'Eve' and 'Ecstasy'

A Report of Five Deaths Associated With the Use of MDEA and MDMA

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3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy"), a synthetic analogue of 3,4-methylenedioxyamphetamine, has been the center of recent debate over its potential for abuse vs its use as a psychotherapeutic agent. Following its emergency classification in Schedule 1 by the Drug Enforcement Administration in 1985, 3,4-methylenedioxyethamphetamine (MDEA, "Eve") has appeared as MDMA's legal replacement. MDMA is thought to be safe by recreational users and by psychotherapists who support its use. The details of five deaths associated with the use of MDMA and MDEA are reported. In three patients, MDMA or MDEA may have contributed to death by the induction of arrhythmias in individuals with underlying natural disease. In another patient, use of MDMA preceded an episode of bizarre and risky behavior that resulted in accidental death. In another patient, MDMA was thought to be the immediate cause of death. Death as a consequence of the use of these drugs appears to be rare, but it does occur; this outcome may be more common in individuals with underlying cardiac disease.

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MDMA (3,4-methylenedioxymethamphetamine, "Ecstasy"), a synthetic analogue of 3,4-methylenedioxyamphetamine (MDA), was first developed as an appetite suppressant in 1914 but was never marketed. In the early 1970s, a small number of psychiatrists began using it as an adjunct to psychotherapy, noting that it appeared to facilitate therapeutic communication, increase patient self-esteem, and limit the use of other drugs (G Greer, MD, unpublished data, 1983; Greer and Strassman[1]; and Shafer[2]).

Since 1983, MDMA has become a popular recreational drug, especially among college students. It is also known as "XTC," "Adam," and "MDM" and is sold as gelatin capsules or loose powder for $10 to $40 per 100-mg dose (*Newsweek*, April 15, 1985, p 96). Users report that the drug is a pleasant way to get in touch with oneself and that it does not produce hallucinations (*Newsweek*, April 15, 1985, p 96; *Life*, August 1985, pp 88-94; and Baum[3]).

Until July 1, 1985, MDMA was not a controlled substance and was legally available for use. At that time, the Drug Enforcement Administration placed MDMA in Schedule 1 on an emergency basis, as a drug with high potential for abuse and without accepted medical use. It was claimed that the abuse potential of MDMA was proved by its widespread use. In addition, because of the structural similarity to MDA, which had been shown to selectively damage serotonin nerve terminals in rat brains,[4] dangerous side effects were felt to be possible.

It was only later that Drug Enforcement Administration officials learned of the therapeutic use of MDMA in psychiatry. While MDMA is still available on the illicit drug market, a related drug, 3,4-methylenedioxyethamphetamine (MDEA, "Eve"), has appeared as a non-scheduled substitute for MDMA, with milder but similar effects.

MDMA is reported to be safe by psychotherapists and users (*Newsweek*, April 15, 1985, p 96, Baum[3]; and Gehlert et al[5]), but the medical literature contains few articles on MDMA or MDEA, and no controlled trials to document and investigate their clinical effects have been completed.[5] One death related to the use of MDMA has been reported in the popular media (*Life*, August 1985, pp 88-94). This article describes five patients, seen over a period of nine months (June 1985 to March 1986) in Dallas County, in which MDMA or MDEA were thought to have [illegible] contributed to death.

METHODS

All cases were examined by the Chief Medical Examiner's Office of Dallas County. Body fluid and tissue samples were screened for the presence of alkaline drugs, including MDMA and MDEA, by the method of Foerster et al.[6] Gas chromatography was used with fused methylsilicone and fused 5% phenylmethylsilicone columns connected to flame ionization detectors. Identification was based on retention times on the two columns and confirmation was by gas chromatography–mass spectrometry. MDMA or MDEA levels were quantitated by gas chromatographic comparison with known standards of these drugs. Body fluids were also screened for the presence of acid and neutral drugs, narcotics, and alcohol.

REPORT OF CASES

CASE 1.—The body of a 22-year-old man was found at the base of an electrical utility tower. He was reportedly last seen alive the previous evening when he ingested an unknown quantity of MDMA. Examination at the scene suggests that he drove his automobile to the utility tower and climbed it to a height of 13 m. At 1:28 AM, he came too close to one of the 138 000-V power lines, was electrocuted, and fell to the ground.

