3,4-METHYLENEDIOXYMETHAMPHETAMINE
CASRN: 42542-10-9

Human Health Effects:

Toxicity Summary:

Many of the risks users face with MDMA are ... Psychological difficulties, including confusion, depression, sleep problems, drug craving, severe anxiety, and paranoia - during and sometimes weeks after taking MDMA (even psychotic episodes have been reported); Physical symptoms such as muscle tension, involuntary teeth clenching, nausea, blurred vision, rapid eye movement, faintness, and chills or sweating; Increases in heart rate and blood pressure, a special risk for people with circulatory or heart disease. Recent research findings also link MDMA to long-term damage to those parts of the brain critical to thought and memory. It is thought that the drug causes damage to the neurons that use the chemical serotonin to communicate with other neurons. ... Also there is evidence that people who develop a rash that looks like acne after using MDMA may be risking severe side effects, including liver damage, if they continue to use the drug. ... Research shows that MDA destroys serotonin-producing neurons in the brain, which play a direct role in regulating aggression, mood, sexual activity, sleep, and sensitivity to pain. It is probably this action on the serotonin system that gives MDMA its purported properties of heightened sexual experience, tranquility, and conviviality.


The stimulant effects of MDMA, which enable users to dance for extended periods, may also lead to dehydration, hypertension, and heart or kidney failure. MDMA can be extremely dangerous in high doses. It can cause a marked increase in body temperature (malignant hyperthermia) leading to the muscle breakdown and kidney and cardiovascular system failures reported in some fatal cases at raves. MDMA use may also lead to heart attacks, strokes, and seizures in some users.


Human Toxicity Excerpts:

... Studies in human (+ or -)3,4-Methylenedioxyamphetamine (MDMA ...) users probing for evidence of brain serotoninergic neurotoxicity indicate that some MDMA users may incur MDMA-related serotonin injury and possibly functional sequelae. In particular, MDMA users have selective decrements in cerebrospinal fluid 5-hydroxyindolacetic acid and brain serotonin transporters, similar to nonhuman primates with documented MDMA induced neurotoxicity. Functional abnormalities seen in MDMA users that may be related to serotonin injury include cognitive defects, altered sleep architecture, altered neuroendocrine function, altered behavioral
The social use of ecstasy (MDMA) and amphetamines is widespread in the United Kingdom and Europe. Deaths have occurred and hepatotoxicity has featured in many cases of intoxication with amphetamine or its methylenedioxy analogs such as ecstasy. Recreational use of these drugs presents an important but often concealed cause of hepatitis or acute liver failure, particularly in young people.

A 53 yr old prisoner expired from multiorgan failure after a suicidal overdose with 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy). Twelve hr after ingestion of MDMA, the patient became severely hyperthermic (107 deg F) with evidence of rhabdomyolysis. He developed acute respiratory distress syndrome (ARDS), disseminated intravascular coagulopathy (DIC) and acute renal failure.

A 37 yr old woman who presented with recurrent hepatitis following the ingestion of ecstasy is detailed. After several months she developed liver cirrhosis shown by biopsy and CT scanning.

A 17 yr old male presented with horizontal diplopia in all directions of gaze after have taken MDMA tablets at 5 day to 7 day intervals during a 2 mo period. Examination detailed bilateral sixth nerve palsey. Ocular motility returned to normal within 5 days without use of MDMA and with no other treatment.

The consumption of the drug ecstasy by young people is incr rapidly. Seizures are among the most common clinical complications of the CNS following the ingestion of ecstasy. This report presents the case of a 21 yr old patient who had a series of grand mal seizures after taking 12 tablets of ecstasy. 36 hr after ingestion the drug was demonstrated at a level of 300 ng/ml in the serum and CSF.

Prospective follow up of 136 babies exposed to ecstasy in utero showed that the drug may be associated with a significantly incr risk of congenital defects (15.4% 95% CI 8.2-25.4). Cardiovascular anomalies (26 per 1000 live births, 3.0-90.0) and musculoskeletal anomalies (38 per 1000, 8.0-109.0) were predominant.

3,4-Methylenedioxymethamphetamine (MDMA) releases serotonin and dopamine. The effect of pretreatment with haloperidol (1.4 mg iv) on psychological and physiological responses to MDMA (1.5 mg/kg po) in 14 healthy volunteers using a
double blind placebo controlled within subject designed /was evaluated/. ... The physiological effects measured were blood pressure, heart rate and body temperature. Side effects were assessed during the session and after 1 and 3 days. Haloperidol attenuated MDMA induced positive and mania mood but had no reducing effect on other subjective changes or cardiovascular effects. ...


Ecstasy is a synthetic amphetamine which causes a wide variety of adverse effects. Hepatic toxicity was only recently demonstrated but can be quite severe. ... A 27 yr old male with no past medical or surgical history developed jaundice without fever. / This individual/ was a regular user of ecstasy and had recently incr the number of doses consumed. No evidence of viral, alcoholic, metabolic or autoimmune mechanism was found which could explain the hepatitis. Complete cure was obtained by discontinuing ecstasy. ... The liver disease has been reported to range from acute regressive hepatitis to fatal liver failure. Iterative exposure can lead to fibrosis. ...


A common undesired effect of MDA is periodic tensing of the muscles in the neck, tightening of the jaw, and grinding of the teeth. Other side effects include erratic behavior, delirium, temporary amnesia, and neuropsychiatric sequelae. Several deaths have been associated with MDA. /3,4-Methylenedioxymethylamphetamine/ [Gossel, T.A., J.D. Bricker. Principles of Clinical Toxicology. 3rd ed. New York, NY: Raven Press, Ltd., 1994., p. 375]**PEER REVIEWED**

MDA has mild sympathomimetic properties, such as mydriasis, and produces stimulatory effects especially on the respiratory center. It produces a sense of physical well-being with heightened tactile sensations. /3,4-Methylenedioxymethylamphetamine/ [Gossel, T.A., J.D. Bricker. Principles of Clinical Toxicology. 3rd ed. New York, NY: Raven Press, Ltd., 1994., p. 375]**PEER REVIEWED**

Five deaths have been associated with finding MDMA or MDEA in the blood. One death was due to trauma; MDMA was found in the blood, but the quantity was not measured. Another death was also due to trauma; butalbital 0.8 mg/l (3.6 umol/l) as well as MDEA 950 ng/mL (4.6 umol/L) was detected in the blood. One death was associated with a history of recent alcohol use; the blood MDMA level was 1.1 mg/L (5.7 umol/L). A fourth fatality was a healthy 18 year old woman who ingested approximately 150 mg of MDMA and an unknown amount of alcohol; she developed ventricular fibrillation and died; her blood showed an MDMA concentration of 1.0 mg/L (5.1 umol/L) and an ethanol level of 40 mg/dL (8.7 umol/l). The fifth death followed ingestion of three capsules (approximately 300 mg), alcohol, and propoxyphene; the postmortem blood level of MDEA was 2.0 mg/l (9.7 umol/l). Thus, one patient appears to have died directly from MDMA (ventricular fibrillation), and the other four deaths may have resulted from trauma or an underlying disease exacerbated by the use of MDMA or MDEA.

[Ellenhorn, M.J., S. Schonwald, G. Ordog, J. Wasserberger. Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning. 2nd ed. Baltimore, MD:
Two patients developed a chronic paranoid psychosis after chronic abuse of repeated (usually high) doses (eg, 80-85 mg) of MDMA. Misuse of MDMA has also been associated with flashbacks, anxiety, panic confusion, suicidal depression, and insomnia.

Acute severe complications may follow use of MDMA and include convulsions, collapse, hyperthermia disseminated intravascular coagulation, rhabdomyolysis, acute renal failure, cerebral infarcts, hemorrhage, and death. Some who take the drug for the first time may experience paranoia, hallucinations, insomnia, tachycardia, or muscle stiffness including trismus and bruxism. These acute effects usually resolve within 48 hours.

... A 34 year old man with a history of Wolff-Parkinson-White syndrome died; postmortem toxicology revealed MDMA in the blood (2,000 ng/ml) and urine (50,000 ng/ml). Ingestion of MDMA may result in life threatening events or exacerbation of coronary artery disease, asthma, or underlying cardiomyopathy.

Tolerance occurs. Some users increase the dose over weeks or months of use to as many as 10 or more tablets during the course of an evening.

Ecstasy use has been followed by sudden hypertensive crises with spontaneous intracerebral hemorrhage, noncardiac chest pain, a toxic hepatitis, an acute or chronic paranoid psychosis, congestive or mild memory impairment in function, cardiac arrhythmias, and death.

