5. HUMAN DEATHS AND TOXIC REACTIONS ATTRIBUTED TO MDMA AND MDEA

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1. INTRODUCTION

3,4-Methylenedioxymethamphetamine (MDMA) and 3,4-methylenedioxyethamphetamine (MDEA) are synthetic amphetamine analogues that have received considerable media attention as recreational drugs popular among college students and young professionals. MDMA, more commonly known as "Ecstasy," has been available on the illicit drug market since 1968 [1], with increasing popularity in the late 1970s and early 1980s. On the other hand, MDEA, also known as "Eve," has only started to gain prominence since the placement of MDMA on Schedule I of the Controlled Substance Act by the Drug Enforcement Administration (DEA) on July 1, 1985. MDMA has been investigated by a small number of psychiatrists for its potential use as a psychotherapeutic agent. Uncontrolled trials of MDMA in clinical settings seem to indicate that it helps to facilitate therapeutic communication and increase patient insight and self-esteem [2, 3]. MDMA in the hands of psychiatrists and both MDMA and MDEA among those who use them recreationally have generally been regarded as safe drugs with some minor short-term side effects [3–5]. Indeed, from 1977 to 1985 the Drug Abuse Warning Network (DAWN) reported only eight admissions to emergency rooms, across the United States, for treatment of individuals who claimed they had taken MDMA [6]. When one considers that the prevalence of MDMA use has been estimated at 10,000 doses nationally in 1976 to more current estimates of 30,000 doses nationally per month in 1985 [7] (and perhaps as high as 30,000

doses per month in one city, as reported by the DEA [8]), then the low number of emergency room admissions is remarkable, to say the least. Likewise, well-documented deaths related to the use of these two drugs are exceptionally rare [9, 10].

Several chapters in this text deal with the potential neurotoxic effects of MDMA and the implications this may have in the long run for individuals who use it either therapeutically or recreationally. This chapter discusses those rare instances of acute toxic reactions and sudden death that have been caused solely by MDMA or MDEA, or where MDMA or MDEA are thought to have contributed significantly to a toxic reaction or death.

2. TOXIC REACTIONS TO MDMA

When MDMA is taken in a therapeutic or recreational setting in the usual dosage range of 75–150 mg orally, a wide variety of minor side effects are often noted. These include increased heart rate, tremor, tightening of the jaw muscles, bruxism, sweating, nauseau, and occasionally vomiting [1, 3, 11, 12]. The side effects are generally short-term in nature, although some individuals complain of residual jaw muscle tension, fatigue, depression, anxiety, nauseau, and occasionally flashbacks, which persist for up to two weeks after a single dose [3, 11–13]. Physiologic side effects that have been documented in uncontrolled studies and that are related to MDMA's sympathomimetic effects include tachycardia and a fairly consistent rise in blood pressure of approximately 15 mm Hg above baseline levels [11, 14]. Generally, as the dose is increased, these side effects become more disturbing, and this has often been cited as a feature that distinguishes MDMA from other drugs of abuse [3, 15, 16]. Although several individuals have noted numbness and tingling in the extremities, increased color acuity, or luminescence of objects, true auditory, visual, or tactile hallucinations are usually not experienced until very high doses are takan [1]. Impairment of judgement, coordination, and the ability to concentrate have all been documented in a clinical setting. For this reason, it is recommended that tasks requiring coordination, concentration, and problem solving skills not be performed by individuals under the influence of MDMA [11].

For the most part, the documentation of severe toxic reactions to MDMA or MDEA has been scanty and primarily anecdotal in nature [17]. As mentioned earlier, only eight admissions to emergency rooms for MDMA-related toxic reactions were reported to DAWN between 1977 and 1985. Perhaps as a reflection of the increasing popularity of MDMA, this number jumped to 28 in 1985, but this still represents only 0.03% of the drugs mentioned most frequently at the time of admission to emergency rooms [18]. The Haight–Ashbury Clinic has reported that these individuals usually present with anxiety and tachycardia. Reassurance is the only treatment necessary; however, on occasion, counselling sessions may be needed for those in whom symptoms of anxiety or paranoia persist [12, 19]. Siegel very briefly described more severe adverse reactions to MDMA in three users [1]. One woman apparently