At autopsy, widespread burning of the clothing and the skin of the face, thorax, abdomen, and both arms was noted, consistent with his having received a high-voltage electrical shock. Other injuries, presumably sustained in the fall, included a complete atlantooccipital dislocation, rib fractures, pulmonary contusions, and lacerations of the liver.

Postmortem toxicology showed MDMA in the blood, but unfortunately, the amount could not be quantitated. No alcohol or other drugs were present.

CASE 2.—A 25-year-old man was seen by his family physician complaining of pleuritic chest pain on inspiration. Physical examination results and chest roentgenogram were unremarkable, and a follow-up appointment was arranged for the next day. While he was driving home, his truck jumped a curb and struck a telephone pole. His only apparent injury was a small laceration of the forehead, but he required cardiopulmonary resuscitation at the scene and en route to the hospital. He was pronounced dead one-half hour after the accident.

At autopsy, the only injury was a 4-cm laceration on the right side of the forehead. The proximal left anterior

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Clinical, Autopsy, and Toxicology Findings in Five Deaths Associated With MDMA and MDEA Use*

Patient No./ Sex/Age, y	Estimated Dose of MDMA or MDEA Taken, mg	Estimated Time Between Dose and Death, h	Cause of Death	Toxicology Findings
1/M/22	Unknown	<8	Electrocution and multiple injuries	MDMA present in blood
2/M/25	Unknown	Unknown	Atherosclerotic cardiovascular disease	Blood: MDEA, 0.95 mg/L (4.6 μmol/L), butalbital, 0.8 mg/L (3.6 μmol/L)
3/M/32	Unknown	Unknown	Acute asthma	Blood, MDMA, 1.1 mg/L (5.7 μmol/L)
4/F/18	160	<2	Acute MDMA intoxication	Blood: MDMA, 1.0 mg/L (5.2 μmol/L), ethanol, 40 mg/dL (8.7 mmol/L)
5/M/21	300	<12	Idiopathic cardiomyopathy	Blood: MDEA, 2.0 mg/L (9.7 μmol/L); propoxyphene, 0.26 mg/L (0.8 μmol/L); norpropoxyphene, 1.0 mg/L (3.1 μmol/L) Liver: MDEA, 4.51 mg/kg (21.8 μmol/kg) Kidney: MDEA, 2.55 mg/kg (12.3 μmol/kg) Heart: MDEA, 1.68 mg/kg (8.1 μmol/kg) Lung: MDEA, 4.54 mg/kg (21.9 μmol/kg) Spleen: MDEA, 3.23 mg/kg (15.6 μmol/kg)

*MDMA indicates 3,4-methylenedioxymethamphetamine; MDEA, 3,4-methylenedioxyethamphetamine.

descending and left circumflex coronary arteries were narrowed to less than 75% of their original area by atherosclerotic plaques, and the lumen of the right coronary artery was narrowed to a pinpoint 5 cm from its origin. The heart was not enlarged (280 g), and there was no evidence of recent or old myocardial infarction. The other organs were unremarkable.

Although the cause of death was listed as atherosclerotic cardiovascular disease, postmortem toxicology revealed 0.95 mg/L (4.6 μmol/L) of MDEA and 0.8 mg/L (3.6 μmol/L) of butalbital in the blood. No alcohol was detected.

CASE 3.—A 32-year-old man with a history of asthma was found dead beside his car. A 0.5% epinephrine inhaler was in his hand. He had been drinking alcohol with friends until two hours prior to the discovery of his body.

Postmortem examination showed gross and histologic features of acute and chronic bronchial asthma, including hyperinflation of the lungs, mucus plugging, peribronchial muscular hyperplasia, submucosal eosinophilic infiltrates, and thickening of bronchial basement membranes. The remaining organs were congested but were otherwise unremarkable.

The cause of death was attributed to asthma; however, postmortem toxicology showed 1.1 mg/L (5.7 μmol/L) of MDMA in the blood. No alcohol or theophylline were detected.

CASE 4.—A healthy 18-year-old woman ingested 1½ "hits" of Ecstasy (approximately 150 mg) and an unknown amount of alcohol within a 60- to 90-minute period. Shortly thereafter, she collapsed, and on arrival of the paramedics, she was found to be in ventricular fibrillation. She was pronounced dead after resuscitation attempts were unsuccessful.