Regular users ... may present with weight loss, exhaustion, jaundice, flashbacks, irritability, paranoia, depression, or psychosis. Repeated use may endanger hepatic function. Chest pain, tachycardia, hyperkalemia, and spontaneous intracranial hemorrhage have been observed.
... The present study utilized positron emission tomography in conjunction with the serotonin transporter ligand (11)C-McN-5652 to assess the status of brain serotonin neurons in human MDMA users. Individuals with a history of MDMA use showed lasting decrements in global brain (11C-McN-5652 binding with decre in (11) C-McN-5652 binding positively correlated to the extent of previous MDMA use. These results suggest that human MDMA use results in brain serotonin neurotoxicity. [Ricaurte GA, et al; Toxicol Lett 15: 112-13, 143-6 (2000)]**PEER REVIEWED**

Ingestion of MDMA (ecstasy) by humans can cause acute toxicity manifested by hyperthermia and death. Demethylenation of MDMA is catalyzed by cytochrome p450 2D6 (CYP2D6) and cytochrome p450 2D1 (CYP2D1) in humans and rats, respectively, and is polymorphically expressed. It has been proposed that CYP2D6 deficiency may account for the unexplained toxicity of MDMA. [Malpass A, et al; Pharmacol Biochem Behav 64 (1): 29-34 (1999)]**PEER REVIEWED**

The cardiovascular and neuroendocrine effects and pharmacokinetics of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") were assessed in a double-blind, randomized, crossover, and controlled (placebo and amphetamine) clinical trial. Eight men with experience in the recreational use of 3,4-methylenedioxymethamphetamine participated in four 10-hr experimental sessions with a 1-week washout period. Single oral doses of 125 mg and 75 mg of 3,4-methylenedioxymethamphetamine, 40 mg of amphetamine, and placebo were given. Both 3,4-methylenedioxymethamphetamine doses significantly increased blood pressure (increases of 40 mm Hg in systolic blood pressure), heart rate (increases of 30 beats/min), and pupillary diameter (mydriasis) as compared with placebo. Oral temperature did not show significant changes in any drug-active condition. Plasma cortisol levels showed a statistically significant increase after 3,4-methylenedioxymethamphetamine administration. Prolactin levels only increased after high dose of 3,4-methylenedioxymethamphetamine. Cmax values for 125-mg and 75-mg 3,4-methylenedioxymethamphetamine doses were 236.4 and 130.9 ng/ml, and Tmax was observed at 2.4 and 1.8 hr, respectively. Elimination half-life was 8.6 h and 7.7 h for high and low 3,4-methylenedioxymethamphetamine doses, respectively. Amphetamine half-life was 15 hr. Between 8 and 9% of the doses of 3,4-methylenedioxymethamphetamine appeared in plasma in the form of 3,4-methylenedioxyamphetamine. The important cardiovascular effects observed after 3,4-methylenedioxymethamphetamine administration in laboratory conditions at rest (increases of 40 mm Hg in systolic blood pressure and 30 beats/min in pulse rate) could be relevant in terms of toxicity in real-life conditions (eg, crowded places and physical activity). [Mas M et al; J Pharmacol Exp Ther 290 (1): 136-45 (1999)]**PEER REVIEWED**

The recreational drug, (+ or -)3,4-methylenedioxymethamphetamine (MDMA, 'Ecstasy'), is a potent serotonin (5-HT) neurotoxin in animals. Whether humans who use 3,4-methylenedioxymethamphetamine incur 5-HT neural injury is unknown. The
present studies utilized positron emission tomography (PET) in conjunction with the 
in human 3,4-methylenedioxymethamphetamine users. Like nonhuman primates 
treated with neurotoxic doses of 3,4-methylenedioxymethamphetamine, humans with 
a history of 3,4-methylenedioxymethamphetamine use showed lasting decrements in 
positively correlated to the extent of previous 3,4-methylenedioxymethamphetamine 
use. These results suggest that human 3,4-methylenedioxymethamphetamine use 
results in brain 5-HT neurotoxicity.
[Ricaurte GA et al; Toxicol Lett 112-3: 143-6 (2000)]
**PEER REVIEWED**

Since the last few years thousands of teenagers and young adults in the Netherlands 
participate in so called "houseparties", mostly during weekends. The majority (ab)uses 
ecstasy during those parties. As a result TIS Bilthoven is frequently consulted about 
ecstasy exposure in pregnancy. The tablets sold as ecstasy may contain pure MDMA 
(methylene dioxy methamphetamine = ecstasy) or MDA (methylene 
dioxyamphetamine), MDEA (methylene dioxy ethyl amphetamine), amphetamine and 
others. To our knowledge there are no published human studies of exposures to 
ecstasy during pregnancy. TIS Bilthoven collected prospectively data on 49 such 
pregnancies. Ecstasy was mostly used in weekends, weekly or incidentally. In 47 cases 
exposure occurred only during the first trimester of pregnancy, while 2 women were 
exposed in the second trimester only. Twenty-one (43%) of the mothers took other 
drugs as well: cocaine (n = 10), cannabis (n = 10) and others. At least 34% used 
alcohol, some of them quite a lot (more than 3 units/day or binge drinking). At least 
63% smoked cigarettes. The mean age of the mothers was 26 (range: 17-44). Only two 
of the pregnancies were known as planned. Before this pregnancy 7 mothers had 
already had an induced abortion once or more (induced abortion ratio: 52/100 
pregnancies). Of the 49 pregnancies, follow-up data are completed for 38 pregnancies.
There were two spontaneous abortions and two elective terminations of pregnancy. 
Post mortem data on one of these induced abortions suggested an omphalocele (this 
mother's first pregnancy was spontaneously aborted). There were 36 liveborn normal 
babies including 6 premature babies (1 triplet) and one with neonatal drug withdrawal 
effects. One term baby had a congenital heart defect and died a few hours after birth, 
this infant was exposed to ecstasy alone. Conclusion: The sample presented here is too 
small to draw conclusions. As yet spontaneous abortion and congenital malformations 
do not seem to occur more frequently. On the other hand, the lifestyle of ecstasy-users 
is potentially harmful for pregnancy and child.
[van Tonningen MR et al; Teratology 58 (1): 33A (1998)]
**PEER REVIEWED**

**Human Toxicity Values:**

Lethal blood concentrations cited have ranged from 0.4 to 2.6 mg/dL. /3,4-
Methylenedioxymethamphetamine/
Toxicology. 3rd ed. New York, NY: Raven Press, Ltd., 
1994., p. 375]**PEER REVIEWED**

**Populations at Special Risk:**
... Individuals with prior psychiatric histories may have an increased susceptibility to the adverse effects of MDMA. In such individuals a single dose of MDMA may be sufficient to produce an enduring psychiatric illness.


It has been proposed that CYP2D6 /cytochrome p450 2D6/ deficiency may account for the unexplained toxicity /SRP: hyperthermia, death/ of MDMA.


Probable Routes of Human Exposure:

The 1998 survey /National Household Survey on Drug Abuse conducted by the Substance Abuse and Mental Health Services Administration/ found that an estimated 1.5 percent (3.4 million) of Americans at least 12 years old had used MDMA at least once during their lifetime. By age group, the heaviest use (5 percent or 1.4 million people) was reported for those between 18 and 25 years old.

National Institute on Drug Abuse Infofax on ECSTASY. Available from

MDMA is used most often by young adults and adolescents at clubs, raves (large, all-night dance parties) and rock concerts.

National Institute on Drug Abuse (NIDA) Infofax on ECSTASY. Available from

Emergency Medical Treatment:

Emergency Medical Treatment:

EMT Copyright Disclaimer:
Life Support:
  o This overview assumes that basic life support measures have been instituted.

Clinical Effects:
0.2.1 SUMMARY OF EXPOSURE

0.2.1.1 ACUTE EXPOSURE

A) AMPHETAMINE ABUSE - By ingestion, injection, nasal insufflation or smoking, commonly causes hypertension, tachycardia, agitation, paranoia, delusions, and hyperactivity. Serious overdose may result in hyperthermia, seizures, dysrhythmias, coma, rhabdomyolysis, renal failure, hepatic injury or coagulopathy.

1) Myocardial infarction, aortic dissection, intracranial bleeding or ischemic stroke are possible complications. Chronic abuse is associated with weight loss, cerebral vasculitis, and bruxism. Inadvertent arterial injection may cause vasospasm and ischemia.

