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BRIEF REPORT

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Acute poisoning with amphetamines (MDEA) and heroin: antagonistic effects between the two drugs

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Abstract A case of oral ingestion of large doses of both the amphetamine-derivative 3,4-methylene dioxyethamphetamine (MDEA) and heroin is reported. Despite high serum levels of both drugs, the patient did not present with the classic signs and symptoms normally seen during intoxication with these drugs. The patient recovered after symptomatic treatment. The possibility that opposite pharmacological properties of the two drugs prevented the patients death is discussed.

Key words Amphetamines (and analogues) · Methylene dioxymethamphetamine (MDMA) · Methylene dioxyeth(yl) amphetamine (MDEA) · Eve · Heroin · Morphine · Poisoning · Intoxication

Introduction

Amphetamines produce strong central nervous system stimulation, primarily via catecholamine release. One amphetamine derivative, 3,4-methylene dioxymethamphetamine (MDMA, Ecstasy or Adam), has become a popular recreational drug. Since the use of MDMA is illegal in most countries, a related drug called 3,4-methylene dioxyethamphetamine (Eve or MDEA) has appeared as a substitute for MDMA [1]. Both drugs share structural similarities with amphetamines and also with mescaline, a hallucinogen.

MDMA, and to a lesser extent MDEA, leads to a "5–6 hour high," which produces increased activity, mood elevation and alterations in perception. The actions of MDEA are thought to be more subtle and shorter (3–4 h) than those of MDMA, but otherwise the two drugs are similar. At first, it was believed that there were few adverse effects from MDMA and MDEA abuse. Recently, however, it has been recognized that both drugs can cause a severe acute reaction, including hyperthermia, alterations in cardiovascular function, respiratory distress, intravascular coagulation, increased muscular activity and rhabdomyolysis, sometimes leading to death [1]. The neurotoxic effect of MDMA, in particular, has led to serious concern about the potential hazards of human exposure to this drug [2].

Since treatment of amphetamine poisoning is usually symptomatic and often associated with a fatal outcome, a search for specific drugs to help the amphetamine-intoxicated victim is sorely needed.

We report a case of a suicidal ingestion of large amounts of MDEA and heroin (diacetylmorphine) and present the hypothesis that the two drugs produce opposing clinical effects. The basic pharmacology of both molecules is discussed.

Case report

A 25-year-old Caucasian male was admitted to the emergency ward because of acute-onset confusion. At presentation, he was agitated and showed increased muscular rigidity. We learned from a friend that he had taken 40 tablets (approximately 4 g) of "Eve" (MDEA) and 12 g of "Smack" (heroin) by oral route approximately 2 h before admission. He had a history of three previous suicide attempts and was known to sell "drugs that were used and sold at dances." No data on previous drug addiction were available.

Clinical investigation showed a normal rectal temperature (36.4 °C), an initial blood pressure of 115/70 mmHg and absence of tachycardia, sweating, mydriasis, myosis or convulsions. Routine biochemical and hematological investigation yielded normal results.

Because of rapidly progressive tachypnea and exhaustion, the patient was intubated, sedated and mechanical ventilation was initiated. Gastric lavage was executed using 10 l of tap water, but no tablet remnants were recovered. Gastric contents, urine and blood were collected for toxicological screening, and 100 g activated charcoal was administered. Arterial blood gas performed while the patient was ventilated ($FiO_2 = 0.4$) showed no metabolic acidosis or alkalosis. Gas exchange under mechanical ventilation quickly returned to normal, indicating that the respiratory insufficiency was of central origin.

Transfer to the ICU was arranged, where maintenance infusions of diazepam and fentanyl were administered. Dantrolene was not given, as there was no hyperthermia. Computed tomography of the brain excluded intracerebral hemorrhage.

Toxicological screening revealed the presence of trace amounts of paracetamol, heroin and "amphetamines" in the gastric lavage fluid. The serum concentration of "Eve" on admission was 1400 ng/ml, as determined by gas chromatography after extraction with dichloromethane. The level of diacetylmorphine (heroin) was measured after acetylation of the sample, thereby reflecting the amount of heroin still present as represented by its natural metabolites morphine and monoacetylmorphine. Trace amounts of cocaine (5 ng/ml) and substantial amounts of heroin (115 ng/ml) were also found in the serum using the same analytical method. The serum level evolution of the different drugs is summarized in Table 1.

Based on theoretical data (pKa) and in the absence of any biochemical sign of rhabdomyolysis, metabolic acidosis or renal insufficiency, acidification of the urine (by means of intravenous administration of up to 6 g vitamin C/24 h) to enhance excretion of amphetamines was used. The urinary pH was monitored regularly to obtain a value between 5.5 and 6.0.

Supportive care, including administration of clonidine (0.6 mg/24 h i.v.) to reduce the central nonadrenergic hyperreactivity of opiate withdrawal was provided for several days. The patient was successfully weaned from the ventilator by day 4 when he was transferred to the psychiatric ward. He recovered without persistent neurobehavioral disturbance and returned home 11 days after admission.

