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# A CASE OF MAO INHIBITOR/MDMA INTERACTION: AGONY AFTER ECSTASY

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## ABSTRACT

After ingesting 3,4-methylene-dioxy-methamphetamine (MDMA) and the monoamine oxidase (MAO) inhibitor phenelzine, a 50 year old male developed marked hypertension, diaphoresis, altered mental status, and hypertonicity lasting 5-6 hours. This clinical course is typical of interaction between MAO inhibitors and some sympathomimetics including amphetamines. Such interaction has not previously been described involving MDMA.

Sympathomimetic-MAO inhibitor interactions can cause excessive release of endogenous bioactive amines (e.g. norepinephrine, serotonin). Hypertensive crisis, intracranial hemorrhage, hypertonicity, and severe hyperthermia have occurred due to sympathomimetic-MAO inhibitor interactions.

MDMA shares structural and pharmacologic features with other agents capable of causing this interaction, and this case suggests that MDMA can cause significant toxicity in patients taking MAO inhibitors.

## INTRODUCTION

3,4 - methylene-dioxy methamphetamine (MDMA) has recently been the focus of tremendous controversy. MDMA (A.K.A. ecstasy, XTC, MDM, Adam, E, doctor, M & M's) is apparently increasing in popularity as a recreational drug. Although there is no scientific evidence to support its use, a small minority of psychotherapists claim dramatic facilitation of patient self-awareness with supervised use of MDMA. Advocates of MDMA use claim that toxicity is exceedingly rare. Despite these claims, the Drug Enforcement Agency (DEA) recently ruled that MDMA has no accepted medical use, has unproven safety, has high abuse potential, and that indirect evidence of significant toxicity exists (1).

Despite the intense debate, current understanding of MDMA toxicity consists of undocumented anecdotes, and speculation based on known effects of related substances (1-3). The medical literature is devoid of documented evidence of either benefits or toxicity from MDMA use. The following is a case of acute toxicity apparently due to the interaction of MDMA and the MAO inhibitor phenelzine.

## CASE DESCRIPTION

A 50 year old male who complained of feeling anxious ingested 1 of 2 identical pills (later identified as MDMA) given to him by a friend as a "natural tranquilizer." He denied any significant initial effect after ingestion. Approximately one hour after the MDMA ingestion he took his usual dose of 15 mg phenelzine sulfate (Nardil®). During the next hour he noted palpitations, associated with a poorly characterized uneasy sense. This was followed by progressive increasing difficulty controlling his movements and speaking. When his speech became unintelligible and he began having slow, sustained, forceful twisting and arching movements he was brought to the emergency department 4 1/2 hours after MDMA ingestion, and 3 1/2 hours after phenelzine.

Medical history was positive for depression, acid peptic complaints, and angina. Medications were cimetidine 300 mg QID, and phenelzine 15-30 mg TID. Because of frequent insomnia, diazepam and other sedative/hypnotics were used occasionally. There had been no changes in medications for several months and no deviation from his usual low tyramine diet.

In the emergency department he was awake, initially able to indicate yes or no answers, but soon was unable to respond. As a result, orientation was not fully assessed. He was profusely diaphoretic with vigorous tonic movements resulting in intermittent, slow twisting, and nearly opisthotonic arching postures. Vital signs were: blood pressure 208/80 mm Hg, heart rate 64/minute, respirations 28/minute, temperature 36.9° (rectal). Pupils were equal, dilated, and reactive. Extraocular movements were intact with intermittent right gaze preference. Funduscopic examination showed no hemorrhages or papilledema. Trismus was noted. Movements of the neck were difficult due to increased tone. Neurologic examination revealed him to be awake but unresponsive to voice. Cranial nerve function was intact. Muscle tone was diffusely increased. Deep tendon reflexes were hyperactive throughout, with unsustained ankle clonus bilaterally. Asymmetry of his deep tendon reflexes was noted transiently, but resolved.

Complete blood count was normal. Serum chemistries were: sodium 138 mEq/L, potassium 4.2 mEq/L, chloride 112 mEq/L, carbon dioxide 17 mEq/L, creatinine 1.3 mg/dl, and glucose 144 mg/dl. The electrocardiogram was normal. Computerized tomography of the head was normal.

Toxicologic testing showed an ethanol level of 14 mg/dl in blood, and traces of benzodiazepines, meprobamate, and cimetidine in the urine. By comparison with a known MDMA standard (> 99% match), an unknown substance in the urine and the uningested second pill were identified later as MDMA by gas chromatographic and mass spectrographic analyses (Hewlitt-Packard GC 5890, MSD 5970 detector, 25 meter 5% phenylmethyl silicone capillary column). Assay of phenelzine metabolites was not attempted.

