

Hematotoxicity and Carcinogenicity of Benzene

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The hematotoxicity of benzene exposure has been well known for a century. Benzene causes leukocytopenia, thrombocytopenia, pancytopenia, etc. The clinical and hematologic picture of aplastic anemia resulting from benzene exposure is not different from classical aplastic anemia; in some cases, mild bilirubinemia, changes in osmotic fragility, increase in lactic dehydrogenase and fecal urobilinogen, and occasionally some neurological abnormalities are found. Electromicroscopic findings in some cases of aplastic anemia with benzene exposure were similar to those observed by light microscopy. Benzene hepatitis-aplastic anemia syndrome was observed in a technician with benzene exposure. Ten months after occurrence of hepatitis B, a severe aplastic anemia developed. The first epidemiologic study proving the leukemogenicity of benzene was performed between 1967 and 1973 to 1974 among shoe workers in Istanbul. The incidence of leukemia was 13.59 per 100,000, which is a significant increase over that of leukemia in the general population. Following the prohibition and discontinuation of the use of benzene in Istanbul, there was a striking decrease in the number of leukemic shoe workers in Istanbul. In 23.7% of our series, consisting of 59 leukemic patients with benzene exposure, there was a preceding pancytopenic period. Furthermore, a familial connection was found in 10.2% of them. The 89.8% of our series showed the findings of acute leukemia. The possible factors that may determine the types of leukemia in benzene toxicity are discussed. The possible role of benzene exposure is presented in the development of malignant lymphoma, multiple myeloma, and lung cancer.

Introduction

The hematotoxicity of chronic benzene poisoning has been well known for nearly a century. The effects of benzene include leukocytopenia, thrombocytopenia, anemia, transitory leukocytosis, lymphopenia, rarely lymphocytosis, very rarely pseudo-Pelger Huet anomaly changes in the leukocyte osmotic resistance, decreased phagocytic function of granulocytes, reduced glucogen content and inhibited activity of peroxidase of neutrophils, an increase in the acid phosphatase and β -glucuronidase activity of the neutrophils, and a decrease of alkaline phosphatase, myeloperoxidase and lipid content of the neutrophils (1). In addition, in chronic benzene toxicity a decrease of the E_a and E_{18} rosetts (T cells) was noted (1). Furthermore, an increase of leukoagglutinins was demonstrated in the sera of some workers exposed chronically to benzene. (1). An increase of eosinophils, basophils, and monocytes in chronic benzene toxicity is a matter of discussion (1). This problem, particularly concerning monocytes, deserves further investigation with modern techniques. In chronic benzene toxicity, some other qualitative abnormalities, such as the presence of giant platelets, has been found (1).

According to Craveri, the hemorrhagic effects of chronic benzene toxicity are not solely due to thrombocytopenia but are also due to increased fibrinolytic activity (2).

Aplastic Anemia or Pancytopenia Resulting from Chronic Benzene Exposure

The clinical and hematologic picture of benzene-induced aplastic anemia which is characterized by pancytopenia, is not different from that of classical aplastic anemia idiopathic or because of different chemicals or other agents (1). In some cases of benzene-induced aplastic anemia, there are characteristics that are absent when this hematologic disorder is caused by other agents, such as mild bilirubinemia, changes in osmotic fragility, shortened erythrocyte survival time, increased serum lactic dehydrogenase activity, increased fecal urobilinogen, and mild reticulocytosis (1). These findings are the result of a hemolytic component in aplastic anemia due to chronic benzene exposure. Additionally, in some cases of benzene-mediated aplastic anemia, absolute and relative lymphocytosis are absent (1). In other words, in addition to aplastic anemia resulting from other causes, absolute lymphopenia is present in this hematologic disorder due to chronic benzene exposure.