B) METHYLPHENIDATE - Central toxic effects may range from restlessness, irritability, and insomnia to marked hyperactivity, seizures, hypertension, and coma. Paranoia and self-destructive behavior has been reported in children.

C) ICE - A form of methamphetamine that has appeared primarily in Hawaii and California. Termed "ice" due to its clear, crystalline appearance, it is smoked, insufflated or injected and produces an almost instantaneous "rush" similar to intravenous methamphetamine. Its effects reportedly last from 8 to 24 hours, and severe psychoses have been reported after its use.

D) CHRONIC USE can result in heart failure, malnutrition, permanent psychiatric illness, and infection.

1) BODY PACKERS/BODY STUFFERS - Please refer to the appropriate management if body packing or body stuffing is known/suspected.

0.2.3 VITAL SIGNS

0.2.3.1 ACUTE EXPOSURE

A) Severe hyperthermia may develop. Hypertension and tachycardia are common.

0.2.5 CARDIOVASCULAR

0.2.5.1 ACUTE EXPOSURE

A) Hypertension and tachycardia are common; cardiovascular collapse may occur in severe intoxications. Dysrhythmias, myocardial ischemia or infarction, ventricular dysfunction and aortic dissection may occur.

0.2.6 RESPIRATORY

0.2.6.1 ACUTE EXPOSURE

A) Tachypnea is common. Pulmonary hypertension has been associated with chronic use or abuse which may result from contaminants. Pulmonary edema and ARDS are unusual complications of severe exposure.

0.2.7 NEUROLOGIC

0.2.7.1 ACUTE EXPOSURE

A) Agitation, confusion, paranoia, delirium, hallucinations, restlessness, hyperactivity, talkativeness, irritability, insomnia, and headache are common. Chorea, dystonia, fasciculations, muscle rigidity, tics, and tremors may develop. Seizures and coma may occur with severe intoxication. Other neurological effects have included stroke and cerebral vasculitis. Serotonin syndrome has occurred.

0.2.8 GASTROINTESTINAL

0.2.8.1 ACUTE EXPOSURE

A) Vomiting, diarrhea, cramps, anorexia and gastrointestinal hemorrhage may occur.

B) Ischemic colitis has occurred with chronic methamphetamine abuse.

0.2.9 HEPATIC

0.2.9.1 ACUTE EXPOSURE
Laboratory:
   A) Monitor core temperature. Hyperthermia above 40 degrees C is life threatening and mandates immediate cooling and sedation.
   B) Monitor serum electrolytes, renal and hepatic function and CPK, obtain an ECG and institute continuous cardiac monitoring in symptomatic patients.

Treatment Overview:
0.4.2 ORAL EXPOSURE

A) Do Not Induce Emesis.

B) ACTIVATED CHARCOAL: Administer charcoal as a slurry (240 mL water/30 g charcoal). Usual dose: 25 to 100 g in adults/adolescents, 25 to 50 g in children (1 to 12 years), and 1 g/kg in infants less than 1 year old.

C) Consider gastric lavage in patients with recent large ingestions.

D) SEIZURES - Administer diazepam IV bolus (DOSE: ADULT: 5 to 10 mg initially, repeat every 5 to 10 minutes as needed. CHILD: 0.2 to 0.5 mg/kg initially, repeat every 5 minutes as needed) or lorazepam IV bolus (DOSE: ADULT: 4 to 8 mg; CHILD: 0.05 to 0.1 mg/kg). Monitor for hypotension, respiratory depression and the need for endotracheal intubation.

1) Consider phenobarbital if seizures are uncontrollable or recur after diazepam 50 mg (adults) or 10 mg (children > 5 years).

E) HYPERTENSION - Hypertension is generally transient and frequently does not require pharmacologic treatment unless severe. Hypertension requiring treatment often responds to sedation with IV benzodiazepines. Administer 5 to 10 mg diazepam every 5 to 10 minutes until agitation is controlled. Hypertension not responding to sedation is best managed with IV nitroprusside. Begin IV infusion at 0.5 to 1 mcg/kg/min and titrate slowly to desired response.

F) ARTERIAL SPASM - Heparinization and intravenous or intra-arterial nitroprusside may be effective.

G) HYPERACTIVITY - Administer 5 to 10 mg of diazepam IV (0.1 to 0.3 mg/kg in children). Repeat every 5 to 10 minutes as needed. Extreme agitation and hallucinations may respond to IV droperidol.

1) CAUTION - DROPERIDOL: Based on cases of QT prolongation and/or torsades de pointes in patients receiving droperidol at doses at or below recommended dosing, it should be reserved for use in patients who fail to show an acceptable response to other agents.

2) A baseline ECG (repeat as indicated), and continuous cardiac monitoring for 3 hours are recommended for all patients receiving droperidol.

H) HYPERTHERMIA - Treat with sedation (IV benzodiazepines) and external cooling. Accelerate evaporative cooling by wetting the patient's skin and putting fans in the room.

I) RHABDOMYOLYSIS: Administer sufficient 0.9% saline to maintain urine output of 2 to 3 mL/kg/hr. Monitor input and output, serum electrolytes, CK, and renal function. Diuretics may be necessary to maintain urine output. Urinary alkalinization is NOT routinely recommended.

J) VENTRICULAR DYSRHYTHMIAS/SUMMARY: Institute continuous cardiac monitoring, obtain an ECG, and administer oxygen. Evaluate for hypoxia, acidosis, and electrolyte disorders. Lidocaine and amiodarone are generally first line agents for stable monomorphic ventricular tachycardia, particularly in patients with underlying impaired cardiac function. Sotalol is an alternative. Amiodarone and sotalol should be used with caution if a substance that prolongs the QT interval and/or causes torsades de pointes is involved in the overdose. Unstable rhythms require cardioversion.

Range of Toxicity:
A) Fatalities have been reported following ingestion as low as 1.3 mg/kg of amphetamine and 5 mg/kg methylphenidate. Clinical observation of toxic effects is more relevant than an estimate of the ingested dose.

B) METHYLPHENIDATE - doses of less than 1 mg/kg in pediatric patients have not been associated with toxicity. A fatality was reported in a young adult following intranasal abuse of methylphenidate.

C) 4-methylthioamphetamine (4-MTA), an amphetamine derivative, has resulted in death in a young adult in the United Kingdom.

Antidote and Emergency Treatment:

Basic treatment: Establish a patent airway. Suction if necessary. Watch for signs of respiratory insufficiency and assist ventilations if needed. Administer oxygen by nonrebreather mask at 10 to 15 L/min. Monitor for pulmonary edema and treat if necessary ... . Monitor for shock and treat if necessary ... . Anticipate seizures and treat if necessary ... . For eye contamination, flush eyes immediately with water. Irrigate each eye continuously with normal saline during transport ... . Do not use emetics. For ingestion, rinse mouth and administer 5 ml/kg up to 200 ml of water for dilution if the patient can swallow, has a strong gag reflex, and does not drool ... . Cover skin burns with dry sterile dressings after decontamination ... .

Advanced treatment: Consider orotracheal or nasotracheal intubation for airway control in the patient who is unconscious, has severe pulmonary edema, or is in respiratory arrest. Positive pressure ventilation techniques with a bag valve mask device may be beneficial. Monitor cardiac rhythm and treat arrhythmias as necessary ... . Start an IV with D5W /SRP: "To keep open", minimal flow rate/. Use lactated Ringer's if signs of hypovolemia are present. Watch for signs of fluid overload. Consider drug therapy for pulmonary edema ... . For hypotension with signs of hypovolemia, administer fluid cautiously. Watch for signs of fluid overload ... . Treat seizures with diazepam (Valium) ... . Use proparacaine hydrochloride to assist eye irrigation ... .

Animal Toxicity Studies:

Toxicity Summary:
Many of the risks users face with MDMA are ... Psychological difficulties, including confusion, depression, sleep problems, drug craving, severe anxiety, and paranoia - during and sometimes weeks after taking MDMA (even psychotic episodes have been reported); Physical symptoms such as muscle tension, involuntary teeth clenching, nausea, blurred vision, rapid eye movement, faintness, and chills or sweating; Increases in heart rate and blood pressure, a special risk for people with circulatory or heart disease. Recent research findings also link MDMA to long-term damage to those parts of the brain critical to thought and memory. It is thought that the drug causes damage to the neurons that use the chemical serotonin to communicate with other neurons. ... Also there is evidence that people who develop a rash that looks like acne after using MDMA may be risking severe side effects, including liver damage, if they continue to use the drug. ... Research shows that MDA destroys serotonin-producing neurons in the brain, which play a direct role in regulating aggression, mood, sexual activity, sleep, and sensitivity to pain. It is probably this action on the serotonin system that gives MDMA its purported properties of heightened sexual experience, tranquility, and conviviality.


