Three Cases of Delirium After "Ecstasy" Ingestion

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Abstract—Three cases of delirium experienced by three young friends after recreational use of "ecstasy" are reported—a syndrome which, to the best of the authors' knowledge, has not been previously observed in MDMA abusers. Special attention is given to the etiological factors and clinical features of the adverse reaction.

Keywords—cocaine, delirium, ecstasy, MDMA

MDMA (3,4-methylenedioxymethamphetamine, also known as "ecstasy") is a drug with high abuse potential classed as an hallucinogenic amphetamine that combines the effects of lysergic acid diethylamide (LSD) and amphetamine; at low doses, it induces a sense of well being, a positive change in mood and a reduction in social anxiety (Peroutka, Newmann & Harris 1988; Climko et al. 1986/87).

The adverse reactions reported after the ingestion of even a single dose may include anorexia, tachycardia, weakness, sweating, trismus or bruxism (Greer & Tolbert 1986). Severe and sometimes fatal adverse reactions have been reported in England, where MDMA is used almost exclusively in discotheques or dancing halls (Henry, Jeffreys & Dawling 1992). Ecstasy has also been associated with serious psychiatric side effects: reports have been published of cases of chronic paranoid psychosis (Mc Guire & Fahy 1991), recurrent paranoid psychosis (Creighton, Black & Hide 1991), panic attacks (Whitaker-Azmitia & Aronson 1989) and depression with suicidal ideation (Benazzi & Mazzoli 1991) following its use.

In spite of the recent reports of severe toxicity following recreational use, the drug has become increasingly popular in northern Italy, where it is commonly represented as being safe. The case of three friends who took some tablets of ecstasy at home and developed psychiatric complications is described.

CASE 1

A 22-year-old man was referred to the Psychiatric Department of L. Sacco Hospital in Milan by the Emergency Room because he looked confused and perplexed; this occurred approximately 30 hours after he had ingested an unknown number of ecstasy tablets. His flow of thought was disturbed, with a loosening of association, incoherence and blocking; he also showed a reduced ability to change focus and sustain attention to environmental stimuli. He had the delusion that the friend with whom he had taken the drug intended to kill him; he also experienced vivid visual hallucinations (eyes and monsters on the wall), auditory hallucinations and delusions of bodily change.

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A blood count, complete blood chemistry, liver and renal function tests, urinalysis and electrocardiogram yielded normal results; urine drug screening revealed the presence of MDMA (5 mg/l) and cocaine (1.22 mg/l); no opioids were present. The patient was treated with diazepam (40 mg daily); his symptoms remitted over a few hours, and no definite abnormalities were found during a mental state examination, although his recall of recent events was poor.

That night, the patient became fearful, agitated and disoriented as to time, place and person; he was treated with a further dose of diazepam (20 mg) and his symptoms cleared up completely and definitely in about three hours.

The patient did not have any personal history of psychiatric disorders; he declared he had been taking MDMA and cocaine on weekends for the previous eight months without experiencing any adverse effects. In terms of his family history, his mother had received a diagnosis of paranoid disorder, and his father met the DSM-III-R diagnostic criteria for a narcissistic personality disorder.

CASE 2

A 21-year-old man, a partner of Cases 1 and 3 in drug misuse, was referred to the Psychiatric Department by the Emergency Room 48 hours after having taken two tablets of ecstasy.

Examination of his mental state revealed agitation, a loosening of association and confusion. The laboratory test results fell within normal parameters except for a plasma creatine kinase value of 2174 u/l; the patient had no history of heavy alcohol or intravenous drug misuse, nor any sign of infectious hepatitis. He was treated with diazepam (40 mg) and forced diuresis, and his symptoms remitted over a few hours.

Thirty hours after hospital admission, the patient became so agitated as to require physical restraint and continued to repeat that someone was trying to kill him; he was given 20 mg of diazepam intravenously and, after two hours, the symptoms disappeared as well as his memory of them. Thirty-seven hours after admission, his speech became incoherent and he once again started to express a fear of being killed (he had visual hallucinations of a threatening man).

His plasma creatine kinase concentration reached 27537 u/l, aspartate aminotransferase 180 u/l, and alanine aminotransferase 50 u/l. After five hours, all of the psychiatric symptoms remitted, the patient became calm, friendly and cooperative, and was unable to recall the experience. Over the next few hours, his plasma creatine kinase rose to 59650 u/l, aspartate aminotransferase to 517 u/l and alanine aminotransferase to 90 u/l. Six days later, all of the biochemical variables had returned to normal.

The patient stated that he had been taking ecstasy and cannabis during weekends for the previous six months without experiencing any adverse effects. He did not have any personal or family history of psychiatric illness.

CASE 3

A 21-year-old man began to feel unwell approximately ten hours after ingesting three tablets of ecstasy in the company of Cases 1 and 2. Upon general hospital admission, the patient manifested extreme anxiety, with physical signs of tremor, mydriasis, tongue protrusion and an oculogyric crisis. MDMA (2.91 mg/l) and cocaine (0.17 mg/l) were detected during the urine screening for psychoactive drugs. His serum creatine kinase concentration was 705 u/l, but the results of the other biochemical and hematological investigations were normal; serological tests for syphilis, hepatitis B and HIV were all negative.

The day after hospital admission the patient felt well and free of symptoms; against the advice of the hospital's physicians, he discharged himself. Two hours later, he was taken back to the same hospital by two policemen, and then was accompanied and admitted to the Psychiatric Department of L. Sacco Hospital.

Examination of his mental state revealed confusion, a reduced attention capacity, loosening of association, visual hallucinations and paranoid delusions (a fear of being killed).