became mute and semicatatonic for three days after ingesting her monthly dose of 130 mg, and two males developed hallucinations and paranoia that lasted 24 and 48 hours (the latter after a dose of 700 mg!). Wolfson states that there are anecdotal reports of seizures occurring with MDMA use, but provides no further details [20]. All of these reports must be tempered by the fact that only rarely are clinical diagnoses of MDMA toxicity confirmed with toxicology. Analysis Anonymous®, a confidential drug testing service that began operating in 1972, found that 58% of 101 samples submitted as MDMA contained only MDMA, 24% contained MDMA plus other substances, and 16% contained drugs other than MDMA [21]. Although these figures are quite good when compared to other illicit drugs, such as cocaine, it is easy to see that individuals who present with a toxic reaction to MDMA may, in fact, be exhibiting symptoms produced by drugs other than MDMA.

There are only three well-documented cases of serious toxic reactions to MDMA and four clinical cases, from Dallas, where the role of MDMA or MDEA in producing toxic reactions is much less clear. These cases are outlined in Table 1.

2.1. Case 1

Case 1 represents an example of toxic psychosis that is supposed to have been caused by MDMA. Unfortunately, the clinical diagnosis could not be confirmed by toxicology. This 34-year-old male presented to a clinic during the course of receiving therapy for opiate and benzodiazepine dependency. He was agitated and hypertensive and admitted to the intravenous administrations of two syringefuls and the ingestion of ½ teaspoonful of MDMA over a period of 48 hours ending two days prior to his presentation. A diagnosis of MDMA toxic psychosis was made, and he received haloperidol and phenobarbital. Five days later he was found to be increasingly agitated, and the following day he was exhibiting a severe reaction with paraonia and auditory hallucinations that required hospitalization. Hayner and McKinney report that generally toxic psychosis, such as that displayed by this patient, only occurs with doses of MDMA in excess of 200 mg, although it is possible that lower doses could trigger a similar response in susceptible individuals [12].

2.2. Case 2

Case 2 is extremely interesting in that a 32-year-old woman presented to hospital one half hour after ingesting only 60–65 mg of MDMA. She was hallucinating and was agitated, diaphoretic, tachycardiac, hyperthermic, and hypotensive. This had apparently been her second experience with MDMA. The first one had been described as "the best time of her life" [12]. Her five day course in hospital was complicated by continuing hallucinations, rhabdomyolysis, and coagulopathy. Serum MDMA levels were 6.5 mg/L (33.7 umol/L) one hour after admission and 7.0 mg/L (36.3 umol/L) three hours

Table 1. Clinical cases of acute toxic reactions involving MDMA and MDEA.

Case no.	Age/sex	Summary of presentation of clinical course	Toxicology
1 [12]	34/M	Agitation and hypertension following intravenous and oral MDMA two days prior to presentation. Five days later developed paranoia and auditory hallucinations requiring hospital admission.	Not obtained
2 [12, 22]	32/F	Agitation, hallucinations, hypotension, hyperthermia, diaphoresis, wheezing 1/2 hour after taking 60–65 mg MDMA p.o. Five day course complicated by continuing hallucinations, rhabdomyolysis, coagulopathy.	Serum: MDMA 6.5 mg/L (33.7 umol/L)
3 [17]	50/M	Hypertension, palpitations, difficulty controlling movements, and unintelligible speech after taking one MDMA tablet and 15 mg phenelzine p.o. Recovered in 15 hours with supportive care.	Blood: Ethanol 0.01 gm% (2.2 mmol/L) Urine: Benzodiazepines, meprobamate, cimetidine, MDMA present
4 [10]	30/M	Unconscious following amitriptyline overdose. Recovered.	Blood: Ethanol 0.16 gm% (34.8 mmol/L) amitriptyline 2.1 mg/L (7.6 umol/L) nortriptyline 0.4 mg/L (1.5 umol/L) Urine: MDEA, amitriptyline, nortriptyline, lidocaine present.
5 [10]	38/M	Bizarre behviour, weakness, dizziness after ingesting MDEA. Released following psychiatric evaluation.	Blood: Ethanol 0.24 gm% (52.2 umol/L) MDEA present.
6 [10]	26/M	Hallucinations and agitation after taking cocaine.	Blood: Cocaine 1.6 mg/L (5.3 umol/L) Urine: MDMA, amphetamine, cocaine present.
7 [10]	32/F	Unconscious after taking ethanol, cocaine, MDMA, and valium. Hospitalized 40 days.	Blood: Diazepam and demethyldiazepam present. Urine: MDMA, cocaine, lidocaine present.