The stimulant effects of MDMA, which enable users to dance for extended periods, may also lead to dehydration, hypertension, and heart or kidney failure. MDMA can be extremely dangerous in high doses. It can cause a marked increase in body temperature (malignant hyperthermia) leading to the muscle breakdown and kidney and cardiovascular system failures reported in some fatal cases at raves. MDMA use may also lead to heart attacks, strokes, and seizures in some users.


Non-Human Toxicity Excerpts:

... The purpose of this ... study was to determine whether brain serotonin deficits persist in squirrel monkeys beyond the 18 month period studied previously and to identify factors that influence recovery of /MDMA/ injured serotonin axons. Seven years after treatment, abnormal brain serotonin innervation patterns were still evident in MDMA treated monkeys although serotonin deficits in some regions were less severe than those observed at 18 months. No loss of serotonin nerve cell bodies in the rostral raphe nuclei was found, indicating that abnormal innervation patterns in MDMA treated monkeys are not the result of loss of a particular serotonin nerve cell group. Factors that influence recovery of serotonin axons after MDMA injury are: the distance of the affected axon terminal field from the rostral raphe nuclei; the degree of initial serotonin axonal injury, and possibly the proximity of damaged serotonin axons to myelinated fiber tracts. ...


The effects of acute admin of 3,4-methylenedioxymethamphetamine ... on anxiety tested in the light/dark box was examined in albino male mice of the OF.1 strain.
Animals were evaluated in the light/dark test 30 min after injection of 3,4-methylenedioxymethamphetamine (1, 8, and 15 mg/kg, ip) or saline. The following parameters were recorded (for 5 min); (a) number of exploratory rearings in the light and dark sections; (b) number of transitions between the lit and dark areas; (c) time spent in the light and dark areas; (d) latency of the initial movement from the light to dark area, and (e) locomotor activity in light area. ... 3,4-Methylenedioxymethamphetamine (8 and 15 mg/kg) produced a significant reduction in exploratory activity (rearings and transitions), without decreas motility, in comparison with saline treated mice. ... Time spent in light/dark compartments was not significantly affected by the drug, which could be a consequence of the anti-exploratory properties of 3,4-methylenedioxymethamphetamine.


... The effect of the serotonin releasing amphetamine ... methylenedioxymethamphetamine ... on immunity in rats. ... MDMA reduced the number of circulating lymphocytes, provoked a suppression of Con A stimulated lymphocyte proliferation and total IFN gamma and IL-10 production in diluted whole blood cultures. ... When Con A stimulated cytokine production was normalized for the number of lymphocytes in culture in order to examine cytokine production at the cellular level ... MDMA had the ability to suppress production of Th2 type cytokine IL-10. ... MDMA incr the secretion of the Th1 type cytokine IL-2 without altering the related Th type cytokine IFN-gamma. ... MDMA inhibited LPS induced TNF-alpha secretion from diluted whole blood cultures suggesting that /MDMA/ impairs macrophage activity following treatment.


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The ... purpose of this study was to examine the effects of single and repeated admin ... of 3,4-methylenedioxymethamphetamine (MDMA) ... on rat liver. Animals were / admin/ (20 mg/kg) and repeated (20 mg/kg, bid) for 4 consecutive days) ip dose of MDMA and at various times after admin the hepatic and serum determinations were made. The effect of acute MDMA admin included incr triglyceride and cholesterol levels and an incr in all enzyme activities 6 hr post admin. ... Glycogen content showed a marked decreas, which was accompanied by a decreas in serum glucose levels. No significant changes in lipid peroxidation and hepatic GSH content were observed. In contrast, multiple MDMA admin produced some evidence of oxidative stress, namely, incr MDA content and decreas GHS content, a small decreas in liver glycogen at 3 hr recovering 6 hr post dose, no effect on blood glucose and incr AST and ALP activities but no effect on ALT activity. Seven days after the last MDMA injection a tendency towards recovery was shown.


Hepatocellular damage has been reported as a consequence of 3,4-methylenedioxymethamphetamine (MDMA) intake. ... The present study was undertaken to evaluate the effects of MDMA on cell viability as well as free calcium levels (Ca2+) in short term cultured hepatocytes. Reduced glutathione (GSH), adenosine-5’-triphosphate (ATP) and lipid peroxidation were investigated to evaluate the toxic effect of MDMA, in vitro using freshly isolated rat hepatocytes. ... A sustained rise of (Ca+2) after injection of MDMA was /noted/. In (Ca+2) free
medium, MDMA caused a reduced incr of (Ca+2). On the other hand, MDMA (0.1-5 mM) induced a concn dependent and time exposure dependent GSH and ATP deletion. Although it did not reach statistical significance, GSH deficits were accompanied by a tendency to incr lipid peroxidation 3 hr after MDMA incubation. ...

Demethylenation of MDMA is catalyzed by cytochrome p450 2D6 (CYP2D6) and cytochrome p450 2D1 (CYP2D1) in humans and rats, respectively, and is polymorphically expressed. It has been proposed that CYP2D6 deficiency may account for the unexplained toxicity of MDMA. The female Dark Agouti rat is deficient in CYP2D1 and serves as a model for the human poor metabolizer. ...
Thermogenic and locomotor actions of MDMA in adult female Sprague-Dawley (CYP2D1 replete) and Dark Agouti rats /were examined in this study/. MDMA (2.5 and 10 mg/kg) and saline were injected sc at ambient temperatures of 22 and 31 deg C. There was no difference in core temperature responses between the two rat strains. Hypothermia occurred in the first 30 min and temperature elevation thereafter. MDMA incr locomotor activity in Sprague-Dawley but not in Dark Agouti rats. ... MDMA had pronounced lethal effects at 31 deg C ambient in Dark Agouti rats only. ...

Direct injection of either 3,4-(:)-methylenedioxyamphetamine (MDMA) or 3,4-(:)-methylenedioxyamphetamine (MDA) into the brain fails to reproduce the serotonergic neurotoxicity seen following peripheral administration. The serotonergic neurotoxicity of 3,4-(:)-methylenedioxyamphetamine and 3,4-(:)-methylenedioxyamphetamine therefore appears to be dependent upon the generation of a neurotoxic metabolite, or metabolites, the identity of which remains unclear. alpha-Methyldopamine (alpha-MeDA) is a major metabolite of both 3,4-(:)-methylenedioxyamphetamine and 3,4-(:)-methylenedioxyamphetamine. We have shown that intracerebroventricular (icv) injection of 2,5-bis(glutathion-S-yl)-alpha-methyldopamine (2,5-bis(glutathion-S-yl)-alpha-MeDA) causes decreases in serotonin concentrations in the striatum, cortex, and hippocampus, and neurobehavioral effects similar to those seen following 3,4-(:)-methylenedioxyamphetamine and 3,4-(:)-methylenedioxyamphetamine administration. In contrast, although 5-(glutathion-S-yl)-alpha-methyldopamine (5-(glutathion-S-yl)-alpha-MeDA) and 5-(N-acetylcysteine-S-yl)-alpha-methyldopamine (5-(N-acetylcystein-S-yl)-alpha-MeDA) produce neurobehavioral changes similar to those seen with 3,4-(:)-methylenedioxyamphetamine and 3,4-(:)-methylenedioxyamphetamine administration, and acute changes in brain 5-HT and dopamine concentrations, neither conjugate caused long-term decreases in 5-HT concentrations. We now report that direct intrastratial and intra cortical administration of 5-(glutathion-S-yl)-alpha-MeDA (4a-MeDA (4a-MeDA (4in striatal and cortical 5-HT concentrations (7 days following the last injection). Interestingly, intrastratial injection of 5-(glutathion-S-yl)-alpha-MeDA or 2,5-bis(glutathion-S-yl)-alpha-MeDA, but not 5-(N-acetylcystein-S-yl)-alpha-methyldopamine, also caused decreases in 5-HT concentrations in the ipsilateral cortex. The same pattern of changes was seen when the conjugates were injected into the cortex. The effects of the thioether conjugates of alpha-MeDA were confined to 5-HT nerve terminal fields, since no significant changes in monoamine neurotransmitter levels were detected in brain regions enriched with 5-HT cell bodies
Our study was aimed at analyzing the basis for the apparent lack of perinatal sensitivity to the serotonergic neurotoxin 3, 4-methylenedioxymethylamphetamine (MDMA, "ecstasy"). 3, 4-methylenedioxymethylamphetamine (20 mg/kg s. c.) repeatedly administered to rat dams during gestation, did not affect [3H]paroxetine-labeled serotonin (5-HT) transporter density and [3H]paroxetine-labeled serotonin content in the offspring. A single dose of 3, 4-methylenedioxymethylamphetamine was then given to pups, not exposed prenatally to 3, 4-methylenedioxymethylamphetamine, at different postnatal ages (PND14, 21, 28 and 35). Long-term significant reductions in [3H]paroxetine-labeled serotonin levels in all the brain regions examined were only found at PND35. In a different set of experiments, 3, 4-methylenedioxymethylamphetamine administered at PND21 alone or in combination with (R)-1-(2, 5-dimethoxy-4-iodophenyl)2-aminopropane (R-DOI, 0.5 mg/kg sc), or L-3,4-dihydroxyphenylalanine (L-DOPA, 80 mg/kg sc), caused a significant hyperthermia in the pups. However, only L-3,4-dihydroxyphenylalanine followed by 3, 4-methylenedioxymethylamphetamine caused a lasting reduction of [3H]paroxetine-labeled serotonin levels and [3H]paroxetine-labeled serotonin transporter density in the hippocampus and in the frontal cortex. In adult animals, no change in [3H]paroxetine-labeled serotonin levels and [3H]paroxetine-labeled serotonin transporter density in different brain regions was either found when 3, 4-methylenedioxymethylamphetamine was given to rats previously lesioned with 6-hydroxydopamine, but a significant reduction was again found in the lesioned animals receiving 3, 4-methylenedioxymethylamphetamine in combination with L-3,4-dihydroxyphenylalanine. These results appear to indicate that the hyperthermia induced by 3, 4-methylenedioxymethylamphetamine is not sufficient to produce lasting neurotoxic effects on the serotonergic system, at least at PND21, and support an important role for dopamine in the mechanism of neurotoxicity of 3, 4-methylenedioxymethylamphetamine, suggesting that an already developed dopaminergic system is necessary for the expression of the serotonergic deficits.