There was no improvement after 50 mg of intravenous diphenhydramine given for a presumed dystonic reaction. Fifty grams of activated charcoal with thirty grams of magnesium sulfate were given by nasogastric tube, and the patient was admitted to the intensive care unit for supportive care and monitoring. He improved rapidly with normalization of mental status and tone within three hours of admission (7 1/2 hours after MDMA, 6 1/2 hours after phenelzine sulfate), and normalization of blood pressure over the subsequent 12 hours. The clinical course is illustrated in Figure 1. He recovered completely and was discharged without apparent sequelae.

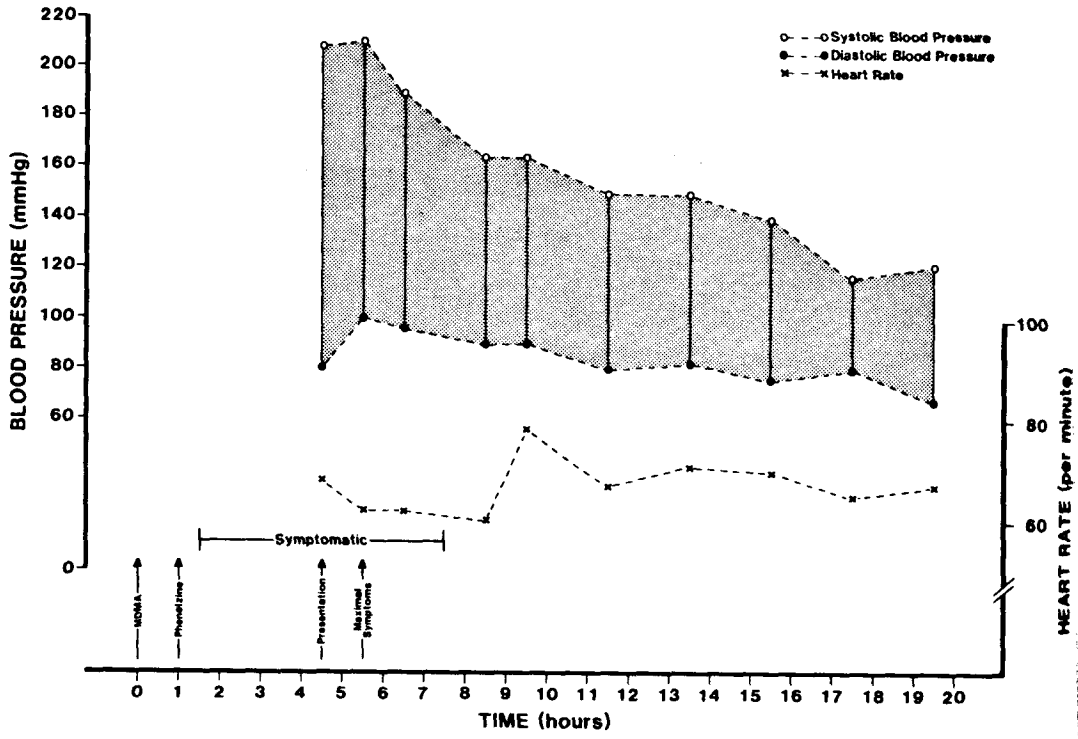
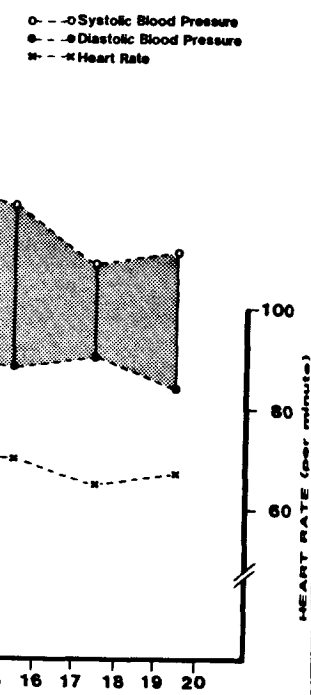



Figure 1 - Summary of the patient's clinical course.

## DISCUSSION

Previous reports of MDMA toxicity have been anecdotal and undocumented (1,2). These reports suggest that at high doses MDMA can cause typical "amphetamine-like" cardiovascular and stimulating effects, and can produce hallucinations. Such effects include: anxiety, agitation, hypertension, and tachycardia, and are not uncommon (2). Serious amphetamine toxicity such as seizures, rhabdomyolysis, renal failure, and acute toxic psychosis have not yet been documented due to MDMA.