Table 1 Serum levels of ingested psychotropic drugs (*ND* not detectable)

	MDEA (ng/ml)	Cocaine (ng/ml)	Heroin (ng/ml)
At admission	1400	5	115
Hours after admission:			
4	1200	1	< 15
8	1000	ND	< 15
12	910	ND	ND
16	840	ND	ND
30	260	ND	ND
42	90	ND	ND
54	40	ND	ND
90	30	ND	ND
102	ND	ND	ND

Discussion

Although MDMA and MDEA were at first considered safe by recreational users and some psychotherapists, later reports of substantial toxicity emerged, implicating a role for both MDMA and MDEA in several fatalities [1].

At a typical dose, both MDMA and MDEA cause euphoria and at higher doses agitation. Both drugs produce stimulant actions similar to their parent compound, amphetamine. These include increased cardiac output, hypertension, induction of arrhythmias, mydriasis, intracranial hemorrhage, increased muscle rigidity, sweating and hepatotoxicity [3, 4]. The pattern of reaction is highly variable between individuals. However, serious side effects, as described above, have been reported after recreational misuse and even after intake of only one tablet [3]. In severe cases, a more chronic pattern of toxicity has been reported, characterized by hyperthermia, disseminated intravascular coagulation, rhabdomyolysis and acute renal failure [3].

The reported blood levels of MDMA and MDEA in acute fatal overdose have ranged from 110 to 1260 ng/ml for MDMA and from 950 to 2000 ng/ml for MDEA, respectively [1, 3, 5]. The patient described herein had a MDEA serum level of 1400 ng/ml, which falls within the lethal range.

In experimental animals, MDMA exerts neurotoxic effects on central serotonergic neurons, resulting in degeneration of serotonin-containing axonal terminals [6]. Some of the properties of MDMA and MDEA are mediated via stimulation of serotonergic pathways. Both drugs induce the release of serotonin (5-hydroxytryptamine, 5HT) from presynaptic terminals, block the reuptake of 5HT into nerve terminals, bind to $5HT_2$ receptors and inhibit tryptophan hydroxylase and hence 5HT synthesis. Neither of these compounds exerts a major long-term effect on dopamine or noradrenaline nerve terminal markers [7–10].

Neurochemical studies showed that MDEA is somewhat less toxic than MDMA [11], being less apt to cause irreversible neuronal damage and being less (approximately 25%) potent in producing a long-term depletion of 5HT [10]. Repeated doses of MDEA also induce a prolonged, selective and dose-related depletion of 5HT in the rat brain [10], and a long-lasting

Table 2 Clinical symptoms and signs after overdose with either amphetamines or opiates

	Amphetamines	Heroin/opiates
Effects on:	Clinical presentation	
Blood pressure	Hypertension	Hypotension
Pulse rate	Tachycardia, arrhythmia	Bradycardia
Temperature	Hyperpyrexia	Hypothermia
Consciousness	Delirium, psychosis, coma	Coma
Muscle	Rhabdomyolysis, muscle rigidity	Rhabdomyolysis
Respiration	Tachypnoe	Respiratory depression
Pupil	Mydriasis	Pinpoint pupils

depletion of 5HT appears to be a good predictor of 5HT neurotoxicity [6]. Therefore, studies on animal behavior have underlined a similarity between MDMA and MDEA [12].

MDEA has been reported to have played a contributory role in causing death in traffic accidents [1], and severe reactions similar to MDMA are reported after recreational use [4]. In humans, an indirect serotonergic mechanism might also be responsible for the observed effects [13]. Volunteers taking only 140 mg MDEA experienced long-lasting increases in systolic blood pressure and heart rate (underlying its sympathicomimetic properties) and increases in plasma cortisol and prolactin (possibly via serotonin pathways) [14]. In view of all these observations, the same caution that is currently being exercised in the use of MDMA seems warranted in the use of MDEA.

Amphetamines in general, and MDMA or MDEA in particular, have clinical effects that are opposite to those of heroin or diacetylmorphine. Table 2 summarizes the clinical effects to be expected after ingestion of large doses of these drugs. None of these was present in the case presented, however, despite the high ingested doses and the high serum levels.

The estimated lethal range of heroin is 200 mg, but addicts may be able to tolerate up to 10 times this amount [15]. Our patient ingested 12000 mg, and heroin-related deaths in addicts have been associated with serum levels ranging from 10 to 1400 ng/ml, with a mean value of 190 ng/ml [15]. Moreover, it is not always possible to compare the potential lethal doses of heroin after i.v. administration and after oral ingestion because the kinetics after these two routes of administration are quite different [16]. The rapid decline in heroin serum level that we observed may be attributable to the short serum half-life of only a few minutes.

The fascinating fact that, apart from the respiratory depression, none of the clinical signs reported after massive overdose with these two drugs (Table 2) was present might be attributed to the opposite pharmacological effects of MDEA and heroin. Indeed, stimulation of so-called "inhibitory" opioid receptors on noradrenergic presynaptic nerve terminals of different cerebral regions and the peripheral sympathetic nervous system diminishes the evoked noradrenaline release in a concentration-dependent manner [17]. Acute administration of morphine or related compounds increases the turnover and synthesis of cerebral 5HT, as detected by measuring the formation of 5-hydroxyindoleacetic acid, the main metabolite of 5HT, in a number of brain regions [18]. This activation of 5HT systems takes place even after the acute administration upon withdrawal from opioids after chronic use.