**Peer Reviewed**

Neonatal 3,4-methylenedioxymethylamphetamine administration to rats was investigated to test the hypothesis that developmental exposures of stimulant drugs of abuse alter the ontogeny of cognitive function. Saline, 5, 10 or 20 mg/kg 3,4-methylenedioxymethylamphetamine was administered sc. twice daily with an eight hour dose interval to rat pups on postnatal days (P) 1-10 or P11-20. The pups began Cincinnati water maze testing at an average age of P63 (range = P59 to P68). Cincinnati water maze testing consisted of two 5 min sessions per day for 4 days on "path B". Dependent measures were latency and errors. 3,4-methylenedioxymethylamphetamine administration at P1-10 did not significantly alter performance in the
maze. In contrast, 3,4-methylenedioxyamphetamine administration at P11-20 resulted in significantly increased latencies (F3,84 = 3.90, p = 0.012) and errors (F3,84 = 3.47, p = 0.020). The mean latencies of pups treated with 5 and 20 mg/kg 3,4-methylenedioxyamphetamine on P11-20 were increased by 19 sec (p = 0.021) and 28 sec (p = 0.002), respectively, in comparison to the saline treated pups (x = 131 sec). The mean number of errors of pups treated with 5, 10 and 20 mg/kg 3,4-methylenedioxyamphetamine were increased by 2.6 (p = 0.019), 2.2 (p = 0.046) and 3.3 (p = 0.003), respectively, in comparison to the saline treated pups (x = 12.4 errors). These results demonstrate for the first time that developmental exposure to 3,4-methylenedioxyamphetamine can disrupt performance in a task of learning and memory. Furthermore these alterations in maze performance appear to be confined to the P11-20 exposure period.

[Broening HW et al; Neurotoxicol Teratol 19 (3): 246 (1997)]**PEER REVIEWED**

Clomethiazole is an effective neuroprotective agent against the degeneration of 5-HT neurones that follows administration of 3,4-methylenedioxyamphetamine (MDMA or 'ecstasy'). Since there is good evidence that free radical formation resulting from auto-oxidation of 3,4-methylenedioxyamphetamine metabolites is responsible for the degeneration we have examined whether clomethiazole is a free radical scavenger. 3,4-methylenedioxyamphetamine (15 mg/kg ip) increased the formation of 2,3- and 2,5-dihydroxybenzoic acids (2,3-DHBA and 2,5-DHBA) from salicylic acid perfused through a microdialysis tube implanted in the hippocampus, indicating increased free radical formation. Clomethiazole (50 mg/kg ip) administered 5 min prior and 55 min post 3,4-methylenedioxyamphetamine prevented both the acute 3,4-methylenedioxyamphetamine-induced hyperthermia and the rise in 2,3- and 2,5-dihydroxybenzoic acids. However, when the temperature of the 3,4-methylenedioxyamphetamine + clomethiazole treated rats was kept elevated to that of the 3,4-methylenedioxyamphetamine treated rats with a homeothermic blanket there was no inhibition of the 3,4-methylenedioxyamphetamine-induced increase in 2,3-dihydroxybenzoic acids or 2,5-dihydroxybenzoic acids. These data suggest firstly that free radical formation is inhibited when the acute 3,4-methylenedioxyamphetamine-induced hyperthermia is prevented. Secondly the data further indicate that clomethiazole has no free radical scavenging activity since the drug produces substantial neuroprotection when 3,4-methylenedioxyamphetamine + clomethiazole treated rats are kept hyperthermic. This conclusion was strengthened by our observation that clomethiazole is a weak inhibitor (IC50 > 1 mM) of lipid peroxidation in synaptosomes when it had been induced by addition of FeCl2 + ascorbic acid.


Administration of 3,4-methylenedioxyamphetamine (4 x 20 mg/kg) to non-transgenic CD-1 mice caused marked depletion in dopamine, 3,4-dihydroxyphenylacetic acid and 5-hydroxytryptamine in the caudate-putamen. There were no significant changes in serotonergic markers in the hippocampus and frontal cortex. Homozygous and heterozygous copper/zinc superoxide dismutase transgenic mice show partial protection against the toxic effects of 3,4-methylenedioxyamphetamine on striatal dopaminergic markers. In addition, 3,4-methylenedioxyamphetamine injections caused marked decreases in copper/zinc superoxide dismutase activity in the frontal cortex, caudate-putamen and hippocampus.
of wild-type mice. Moreover, there were concomitant 3,4-
methylenedioxymethamphetamine-induced decreases in catalase activity in the
caudate-putamen and hippocampus, decreases in glutathione peroxidase activity in the
frontal cortex as well as increases in lipid peroxidation in the frontal cortex, caudate-
putamen, and hippocampus of wild-type mice. In contrast, administration of 3,4-
methylenedioxymethamphetamine to homozygous superoxide dismutase transgenic
mice caused no significant changes in antioxidant enzyme activities nor in lipid
peroxidation. These results provide further substantiation of a role for oxygen-based
radicals in 3,4-methylenedioxymethamphetamine-induced neurotoxicity. The present
data also suggest that free radicals generated during 3,4-
methylenedioxymethamphetamine administration may perturb antioxidant enzymes.
Consequently, there might be further overproduction of free radicals with associated
peroxidative damage to cell membranes and associated terminal degeneration.

[Jayanthi S et al; Neuroscience 91 (4): 1379–87 (1999)]**PEER REVIEWED**

Ingestion of 3,4-methylenedioxymethamphetamine ("ecstasy") by humans can cause
acute toxicity manifested by hyperthermia and death. Demethylation of 3,4-
methylenedioxymethamphetamine is catalyzed by cytochrome p450 2D6 (CYP2D6)
and cytochrome p450 2D1 (CYP2D1) in humans and rats, respectively, and is
polymorphically expressed. It has been proposed that CYP2D6 deficiency may
account for the unexplained toxicity of 3,4-methylenedioxymethamphetamine. The
female Dark Agouti rat is deficient in CYP2D1, and serves as a model for the human
poor metabolizer. We investigated thermogenesis in Sprague-Dawley but not in Dark
Agouti rats. However, 3,4-methylenedioxymethamphetamine had pronounced lethal
effects at 31 deg C ambient in the Dark Agouti rats only. We conclude that the poor
metaboliser phenotype may predispose to lethality, but the mechanism is as yet
unknown.


