Case Report: Hexachloroethane Smoke Inhalation: A Rare Cause of Severe Hepatic Injuries

Ching-Hui Loh,1 Yaw-Wen Chang,1 Saou-Hsing Liou,2,3 Jun-Hei Chang,1 and Hong-I Chen4,5

1Department of Family Medicine and Community Health, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC; 2Department of Public Health, National Defense Medical Center, Neihu, Taipei, Taiwan, ROC; 3Division of Environmental Health and Occupational Medicine, National Health Research Institutes, Kaohsiung, Taiwan, ROC; 4Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC; 5Medical Bureau, Department of National Defense, Taipei, Taiwan, ROC

Hexachloroethane/zinc oxide (HC/ZnO) smoke, also known as white smoke, has many military and civilian applications, such as in training exercises and on the battlefield. In addition to pulmonary effects of HC/ZnO smoke, the hepatotoxic effect was attributed to inhalation of high-concentration HC/ZnO smoke in an enclosed area, where several hepatotoxicants, including ZnCl2, HC, and chlorinated vapors, could have been generated and mixed in the smoke.

**Case Presentation:** The patients had been healthy previously and denied any history of alcohol or drug abuse. Hematologic tests revealed leukocytosis with neutrophils predominant. The respiratory conditions of both patients improved after steroid therapy and oxygen support, but deterioration of liver function was found. The laboratory results showed that alanine aminotransferase (ALT) and γ-glutamyl transpeptidase (GGT) levels were elevated about 1.5-fold the normal limits and that aspartate aminotransferase (AST) levels were marginally elevated. The elevation of liver aminotransferase started from day 1 and day 2 and peaked from day 18 to 22. ALT/AST levels then returned to normal in 6 weeks.

**Discussion:** The hepatic toxicity was attributed to inhalation of high-concentration HC/ZnO smoke in an enclosed area, where several hepatotoxicants, including ZnCl2, HC, and chlorinated vapors, could have been generated and mixed in the smoke.

**Relevance to Clinical Practice:** These case reports elaborate the hepatic effects that may occur in addition to pulmonary effects of HC/ZnO smoke.

**Key Words:** hepatotoxicity, hexachloroethane, white smoke, zinc oxide. Environ Health Perspect 114:763–765 (2006). doi:10.1289/ehp.8635 available via [Online 24 January 2006]
levels. Two weeks later (6 weeks after the accident), the patient’s liver function returned to normal. In addition, in serial follow-up studies we failed to find any evidence of HIV or autoimmune disease for 18 months.

**Patient 2.** The second patient, a 24-year-old man with an unremarkable medical history, was admitted to our hospital on the same day from the same accident described for patient 1. He had been healthy previously and denied any history of alcohol or drug abuse. He also had dyspnea, cough, chest distress, and a sore throat. Physical examination revealed blood pressure of 120/74 mmHg, heart rate of 84 bpm, and oral temperature of 37.4°C (99.3°F). Arterial blood gas analysis and blood chemistry tests were within the normal ranges. Hematologic tests revealed leukocytosis with neutrophils predominant (Table 1). The leukocytosis returned to normal on the 9th day after the event.

Oxygen was given by face mask after admission. Two days later, the patient experienced progressive respiratory distress. Chest auscultation revealed bilateral expiratory wheezes. A chest radiograph revealed diffuse interstitial infiltrates. High-resolution computed tomography of the chest showed acute inhalation pneumonitis with patchy and small ill-defined nodular areas of ground-glass opacity over all lung fields. Respiratory supports, including steroid therapy and antibiotic prophylaxis were administered as for patient 1. Three days after treatment, his respiratory condition improved and we began to gradually decrease the steroid.

The AST and ALT concentrations increased to a peak of 92 and 195 U/L, respectively, on day 18 (Figure 1). Serologic tests for hepatitis B and C and abdominal sonography showed no abnormal findings. The ALT level decreased to 95 U/L before discharge on the 27th day. Two weeks after discharge, the patient’s liver function returned to normal. In addition, serial follow-up studies failed to find any evidence of HIV or autoimmune disease for 18 months.