Briefly, we believe that the patient unwittingly may have saved his own life by the oral coingestion of both MDEA and heroin. Our clinical data raise an interesting point about the pharmacological treatment of acute poisoning with amphetamine derivatives. Until now, MDMA-induced 5HT-uptake has been reported to be inhibited in vitro by cocaine, a more general monoamine (including 5HT) uptake blocker [19]. MDMA-induced hyperpyrexia is attenuated by blocking the $5HT_2$ receptor [9]. We do not proclaim the use of heroin (or morphine) in amphetamine poisoning, but we believe that this observation suggests that both in vitro and in vivo experiments with well-known opioids may be worthwhile. It would indeed appear from this case that stimulating opposite and alternative pharmacological pathways might modulate the clinical response.

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References

1. Dowling GP, McDonough ET III, Bost RO (1987) "Eve" and "Ecstasy." A report of five deaths associated with the use of MDEA and MDMA. JAMA 257: 1615–1617
2. Rattray M (1991) Ecstasy: towards an understanding of the biochemical basis of the actions of MDMA. Essays Biochem 26: 77–87
3. Henry JA, Jeffreys KJ, Dawling S (1992) Toxicity and deaths from 3,4-methylene dioxymethamphetamine ("Ecstasy"). Lancet 340: 384–387

4. Tehan B, Hardern R, Bodenham A (1993) Hyperthermia associated with 3,4-methylene dioxyethamphetamine ("Eve"). Anaesthesia 48: 507–510
5. Chadwick IS, Linsley A, Freemont AJ, Doran B (1991) Ecstasy, 3,4-methylene dioxymethamphetamine (MDMA), a fatality associated with coagulopathy and hyperthermia. J R Soc Med 84: 371
6. Ricaurte G, Bryan G, Strauss L, Seiden L, Schuster C (1985) Hallucinogenic amphetamine selectively destroys brain serotonin nerve terminals. Science 229: 986–988
7. Johnson MP, Hoffman AJ, Nichols DE (1986) Effects of the enantiomers of MDA, MDMA and related analogues on [^{3}H] serotonin and [^{3}H] dopamin release from superfused rat brain slices. Eur J Pharmacol 132: 269–276
8. Rudnick G, Wall SC (1992) The molecular mechanism of "ecstasy" [3,4-methylene dioxymethamphetamine (MDMA)]: serotonin transporters are targets for MDMA-induced serotonin release. Proc Natl Acad Sci USA 89: 1817–1821
9. Schmidt CJ, Taylor VL, Abbate GM, Nieuduzak TR (1991) $5HT_2$ antagonists stereoselectively prevent the neurotoxicity of 3,4-methylene dioxymethamphetamine by blocking the acute stimulation of dopamine synthesis: reversal by L-dopa. J Pharmacol Exp Ther 256: 230–235
10. Ricaurte GA, Finnegan KF, Nichols DE, DeLamey LE, Irwin I, Langston JW (1987) 3,4-Methylene dioxyethylamphetamine (MDE), a novel analogue of MDMA, produces long-lasting depletion of serotonin in the rat brain. Eur J Pharmacol 137: 265–268
11. Schmidt CJ (1987) Acute administration of methylene dioxymethamphetamine: comparison with the neurochemical effects of its N-desmethyl and N-ethyl analogues. Eur J Pharmacol 136: 81–88
12. Boja JW, Schechter M (1987) Behavioral effects of N-ethyl-3,4-methylenedioxyamphetamine (MDE; "Eve"). Pharmacol Biochem Behav 28: 153–156
13. Price LP, Ricaurte GA, Krystal JH, Heninger GR (1989) Neuroendocrine and mood response to intravenous L-tryptophan in 3,4-methylenedioxymethamphetamine (MDMA) users. Arch Gen Psychiatry 46: 20–28
14. Gouzoulis E, van Bardeleber U, Rupp A, Kovar KA, Hermle L (1993) Neuroendocrine and cardiovascular effects of MDE in healthy volunteers. Neuropsychopharmacology 8: 187–193
15. Moffat AC (ed) (1986) Clarke's isolation and identification of drugs. Pharmaceutical Press, London
16. Ellenhorn MJ, Barceloux DG (eds) (1988) Medical Toxicology. Diagnosis and treatment of human poisoning. Elsevier, New York
17. Hertting G, Wurster S, Allgaier C (1990) Regulatory proteins in presynaptic function. Ann NY Acad Sci 604: 289–304
18. Sawynok J (1989) The role of ascending and descending noradrenergic and serotonergic pathways in opioid and non-opioid antinociception as revealed by lesion studies. Can J Physiol Pharmacol 167: 975–988
19. Richelson E, Pfenning M (1984) Blockade by antidepressants and related compounds of biogenic amine uptake into rat brain synaptosomes: most antidepressants selectively block norepinephrine uptake. Eur J Pharmacol 104: 277–282