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On the other hand, although there are no symptoms and findings relating to the nervous system in aplastic anemia, idiopathic or because of different agents, in some cases of aplastic anemia resulting from chronic exposure to benzene, there are some findings relating to the nervous system (3). Although as early as 1967 Truhaut has indicated in his reports on benzene the possibility of long-term effects of this chemical agent on the nervous system such as polyneuritis of the lower extremities, there are very few reports on this subject (3,4). Baslo and Aksoy performed neurological, electromyographical, and motor conduction velocity examinations in six patients with aplastic anemia and two patients with preleukemia caused by chronic exposure to benzene (3). In addition, sensory conduction velocities were measured in three patients. Neurological abnormalities such as global atrophy and decreased sensory vibration of lower extremities (in one case), distal latency lengthening of median nerve (in one case), decrease in the sensory conduction velocities of the lower extremities (in one case) were found (3). There was a certain relationship between the presence of neurological abnormalities and the period of the exposure.

The findings of bone marrow examination in chronic benzene toxicity are extremely variable. The picture ranges from complete aplasia to highly hyperplastic bone marrow. In some patients, the bone marrow is fully acellular in the terminal stage (1). According to Mallory et al. the effects of benzene on the bone marrow will vary with the individual and are independent of the length of exposure (5). More than one type of foci can be encountered in the bone marrow. Using ³H-methylthymidine autoradiography, Moeschlin and Speck studied the bone marrow of animals poisoned by benzene and found that the results varied from animal to animal: 4 very hypoplastic, 6 hypoplastic, 5 normocellular, and 4 hypercellular (6). No correlation was found between cellularity of the bone marrow and duration of exposure to benzene.

A follow-up study was performed in 44 pancytopenic patients with chronic benzene toxicity (7). Only 21 patients had hypocellular bone marrow. It was normocellular in 13 patients and hypercellular in 8. Contrary to the findings of peripheral blood, there was a relationship between the types of cellularity of the bone marrow and the outcome, including the development of leukemia. Out of 21 patients with hypocellular bone marrow, 11 died (52.4%), and in 5 patients (23.8%) leukemia developed later. Contrary to this, only 1 out of 13 (7.7%) pancytopenic patients with normocellular bone marrow died. On the other hand, 4 out of 8 patients with hypercellular bone marrow recovered completely (50%). Two died from the complications of aplastic anemia. In 1 of the remaining 2, leukemia developed and in the second 8 years after complete recovery, the occurrence of myeloid metaplasia was the cause of death.

Ultrastructural studies in 4 patients with aplastic anemia and leukocytopenia were performed by Erbençi and Aksoy (8). Electronmicroscopic findings were in accordance with the changes in the bone marrow observed by light microscopy. Additionally, there was an increase in

plasma cells with maturation arrest in the later phases of the erythroid series. Ultrastructural studies shed some light on phagocytic activity of the reticulum cells. This study showed a hyperactivation in the bone marrow of one case and a depression in the erythroid elements in the second patient. These different findings may give the impression that the effect of benzene on the bone marrow may change from patient to patient.

Benzene-Hepatitis-Aplastic Anemia Syndrome

The occurrence of aplastic anemia in chronic benzene toxicity may be accelerated by the occurrence of viral hepatitis. Recently we have observed a severe case of aplastic anemia associated with chronic benzene toxicity 10 months after the appearance of hepatitis B. The propositus was a 32-year-old technician working in a petroleum plant (1). A sample of the product disclosed 2.2% benzene. Two years ago he had hepatitis B for a duration of 1 month. At that time he was not anemic and there was no leukocytopenia or hemorrhagic diathesis. Approximately 10 months later the signs of aplastic anemia appeared. He had severe pancytopenia. The bone marrow was very hypocellular, and the findings were consistent with the diagnosis of severe aplastic anemia. The tests for hepatitis B-virus antigens determined by ELISA showed that anti-HBs, anti-HBe, and anti-HBc were positive. The clinical and hematologic picture of the patient was similar to those of chloramphenicol-hepatitis-aplastic anemia syndrome first described by Hodgkinson (9). Following the failure of oxymetholon therapy, a trial with anti-lymphocytic serum, the patient's clinical and hematological picture improved considerably. He is in remission at the present. We call this syndrome "benzene-hepatitis-aplastic anemia syndrome" (1).