**Discussion**

HC/ZnO smoke is used by the military to conceal troops, for crowd dispersal, and occasionally in military and civilian fire-fighting. The acute toxic effects of HC/ZnO smoke on the respiratory tract are primarily attributed to inhalation of hydrated ZnCl₂ vapor. The vapor is very corrosive and rapidly damages the respiratory mucosal surface (Cullumbine 1957; Greenfield et al. 2002; Hjortso et al. 1988). To the best of our knowledge, the hepatic effects of HC/ZnO are very limited. Pettila et al. (2000) reported three patients with ZnCl₂ inhalation; all three patients had severe acute respiratory distress syndrome (ARDS). Acute exposure causes the elevation of liver enzymes by day 1 or 2, which peaks from day 18 to day 21 and then returns to normal in 6 weeks (Figure 1). The mechanism of hepatotoxicity of HC/ZnO smoke is still unknown. Several compounds, including ZnO, ZnCl₂, HC, chlorinated vapors, and medications, may cause hepatic toxicity.

ZnO has not been reported to cause hepatic damage, whereas ZnCl₂, HC, and chlorinated compounds have great potential to induce hepatotoxicity. Among 12 workers with 4–21 years of exposure to ZnO fumes in the production of brass alloys, no liver disease was reported (ATSDR 2003b; Hamdi 1969). Pettila et al. (2000) reported abnormal liver function (ALT of 119, 131, and 2,570 U/L) in three patients; however, because there was no detailed personal history (e.g., transfusion, alcohol consumption) or viral markers, it was difficult to evaluate the potential hepatotoxicity. Marts et al. (1988) observed a significant increase in the incidence of fatty liver in mice after repeated exposure to ZnCl₂ smoke, but the incidence did not increase with the dose, and hepatic toxicity was not observed in the liver of rats and guinea pigs using the same exposure paradigm.

About 5% or less of the compounds in HC/ZnO smoke are released into the air as HC. In one study, Selden et al. (1993) reported that liver function tests were not affected in HC-exposed workers who wore protective clothing. Animal studies have shown that hepatic tissues are moderately vulnerable to HC exposure, especially when exposure occurs by the oral route. Increases in liver weight, increases in serum levels of liver enzymes, centrilobular necrosis, fatty degeneration, hemosiderin-laden macrophages, and hemorrhage were seen in animals exposed to HC (ATSDR 1997; Fowler 1969; Gorzinski 1985; National Toxicology Program (NTP) 1989; Weeks et al. 1979). In these studies, effects on the liver and kidneys were mild with inhalation exposure and more pronounced with oral exposure. In a study of acute and intermediate-duration inhalation exposure, the only effect noted by Weeks et al. (1979) after 6 weeks of exposure to 260 ppm HC was an increase in liver weight in rats and guinea pigs but not in quail.

About 10% of HC/ZnO smoke is composed of chlorinated compounds (Holmes 1999; Katz et al. 1980; National Research Council 1997). The chlorinated compounds include tetrachloromethane (i.e., carbon tetrachloride, CCl₄), tetrachloroethylene, and hexachloroethane. CCl₄ has long been known to be a powerful hepatotoxic agent in humans and animals. The principal clinical signs of liver injury in humans who inhale CCl₄ are a swollen and tender liver, elevated levels of hepatic enzymes in serum, elevated serum bilirubin levels and the appearance of jaundice, and decreased serum levels of proteins such as albumin and fibrinogen (ATSDR 2003a). Liver necrosis was reported in one fatal case involving an alcoholic patient who was exposed to 250 ppm for 15 min (Norwood et al. 1950). High CCl₄ vapor concentration might have produced liver injury in our patients. However, we could not identify any right upper quadrant tenderness or liver enlargement in either of our patients.

Toxicant- or drug-induced liver injury is a potential complication of nearly every medication (Lee 1995). We needed to rule out the possibility that the observed hepatic toxicity was due to therapeutic drugs. For our cases, we prescribed acetaminophen for fever, steroids, antibiotics, bambuterol, aminophylline, ipratropium, mucolytics for pulmonary symptoms, and a mild sedative for sleeping. The three potential hepatic toxicants are acetaminophen, steroids, and antibiotics; however, acetaminophen taken at recommended doses (0.5–3 g daily) is relatively safe (Norris 2000). One of our cases took < 0.5 mg/day for 2 days, and the other never took it.

