Accidental intoxication with methylene dianiline p,p'-diaminodiphenylmethane: acute liver damage after presumed ecstasy consumption.

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Background: MDA is the abbreviation for methylene dianiline (p,p' diaminodiphenylmethane; 4,4'-methylenedianiline; CAS 101-77-9); and for methylendioxyamphetamine (MDMA, N, [Alpha]-dimethly-1,3-benzodioxole-5-ethanamine; CAS42512-10-9. While the former is used for the production of polyurethane foams, the latter is a psychmnetric drug, which is becoming increasingly popular in the techno scene. Methods: We report six participants of a technoparty (1 female, 5 males, ages 17-25) who were admitted to the hospital with severe colicky abdominal pain and subsequently developed symptoms of hepatotoxicity. They had ingested an alcoholic beverage that had been spiked with a powdery substance they dubbed MDA. Results: All patients showed similar clinical symptoms, with an identical time course. Acute jaundice developed within 2 days after ingestion. Enzymes indicating cholestasis increased steadily over 7 days and reached peak values of 800 U/L (AP) and 380 U/L (GGT), whereas transaminases remained moderately elevated. Between days 5 and 7, all patients became febrile for one day, their body temperatures rising up to 40 [degrees] C. There was no evidence for hemolysis or an infectious hepatitis. Toxicological analysis revealed the presence of p,p'-diaminophenyhmethane (4,4'-methylenedianiline) at a concentration of 130 mg/L in one of two urine MM owned. Conclusions: The analytical data indicate that the participants of the technology assumed the aniline-derivative, the cause of Epping Jaundice, was methylendioxyamphetamine because the same abbreviation, MDA, is used for both compounds. An overview of the acute liver toxicity of aniline derivatives is given and the possibility of amphetamine-induced liver damage is discussed.

INTRODUCTION

The aromatic amine 4,4'-methylenedianiline (MDA) CAS 101-77-9 is used in the production of polyurethane foams and resins as well as an epoxy resin hardener.[1] This compound produces cholestasis, bile duct proliferation, and hepatic necrosis in animal experiments.[1-3] It induces DNA damage in short-term tests, and is carcinogenic in several animal species.[1,3,6] Although MDA has structural similarities to benzidine and 4-amino-biphenyl, two known human carcinogens, the carcinogenicity of MDA in humans is not established.[1,3,4,7,8] In occupational medicine the toxic effects of MDA in humans usually follow after subacute or subchronic exposure by transdermal or inhalatory routes.[7-11] Common adverse effects observed include hepatotoxicity, cholestasis and contact dermatitis.[1,9-14] The classical case of accidental, acute oral intoxication with MDA is the so-called Epping Jaundice, where at least 80 people reported abdominal complaints after ingestion of MDA contaminated bread.[15,16] Here we report another oral mass intoxication with MDA, 30 years after the Epping Jaundice incident, of young adults belonging to the current techno-scene.

The abbreviation MDA is not exclusively used for the aniline derivative 4,4'-methylenedianiline but also for the amphetamine-derivative 3,4-methylendioxyamphetamine. The latter, as well as methylenedioxymethamphetamine (MDMA) CAS 42542-10-9 and 3,4-methylenedioxy-N-ethylamphetamine (MDE), are compounds frequently sold as Ecstasy. Over the last decade, Ecstasy has enjoyed an increasing popularity as a recreational drug, used as a dance drug at the techno or rave parties. Although these psychoactive compounds are generally regarded as safe, a number of cases of Ecstasy-induced adverse effects have been reported including hyperthermia, kidney failure, and liver injury.[17-22] The Ecstasy-associated liver damage appears to be rare and, to date, no experimental evidence is available to support a causative relation between Ecstasy consumption and hepatotoxicity. However, the clinical characteristics of liver injury in patients, whose anamnesis indicated the consumption of Ecstasy,[23,24] can easily be differentiated from those caused by MDA.

