

Benzene-Induced Myelodysplastic Syndrome

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In various industries benzene is used for cleaning, stain removal, and dilution and as an adhesive. The petrochemical industry uses benzene as a raw material for styrene, alkyl benzene, and caprolactam. Moreover, aromatic compounds are added to gasoline as a substitute for alkyl lead compounds. Although atmospheric lead pollution is reduced, the concentration of benzene released into the air is increased. Because benzene is widely used in industry, exposure of workers to benzene is a health concern that deserves attention.^{1,2}

During the late 19th century, it was found that continuous exposure to benzene can lead to aplastic anemia and leukemia. There were also cases of acute myeloblastic leukemia reported during this period.³ This association brought attention to the toxicity of benzene to the bone marrow. Additional studies in Italy and Turkey showed that the standardized mortality ratio of leukemia among workers exposed to benzene is higher than that of non-exposed civilians.⁴ The threshold limit values for benzene have become more stringent. Threshold limit values refer to airborne concentrations of substances and represent conditions under which it is believed that nearly all workers may be exposed on a daily basis without adverse health effects.

The Department of Occupational Disease in Tri-Service General Hospital was established in 1994. Its goal is "to find and identify patients with occupational diseases, and to perform research in occupational medicine." The patient prompting this case report came to our hospital with benzene-induced myelodysplastic syndrome in 1996.

Case Report

The patient was a 45-year-old man who had started working at a petrochemical plant in 1977. That

petrochemical plant used benzene as a raw material for the production of caprolactam needed by the downstream factories for making nylon and plastic products. This man's job was adding benzene into the reactive kiln. He did not have any history of special medications or diseases, nor was he afflicted by any apparent toxic contamination or radioactive injuries. Each year the patient submitted to a regular medical checkup for workers. The results of routine blood studies are displayed in Table 1. These findings show that the patient had anemia, leukocytopenia, and thrombocytopenia since May 1994.

The patient was transferred to Magei hospital for diagnosis. Results of a bone marrow aspiration showed myelodysplastic syndrome. The patient was then referred to the Department of Occupational Diseases of the Tri-Service General Hospital in February 1996, where he has been given regular follow-up care. He was hospitalized again for pneumonia and pancytopenia in October 1996. At that time he was given antibiotics and a transfusion of red blood cells and platelets. When he was released from the hospital, he retired from the plant and has been unemployed at home. He still has pancytopenia, together with weakness, fatigue, dizziness, palpitation, and excessive bleeding after a minor injury. He cannot work because of his poor health. The results of blood studies since 1996 are displayed in Table 1.

Discussion

Benzene used in the plant was the principal ingredient for caprolactam, the basic material for nylon fibers. It is an important portion of the petrochemical industry. The production of caprolactam can recycle vitriolic fertilizers and supplement the domestic fertilizer supply for farming. Production was officially started in 1978. The time-weighted average of benzene has been 1 to 2 ppm around the reactive kiln in this factory since 1978. Time-weighted average means the average concentration in daily 8-hour work shifts. Aside from benzene, the other principal raw materials are hydrogen, liquid ammonia, sulfuric acid, and cyclohexane.

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Table 1. Blood Test Results of Worker.

Date	Hemoglobin g/dL	Hematocrit %	Mean Corpuscular Volume \times $10^3/\mu\text{L}$	Mean Corpuscular Hemoglobin Pg	Mean Corpuscular Hemoglobin Concentration G/dL	White Cell Count/ μL	Platelet Count $10^3/\mu\text{L}$
3/20/80	14.1					4,500	
3/28/89	13.9	43.4	103.0	33.1	32.0	2,300	
4/10/91	12.6					3,400	
1/16/93	15.2	44.2	92.3	30.0	37.0	5,200	183,000
5/12/94	11.0					3,500	
5/1/95	10.5	33.3	87.6	27.6	31.5	2,100	169,000
12/19/95	11.3	34.4	84.7	27.8	32.8	2,880	188,000
2/16/96	11.5	36.4	85.2	26.9	31.6	3,000	140,000
10/3/96	7.2	31.6	78.2	25.7	31.2	2,060	72,500
7/26/97	11.6	33.6	86.2	27.9	31.8	3,600	126,000
4/11/98	12.0	38.4	83.2	28.6	33.2	3,720	167,000
6/23/99	10.2	32.5	82.1	25.2	32.3	2,670	145,000
4/95	Bone marrow aspiration: myelodysplasia						
12/95	Bone marrow aspiration: Mild myeloid hypoplasia with maturation disturbance						

These materials might not be additive or synergistic to benzene toxicity.

