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CASE REPORTS

Dimethylacetamide, Ethylenediamine, and Diphenylmethane Diisocyanate Poisoning Manifest as Acute Psychosis and Pulmonary Edema: Treatment with Hemoperfusion

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ABSTRACT

Case Report: A 27-year-old man, employed by a synthetic fiber company, had been exposed to dimethylacetamide, ethylenediamine, and diphenylmethane diisocyanate in a confined space continuously for 4–6 hours per day for 3 days before admission. Hallucinations and delusions were noted at admission; pulmonary edema developed subsequently. The electroencephalogram showed diffuse moderate cortical dysfunction and slow waves at 4–7 Hz, 20–80 μ V. Seizures, liver injury, and rhabdomyolysis were noted on the 4th hospital day. The patient was treated by hemoperfusion with a decrease in urine dimethylacetamide from 3265 mg/g to 4 mg/g creatinine over 4 days. Serial urinary dimethylacetamide and electroencephalogram correlated with the clinical condition.

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INTRODUCTION

Dimethylacetamide (DMAC) (CAS No. 127-19-5), an excellent dipolar and versatile industrial solvent with wide organic and inorganic solubility and water miscibility has been widely applied in the manufacturing industry.¹ DMAC is well absorbed by the dermal and inhalational routes.² Animal studies have shown liver damage in acute DMAC intoxication;³ however, the human data on DMAC toxicity remain limited.

Urinary *N*-methylacetamide (MMAC), assayed by gas chromatography, is commonly used to monitor occupational exposure to DMAC. Biomonitoring is superior to airborne concentration monitoring in the detection of excessive DMAC exposure.⁴

We report a case of severe DMAC, ethylenediamine (EDA), and diphenylmethane diisocyanate (MDI) intoxication with a description of the serial changes in the electroencephalogram (EEG) and urinary MMAC measurements. The response to treatment by hemoperfusion is discussed.

Case Report

A previously healthy 27-year-old man had been employed for 1 year by a chemical factory where synthetic elastic fiber was synthesized from polytetramethylene glycol (PTG) (CAS No. 25190-06-1) and diphenylmethane diisocyanate (MDI) (CAS No. 101-68-8). In the manufacturing process, EDA (CAS No. 107-15-3) was used as a catalyzer and DMAC as the solvent. After polymerization, DMAC was used to clean the reaction tank and collected into a recycling tank where the solid remains (2%) were separated from DMAC (98%). There was no further analysis of the 2% solid remains, which were described as elastic fiber polymer. It is presumed that small amounts of EDA, MDI, PTG, and their incomplete reaction products were also part of the solid remains. The recycling tank was an enclosed cylindrical container with limited ventilation. Since cleaning was not performed regularly, the reaction debris of solid compounds had accumulated and obstructed the container outlet. The employee had been assigned to clean up the debris in the

Figure 1. Urinary *N*-methylacetamide concentration after exposure to the DMAC mixture and clinical course before and after hemoperfusion treatment. Arrow ✓ marks the 1st hospital day.

closed tank without respiratory or skin protection for 3 consecutive working days, 4 to 6 hours each day. The patient reported that he had leaned against or sat in the solid debris while working because of the limited space in the cylinder.

Delusion and paranoia with visual hallucination developed in the early morning of day 4 (hospital day 1). At this time, ulceration of the entire buttocks was noted. Laboratory tests revealed leukocytosis, mildly elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and markedly increased creatinine phosphokinase (CPK) of 7049 IU/L.

On hospital day 2, the patient became drowsy and delirious with poor attention span, agitation, and incoherent speech. He had tachycardia with mild respiratory distress. The chest X-ray and pulmonary computed tomography (CT) scan showed bilateral diffuse interstitial infiltrate. The EEG revealed diffuse slow (theta) waves at 2.5–7 Hz, 20–80 μ V with generalized beta activities at 15–17 Hz, 10–20 μ V.

On hospital day 3, he had recurrent generalized tonic-clonic seizures followed by deterioration of consciousness. This was ascribed to pulmonary edema with hypoxemia (pH 7.37, PaCO₂ 34.4 mmHg, PaO₂ 36.1 mmHg, HCO₃⁻ 19.5 mEq/L, and base-excess -4.5). CT scan of the brain on hospital day 4 revealed diffuse mild brain swelling. Glycerol and steroids but no sedatives were given. Bronchoscopy on hospital day 4 showed hyperemic edema of the tracheobronchial tree, consistent with inhalational injury. Intubation was not performed. Upper gastrointestinal (UGI) bleeding and conjunctivitis were noted on the 5th to 9th hospital days. Panendoscopy for evaluation of UGI bleeding revealed oral mucositis, fungal esophagitis, and gastric erosion, which were treated with famotidine and fluconazole.