Based on current knowledge, our case is atypical of "amphetamine-like" toxicity that might be expected from MDMA overdose for several reasons. The dose of MDMA ingested by history would be unlikely to cause overdose symptoms. Street-available MDMA, as in this case, is usually in 50-100 mg doses (2). Psychiatrists who advocate MDMA use suggest an initial dose of 75-125 mg (2). Recreational doses are usually 50-100 mg (2). At these doses

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significant toxicity is apparently not seen (2). Before the desired effects occur, stimulation, anxiety, and jaw-clenching do occur after the above MDMA doses, but are maximal 30-60 minutes after ingestion, and transient, lasting less than an hour (2). These adverse effects are not delayed (1 1/2 -2 hours post-ingestion) or persistent (6 hours) as in our patient. The possibility of an erroneous dose history and a significant overdose must be considered. The absence of typical central nervous system stimulation in this case before or after the prominent hypertonicity is atypical of amphetamine overdose (4). MDMA overdose would seem unlikely to cause this picture, since adverse effects after high doses of MDMA apparently mimic other amphetamine toxicity.

The course is similarly atypical of phenelzine overdose. MAO inhibitor overdoses often cause hypertension, diaphoresis, and hypertonicity as seen in our case, but with a characteristically different time course (5). The onset of MAO inhibitor overdose toxicity is delayed, often 6-12 hours after ingestion, and then persistent due to the sustained effects of MAO inhibitors. MAO inhibitors act as irreversible inhibitors of MAO with MAO activity returning only after enzyme regeneration, which may take weeks to complete (6). After serious overdose, acute toxicity may persist for days. Rapid resolution, as in our patient, is distinctly atypical in MAO inhibitor overdose.

Sympathomimetic-MAO Inhibitor Interaction

The clinical course in our patient is quite typical of toxicity due to the interaction between MAO inhibitors and many sympathomimetics. After MAO inhibitor use, indirect-acting sympathomimetics, i.e. those that act by stimulating release of bioactive amines, produce an exaggerated response. This response apparently results from release of the excessive pool of MAO substrate (e.g. epinephrine, norepinephrine, dopamine, serotonin [5-hydroxytryptamine]) which accumulates after MAO inhibitor use (7,8).

The peripheral manifestations of this exaggerated response include hypertension, tachycardia (variable), and diaphoresis (9-14). Absence of tachycardia or reflex bradycardia due to hypertension is common (15,16). Central effects include agitation, hyperreflexia, hypertonicity, and in severe cases rigidity, seizures, and coma (9,13). Secondary toxicity such as hyperpyrexia (9) and intracranial hemorrhage (10,17) may occur and lead to

death. Rhabdomyolysis, although expected, is not well documented after such interactions. The actual incidence of rhabdomyolysis and myoglobinuria is not clear since most case reports do not document creatinine phosphokinase levels or urinalysis results.

Toxic interactions of varying severity have been reported with MAO inhibitors and amphetamine (9,10,17), methamphetamine (11), phenylpropanolamine (12), metaraminol (13), mephenteramine (14), and methylphenidate (18). Experimentally, dopamine (19), ephedrine (15), and phenylephrine (15) have also been shown to trigger exaggerated sympathomimetic effects after pre-treatment with MAO inhibitors. MDMA has not previously been described in this role, but in view of its similarities to other amphetamine sympathomimetics (see Figure 2), similar interaction would not be unexpected.

The common feature of sympathomimetics capable of triggering at least this response is their indirect action. Some (e.g. phenylephrine) have only slight indirect activity, but all the agents mentioned above are capable of triggering some release of endogenous amines (20). Agents with direct receptor action only (e.g. levarterenol [norepinephrine]) are well tolerated by patients on MAO inhibitors and do not cause a markedly exaggerated response (16). The ability of MDMA to act indirectly is not fully resolved. Limited in vitro data suggest that MDMA can trigger release of endogenous serotonin (21). From its structure, indirect action would be expected from MDMA. Although many variations exist, the most potent indirect sympathomimetics are those with a methyl substitution on the alpha carbon and no substitution on the beta carbon of their side chain (20,22). MDMA has both of these structural characteristics (see Figure 2).

In addition to their indirect sympathomimetic effects, amphetamines exhibit their own MAO inhibitory action due to the methyl substitution on the alpha carbon (20,22). Whether the potential for toxic interaction between amphetamines and MAO inhibitors is affected by this intrinsic MAO inhibitory action of amphetamines is unknown.