later. These are the highest human blood levels of MDMA reported to date. Interestingly enough, a friend of the patient ingested a similar quantity of MDMA from the same packet as the patient and suffered no ill effects. The clinical course of this individual is remarkably similar to the hospital course described in individuals with toxic reactions to large doses of amphetamines [23, 24] and 3,4-methylenedioxyamphetamine (MDA) [24, 25]. The complications are also similar to those seen in cases of hyperthermia due to heat exposure, and it has been postulated that the hyperthermia seen in all of these instances may be the underlying mechanism by which rhabdomyolysis and coagulopathy come into play [23]. If one looks only at the blood levels of MDMA reported in this case, it seems to be an example of an extreme overdose [26]. Yet, judging from the alleged dose taken and the absence of toxic effects on the part of the patient's friend, this case has the appearance of an idiosyncratic response to MDMA's sympathomimetic effects. Thus, it is not entirely clear whether this patient's complications were the result of an overdose or an idiosyncratic reaction to MDMA.

2.3. Case 3

The last example of a serious toxic reaction to MDMA (Case 3) actually represents an interaction between MDMA and a monoamine oxidase inhibitor (MAOI). This individual presented to hospital with hypertension, diaphoresis, altered mental status, and hypertonicity 3½ hours after taking his usual 15 mg dose of phenelzine and 4½ hours after ingesting one tablet of MDMA. His symptoms resolved with supportive care in 15 hours. The presence of MDMA was confirmed in urine samples. The clinical picture was that of a fairly typical interaction between an MAOI and a sympathomimetic agent, which results in the exaggerated release of monoamine oxidase substrates, such as epinephrine and norepinephrine. Such reactions have been documented with MAOIs and amphetamine, methamphetamine, and several other sympathomimetic agents [17]. Thus it appears that the use of MDMA should be avoided by those on MAOIs.

2.4. Other cases

The four clinical cases reported from Dallas by Bost [10] are difficult to interpret as toxic reactions caused by MDMA or MDEA. In each instance, either ethanol or some other drug was present in sufficient quantities to account for the patient's symptoms. Thus it is impossible to sort out what role, if any, MDMA or MDEA played in their symptomatology.

In summary, it would appear that although minor side effects produced by MDMA are quite common, serious toxic reactions are exceptionally rare. These can take the form of toxic psychosis, drug interactions, and complications of MDMA's sympathomimetic effects, either in an overdose situation or possibly as an idiosyncratic reaction. These toxic reactions are generally managed with supportive care only, but they can be life-threatening.

3. HUMAN DEATHS AND MDMA

As with toxic reactions, the topic of human deaths related to MDMA and MDEA use has, until recently, been anecdotal and poorly documented. For example, in 1985 it was commonly believed that at least two and possibly three deaths had been caused by MDMA. Later, it was found that one of the cases was, in fact, an MDA overdose, and in the second instance the presence of MDMA by toxicology was not confirmed [14]. Likewise, in 1985 the DEA reported that there were 22 Medical Examiner cases where the presence of MDMA was cited [27], but the details of these cases have not been published. Five deaths related to the use of MDMA and MDEA were reported by Dowling et al. in 1987 [9]. These five deaths occurred in Dallas, Texas, and its surrounding counties between July, 1985 and March, 1986. Table 2 summarizes these cases together with the details of 11 other deaths in which MDMA or MDEA was detected by postmortem toxicology. These cases were compiled by review of the available literature, by obtaining the most recent information on human deaths related to MDMA and MDEA use from DAWN, and by review of records at the Office of the Chief Medical Examiner in Dallas County. It should be stated at the outset that this list is likely to be incomplete, as most of the cases are from Dallas, and other major centers where MDMA and MDEA use have been reported, including Florida, New York, California, and New England [1], are underrepresented. It is probable that deaths have occurred in these states, but they have not been reported in the literature or to DAWN. The 16 cases are divided in Table 2 into those cases where MDMA or MDEA were the underlying cause of death, those cases where MDMA or MDEA are thought to have contributed to death, and those cases where the drugs were simply incidental findings at autopsy or where their role in contributing to death is uncertain. Not included in Table 2 is the recent death of a young woman in Santa Clara County, California, wherein MDMA is thought to have caused death; however, this has not yet been confirmed by toxicology [28].