Rationale: A variety of animal models have shown MDMA (3,4-
methylenedioxymethamphetamine) to be a selective 5-HT neurotoxin, though little is
known of the long-term behavioural effects of the pathophysiology. The widespread
recreational use of 3,4-methylenedioxymethamphetamine thus raises concerns over
the long-term functional sequelae in humans. Objective: This study was designed to
explore both the acute- and post-treatment consequences of a 3-day neurotoxic
exposure to 3,4-methylenedioxymethamphetamine in the rat, using a variety of
behavioural para Finally, post mortem biochemical analyses of (3H) citalopram
binding and monoamine levels were performed. Results: During the 3,4-
methylenedioxymethamphetamine treatment period, an acute 5-HT-like syndrome
was observed which showed evidence of tolerance. Once drug treatment ceased the
syndrome abated completely. During the post-treatment phase, a selective, delay-
dependent, deficit in DNMTP performance developed. Post-mortem analysis
confirmed reductions in markers of 5-HT function, in cortex, hippocampus and
striatum.


Rat whole-brain spheroids were used to assess the intrinsic neurotoxicity of
methylenedioxy-methamphetamine (MDMA, Ecstasy) and two of its metabolites,
dihydroxymethamphetamine (DHMA) and 6-hydroxy-MDMA (6-OH MDMA). Exposure of brain spheroids to MDMA or the metabolite 6-OH MDMA (up to 500 umol/L) for 5 days in culture did not alter intracellular levels of glutathione (GSH), glial fibrillary acidic protein (GFAP) or serotonin (5-HT). In contrast, exposure to the metabolite DHMA, which can deplete intracellular thiols, significantly increased GSH levels (up to 170% of control) following exposure to 50 and 100 umol/L DHMA. There was also a significant reduction in the levels of glial fibrillary acidic protein (GFAP) and GSH by DHMA at the highest concentration tested (500 umol/L) but there was no effect on 5HT. This may constitute a sublethal neurotoxic compensatory response to DHMA in an attempt to replenish depleted intraneural GSH levels following metabolite exposure. Rat whole-brain spheroids may thus be a useful in vitro model to delineate mechanisms and effects of this class of neurotoxin. [Walker TM et al; Cell Biology and Toxicology 15 (3): 137-142 (1999)] **PEER REVIEWED**

This study investigated the effects of chlorpheniramine (CPA, 10-25 mg/kg), diphenhydramine (DIPH, 20 mg/kg), tripelennamine (TRIP, 20 mg/kg), and pyrilamine (PYRI, 20 mg/kg) on 3, 4-methylenedioxymethamphetamine (MDMA, 20 mg/kg x 2)-induced hyperthermia and depletion of indoles in rat brains, on the uptake of serotonin and dopamine into rat synaptosomes, on the binding affinity of chlorpheniramine for biogenic amine transporters in the synaptosomes of rat brain, and on the scavenging hydroxyl free radicals activity. Rats were treated with two injections of 3, 4-methylenedioxyamphetamine, chlorpheniramine, diphenhydramine, tripelennamine, pyrilamine, and saline, alone or in combination of 3, 4-methylenedioxyamphetamine with one of the antihistamines, 6 hr apart and sacrificed 5 days later. Rectal temperature was measured prior to and hourly following the drug injections for 13 hr. As compared to saline controls, 3, 4-methylenedioxyamphetamine increased body temperature and decreased levels of indoles, measured by HPLC, in several brain regions of rats. Chlorpheniramine attenuated and diphenhydramine had no effect on 3, 4-methylenedioxyamphetamine-induced hyperthermia, yet both attenuated the depletion of indoles, whereas pyrilamine and tripelennamine potentiated these effects. Chlorpheniramine inhibited the binding of [(3)H]paroxetine and [(3)H]nisoxetine to the synaptosomes of cerebral cortex and of [(3)H]win 35,428 to the synaptosomes of striatum. Chlorpheniramine, diphenhydramine, tripelennamine, and pyrilamine inhibited [(3)H]serotonin uptake. Chlorpheniramine, pyrilamine, and tripelennamine, but not diphenhydramine, scavenge hydroxyl radicals. Possible mechanisms of the different effects of the antihistamines on 3, 4-methylenedioxyamphetamine-induced hyperthermia and depletion of serotonin are discussed. [Yeh SY et al; Synapse 33 (3): 207-17 (1999)] **PEER REVIEWED**

**Metabolism/Pharmacokinetics:**

**Metabolism/Metabolites:**

A clinical trial was designed for the evaluation of 3,4-methylenedioxyamphetamine (MDMA) pharmacological effects and pharmacokinetics in healthy volunteers. ... A total of 14 subjects were included. In the pilot phase 6 received MDMA at 50 (n=2) and 150 mg (n=2). In the second phase 8
received MDMA at both 75 and 125 mg (n=8). Subjects were phenotyped for CYP2D6 activity and were classified as extensive metabolizers for substrates, such as MDMA whose hepatic metabolism is regulated by this enzyme. Plasma and urine samples were collected throughout the study for the evaluation of MDMA pharmacokinetics. Body fluids were analyzed for the determination of MDMA and its main metabolites 3,4-methylenedioxyamphetamine, 4-hydroxy-3-methoxy-methamphetamine and 4-hydroxy-3-methoxy-amphetamine. As the dose of MDMA admin was incr, volunteers showed rises in the MDMA concn that did not follow the same proportionality which would be indicative of nonlinearity. In the full range of doses tested the constant recovery of 4-hydroxy-3-methoxy-methamphetamine in the urine combined with incr MDMA recovery ... /indicates/ a point towards a saturation or inhibition of MDMA metabolism (the demethylenation step). ... Urinary clearance was rather constant while nonrenal clearance was dose dependent. ...

Absorption, Distribution & Excretion:

A 32 year old woman ingested between 100 and 150 mg of MDMA developed a serum level of 6500 ng/mL, and lived. A 40 year old man ingested a single 50 mg dose, and hours later, his MDMA plasma level peaked at 105.6 ng/ml. [Ellenhorn, M.J., S. Schonwald, G. Ordog, J. Wasserberger. Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning. 2nd ed. Baltimore, MD: Williams and Wilkins, 1997., p. 347]**PEER REVIEWED**

3,4-Methylenedioxymethamphetamine (MDMA, commonly called ecstasy) is a synthetic compound increasingly popular as a recreational drug. Little is known about its pharmacology, including its metabolism and pharmacokinetics, in humans in controlled settings. A clinical trial was designed for the evaluation of 3,4-methylenedioxymethamphetamine pharmacological effects and pharmacokinetics in healthy volunteers. METHODS: A total of 14 subjects were included. In the pilot phase six received 3,4-methylenedioxymethamphetamine at 50 (n=2), 100 (n=2), and 150 mg (n=2). In the second phase eight received 3,4-methylenedioxymethamphetamine at both 75 and 125 mg (n=8). Subjects were phenotyped for CYP2D6 activity and were classified as extensive metabolizers for substrates, such as 3,4-methylenedioxymethamphetamine, whose hepatic metabolism is regulated by this enzyme. Plasma and urine samples were collected throughout the study for the evaluation of 3,4-methylenedioxymethamphetamine pharmacokinetics. Body fluids were analysed for the determination of 3,4-methylenedioxymethamphetamine and its main metabolites 3,4-methylenedioxyamphetamine (MDA), 4-hydroxy-3-methoxy-methamphetamine (HMMA) and 4-hydroxy-3-methoxy-amphetamine (HMA). RESULTS: As the dose of 3,4-methylenedioxymethamphetamine administered was increased, volunteers showed rises in 3,4-methylenedioxymethamphetamine concentrations that did not follow the same proportionality which could be indicative of nonlinearity. In the full range of doses tested the constant recovery of HMMA in the urine combined with the increasing 3,4-methylenedioxymethamphetamine recovery seems to point towards a saturation or an inhibition of 3,4-methylenedioxymethamphetamine metabolism (the demethylenation step). These observations are further supported by the fact that urinary clearance was rather constant while nonrenal clearance was dose dependent.
CONCLUSIONS: It has previously been postulated that individuals genetically deficient for the hepatic enzyme CYP2D6 (about 10% of the Caucasian people) were at risk of developing acute toxicity at moderate doses of 3,4-methylenedioxymethamphetamine because the drug would accumulate in the body instead of being metabolized and inactivated. The lack of linearity of 3,4-methylenedioxymethamphetamine pharmacokinetics (in a window of doses compatible with its recreational use) is a more general phenomenon as it concerns the whole population independent of their CYP2D6 genotype. It implies that relatively small increases in the dose of 3,4-methylenedioxymethamphetamine ingested are translated to disproportionate rises in 3,4-methylenedioxymethamphetamine plasma concentrations and hence subjects are more prone to develop acute toxicity.