Benzene enters the body mainly by inhalation; little is absorbed by the skin. Once inside the body, benzene penetrates the tissues. Concentrations in adipose tissue, bone marrow, and urine are about 20 times greater than in the blood. About 30% to 50% of the benzene inside the body is exhaled from system; the rest is processed in the liver. Generally, organic solvents inside the human body are processed in the liver, which converts them from fat-soluble to water-soluble compounds, and are then excreted through the kidney. The process is usually divided into two steps. First, the organic solvent is converted into a water-soluble product primarily through hydrolyzation, oxygenation, or deoxygenation. Next, when the organic solvent or primarily product undergoes biosynthesis, it will combine with such endogenous molecules as glucuronic acid and sulfate and form a secondary product. The secondary product is even more water soluble and is readily excreted by the kidney.⁵

When metabolized in the liver, benzene is first processed through mixed function oxidase. The energy needed for mixed function oxidase metabolism is supplied by cytochrome P-450. Often cytochrome P-450 is used as the active indicator of mixed function oxidase. The effect of mixed function oxidase on the benzene chain serves as the epoxide intermediate. When further hydrolyzed, it

metabolizes into phenol, catechol, hydroquinone, and 1, 2, 4-trihydroxybenzene. These intermediate metabolites, especially hydroquinone, are currently recognized as the principal cause of benzene-induced bone marrow toxicity.^{6,7} Epoxide intermediate can combine with glutathione and turn into mercapturic acid. It can combine with endogenous molecules, such as glucuronic acid and sulfate, and reduce benzene toxicity by means of excretion of benzene in the urine. A small amount of muconic acid found in the urine shows that the benzene chain structure has been broken. The metabolic products found in urine are mostly phenol.^{5,8,9}

Symptoms from chronic benzene exposure are mostly nonspecific. Generally, benzene is a central nervous system stimulant, while its metabolites damage the hematopoietic system. Since the end of the 19th century, numerous workers exposed to benzene suffered from serious and fatal aplastic anemia. Usually this condition is the result of high-dosage exposure. Aplastic anemia has a poor prognosis, and some cases would develop into leukemia. For more than 50 years, the link between benzene and leukemia has been debated, because supporting evidence was lacking, and animal experiments were unable to show cancer-causing effects. Then in the 1970s, reports from Turkey and Italy showed that benzene does increase the risk for leukemia, especially acute myeloblastic leukemia. Erythrocytic leukemia (M_6) and bone marrow monocyte leuke-

mia (M_4) are also forms of acute myeloblastic leukemia.^{10,11} Benzene exposure can be toxic to erythrocytes, leukocytes, and platelets. Basic animal experimental research has shown that benzene metabolism mainly occurs in the liver.^{12,13} Its metabolites include phenol, hydroquinone, catechol, and benzoquinone, all of which are capable of inhibiting the hematopoietic functions of the stem cells.

The stereotypical incubation period for leukemia resulting from benzene exposure is 5 to 15 years. The stage before the condition deteriorates to aplastic anemia and acute myeloblastic leukemia is myelodysplasia. When myelodysplasia occurs, the stem cells of the bone marrow are inhibited, causing poor hematopoietic functions. This condition would sometimes progress to aplastic anemia or a preleukemic stage, then later to acute myeloblastic leukemia. Hence, workers in operations exposed to benzene should undergo regular blood tests to monitor their health.

The International Agency for Research on Cancer (IARC) has listed benzene as a human carcinogen.¹⁴⁻¹⁶ The mission of IARC is to coordinate and conduct research on the causes of human cancer and the mechanisms of carcinogenesis and to develop scientific strategies for cancer control. The agency is involved in both epidemiologic and laboratory research and disseminates scientific information through publications, meetings, courses, and fellowships.

Environmental scanning is effected through area sampling. A simulation of the worker's respiratory conditions determines the exposure dosage. Test findings are called external dose. The US Occupational Safety and Health Administration standard is 1 ppm.¹⁷ The standard in Taiwan is 5 ppm. In terms of biologic surveillance, the short half-life of benzene makes it difficult to determine the benzene concentration in blood. Usually, benzene biologic surveillance is conducted by measuring the phenol concentrations in the urine. This measurement, however, is affected by the presence of phenol in food, medicines, or atmosphere. Consequently, low benzene exposure levels shown by urine phenol concentrations do not represent the biologic surveillance dosage.

In the United States, the American Conference of Governmental Industrial Hygienists (ACGIH) has ruled that the phenol concentrations of urine passed by workers before the end of their shift should meet a biologic surveillance standard of

50 mg/1 g of creatinine.² The original goal of ACGIH has been "to encourage the interchange of experience among industrial hygiene workers and to collect and make accessible such information and data as might be of aid to them in the proper fulfillment of their duties." ACGIH offers full membership to all industrial hygiene personnel within their agencies as well as to governmental industrial hygiene professionals in other countries. Today, membership is open to all practitioners in industrial hygiene, occupational health, environmental health, or safety.

Conclusion

Because of the wide industrial applications of benzene, it has been estimated that in the United States alone, about 2 million workers are exposed to benzene at their work sites. The bone marrow toxicity of benzene is well documented. In Taiwan there are few case studies reported on this subject. Naturally, benzene is not the only cause of bone marrow toxicity; other factors include radiation and a number of medicines. Persons working in work sites with benzene exposure should have regular blood monitoring through routine blood examinations and checkups.

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