Autopsy findings included pulmonary congestion and edema, associated with congestion of other viscera. Postmortem toxicology revealed 1.0 mg/L (5.2 μmol/L) of MDMA and 40 mg/dL (8.7 mmol/L) of ethanol in the blood.

CASE 5.—A 21-year-old man was found unconscious after ingesting three Ecstasy capsules (approximately 300 mg), one propoxyphene capsule (65 mg), and several drinks over a period of ten to 11 hours. Attempts at resuscitation were unsuccessful.

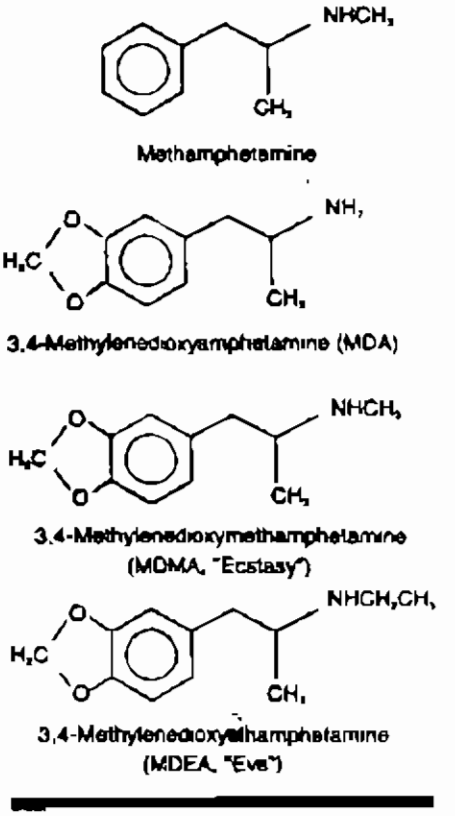
Significant autopsy findings were confined to the heart, which was enlarged (420 g) due to concentric left ventricular hypertrophy and slight dilatation. The coronary arteries contained scattered, nonocclusive, atheromatous plaques, and the valves were unremarkable. Histologically, some myocytes showed enlarged, hyperchromatic nuclei, but there was no evidence of the bizarre cells found in hypertrophic cardiomyopathy.

Given the absence of coronary atherosclerosis and valvular abnormalities and the lack of history of hypertension, the cause of death was attributed to idiopathic cardiomyopathy. Postmortem toxicology showed the following drug levels in the blood: MDEA, 2.0 mg/L (9.7 μmol/L); propoxyphene, 0.26 mg/L (0.8 μmol/L); and norpropoxyphene, 1.0 mg/L (3.1 μmol/L). MDEA levels in other body fluids and tissues are shown in the Table. No MDMA (the drug the decedent thought he was taking) or alcohol was present.

COMMENT

MDMA and MDEA are structurally related to MDA, as shown in the Figure. All three drugs share structural similarities to methamphetamine, which has sympathomimetic properties, and to mescaline, a hallucinogen. MDA was a popular drug of abuse during the 1960s, and although several deaths related to MDA overdose were reported,[1-3] these appeared to be rare occurrences.[4]

MDMA and MDEA apparently cause euphoria and enhanced sociability as MDA does,[5] but they are not thought to be hallucinogenic.[6] Both have a rapid



Structural formulas of MDMA, MDEA, and related compounds

onset of action of approximately one-half hour.[5] MDMA users describe three phases of action: an initial period of disorientation, followed by a rush during which the user experiences tingling and may exhibit spasmodic jerking motions, and finally a period of "happy sociability" (*Life*, August 1985, pp 88-94). Generally, MDMA's effects wear off in four to six hours[5]; however, confusion, depression, and anxiety have been reported by some users for several weeks after a single dose.[5]

To date, there have been no reports of MDMA- or MDEA-related deaths in the medical literature, but one death has

been described in the popular press (*Life*, August 1985, pp 88-94). The five cases reported herein and associated with MDMA and MDEA use were seen in Dallas and surrounding counties within a period of nine months (June 1985 to March 1986). In four patients, MDMA or MDEA appears to have played only a contributory role in causing death, while in the fifth, MDMA was the immediate cause of death.

Although MDMA has not been described as causing bizarre behavior (*Newsweek*, April 15, 1985, p 96; *Life*, August 1985, pp 88-94; Shafer[2]; and Baum[3]), case 1 illustrates that such behavior is possible. Although it is not possible to rule out suicidal intent, information available from relatives and friends indicates that this individual's behavior was motivated solely by his use of MDMA.