[de la Torre R et al; Br J Clin Pharmacol 49 (2): 104-9 (2000)] **PEER REVIEWED**

Background: Little is known concerning the enantioselective disposition of 3,4-methylenedioxymethamphetamine (MDMA; ecstasy) in humans. In addition, the potential of utilizing the stereochcmical composition of an analyte in biological media for forensic purposes requires investigation. Methods: The enantiomers of 3,4-methylenedioxymethamphetamine and its demethylated metabolite, 3,4-methylenedioxyamphetamine (MDA), present in plasma and urine extracts were derivatized with (-)-(R)-alpha-methoxy-alpha-trifluoromethyl-phenylalif of (R)-3,4-methylenedioxymethamphetamine (5.8 : 2.2 hr) was significantly longer than that of the S-enantiomer (3.6 : 0.9 hr). The majority of the recovered material in urine was excreted within 24 hr after dosing, with the recovery of (R)-3,4-methylenedioxymethamphetamine (21.4% : 11.6%) being significantly greater than that of (S)-3,4-methylenedioxymethamphetamine (9.3% : 4.9%), and with (S)- and (R)-MDA accounting for 1.4% : 0.5% and 1.0% : 0.3% of the dose, respectively. Mathematical modeling of plasma enantiomeric composition vs sampling time demonstrated the applicability of composition may be applicable for forensic purposes.

[Kicman AT et al; Clinical Chemistry 45 (7): 1058-69 (1999)] **PEER REVIEWED**

The cardiovascular and neuroendocrine effects and pharmacokinetics of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") were assessed in a double-blind, randomized, crossover, and controlled (placebo and amphetamine) clinical trial. Eight men with experience in the recreational use of 3,4-methylenedioxymethamphetamine participated in four 10-hr experimental sessions with a 1-week washout period. Single oral doses of 125 mg and 75 mg of 3,4-methylenedioxymethamphetamine, 40 mg of amphetamine, and placebo were given. Both 3,4-methylenedioxymethamphetamine doses significantly increased blood pressure (increases of 40 mm Hg in systolic blood pressure), heart rate (increases of 30 beats/min), and pupillary diameter (mydriasis) as compared with placebo. Oral temperature did not show significant changes in any drug-active condition. Plasma cortisol levels showed a statistically significant increase after 3,4-methylenedioxymethamphetamine administration. Prolactin levels only increased after high dose of 3,4-methylenedioxymethamphetamine. Cmax values for 125-mg and 75-mg 3,4-methylenedioxymethamphetamine doses were 236.4 and 130.9 ng/ml, and Tmax was observed at 2.4 and 1.8 hr, respectively. Elimination half-life was 8.6 h and 7.7 h for high and low 3,4-methylenedioxymethamphetamine doses, respectively. Amphetamine half-life was 15 hr. Between 8 and 9% of the doses of 3,4-
methylenedioxymethamphetamine appeared in plasma in the form of 3,4-methylenedioxyamphetamine. The important cardiovascular effects observed after 3,4-methylenedioxymethamphetamine administration in laboratory conditions at rest (increases of 40 mm Hg in systolic blood pressure and 30 beats/min in pulse rate) could be relevant in terms of toxicity in real-life conditions (eg, crowded places and physical activity).

[Mas M et al; J Pharmacol Exp Ther 290 (1): 136-45 (1999)]**PEER REVIEWED**

**Mechanism of Action:**

Methylenedioxymethamphetamine (MDMA) is known to damage brain presynaptic serotonin (5-HT) neurons. ... Brain cortical 5-HT2A receptor densities were studied with (121)I-5-I-R91150 SPECT in 5 abstinent MDMA users and nine healthy controls. Memory performance was assessed using RAVLT. ... The (123)I-5-I-R91150 binding ratios were significantly higher in the occipital cortex of MDMA users than in controls, indicating up-regulation. Mean cortical 5-HT2A receptor binding correlated positively with RAVLT recall in MDMA users. ... Preliminary results indicate altered 5-HT neuronal function with correlated memory impairment in abstinent MDMA users.


... The activity of cytochrome oxidase, complex IV of the electron transport chain was determined at three different time points following admin of high doses of methamphetamine or 3,4-methylenedioxymethamphetamine (MDMA) (four injections 10-15 mg/kg admin over 8 hr). There was a rapid decr in cytochrome oxidase staining in the striatum (23-29%), nucleus accumbens (29-30%) and substantia nigra (31-43%), 2 hr following admin of either /drugs/. This decr in cytochrome oxidase activity was transient and returned to control levels within 24 hr. Since ... /the two drugs/ induced decr in cytochrome oxidase activity was localized to dopamine rich regions, incr extracellular concn of dopamine may contribute to the inhibition of metabolic function via its metabolism to quinones or other reactive oxygen species. ...


... Serotonergic neurotoxins like MDMA exert their neurodegenerative effects indirectly via dopaminergic neurones.


**Interactions:**

Neurotoxicity induced by different substituted amphetamines has been associated with the exhaustion of intracellular energy stores. ... 2-deoxy-D-glucose (2-DG) a competitive inhibitor of glucose uptake and metabolism and nicotinamide, an agent that improves energy metabolism, on 3,4-methylenedioxymethamphetamine (MDMA) induced 5-hydroxytryptamine (5-HT; serotonin) deficits. Admin of MDMA (15 mg/kg ip) produced significant hyperthermia, whereas 2-DG caused a profound hypothermia that lasted throughout the experiment. When MDMA was given to 2-DG
treated rats, an immediate but transient hyperthermia occurred and was followed by a return to hypothermia. 2-DG had no effect on 5-HT concn in the frontal cortex, hippocampus and striatum but prevented the neurotoxicity induced by MDMA. When rats were injected with 2-DG/MDMA and were warmed to prevent hypothermia, the protection afforded by 2-DG was abolished. Nicotinimide had no effect on body temperature of the rats and the hyperthermia induced by nicotinimide/MDMA treatment was similar to that of the saline/MDMA treated rats. ... The longterm 5-HT deficits induced by MDMA were potentiated by nicotinamide in all the brain regions examined. ... No change on ATP concn in the frontal cortex, hippocampus and striatum was observed up to 3 hr after a single dose of MDMA....


**PEER REVIEWED**

After ingesting MDMA and the monoamine oxidase inhibitor phenelzine, a 50 year old man developed marked hypertension, diaphoresis, altered mental status, and hypertonicity lasting 5 to 6 hours; he recovered with supportive treatment ... Similar effects might be expected with MDMA.


Human immunodeficiency virus 1 (HIV-1) protease inhibitors have dramatically reduced the morbidity and mortality due to HIV-1 infection. However, most of these antiretrovirals are also potent inhibitors (and occasionally inducers) of hepatic and intestinal cytochrome p450 systems and, therefore, have the potential to alter the elimination of any substance that utilizes these metabolic pathways. We describe a patient infected with HIV-1 who was treated with ritonavir and saquinavir and then experienced a prolonged effect from a small dose of methylenedioxymethylamphetamine (MDMA or ecstasy) and a nearly fatal reaction from a small dose of gamma-hydroxybutyrate (GHB). We also discuss the potential for HIV-1 protease inhibitors to alter the metabolism of other abusable prescribed and illicit substances.