Benzene and Malignancies

Benzene is a suspected leukemogenic and carcinogenic agent since the first description of a case of leukemia by Le Noire and Claude in 1897 (10). Recently, Maltoni and Scarnato showed in rats and mice that oral intake of high doses of benzene causes malignancies in several tissues (11). Any agent toxic to pluripotent stem cells can cause an alteration in two important capabilities of the colony forming cells (12): self-renewal and differentiation to produce a variety of lineage restricted progenitor cells, in other words, the long-term maintenance of self-renewal and differentiation. Any block or disturbance in these capabilities will cause either aplastic anemia (a block in self-renewal) or leukemia (a block in differentiation). Therefore, benzene as a toxic agent for stem cells, may cause aplastic anemia or leukemia.

Although there were numerous case reports showing the possible role of benzene in the development of leukemia, the first epidemiologic study on this problem appeared in 1974 (13). From 1967 to September 1973, 26 patients with leukemia or pre-leukemia were seen among

Table 1. Annual number of leukemic shoe workers in Istanbul between 1967 and 1978.

Year	No. of leukemic shoe workers
1967	1
1968	1
1969	3
1970	4
1971	6
1972	5
1973	7
1974	4
1975	3
1976	0
1977	0
1978	0

28,500 shoe-slipper and handbag workers chronically exposed to benzene in Istanbul. At that time, the concentration of benzene was found to reach a maximum of 210 to 650 ppm during working hours in workplaces. The content of benzene in adhesives and thinners was between 9% and 88% (7,14). Of these leukemic workers, 17 were investigated at the Second Internal Clinic of Istanbul Medical School. The remaining 9 leukemic workers were studied in other hospitals in Istanbul. As explained in this study, another worker with acute lymphoblastic leukemia resulting from benzene exposure was not included in this series because his profession was different. In 1974, the number of the leukemic shoe workers in Istanbul increased to 31 (15). Thus the incidence of leukemia among them was 13.59 per 100,000, which is a markedly and statistically significant increase over that of leukemia in general population, 6 per 100,000.

In Turkey, according to the official Year Book of Health Statistics, the incidence of leukemia is between 2.25 and 2.80 per 100,000 (16). As can be seen from Table 1, the peak incidence among shoe workers in Istanbul occurred between 1971 and 1973 (17). It was 21.7 per 100,000. The number of leukemic shoe workers in Istanbul started to decrease after the prohibition and discontinuation of the use of benzene since 1969 (17). The number of new leukemic shoe workers has decreased in 1974 to 1975 to the level of 1969 to 1970, and none were recorded in subsequent 3 years. But between 1979 and 1987, we observed 22 new cases of leukemia associated with chronic exposure to benzene. Only 3 of them were shoe workers living in Istanbul. The decline in the annual occurrence of leukemia in the series of shoe workers in Istanbul may

be attributed to the prohibition and gradual discontinuation of benzene in this city starting in 1969. On the other hand, the reappearance of leukemia after 1979 in Istanbul and other Turkish cities may be attributed either to the variation in the interval between the occurrence of leukemia and exposure or the continued use of materials containing benzene (17).

The evidence for the use of benzene in Istanbul and other cities of Turkey following the prohibition of this chemical is shown in the following study (18). To illustrate the etiologic role of drugs and chemicals in the development of aplastic anemia, we analyzed 108 cases of aplastic anemia among 3175 hematologic patients during a 10-year period (1973-1982) in the hematology section of the Istanbul Medical School (18). In 25 (23.1%) of the cases, benzene was responsible for the development of aplastic anemia. On the other hand, a recent study performed in the period between 1983 and 1985 in Istanbul and Izmit showed that despite the considerable decrease in the content of benzene in most of the materials, they were still above permissible limits (19). During the study mentioned above we have encountered 2 cases of acute leukemia in a modern tire cord fabric in Izmit (19). Approximately 550 workers were employed. The working conditions were good and properly ventilated. The concentration of benzene in one part of the plant was 110 ppm, and in one solvent used in the auxiliary repair shop the benzene content was nearly 5%. The incidence of leukemia was 60.6 per 100,000 in a period of 6 years.