At the present time, there are only two documented cases where the acute toxic effects of MDMA were thought to be the underlying cause of death. No deaths solely related to MDEA use have been reported. The first case (Case 8) involved an 18-year-old previously healthy female who allegedly ingested 1 ½ "hits" (approximately 150 mg) of MDMA at a Dallas bar. A short time later, she collapsed and was found to be in ventricular fibrillation upon the arrival of paramedics. No natural disease processes were identified at autopsy that would account for death, and the only finding of significance was an MDMA level of 1.0 mg/L (5.2 umol/L) in postmortem blood, together with a small amount of ethanol. The second case (Case 9) was that of a 34-year-old male who appeared at his physician's home claiming that he had ingested LSD, MDMA, and valium. He suddenly collapsed, and all attempts at resuscitation were unsuccessful. Again, there was no anatomical cause of death identified at autopsy, but 1.46 mg/L (7.6 umol/L) of MDMA was found in postmortem

blood. Unfortunately, the detection and quantitation of LSD is exceptionally difficult and was not attempted in this case. Therefore, it is not possible to clarify the role, if any, that LSD played in this individual's death.

Both of these deaths occurred very suddenly in previously healthy individuals, and it would appear that in both instances the mechanism of death was a cardiac arrhythmia induced by MDMA. Such arrhythmias are well-recognized mechanisms of sudden deaths attributed to amphetamine overdoses [24, 29]. What is not clear in both cases is whether these deaths were the result of true overdoses or of an idiosyncratic reaction to MDMA. The estimated dose of MDMA taken in Case 8, 150 mg, is well within the range of this drug taken therapeutically and recreationally. However, this estimate was derived from witnesses at the scene and, therefore, may be misleading. There is a small but growing body of evidence, to be discussed later in this chapter, that indicates that the levels of MDMA found in these cases are quite high. Thus these may, in fact, be examples of overdoses.

As can be seen in Table 2, there are six cases where MDMA or MDEA are thought to have contributed significantly to death. Cases 10–13 have been described in detail by Dowling et al. [9] and only their salient features will be repeated here. In three of these four cases, MDMA or MDEA was found in individuals whose deaths could be accounted for by underlying natural disease processes. These diseases include coronary atherosclerosis (Case 11), an idiopathic cardiomyopathy (Case 13), and asthma (Case 12). The sympathomimetic effects of MDMA have been documented in an uncontrolled clinical trial and include mild tachycardia together with a consistent elevation of blood pressure [11]. Therefore, in individuals like those in Cases 11 and 13 with significant underlying cardiovascular disease, it is not unreasonable to suggest that MDMA or MDEA could precipitate a fatal arrhythmia. In fact, as a result of its documented sympathomimetic effects, Greer has recommended that MDMA not be administered to those suffering from "hypertension, heart disease, hypothyroidism, diabetes mellitus, hypoglycemia, seizure disorder, glaucoma, diminished liver function, and actual or possible pregnancy" [3]. These would seem to be reasonable guidelines in view of the postulated role played by MDEA in these two deaths. The contributory role of MDMA in the death of the asthmatic (Case 12) is perhaps more tenuous. This individual's asthma was poorly controlled, which is one finding noted in those who die suddenly of asthma [30]. One cannot rule out the possibility, however, that MDMA potentiated a cardiac arrhythmia in an individual who was already compromised as a result of his asthma. It is interesting to note that the young asthmatic woman who suffered a severe toxic reaction to MDMA (Case 2) developed wheezes and respiratory distress requiring treatment with methylprednisolone and isoetharine [12, 22]. Thus MDMA may play some as yet undefined role in the exacerbation of asthma.