The patient was treated with diazepam (60 mg daily) and his psychotic symptoms remitted over a few hours. Over the subsequent 48 hours, he had visual hallucinations (people staring and ridiculing him) and persecutory delusions at night, but during the day was quiet, collaborative and could not remember the nocturnal psychotic symptoms. Five days after admission, his psychiatric and somatic symptoms remitted completely, his plasma creatine kinase concentration returned to normal, and the patient was discharged. He had a history of intravenous opioid abuse for four years and was on methadone treatment at the time of his ingestion of ecstasy. His mother had suffered from schizophrenia.

DISCUSSION

All three subjects developed similar psychiatric symptoms after MDMA ingestion, and a diagnosis of delirium was made on the basis of DSM III-R criteria. To the best of the authors' knowledge, this is the first time that delirium has been observed in MDMA abusers, though it is a recognized complication of amphetamine abuse.

Even in the best of circumstances, it is generally quite difficult to establish a direct causal relationship between the use of a psychoactive drug and subsequent adverse

reactions. In these cases, MDMA ingestion was confirmed by the detection of the drug in the urine specimens of two patients, and the third young man reported that he took MDMA from the same source; however, separate toxic effects due to possible contaminants in the clandestine drug itself cannot be excluded.

Only Cases 1 and 3 underwent urine toxicology screening, which in both cases revealed the presence of MDMA and cocaine. If it is assumed that Case 2 also made use of cocaine, the possibility that the clinical picture of delirium was induced by cocaine use cannot be excluded.

Furthermore, it should be noted that the repeated use of cocaine reported by Cases 1 and 3 in any event probably played an important part in promoting the onset of delirium, because there is evidence that chronic cocaine use produces adaptive changes involving dopamine transporters. In comparison with drug-free controls, the brains of nonpsychotic cocaine users contain a large number of cocaine recognition sites on the striatal dopamine transporter (Staley, Hearn & Ruttenber 1994). As no such increase is observed in cocaine users who are agitated delirium victims (Staley et al. 1994), it is possible that they cannot clear dopamine from their synapses, and that this could lead to agitation and delirium.

Moreover, a clinical picture of delirium could possibly be induced by MDMA itself. Although the serotonergic neurotoxicity of MDMA is now well established, it is worth noting that the interruption of the normal route of dopamine catabolism due to MDMA-induced blockade of monoamine oxidase could lead to high concentrations of extracellular dopamine adjacent to 5HT neurons, thus enhancing carrier-mediated dopamine uptake and producing an increased level of intrasynaptic dopamine (Gibb et al. 1989).This effect is specifically blocked by fluoxetine, a 5HT uptake inhibitor that provides protective effects against MDMA-induced neurotoxicity.

None of the three subjects had a history of alcohol abuse, and none of them reported the concurrent ingestion of alcohol. The possibility can therefore be excluded that alcohol played a part in the onset of the described symptoms. With regard to Case 2, the possibility cannot be excluded that the chronic use of cannabis or the repeated combination of cannabis and MDMA he had taken each weekend for six months may have been important elements in increasing his vulnerability to delirium.

Pearlson and colleagues (1989) have reported a case of cocaine-induced delirium in a subject with a long history of using marijuana and intravenous cocaine, and they hypothesized that the repeated use of these two drugs in combination may increase susceptibility to cocaine delirium.

A number of studies have suggested that delta-9-tetrahydrocannabinol, the psychoactive principle of cannabis, facilitates mesolimbic dopamine neurotransmission, an *in vivo* effect that has been attributed to the inhibition of dopamine uptake and/or the facilitation of dopamine release by nerve terminals (Sakurai Yamashita et al. 1989). However, low concentrations of delta-9-tetrahydrocannabinol have been shown to produce the opposite effects of stimulating dopamine uptake and inhibiting dopamine release in a synaptosomal preparation (Poddar & Dewey 1980). It can be hypothesized that, as with low doses of delta-9-tetrahydrocannabinol, the repeated use of cannabis may increase intrasynaptic levels and thus lead to agitation and delirium. It is possible that cannabis itself, like cocaine, can directly induce delirium (Hollister 1988).

The patients cited in the above case studies had a similar pattern of psychiatric symptoms, with a prevalence of persecutory delusions (all believed that someone was trying to kill them) and experiences of bodily changes. All of them were treated only with repeatedly administered intramuscular and intravenous diazepam, which led to the remission of the psychiatric and somatic symptoms after a period of no longer than six days. In order to avoid the risk of hyperthermia, no neuroleptic agents were used.

It is worth noting that the three clinical pictures were comparable in terms of their features, severity and duration, but were very different in terms of their somatic involvement. Despite the large quantity of MDMA found in his urine, Case 1 showed no physical effects and the results of the laboratory investigations were normal, whereas the second case may have experienced rhabdomyolysis and hepatotoxicity (recognized complications of MDMA misuse), as suggested by the presence of increased creatine kinase and aspartate aminotransferase concentrations. Since 1987, more than 20 case reports of cocaine-associated rhabdomyolysis (CAR) have been reported in the medical literature, in many of which the patients also showed the classical features of excited delirium, hyperthermia or both. Ruttenber and colleagues (1997) suggest that rhabdomyolysis and excited delirium are both caused by the same aberrant dopaminergic function which causes a spectrum of clinical severity, ranging from rhabdomyolysis with no excited delirium or hyperthermia to various combinations of the three conditions.

The present report suggests that clinically important and unpredictable effects may occur after MDMA ingestion, especially if combined with other drugs. Given the increasing popularity of the drug in northern Italy, the authors hope to stimulate further reports and research in this area.

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