Since consciousness was not restored, a therapeutic trial of hemoperfusion with activated charcoal was performed for 5 hours per day $\times$ 3 on the 6th through the 8th hospital days, employing hemoperfusion cartridges of Gambro Adsorba 300C (Gambro Dialysatoren GmbH & Co KG, Hechingen, Germany) at a blood flow of 150 mL/min with 300 units heparin/h. Subsequently, his condition improved and he was discharged on the 29th hospital day with good recovery.

Measurement of Urinary N-methylacetamide

Cold methanol 2 mL was added to 1 mL urine to denature the proteins, which were then removed by a brief centrifugation. The supernatant was analyzed with China

GC 8700F on a DB-264 column using flame ionization detection.⁵ The patient's urine was collected for MMAC testing on the 4th, 6th, 8th–10th, and 12th–16th day after initial DMAC exposure.

The biological exposure index (BEI) of MMAC is 35 mg/g creatinine (Cr).⁴ The urinary MMAC level on admission was 4609 mg/g Cr, decreasing to 3265 mg/g Cr before hemoperfusion. After the 1st, 2nd, and 3rd course of hemoperfusion, the MMAC levels decreased to 936, 115, and 4 mg/g Cr, respectively. The MMAC levels were no longer detectable on the 5th day after hemoperfusion (Figure 1).

EEG Recordings and Findings

All EEGs were recorded digitally with subsequent quantitative analysis. Nonsleep, artifact-free EEG segments were selected and then underwent spectrum analyses through fast Fourier transformation (FFT). Peak frequencies and summation amplitudes of different frequency bands were obtained. The frequency bands were conventionally defined, i.e., delta band 0.5–3 Hz, theta band 4–7 Hz, alpha band 8–13 Hz, and beta band 14–24 Hz.

On day 5, there were frequent intermittent diffuse theta waves at 4–7 Hz, 20–80 μ V and occasional intermittent diffuse delta waves at 2.5–3 Hz, 30–70 μ V with

Figure 2. Distribution of the amplitude spectra in the different EEG recordings. The EEG on day 5 after the initial DMAC exposure, the band percentages were delta 24.3%, theta 31.8%, alpha 20.0%, and beta 24.0%. After clinical deterioration, the delta band increased to 50.4%, and the fast activities decreased to alpha 13.2% and beta 15.0% by day 11. By day 17, the delta band shrank to 8% and fast activity increased to alpha 20.1% and beta 25.3%.

generalized beta activities at 15–17 Hz, 10–20 μ V. The follow-up on day 11 showed deterioration of the cortical function with nearly continuous diffuse theta waves at 4–7 Hz, 20–50 μ V intermixed with or intervened by occasional bursts of generalized sharp waves or delta waves at 1–3 Hz, 30–90 μ V. The EEG on day 17, after improvement of the consciousness, showed intermittent diffuse theta waves at 4–7 Hz, 20–50 μ V, occasional diffuse intermittent delta waves at 2–3 Hz, 30–60 μ V against a background of low cerebroelectric activities, and diffuse beta activities at 15–20 Hz, 5–10 μ V mostly in the frontocentral regions. Attenuation of alpha activities was observed in all three recordings.

Peak frequencies shifted from 5.0 ± 0.9 Hz on day 5 to 1.2 ± 0.4 Hz on day 11 and to 3.3 ± 1.2 Hz on day 17. The distribution of the normalized amplitude spectrum for different frequency bands showed a similar evolution (Figure 2).

DISCUSSION

This patient manifested hallucinations, delusions, skin burns, hepatitis, inhalational injury and rhabdomyolysis, similar to those of a case of combined exposure of DMAC and EDA.⁶ However, the clinical course in this case was further complicated by pulmonary edema and disturbed consciousness 48 hours after the cessation of exposure.

EDA and MDI are both respiratory sensitizers and can induce dyspnea, wheezing, runny nose, and coughing. DMAC has been reported to be associated with bronchitis; however, pneumonitis with pulmonary edema has not been reported after pure DMAC exposure in humans. Pulmonary edema and bronchopneumonia have been observed in animals exposed to high concentrations of EDA.⁷ High aerosol concentrations of MDI could cause chemical pneumonitis and pulmonary edema, which can develop in several hours or be delayed up to 48 hours after exposure and are aggravated by physical exertion.⁸ Thus, EDA or MDI could be responsible for inhalational injury and pulmonary edema.