Of the remaining three cases in Section B of Table 2, only Case 10 has been described previously in the literature. This 22-year-old male was apparently

Table 2. Deaths associated with MDMA and MDEA use.

Case no.	Age/sex/ city reported	History	Cause of death	Toxicology
		A. Cases where MDMA or MDEA are sole cause of death		
8 [9]	18/F Dallas	Sudden collapse after ingesting 1½ "hits" MDMA with ethanol.	Acute MDMA intoxication	Blood: Ethanol 0.04 gm% (8.7 mmol/L) MDMA 1.0 mg/L (5.2 umol/L)
9 [10]	35/M Berkeley	Sudden collapse after allegedly ingesting LSD, valium, MDMA.	Acute MDMA intoxication	Blood: MDMA 1.46 mg/L (7.6 umol/L) MDA 0.03 mg/L (0.2 umol/L) LSD not determined.
		B. Cases where mDMA or MDEA contributed to death		
10 [9]	22/M Dallas	Climbed electrical utility tower at 0130 hours. Electrocuted and fell.	Electrocution and multiple injuries.	Blood: MDMA present.
11 [9]	25/M Dallas	Collapsed while driving vehicle.	Atherosclerotic cardiovascular disease	Blood: MDEA 0.95 mg/L (4.6 umol/L) Butalbital 0.8 mg/L (3.6 umol/L)
12 [9]	32/M Dallas	Found dead beside car after evening of bar-hopping.	Asthma	Blood: MDMA 1.1 mg/L (5.7 umol/L) Ethanol not present.
13 [9]	21/M Dallas	Found dead in shower after ingesting 3 "MDMA" capsules, 65 mg propoxyphene, and ethanol.	Idiopathic cardiomyopathy	Blood: MDEA 2.0 mg/L (9.7 umol/L) MDMA not present. Propoxyphene 0.26 mg/L (0.8 umol/L) Norpropoxyphene 1.0 mg/L (3.1 umol/L)
14[a]	49/M Oklahoma City	Found dead at home with car running in garage and exhaust fumes in house. Had been snorting cocaine and taking MDMA.	Carbon monoxide intoxication	Blood: MDMA 1.4 mg/L (7.3 umol/L) Cocaine — trace Carboxyhemoglobin 43%
15[b]	25/M Dallas	Involved in motor vehicle collision after running red light.	Multiple injuries	Blood: Ethanol 0.23 gm% (50 mmol/L) MDEA 0.33 mg/L (1.6 umol/L)

C. Cases where MDMA or MDEA not related to cause of death

16[b]	34/M Dallas	History of depression and drug abuse. Found dead at home.	Gunshot wound of head	Blood:	Ethanol 0.17 gm% (37.0 mmol/L) MDMA present. Acetaminophen 430 mg/L (2.8 mmol/L) Cocaine 0.4 mg/L (1.3 umol/L)
17[b]	22/M Dallas	Struck by car while crossing freeway.	Multiple injuries	Blood:	Ethanol 0.24 gm% (52.2 mmol/L) MDMA present.
18[b]	34/F Dallas	Lost control of vehicle, rolled, ejected.	Multiple injuries	Blood:	Ethanol 0.05 gm% (10.9 mmol/L) MDMA present. Cocaine 0.11 mg/L (0.3 umol/L) Dextromethorphan 0.11 mg/L (0.4 umol/L)
19[b]	21/F Dallas	Found dead in garage with car running. Suicide note present.	Carbon monoxide intoxication	Blood:	MDMA 0.26 mg/L (1.35 uol/L) Carboxyhemoglobin 90%
20[b]	20/M Dallas	Found dead in bed with plastic bag over head and cylinder of nitrous oxide nearby.	Smothering and inhalation of nitrous oxide	Blood:	Nitrous oxide detected. MDMA 0.08 mg/L (0.41 umol/L)
21[b]	18/F Dallas	Girlfriend of Case 20, found at same scene.	Smothering and inhalation of nitrous oxide	Blood:	Nitrous oxide detected. MDMA 0.39 mg/L (2.0 umol/L)
22[b]	20/M Dallas	Unwitnessed hit-and-run.	Multiple injuries	Blood:	Ethanol 0.22 gm% (47.9 mmol/L) MDMA 0.38 mg/L (2.0 umol/L)
23[b]	34/M Dallas	Suspect in a theft, shot by police.	Multiple gunshot wounds	Blood:	Cocaine 0.03 mg/L (0.1 umol/L) MDMA 0.27 mg/L (1.4 umol/L)