[Harrington RD et al; Arch Intern Med 159 (18): 2221-4 (1999)]**PEER REVIEWED**

Neurotoxicity induced by different substituted amphetamines has been associated with the exhaustion of intracellular energy stores. Accordingly, we examined the influence of 2-deoxy-D-glucose (2-DG), a competitive inhibitor of glucose uptake and metabolism, and nicotinamide, an agent that improves energy metabolism, on 3,4-methylenedioxymethylamphetamine (MDMA)-induced 5-hydroxytryptamine (5-HT; serotonin) deficits. Administration of 3,4-methylenedioxymethylamphetamine (15 mg/kg ip) produced a significant hyperthermia, whereas 2-deoxy-D-glucose caused a profound hypothermia that lasted throughout the experiment. When 3,4-methylenedioxymethylamphetamine was given to 2-deoxy-D-glucose-treated rats, an immediate but transient hyperthermia occurred and was followed by a return to hypothermia. 2-Deoxy-D-glucose had no effect on 5-hydroxytryptamine concentrations in the frontal cortex, hippocampus, and striatum but prevented the neurotoxicity induced by 3,4-methylenedioxymethylamphetamine. When rats were injected with 2-deoxy-D-glucose/3,4-methylenedioxymethylamphetamine and were warmed to prevent hypothermia, the protection afforded by 2-deoxy-D-glucose was abolished. Nicotinamide had no effect on body temperature of the rats, and the
hyperthermia induced by the nicotinamide/3,4-methylenedioxymethamphetamine treatment was similar to that of the saline/3,4-methylenedioxymethamphetamine-treated rats. However, the long-term 5-hydroxytryptamine deficits induced by 3,4-methylenedioxymethamphetamine were potentiated by nicotinamide in all the brain regions examined. Finally, no change on ATP concentrations in the frontal cortex, hippocampus, and striatum was observed up to 3 hr after a single dose of 3,4-methylenedioxymethamphetamine. These results suggest that an altered energy metabolism is not the main cause of the neurotoxic effects induced by 3,4-methylenedioxymethamphetamine.

[Hervias I et al; J Neurochem 75 (3): 982-90 (2000)]

**PEER REVIEWED**

**Pharmacology:**

**Therapeutic Uses:**

Adrenergic uptake inhibitors

**PEER REVIEWED**

**Interactions:**

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reduced the morbidity and mortality due to HIV-1 infection. However, most of these antiretrovirals are also potent inhibitors (and occasionally inducers) of hepatic and intestinal cytochrome p450 systems and, therefore, have the potential to alter the elimination of any substance that utilizes these metabolic pathways. We describe a patient infected with HIV-1 who was treated with ritonavir and saquinavir and then experienced a prolonged effect from a small dose of methylenedioxymetamphetamine (MDMA or ecstasy) and a nearly fatal reaction from a small dose of gamma-hydroxybutyrate (GHB). We also discuss the potential for HIV-1 protease inhibitors to alter the metabolism of other abusable prescribed and illicit substances.

[Harrington RD et al; Arch Intern Med 159 (18): 2221-4 (1999)]

Neurotoxicity induced by different substituted amphetamines has been associated with the exhaustion of intracellular energy stores. Accordingly, we examined the influence of 2-deoxy-D-glucose (2-DG), a competitive inhibitor of glucose uptake and metabolism, and nicotinamide, an agent that improves energy metabolism, on 3,4-methylenedioxymethamphetamine (MDMA)-induced 5-hydroxytryptamine (5-HT; serotonin) deficits. Administration of 3,4-methylenedioxymethamphetamine (15 mg/kg ip) produced a significant hyperthermia, whereas 2-deoxy-D-glucose caused a profound hypothermia that lasted throughout the experiment. When 3,4-methylenedioxymethamphetamine was given to 2-deoxy-D-glucose-treated rats, an immediate but transient hyperthermia occurred and was followed by a return to hypothermia. 2-Deoxy-D-glucose had no effect on 5-hydroxytryptamine concentrations in the frontal cortex, hippocampus, and striatum but prevented the neurotoxicity induced by 3,4-methylenedioxymethamphetamine. When rats were injected with 2-deoxy-D-glucose/3,4-methylenedioxymethamphetamine and were warmed to prevent hypothermia, the protection afforded by 2-deoxy-D-glucose was abolished. Nicotinamide had no effect on body temperature of the rats, and the hyperthermia induced by the nicotinamide/3,4-methylenedioxymethamphetamine treatment was similar to that of the saline/3,4-methylenedioxymethamphetamine-treated rats. However, the long-term 5-hydroxytryptamine deficits induced by 3,4-methylenedioxymethamphetamine were potentiated by nicotinamide in all the brain regions examined. Finally, no change on ATP concentrations in the frontal cortex, hippocampus, and striatum was observed up to 3 hr after a single dose of 3,4-methylenedioxymethamphetamine. These results suggest that an altered energy metabolism is not the main cause of the neurotoxic effects induced by 3,4-methylenedioxymethamphetamine.

[Hervias I et al; J Neurochem 75 (3): 982-90 (2000)]

Environmental Fate & Exposure:

Probable Routes of Human Exposure:

The 1998 survey /National Household Survey on Drug Abuse conducted by the Substance Abuse and Mental Health Services Administration/ found that an estimated 1.5 percent (3.4 million) of Americans at least 12 years old had used MDMA at least once during their lifetime. By age group, the heaviest use (5 percent or 1.4 million people) was reported for those between 18 and 25 years old.

[National Institute on Drug Abuse Infofax on ECSTASY.
MDMA is used most often by young adults and adolescents at clubs, raves (large, all-night dance parties) and rock concerts.

Environmental Standards & Regulations:

FDA Requirements:

Schedules of controlled substances are established by section 202 of the Controlled Substances Act (21 U.S.C. 812). Schedule I includes 3,4-methylenedioxymethamphetamine (MDMA), DEA Code #7405; Drug class: Hallucinogenic substances.

Chemical/Physical Properties:

Molecular Formula:

C11-H15-N-O2

Molecular Weight:

193.25

Color/Form:

Oil

Boiling Point:

100-110 deg C at 0.4 mmHg
Crystals from isopropanol/n-hexane, mp 147-148 deg C ... Crystals from propanol/ether, mp 152-153 deg C ... UV max (ethanol): 286 nm (E 3843). /MDMA Hydrochloride/

MDA is only one-third as potent as amphetamine, and three times more potent than mescaline. /3,4-Methylenedioxymethamphetamine/

**Chemical Safety & Handling:**

**Disposal Methods:**

SRP: At the time of review, criteria for land treatment or burial (sanitary landfill) disposal practices are subject to significant revision. Prior to implementing land disposal of waste residue (including waste sludge), consult with environmental regulatory agencies for guidance on acceptable disposal practices.

**Occupational Exposure Standards:**

**Manufacturing/Use Information:**

**Major Uses:**

... has no approved medical use in the U.S.

/3,4-Methylenedioxymethamphetamine/ ... has been recommended by some therapists as an aid to the process of therapy, although no controlled data exist to support this contention.

Ecstasy is the popular name for the illicit drug MDMA and is widely used at dance parties or "raves." It is usually consumed orally in tablet or capsule form ... Its primary effect is to produce a positive mood state with euphoria, intimacy, and closeness to others.
[Ellenhorn, M.J., S. Schonwald, G. Ordog, J. Wasserberger. Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning. 2nd ed. Baltimore, MD:
Methods of Manufacturing:

Prepn: Ger pat 274,350 (1914 to E. Merck), C.A. 8,3350 (1914); U. Baum et al., J Pharm Sci 69, 192 (1980).

General Manufacturing Information:

This is a controlled substance (hallucinogen) listed in the U.S. Code of Federal Regulations, Title 21 Part 1308.11 (1995).

It was intended as a weight-loss (anorectic) drug, but because of its side-effects /3,4-methylenedioxymethamphetamine/ was never marketed.

It was first developed as an appetite suppressant in 1914 after it was synthesized in Germany by E. Merck and Company, but it was never marketed.

Tablets or capsules sold as Ecstasy may contain caffeine, ketamine, amphetamine, acetaminophen, or MDEA.

Formulations/Preparations:

Tablet, capsule, or powder form

Laboratory Methods:
**Clinical Laboratory Methods:**

[Haddad LM et al, eds; Clinical Management of Poisoning and Drug Overdose. 3rd ed. Philadelphia, PA: W.B. Saunders Co p. 577 (1998)] Urine toxicology screening may suggest phenylethylamine use. Commercially available immunoassays including radioimmunoassay, enzyme-multiplied immunoassay technique, and fluorescence polarization immunoassay for amphetamines, have been demonstrated to have cross-reactivity to ... MDMA ...


**Special References:**

**Special Reports:**


**Synonyms and Identifiers:**

**Synonyms:**

Adam
**PEER REVIEWED**

1,3-Benzodioxole-5-ethanamine, N-alpha-dimethyl-
**PEER REVIEWED**

N,alpha-Dimethyl-1,3-benzodioxole-5-ethanamine
**PEER REVIEWED**

Ecstasy
**PEER REVIEWED**

MDMA
**PEER REVIEWED**

N-Methyl-3,4-methylenedioxyamphetamine
**PEER REVIEWED**

XTC
**PEER REVIEWED**

**Associated Chemicals:**

Methylenedioxyethylamphetamine;82801-81-8
Formulations/Preparations:

Tablet, capsule, or powder form