Case Report

An 18-year-old man (#1) was admitted to the hospital because of abdominal pain, vomiting, jaundice, arthralgia, myalgia,

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and weakness. The day before admission he had attended a techno party, where he consumed 3-4 glasses of a punch. Anamnesis indicated that this beverage had been spiked with a substance presumed to be Ecstasy.

On physical examination, the patient appeared ill with jaundice and pain in the upper abdomen evoked by palpation. No further physical abnormalities were found. The ultrasound examination of the abdomen showed a diffuse enhancement of the hepatic echoes without evidence for enlargement of the liver or obstruction of the biliary ducts. Red blood cell count and thrombocyte rate were normal. Leucocyte count was mildly elevated to 10,700/ [Mu] L. Blood sedimentation rate was normal, but C-reactive protein was elevated to 71 mg/L. Normal values were obtained for electrolytes, kidney function, and liver synthesis parameters. However, bilirubin was 185 [Mu] mol/L and liver enzyme activities were elevated (AST 79 U/L, ALT 77 U/L, GGT 52 U/L and AP 344 U/J and increased steadily over 7 days. LDH was elevated, while haptoglobin values were in normal range. CK was elevated to 372 U/L with normal CK-MB.

Nausea, vomiting, abdominal pain, and fever persisted for another 24 h. Hereafter, the patient was free from complaints, but there was proteinuria and erythrocyturia. Then fever recurred with chills. Temperature rose to 39.2 [degrees] C on the seventh day, although blood cultures remained sterile and further microbiological investigations were negative. Once more, he experienced nausea, vomiting, upper abdominal pain and he developed a rash. With the disappearance of the fever (day 9) all other complaints cleared as well. During the stay in hospital the jaundice vanished and the bilirubin was close to normal on discharge (day 15). Liver syntheses remained normal, however the cholinesterases decreased from 3739 to 2781 U/L.

During the same period, 5 other patients (4 males and 1 female, aged 17-25), who all attended the same party, sought medical attention with similar complaints. The frequency of symptoms is presented in Table 1 and the fever curves of the 6 patients are given in Figure 1.

Table 1 Frequency of Symptoms

	Oral Intoxicationt [dagger]	Occupational Exposuret (??)
Malaise	5/6	13/13
Icterus	6/6	13/13
Dark urine	6/6	13/13
Abdominal pain	6/6	11/13
Nausea	6/6	11/13
Fever St Chills	6/6	10/13
Rash	0/6	3/13
Myalgia	0/6	5/13

[dagger] 6 patients with oral intoxication by MDA. (??) 13 patients with MDA-induced hepatitis after occupational exposure.(11)

Toxicological Analysis

Three mL urine and 1 mL serum of the patient (#1) sampled about 24 h after ingestion of the punch, were alkalinized by adding [Mu] L 2 N ammonia. Both samples were extracted successively with 2 mL of n-heptane and 2 mL of diethylether/ethylacetate. The pooled organic phases were evaporated to dryness, the residue was dissolved in toluene/ethanol and 1 [Mu] L of each extract was analyzed by GC/MS. While no toxic agents were found in the serum, the urine extract yielded two large signals. With the aid of the NIST/EPA/NIH75k mass spectral database one of these signals could be identified as 4,4'-methylenebisbenzenamine. Synonyms are 4,4'-diaminodiphenylmethane and methylenedianiline (MDA). Methylenedianiline (Fluka, Buchs, Switzerland) was used as a reference standard. The urine concentration of MDA was 130 [Mu] g/L. The second signal appeared to be a monoacetylated metabolite of MDA. Two days later results were double-hecked by reanalyzing the sample (stored at 4 [degrees] C). There was no change in concentration. The immunological drug screening using the ADx system (Abbott Laboratories, North Chicago, IL) was

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negative. Ingestion of MDA was confirmed by identification of the parent compound and its major metabolite N-acetyl-MDA.