[a] Personal communication, L. Balding, M.D., Office of the Chief Medical Examiner, Oklahoma City, 1988.
[b] Personal communication, C.S. Petty, M.D. and R. Bost, Ph.D., Office of the Chief Medical Examiner, Dallas, 1988.

climbing an electrical utility tower at 1:30 a.m., when he was electrocuted and fell to his death. In view of the fact that there was no evidence that his actions were suicidal in nature, it was concluded that MDMA was the cause of his bizarre behavior. Unfortunately, the MDMA was not quantitated in postmortem blood samples. In Case 15, a 25-year-old male died of multiple injuries received when he drove through a red light and collided with another vehicle. Although a high level of ethanol was detected in his blood, the Medical Examiner was of the opinion that MDEA contributed to his state of intoxication and thus was a factor in causation of the accident. Finally, Case 14 is interesting in that this 49-year-old male was found dead in his home, with a car running in the attached garage. He had apparently been snorting cocaine and taking MDMA several hours prior to the time his body was found. The circumstances surrounding this death were such that the manner of death (i.e., suicide or accident) could not be determined. The cause of death was thought to be carbon monoxide intoxication. However, the carboxyhemoglobin level of 43% was substantially below the level of 60%–70%, which causes death in healthy individuals [31]. Although this may be partially accounted for by the fact that the patient was actively resuscitated, it is also likely that the relatively high blood level of MDMA was a significant factor in this man's death.

The final eight cases listed in Table 2 represent instances where the presence of MDMA or MDEA was an incidental finding during postmortem drug screening or cases where the role that these drugs played in contributing towards death is unclear. It might reasonably be argued that MDMA contributed to the state of intoxication of the individuals in Cases 17, 18, and 22, and that this, in turn, may have been a factor in the motor vehicle and pedestrian deaths. However, the MDMA was not quantitated in Cases 17 and 18, and the circumstances surrounding the hit-and-run incident in Case 22 were unknown. Therefore, these cases are considered to be instances where the role that MDMA played in contributing towards death is not known.

When the level of MDMA and MDEA found in postmortem blood samples from those cases in Sections A and B of Table 2 is compared with those of Section C, an interesting difference becomes apparent. With the exception of case 10, in which MDMA was not quantitated, and Case 15, in which MDMA was only thought to have contributed to a general state of intoxication, all of the cases in which MDMA is thought to have caused or contributed significantly towards death have shown levels of this drug in excess of 1.0 mg/L (5.2 umol/L), with a mean of 1.2 mg/L (6.4 umol/L) (N = 4). In contrast, those cases in which MDMA was simply an incidental finding have shown a maximum MDMA level of 0.39 mg/L (2.0 umol/L), with a mean of 0.28 mg/L (1.4 umol/L) (N = 5). Likewise, the MDEA levels in Cases 11 and 13, where MDEA contributed significantly towards death, are 0.95 mg/L (4.6 umol/L) and 2.0 mg/L (9.7 umol/L), respectively. Although there have been no deaths described in which MDEA was simply an incidental finding, Bost has reported the blood levels of MDEA found in four living

individuals who were arrested for driving while under the influence of drugs [10]. The maximum MDEA level found was 0.59 mg/L (2.9 umol/L), with a mean of 0.31 mg/L (1.5 umol/L) (N = 4). Thus, although the number of cases is relatively small, it is apparent that a blood level of MDMA or MDEA in excess of 1.0 mg/L has the potential to cause or contribute significantly towards death, whereas levels below approximately 0.6 mg/L appear to be consistent with a state of MDMA or MDEA intoxication. In fact, one is left to speculate whether or not the high levels of MDMA or MDEA found in Cases 11, 12, and 13 represent the actual cause of death, with the natural disease processes being contributory factors.