The role of MDMA and MDEA in patients 2 and 5 is more difficult to delineate, particulary in the presence of low concentrations of other drugs (butalbital in patient 2, propoxyphene in patient 5). Both individuals suffered from underlying cardiac diseases, which could have been responsible for death without MDMA or MDEA use. However, MDMA is known to have sympathomimetic actions, including mydriasis and hyperhidrosis (*Life*, August 1985, pp 88-94; Greer and Strassman[1]; Shafer[2]; and Riedlinger[10]). Although their cardiovascular effects are unknown, MDMA and MDEA may well have actions similar to their parent amphetamines, including increased cardiac output, hypertension, and induction of arrhythmias.[14] Arrhythmias are a recognized mechanism in amphetamine-related deaths,[15] and are thought to be the mechaniam of death in both patients 2 and 5.

These two cases are not unlike an MDMA-related death, reported in the popular press (*Life*, August 1985, pp 88-94) wherein an individual with known cardiac disease died suddenly, shortly after taking a large dose of MDMA. Therefore, it is possible that these drugs can induce or augment potentially fatal arrhythmias in those individuals with predisposing cardiac diseases. Clearly, this is an area that needs further study.

In patient 3, MDEA use was associated with the sudden death of an individual who had asthma. The absence of theophylline in postmortem blood samples and his use of an over-the-counter epinephrine inhaler indicate that the individual was not likely receiving adequate medical therapy. Inadequate treatment is a major finding reported in those dying suddenly of asthma,[16] so it is possible that this individual would have suffered his fatal attack even if he had not taken MDEA. Amphetamines, in general, relax bronchial smooth muscle, which would tend to argue against MDEA's playing a contributory role in initiating the acute attack.[14] However, based on the previous discussion, one cannot rule out the possibility that MDEA potentiated a cardiac arrhythmia in this individual whose cardiopulmonary function was already impaired as a result of asphyxia induced by his asthma attack.

Use of MDMA was thought to be the immediate cause of death in patient 4. This 18-year-old woman was healthy prior to her death. Autopsy revealed that she had no underlying natural disease that would predispose her to sudden death. If the witnesses to the event are reliable, she did not take an extraordinarily large amount of MDMA (approximately 150 mg). The mechanism of death was clearly a cardiac arrhythmia, as she was determined to be in ventricular fibrillation on the arrival of paramedics. The low dose of MDMA ingested resulting in sudden death may be an example of an idiosyncratic reaction, or may suggest that the toxic-to-therapeutic ratio of MDMA is low.

To our knowledge, levels of MDMA and MDEA in human blood and tissues have not previously been reported, so it is difficult to interpret the significance of the drug concentrations found. It is interesting to note that the blood MDMA level of 1.0 mg/L (5.2 μmol/L) in patient 4, where the cause of death was attributed to MDMA intoxication, is slightly lower than that in patient 3 of 1.1 mg/L (5.7 μmol/L), where an anatomic cause of death (ie, asthma) was found. At the present time, it is not known whether these represent unusually high or just "therapeutic" levels of MDMA. The tissue distribution of MDEA in patient 5 shows the highest concentrations of this drug in liver and lung. Amphetamines are metabolized in the liver and are also excreted in the urine in varying proportions, depending on urine pH.[14] Metabolism of MDEA in the liver may account for the relatively high levels found in this organ; however, the significance of the high lung and lower kidney concentrations is unknown.

Unfortunately, these five cases do little to resolve the present controversy as to the abuse potential and dangers of MDMA and MDEA vs the possible therapeutic usefulness of MDMA in psychotherapy. Deaths directly and indirectly related to the use of MDMA and MDEA do occur; however, they appear to be rare at this time. Their rarity is confirmed by the recently published statistics of the Drug Abuse Warning Network for 1985. Neither MDMA nor MDEA was included in the list of drugs found most frequently by 73 medical examiner facilities across the United States (drugs reported less than 10 times were excluded from this list).[17] It would appear that preexisting cardiac disease may be one factor that predisposes individuals to sudden death while using these drugs. It is hoped that the reporting of these cases will inaugurate a search for more objective information about MDMA and MDEA.

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