Steroid therapy is a standard treatment of ARDS and is applied universally. A thorough

---

**Table 1. Characteristics and biochemical data of patients 1 and 2 at 4 hr after the event.**

| Patient | Normal range for males |
|---------|------------------------|
| Age (years) | 23 | 24 |
| Body weight (kg) | 64.5 | 67 |
| Body mass index (kg/m²) | 19 | 21 |
| White blood cell count (L/mm³) | 21,900 | 17,100 |
| Neutrophils (%) | 93 | 91 |
| Lymphocytes (%) | 3.8 | 3.4 |
| ALT (U/L) | 60 | 24 |
| AST (U/L) | 47 | 31 |
| ALP (U/L) | 176 | 123 |
| GGT (U/L) | 61 | 25 |

ALT, alkaline phosphatase.

**Figure 1. Changes in ALT levels of patients 1 and 2.**
search of the literature revealed only a few case reports of suspected corticosteroid-induced hepatomegaly (Nanki et al. 1999). Based on limited data, it is difficult to justify any correlation between corticosteroid use and the hepatitis seen in our patients.

Elevations in liver enzymes and bilirubin have occurred during treatment with cefazidime. The incidence appears similar to that with other cephalosporins (Meyers 1985). In most cases, liver enzyme elevations have been transient, with levels returning to normal after withdrawal of treatment. Our patients received a 5-day course of cefazidime for prophylaxis. However, continued deterioration of liver function was observed after cefazidime was discontinued.

The diagnosis of toxicant-induced liver injury is often obscured by difficulty in determining the precise timing of toxicant ingestion and lack of specific symptoms (Lee 1995; Norris 2000). Central to the diagnosis is a thorough history, including drug exposure and occupational hazards with exposure to chemicals. In addition, the changes of liver enzymes may represent progression on underlying disease, a complication of the underlying disease, or an unrelated episode, such as sepsis or shock (Norris 2000). Confirmation of the diagnosis by a toxicant rechallenge is reliable but rarely justifiable (Lee 1995; Maria et al. 1997; Norris 2000). However, given that these two individuals inhaled the same gas, it is more likely that the effects were due to either the chemicals in the smoke or a combination of the chemicals in the smoke and the drugs, rather than the drugs alone.

The main treatment for toxicant-induced hepatotoxicity is the withdrawal or removal of the agent, supportive care, and alleviation of the symptoms (Lee 1995; Norris 2000). In our cases, there was no treatment beyond what was done for the respiratory effects.

**Conclusion**

Inhalation of HC/ZnO smoke may have hepatic effects in addition to the effect of pulmonary distress. The hepatotoxic effect in our patients was attributed to inhalation of high-concentration HC/ZnO smoke in an enclosed area, where several compounds including ZnCl₂, HC, and chlorinated vapors may have been generated and mixed in the smoke.

**REFERENCES**

ATSDR. 1997. Toxicological Profile for Hexachloroethane. Atlanta, GA:Agency for Toxic Substances and Disease Registry. Available: http://www.atsdr.cdc.gov/toxprofiles/tp97.html [accessed 6 May 2005].

ATSDR. 2000a. Toxicological Profile for Carbon Tetrachloride (Draft). Atlanta, GA:Agency for Toxic Substances and Disease Registry. Available: http://www.atsdr.cdc.gov/toxprofiles/tp30.html [accessed 6 May 2005].

ATSDR. 2000b. Toxicological Profile for Zinc (Draft). Atlanta, GA:Agency for Toxic Substances and Disease Registry. Available: http://www.atsdr.cdc.gov/toxprofiles/tp46.html [accessed 6 May 2005].

Cichowicz JJ. 1983. Environmental Assessment. Programmatic Life Cycle Environmental Assessment for Smoke/Obscurants. HC Smoke, Vol. 4. ARSCL-83007. Edgewood, MD:Chemical Research and Development Center, U.S. Army Armament, Munitions and Chemical Command, U.S. Army Aberdeen Proving Ground. Cullumhine H. 1957. The toxicity of screening smokes. J R Army Med Corps 102:119–122.