Abnormal mental states, including various levels of confusion, disorientation, or hallucination were found in all 15 patients with advanced malignancies treated with DMAC 400 mg/kg for 3 or more days.^{9,10} Elevation of serum transaminase was also seen in 7 of 15 patients in the same study. The elevation of liver enzymes in this patient was relatively mild.

Extracorporeal perfusion for the treatment of DMAC intoxication has not been reported.⁶ The patient presented

with acute pulmonary edema due to chemical pneumonitis, had a progressive deterioration of consciousness, and the urinary MMAC level was over 100 times the BEI. We attempted to supplement the renal clearance of lipid soluble DMAC, EDA, and MDI by activated charcoal hemoperfusion.¹¹ The urinary concentration of MMAC did decrease rapidly during hemoperfusion, and was non-detectable on day 5 after hemoperfusion. The slope of urinary MMAC level before hemoperfusion was -336 mg/g Cr per day or about one-fifth of that during hemoperfusion (slope = -1575 mg/g Cr per day), as shown in Figure 1.

A study by Kennedy *et al.* concluded that changes in DMAC exposures could be quantitatively reflected by urinary MMAC.¹² Although there were no direct measurements of blood DMAC levels before and after hemoperfusion in this study, the urinary MMAC levels before and after hemoperfusion (24-hour interval) were only a biomonitoring index. This patient's pulmonary edema was resolved and his consciousness and general condition improved simultaneously after hemoperfusion. The relation of the possible removal of EDA and MDI, both potent respiratory sensitizers and irritants, to the pulmonary status improvement remains speculative.

The CNS toxicity in our patient included delirium, hallucinations, and impaired consciousness, consistent with previous reports of DMAC intoxication; it resembled the syndrome produced by lysergic acid diethylamide characterized by increased beta activities on EEG.¹³

REFERENCES

1. Kennedy GL. Biologic effects of acetamide, formamide, and their monomethyl and dimethyl derivatives. *CRC Crit Rev Toxicol* 1986;**17**:129–182.
2. Maxfield ME, Barnes JR, Azar A, *et al.* Urinary excretion of metabolite following human exposure to dimethylformamide or dimethylacetamide. *J Occup Med* 1975;**17**:506–511.
3. Kennedy GL, Sherman H. Acute and subchronic toxicity of dimethylformamide and dimethylacetamide following various routes of administrations. *Drug Chem Toxicol* 1986;**9**:147–170.
4. Spies GJ, Rhyne RH, Evans RA, *et al.* Monitoring acrylic fiber workers for liver toxicity and exposure to dimethylacetamide. *J Occup Environ Med* 1995;**37**:1093–1101.
5. Scailteur V, deHoffmann E, Buchet JP, Lauwerys R. Study on *in vivo* and *in vitro* metabolism of dimethylformamide in male and female rats. *Toxicology* 1984;**29**:221–234.

6. Marino G, Anastopoulos H, and Woolf AD. Toxicity associated with severe inhalational and dermal exposure to dimethylacetamide and 1,2-ethanediamine. *J Occup Med* 1994;**36**:637-641.
7. Pozzani UC, Carpenter CP. Response of rats to repeated inhalation of ethylenediamine vapors. *Arch Ind Hyg Occup Med* 1954;**9**:223-226.
8. Karol MH. Respiratory effects of inhaled isocyanates. *CRC Crit Rev Toxicol* 1986;**16**:349-379.
9. Weiss AJ, Mancall EL, Koltes JA, White JC, Jackson LG. Dimethylacetamide: A hitherto unrecognized hallucinogenic agent. *Science* 1962;**136**:151-152.
10. Weiss AJ, Jackson LG, Carabasi RA, Mancall EL, White JC. A phase I study of dimethylacetamide. *Cancer Chem Rep* 1962;**16**:477-485.
11. Goldfarb DS, Pond SM. Principles and techniques applied to enhance elimination of toxins. In: *Goldfrank's Toxicologic Emergencies, 6th Ed.* Goldfrank LR, Flomenbaum NE, Lewin NA, *et al.*, eds., East Norwalk: Appleton & Lange 1998:53-62.
12. Kennedy GL, Pruett JW. Biologic monitoring for dimethylacetamide: Measurement for 4 consecutive weeks in a workplace. *J Occup Med* 1989;**31**:47-50.
13. Brown BB. Subjective and EEG responses to LSD in visualizer and non-visualizer subjects. *Electroencephalogr Clin Neurophysiol* 1968;**25**:372-379.

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