Samples of another patient (#2) were also analyzed but neither MDA nor any one of its metabolites or other toxic compounds could be detected in serum or urine.

DISCUSSION

Toxicological analysis of urine extracts from patient #1 revealed the presence of methylenedianiline whereas this compound could not be detected in the sample obtained from the patient #2 consistent with the report that patient #1 consumed much more spiked punch than patient #2. The quantity ingested could not be accurately estimated because of the heterogeneous distribution in the punch due to the weak solubility of the compound in aqueous medium.

Several facts indicate that this compound was the common source of intoxication. All patients attended the same party prior to the complaints and admitted to have consumed the spiked punch. They presented with the same clinical picture and an almost identical time course. A typical fever spike was observed in all patients between day 5 and day 7, while microbiological investigations excluded an infectious agent as the cause of the phenomenon. The elevated LDH levels originated in liver damage. Severe hemolysis could be excluded because haptoglobin was normal, and the number of red cells remained stable. Aniline derivate-induced methemoglobinemian[25] could be excluded because of the absence of headache, dyspnea, or tachycardia.

In the epidemic of Epping Jaundice, Koppelman distinguished three types of the disease according to the time of onset. In the majority of patients, the first symptoms were severe, acute, and intermittent abdominal pain accompanied by rather severe colicky pain and jaundice lasting for up to 36 h. During the following five days most of these patients became febrile. In some patients the jaundice persisted even after disappearance of the other symptoms. The second form was characterized by similar symptoms, but they were less severe initially. The least common form occurred in elderly patients who had severe jaundice, although preceding symptoms were minimal.

MDA-induced hepatotoxicity occurs in a dose- and time-dependent manner, leading to cholestasis, bile duct epithelial damage, and insults of hepatic parenchyma.[26] Within hours, the bile flow diminishes, and bile composition changes resulting in highly injurious fluid to biliary epithelial cells.[27] The amount of MDA in the urine of patient #1 was much larger than the amount seen in workmen constantly exposed to MDA who do not develop toxicity.[28]

Although, there are multiple reports concerning liver damage after MDMA consumption,[17,22-24] there have never been a number of persons affected at the same time as in this incident. While an idiosyncratic reaction to Ecstasy might be considered, the simultaneous involvement of multiple persons suggests a direct toxic effect. In addition, none of the patients reported any psychomimetic effects after consuming the punch, which was presumed to be spiked with Ecstasy. In addition we did not detect any amphetamines in the patients, urine or serum. Ecstasy-induced liver damage is associated with much greater increase of ALT than the GGT values;[22,24,29] the reverse was seen in our patients.

The clinical status of all patients normalized after the fever spike; laboratory values returned to normal within 6 weeks, except for one patient, whose GGT value remained elevated due to the chronic consumption of alcohol. The long term prognosis appears to be favorable. All patients with Epping Jaundice recovered, and there were no further reports of recurring illnesses attributable to the 4,4'-diaminodiphenylmethane intoxication, although animal models indicate a potential risk for cancer.[30]

Little information is available on the pharmacokinetics of MDA after oral administration in humans. However, a recent pharmacokinetic study in five volunteers indicated an elimination half-life of 9 to 19 hours.[31] When ingestion of MDA has occurred no longer than a few hours before, gastric lavage might still be useful. The instillation of active carbon or cholestyramine may diminish initial absorption and reabsorption via the entero-hepatic circulation. Dialysis is not projected as beneficial since the substance is poorly soluble in water, but urine acidification might enhance the elimination rate.

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The decrease in acetylcholinesterase activity in all patients suggests the possibility of severe liver damage, which might lead to fulminant liver failure. When a large amount of MDA is ingested, liver transplantation may become a consideration.

ACKNOWLEDGEMENTS

Dr. Frank van Pelt was supported by a Research Fellowship from the Alexander von Humboldt Foundation, Bonn, Germany. We thank Drs. Erdmann, Bigalke and Obermeyer-Straub for discussion and their assistance in preparing the manuscript.

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