In most cases of significant interactions, symptoms have immediately followed a sympathomimetic dose given to a patient on chronic MAO inhibitor therapy. In volunteers taking MAO inhibitors who were then given sympathomimetics by mouth, the onset of hypertension was between

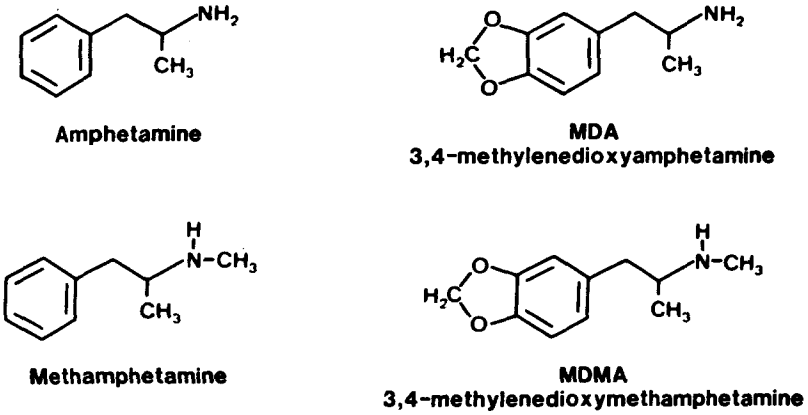


Figure 2 - Structures of amphetamine, methamphetamine, 3,4-methylene-dioxy-amphetamine (MDA), and MDMA.

30-90 minutes after the sympathomimetic with peak effect approximately three hours after ingestion (23). Blood pressure returned to normal over the subsequent few hours in these subjects. This time course is typical for reported cases of MAO inhibitor-sympathomimetic interaction.

Interestingly, our patient experienced no adverse effects after MDMA until ingesting a dose of phenelzine. In addition to toxicity seen immediately after sympathomimetic dosing, experimental (24) and clinical (9) evidence suggests that MAO inhibitor-sympathomimetic interaction can also be exaggerated acutely following MAO inhibitor dosing. In these reports, amphetamines given between doses of MAO inhibitors apparently triggered insignificant responses. When the same amphetamine dose was given simultaneously with the MAO inhibitor a dramatic response was seen. Since peak MAO inhibition is delayed 5-10 days after dosage (6), this mechanism alone is unlikely to explain the acute additive effects seen after MAO inhibitor dosage. The course of these acute effects more closely parallels MAO inhibitor acute dose kinetics (5,25). Peak levels of phenelzine in plasma occur 3-4 hours after a dose, followed by a rapid fall by 6-8 hours post-ingestion (25). The correlation between the kinetics of phenelzine levels and the clinical course in these few cases suggests some short-term effect related to direct action of phenelzine. Phenelzine and other MAO

inhibitors have many actions other than MAO inhibition (6-8). They inhi it other enzyme systems, slow hepatic metabolism of other agents, and have their own "amphetamine-like" actions (8). Which, if any, of these mechanisms are involved with acute potentiation of sympathomimetic effects is completely unknown.

The clinical course of sympathomimetic-MAO inhibitor interaction is similar whether it temporally follows a dose of a sympathomimetic or an MAO inhibitor. The history in our patient suggests the latter, but given the unreliability of drug histories this cannot be proven.

## TREATMENT

Optimum treatment of MAO inhibitor-sympathomimetic interaction toxicity is prevention. Patients taking MAO inhibitors should be cautioned against eating foods high in tyramine (e.g. cheeses, beer, wine, yogurt), and should be told to consult their physician before using any other medication. Treatment of toxicity due to sympathomimetic-MAO inhibitor interaction is directed at controlling the life-threatening sequelae rather than at removal of the involved drugs. Although MAO inhibitor effects persist, the agents themselves are rapidly eliminated without intervention (5,25). Although not studied for MDMA, based on its similarity to other amphetamines, enhanced elimination is unlikely to be indicated. For other amphetamines, extracorporeal treatment is ineffective (4). Urinary acidification enhances urinary elimination of other amphetamines, but has not been shown to improve the clinical course after overdose (4). Renal toxicity due to myoglobinuria may be increased in the face of an acid urine. In view of the unproven clinical benefits, and the possible risk of rhabdomyolysis and myoglobinuria in these patients, urinary acidification should be avoided. Standard therapies for hypertensive crisis (nitroprusside, phentolamine) hyperpyrexia (cooling measures, dantrolene, pancuronium), seizures (diazepam, phenytoin), and rhabdomyolysis (hydration, mannitol) should be instituted when indicated. Intracranial hemorrhage is the most common cause of death from MAO inhibitor-sympathomimetic interactions, and must be considered early.

## CONCLUSION

With a resurgence in the use of MAO inhibitors as antidepressants, and the rising popularity of MDMA, physicians must be aware of the potential toxicity which may result from taking these two agents in combination. This case report illustrates this toxicity, but the dosing requirements needed to cause such interactions remain speculative. In view of the serious potential for toxicity, patients on MAO inhibitors should be educated to avoid MDMA completely.

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