Development of Leukemia in Pancytopenic Patients with Chronic Benzene Toxicity

In our series comprising 59 leukemic patients with benzene exposure, a preceding pancytopenic period was present in 14 leukemic patients (23.7%) (20). The interval between the onset of the preceding pancytopenic period and that of leukemia varied between 6 months and 6 years. Furthermore, in a follow-up study in 44 pancytopenic patients with chronic benzene toxicity, leukemia developed in 6 (13.6%) and myeloid metaplasia in 1 (2.8%) (7).

Familial Connection and Individual Susceptibility

As can be seen from Table 2, in 6 leukemic patients associated with chronic benzene exposure, in our series, a

Table 2. Genetic relationship between eight leukemic patients with chronic exposure to benzene or colchicine and saccharin.

Case no.	Age	Duration of exposure, years	Occupation	Type of leukemia	Genetic relationship
1	43	6	Shoe worker	AML	Paternal uncle of case 2
2	24	4	Shoe worker	AML	Nephew of case 1
3	36	7	Shoe worker	AML	Maternal cousin of case 4
4	48	3	Painter	AML	Maternal cousin of case 3
5	36	15	Shoe worker	Erythroblastic leukemia	Son of case 6
6 ^a	65	35	Shoe worker	Unidentified type of leukemia	Father of case 5
7	43	2	Owner of a wallpaper and printing shop	Chronic lymphoid leukemia	Son of case 8
8 ^b	77	10-20 tablets daily	Stationer	Chronic lymphoid leukemia	Father of case 7

^aThis case was not included in our series of leukemia because he was not studied before his death.

^bUsed colchicine and saccharin.

familial connection was established (1,15,21).^{*} Two were an uncle and his nephew, and 2 were cousins (15). The father of the fifth leukemic patient, a 65-year-old shoe worker with a long history of benzene exposure, died in a hospital with the diagnosis of myelosclerosis, but re-evaluation of the case report showed that this patient had acute leukemia of an unidentified type (15). The father of the seventh patient with chronic benzene exposure also had the same hematologic malignancy associated with the use of colchicine and/or saccharin (21). These 6 leukemic patients among the first- and second-degree relatives constituted 10.2% of the leukemic patients with chronic exposure to benzene.^{*} In these 6 patients including case 7, the development of leukemia possibly resulted from simultaneous presence of genetic determinants, in addition to benzene as an extraneous or environmental factor. This suggestion is in accordance with the view that leukemia may be caused by the combination of various intrinsic and extrinsic factors (22). On the other hand, family susceptibility in the development of various disorders of chronic benzene toxicity suggested by numerous investigators were evident in our studies concerning benzene toxicity (1,17).

Types of Leukemia in Chronic Benzene Toxicity

It is evident from the literature that there is a significant difference in the distribution of leukemia types caused by benzene exposure (1,15,20,23). In one group, acute types of leukemia, mostly myeloblastic or erythroblastic, predominate, and in the other chronic leukemia, myeloid and lymphoid take the most important place. Although in our series, acute leukemia was 89.8%, the percentage of chronic types comprising myeloid, lymphoid, and hairy cell leukemia was 10.2% (20). Considering these facts we have tried to explain the possible factors that may determine the types of leukemia in chronic benzene toxicity (23).

