Thus, the anamnestic data in this case appears erroneous and the reported ingestion of two and a half 'Ecstasy' tablets cannot be relied upon. Amphetamine was not detected in this case. The literature on the concentrations of MDA, MDMA and MDEA found in fatalities is sparse. The results of analysis suggest that MDEA may have been ingested during the early part of the evening and that a second ingestion of MDMA occurred later that night. The MDA detected likely represents a metabolite of MDEA and/or MDMA rather than ingested drug. Few, if any, deaths caused by 'EVE' have been reported. The results, however, suggest that MDEA ('EVE') is likely to have been the primary toxic agent. This case illustrates the considerable difficulties inherant in the investigation and interpretation of these deaths.

Diagnostic difficulties may also arise because of the methods used in toxicological analysis. The specificity of some immunological diagnostic kits for the determination of amphetamine is such that they may not demonstrate the presence of related compounds, including MDEA and MDMA, unless present at high concentrations. Thus, clinicians, forensic pathologists and laboratory personnel must be aware of the similarity of the clinical presentation secondary to ingestion of all these compounds, so that the appropriate analyses are performed to permit an accurate diagnosis.

6. Conclusion

These two cases illustrate how similar the clinical presentation may be in deaths related to all the amphetamines. This supports the postulated mechanism of death related to pharmacological properties common to these amphetamine analogues. These cases highlight the difficulties inherent in interpreting the results of toxicological analysis of 'designer' drugs and in determining the role of 'therapeutic' concentrations of these drugs in causing or contributing to death. This reinforces the contention that social use of any of the amphetamines carries a risk and there is almost certainly no one member of this drug group which can be considered safer than the others. It also highlights the care which must be taken in the medico-legal investigation of deaths which may subsequently be subject to judicial examination. The importance of good communications between all the agencies and individuals involved in investigating these deaths is reinforced, although the role of anamnestic data in directing these investigations must be questioned, particularly with regard to the specific toxicological analyses to be requested or performed.

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