DeVauill DE, Dunn WE, Liljegren JC, Pochastro AJ. 1989. Field Measurement and Model Evaluation Program for Assessment of the Environmental Effects of Military Smokes: Analysis Methods and Results of Hexachloroethane Smoke Dispersion Experiments Conducted as Part of Aberdeen-97 Field Studies. AD-A216048. Frederick, MD:U.S. Army Medical Research and Development Command.

Fowler JS. 1989. Some hepatotoxic action of hexachloroethane and its metabolites in sheep. Br J Pharmacol 35:530–542.

Gorzinski SJ, Wade CE, McCollister SB, Kociba RJ, Mattsson JL. 1985. Subchronic oral toxicity, tissue distribution and clearance of hexachloroethane in the rat. Drug Chem Toxicol 8:155–169.

Greenfield RA, Brown BR, Hutchins JB, llandolo JJ, Jackson R, Slater LN, et al. 2002. Microbiological, biological, and chemical weapons of warfare and terrorism. Am J Med Sci 323:328–340.

Hamdi EA. 1989. Chronic exposure to zinc of furnace operators in a brass foundry. Br J Ind Med 26:126–134.

Hjortso E, Qvist J, Bud MI, Thomsen JL, Andersen JB, Wiberg-Jorgensen F, et al. 1988. ARDS after accidental inhalation of zinc chloride smoke. Intens Care Med 14:17–24.

Holmes PS. 1998. Pneumomediastinum associated with inhalation of white smoke. Mitt Med 164:751–752.

Kats S, Snelson A, Farlow R, Welker R, Mainer S. 1980. Physical and Chemical Characterization of Fog Oil Smoke and Hexachloroethane Smoke. DAMD 77-8-C-0085. AD-A080 936. Chicago, IL:IIIT Research Institute.

Lee WM. 1995. Drug-induced hepatoxicity. N Engl J Med 333(17):1118–1127.

Maria VA, Victorino RMM. 1997. Development and validation of a clinical scale for the diagnosis of drug-induced hepatitides. Hepatology 26:664–669.

Marrs TC, Colgrave HF, Edington JA, Brown RF, Cross NL. 1988. The repeated dose toxicity of a zinc oxide/hexachloroethane smoke. Arch Toxicol 62:123–132.

Meyers BR. 1985. Comparative toxicities of third-generation cephalosporins. Am J Med 79(2A):96–103.

Nanki T, Koike R, Miyasaka N. 1999. Subacute severe steatosis during prednisolone therapy for systemic lupus erythematosus [Letter]. J Am Gastroenterol 94:3379.

Rapacioli E, Qvist J, Bud MI, Thomsen JL, Andersen JB, Wiberg-Jorgensen F, et al. 1988. ARDS after accidental inhalation of zinc chloride smoke. Intens Care Med 14:17–24.

National Research Council. 1997. Hexachloroethane smoke. In: Toxicity of Military Smoke and Obscurants. Vol 1. Washington, DC:National Academy Press, 127–159.

Norris S. 2000. Drug and toxic-induced liver disease. In: Comprehensive Clinical Hepatology (O’Grady JG, Lake JL, Howdilder PD, eds). London: Mordby, 3/291–2.

Nonwood WD, Fuqua PA, Scudder BC. 1980. Carbon tetrachloride poisoning. Arch Ind Hyg Occup Med 30:1–100.

NTP. 1989. Toxicology and Carcinogenesis Studies of Hexachloroethane (CAS No. 67-72-1) in F344/N Rats (Gavage Studies). Technical Report 361. Research Triangle Park, NC:National Toxicology Program.

Pettila V, Takkunen O, Tukiainen P. 2000. Zinc chloride smoke inhalation: a rare cause of severe acute respiratory distress syndrome. Intensive Care Med 26:215–217.

Selden A, Nyrén M, Kvarnström A, Sundell K, Spangberg O. 1993. Biological monitoring of hexachloroethane. Int Arch Occup Environ Health 65(suppl 1):S111–S114.

Slater LN, et al. 2002. Microbiological, biological, and chemical weapons of warfare and terrorism. Am J Med Sci 323:328–340.