One factor may be the differences in the content of benzene in the material used. The benzene content of the adhesives and thinners used by workers with acute leukemia in our series was very high (13,15,17,23). In contrast, it was very low (2.8%) in a worker with chronic lymphoid leukemia (23). Second, the adhesives and thinners that were used by nearly all the workers with acute leukemia contained only benzene (13,15,23). Contrary to this, the solvent used by a worker with chronic lymphoid leukemia had a low level of benzene and a high percentage of toluene (23). Third, the great majority of the individuals with acute leukemia in the series was exposed to high concentration of benzene ranging between 150 and 210 ppm during all working hours (13,15,23). Contrary to this, 5 out of 6 patients with chronic leukemia, 2 with chronic myeloid, 2 with chronic lymphoid, and one with hairy cell

leukemia were exposed to benzene intermittently and for a short time during the daily work. Fourth, the possible role of genetic factors may help to explain the development of different types of leukemia. As can be seen from Table 2, 6 patients in 3 families had acute types of leukemia. In the fourth family, despite different extraneous factors such as chronic benzene exposure and the use of colchicine and/or saccharin, the same type of leukemia, namely chronic lymphoid, developed at different ages (21).

Benzene, Malignant Lymphoma, Multiple Myeloma, and Lung Cancer

There are a few investigations that suggest a possible role of benzene in the etiology of malignant lymphoma, multiple myeloma, and lung cancer. In 1961, Wirtschafter and Bichell showed that tissue responses could be observed in lymph nodes, spleen, thymus, and bone marrow of the rat after a single injection of benzene (24). Recently, Irons et al. showed that the effects of benzene administration in mice on lymphocyte function are at the doses of the compound that produce little or no measurable differences in the number of circulating cells (25). In 1974, we described 6 cases of Hodgkin's disease with chronic exposure to benzene (26). Despite the lack of statistical data, we suggested that chronic exposure to benzene might play a role in the development of Hodgkin's disease.

In the last few years we have studied 7 more cases of different types of malignant lymphoma with benzene exposure (1,17,19). In 1979, Vianna and Polan performed a comparative study on the mortality rates of different types of malignant lymphoma among workers exposed to benzene (27). According to the investigators, their results are consistent with the possibility that chronic exposure to benzene might be important in the etiology of malignant lymphoma. A recent study of Norseth et al. is also in favor of this assumption (28). Furthermore, there are several studies showing a high mortality rate from different types of malignant lymphoma among pathologists, chemists, and persons handling chemicals containing benzene (29).

Multiple Myeloma

As early as 1970, Torres et al. reported 2 cases of multiple myeloma with chronic benzene exposure (30). In 1980 and 1984, we described 4 cases of multiple myeloma with chronic benzene exposure (31,32). Only one of these patients had a short period of pancytopenia with hypoplastic bone marrow. The mean exposure time to benzene was longer than that of cases of leukemia and malignant lymphoma: 18 years in the former and 10.5 in the latter (1). In an epidemiologic assessment study of Rinsky et al. in 1987, there was a statistically significant increase in deaths from leukemia and multiple myeloma (33).

^{*}Cases 6 and 8 were not included in this series because one (case 6) was studied in another hospital and the second (case 8) was not exposed to benzene (15,21).

Lung Cancer

In 1976, we considered 5 individuals with lung cancer associated with chronic benzene exposure and suggested that there is a causal relationship between this chemical and lung cancer (34). In our series of malignancies resulting from chronic exposure to benzene, there are 7 cases of lung cancer (1,17). Only 3 showed mild hematologic findings of chronic benzene toxicity. Because benzene available in Turkey did not contain benzo[a]pyrene determined by ultraviolet spectrophotometry, lung cancer in these 7 patients cannot be attributed to this carcinogenic agent (1,7). Benzene is mainly absorbed via the lungs, and about 40% of the absorbed portion is exhaled unchanged (35). After 24 hr, a small percentage of benzene can still be detected in the expired air (35). Therefore, a carcinogenic effect of benzene in the lung is possible. Because our patients were also smokers, a contributory role of smoking in the development of lung cancer is possible.

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