If one assumes that the high levels of MDMA and MDEA found in Cases 11, 12, and 11–14 are the result of overdoses of these drugs, then the question remains: What amount of MDMA or MDEA taken orally represents an overdose? The cases themselves are not enlightening in this regard. Only Cases 8 and 13 provide any information as to the amount of MDMA or MDEA taken, but there is no way to be certain of the actual dose and purity of the drugs ingested. Taken at face value, the estimated doses of 150 mg of MDMA in Case 8 and 300 mg of MDEA in Case 13 are not particularly large, when one considers that some individuals have allegedly taken 700 mg of MDMA orally in one session and survived [1]. Thus individual susceptibility is probably a major factor in determining whether any given dose of MDMA or MDEA is potentially lethal.

Regrettably, virtually nothing is known about the pharmacokinetics of MDMA or MDEA. Only one study has been reported in humans [26], in which a healthy 74 kg 40-year-old male ingested 50 mg (0.68 mg/kg) of MDMA. The peak plasma MDMA level was 0.106 mg/L (0.55 umol/L), measured two hours after administration of the dose. Sixty-five percent of the 50 mg dose was recovered from the urine as unchanged MDMA and 7% as MDA. Although it is not possible to draw any definitive conclusions from a single case study, the peak serum MDMA level of 0.106 mg/L (0.55 umol/L) following a 50 mg dose does tend to support the idea that blood levels of MDMA in excess of 1.0 mg/L (5.2 umol/L) result from the ingestion of large quantities of this drug.

Turning to animal studies of MDMA toxicity, Hardman et al. determined the mean lethal dose (LD50) of MDMA in several animal species [32]. The LD50 was 97 mg/kg i.p. in mice, 49 mg/kg i.p. in rats, 14 mg/kg i.v. in dogs, and 22 mg/kg i.v. in monkeys. Orally administered, MDMA appears to be much less toxic, with an LD50 of 325 mg/kg p.o. reported in rats [33]. Although it is difficult to extrapolate animal data to humans, the orally effective dose of MDMA in humans is 1.5 mg/kg, which is less than one-tenth of the parenteral LD50 reported in animals [14]. Thus it would appear that there should be a high margin of safety between therapeutic and lethal doses of MDMA. It is interesting to note, however, that Frith et al. described the sudden death of one experimental dog following a single oral dose of 15

mg/kg MDMA [34]. This same dose was tolerated once daily for 28 days by five other dogs in the same study, thus supporting the concept that individual susceptibility is an important factor to consider when trying to establish what a so-called lethal dose of MDMA is in humans.

4. CONCLUSIONS

Human deaths that can be attributed to MDMA or MDEA appear to be exceedingly rare, especially when one considers the widespread use of these drugs in the United States. There is evidence to suggest that deaths can occur either as a result of the direct toxic effects of high doses of MDMA or MDEA (especially in those with underlying cardiovascular diseases) or as a result of the intoxicating effects of these drugs upon individuals who are engaged in activities requiring intact concentration, judgment, and coordination (e.g., driving an automobile). The possibility that some deaths arise as an idiosyncratic reaction to low doses of MDMA or MDEA cannot be ruled out at this time. Although the rarity of serious toxic reactions and deaths may indicate that these drugs are safe to use, one must always exercise caution in making such a judgment. For one thing, the long-term sequelae of their use is still unknown, and this is a matter of considerable debate, given the present findings which suggest that MDMA is neurotoxic [35, 36]. Secondly, one must always keep in mind the lessons taught to us by drugs such as cocaine, which only ten years ago was generally considered to be safe [37]. Clearly, more research is needed into the pharmacokinetics and toxicity of MDMA and MDEA, together with the continued documentation of toxic reactions and deaths related to their use, before we can be assured of their safety.

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