Case Study

Two Offset Printing Workers with Cholangiocarcinoma

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Abstract: Two Offset Printing Workers with Cholangiocarcinoma: Shinji KUMAGAI. Department of Management of Occupational Safety and Health, University of Occupational and Environmental Health, Japan—Objectives: Previously, the author reported a cluster of 11 cholangiocarcinoma cases exposed to 1,2-dichloropropane (1,2-DCP) and/or dichloromethane (DCM) in an offset proof-printing company. Before that report, the association between the two chemicals and cholangiocarcinoma had not been known. The current study describes two cholangiocarcinoma patients exposed to 1,2-DCP or DCM in different offset printing companies. Methods: The author obtained medical records for the patients, and interviewed the surviving patient and a relative of the deceased patient about their occupational history. Results: Case 1 was a man born in 1950. He worked in the printing section in a proof-printing company for 26 years. He was diagnosed as cholangiocarcinoma in 1998 and died in 2000. In proof-printing operations, he used gasoline for 14 years and 1,2-DCP for 11 years to remove ink from a rubber transcription roller (blanket). The exposure concentration of 1,2-DCP was estimated to be between 72 and 5,200 ppm. Case 2 was a man born in 1963. He worked in the printing section in a general offset printing company for 11 years. He was diagnosed with cholangiocarcinoma in 2007. In printing operations, he used both kerosene and a mixture of 50% DCM and 50% 1,1,1-trichloroethane (1,1,1-TCE) for 11 years to remove ink from a blanket. The exposure concentration of DCM was estimated to be between 240 and 6,100 ppm. He was simultaneously exposed to similar levels of 1,1,1-TCE. Conclusions: Because the offset printing process may cause cholangiocarcinoma, occupational history should be examined for patients with this cancer. (J Occup Health 2014; 56: 164–168)

Keywords: 1,2-Dichloropropane, Cholangiocarcinoma, Dichloromethane, Printing

Previously, I found a cluster of 11 cholangiocarcinoma cases among 62 employees in the proof-printing section of a printing company in Osaka, Japan, and reported a standardized mortality ratio (SMR) of 2,900 as a crude estimate1. The frequent occurrence of cholangiocarcinoma could not be explained by known risk factors for this cancer1. Up to now, 17 employees have developed cholangiocarcinoma in the company, and all patients had been exposed to high concentrations of 1,2-dichloropropane (1,2-DCP) over a long-term period, including 12 who had also been exposed to high concentrations of dichloromethane (DCM)2. The Ministry of Health, Labour and Welfare recognized cholangiocarcinoma in the cases to be an occupational cancer, probably caused by the long-term exposure to high concentrations of 1,2-DCP2.

Other than the above study1, no cancer epidemiological study or cancer case report of 1,2-DCP exposed workers has been published. There have been four cohort studies of DCM exposed workers in two cellulose triacetate-film production plants3,4 and two cellulose triacetate-fiber production plants5,6, but of these, only Lane’s original study found a significantly increased mortality risk for biliary tract cancer7. Consequently, the association between these chemicals and cholangiocarcinoma should be studied further. This report concerns two cholangiocarcinoma patients who were exposed to 1,2-DCP or DCM in small printing companies. The surviving patient and a relative of the deceased patient provided informed consent regarding study publication.

Case 1

1) Patient characteristics and occupational and medical histories

The patient was a man born in July 1950 with no drinking history. He smoked 20 cigarettes a day from 19 to 47 years old. He worked in the color proof-printing section of an offset proof-printing company
in Fukuoka, Japan, from 1970 to 1973. He then worked for a construction company, operating a crane truck, from 1973 to 1975. He was subsequently re-employed by the same offset proof-printing company and worked from 1975 to 1998.

In March 1998, he visited a nearby hospital due to epigastric pain and back pain. Abdominal CT and abdominal ultrasonic echo revealed neoplastic lesions in the S4 and S6 segments of the liver. In the same month, he visited a university hospital and received a diagnosis of intrahepatic bile duct cancer. The blood test at diagnosis showed increased levels of biliary enzymes \( \gamma \)-GTP (294 IU/l) and ALP (1,017 IU/l) and a high level of tumor marker CEA (11.2 ng/ml). Tests for hepatitis B and for hepatitis C were negative. Moreover, lymph node metastasis in the pancreatic head was observed. He was transferred to a municipal hospital, where he received chemotherapy and underwent hepatic trisegmentectomy in November. However, due to a recurrence, he underwent partial hepatectomy in November. Thereafter, he continued to receive chemotherapy but died in March 2000.

2) Operations at the offset proof-printing company

The proof-printing room was 10.5 m \( \times \) 7.4 m with a ceiling height of 2.7 m and was located on the first floor of the building; two offset color proof-printing machines were located in the room. The windows in the room were always closed. The room was equipped with three ventilators; all three were running during summer, while two of the three were used during winter. One printing worker and one assistant (e.g., for plate exchange) were allocated to each proof-printing machine, i.e., a total of four workers in the room. The workers printed color proofs for catalogs and brochures. Color proofs are a set of a few preprinted sheets used to show how the colors will look in final printing.

The color proof-printing procedure was as follows:
1) A sheet of paper and a plate were set on the machine. 2) The ink roller was charged with red ink and rotated so that the ink was rolled in. 3) The plate surface was wet with a sponge soaked in tap water. 4) The ink was spread over the plate by the rolling motion of the ink roller on the plate surface. 5) The rubber transcription roller (blanket) was rolled over the plate surface as well as the paper surface to print a proof, with this procedure repeated about 10 times. 6) The ink roller was wiped off with ink-removal cleaner (a mixture of kerosene and water with surfactant) and with white gasoline. 7) Finally, the blanket was wiped off with blanket cleaner. The same procedure was repeated for blue ink, yellow ink and then black ink. After black ink was used, cleaning was sometimes repeated twice in order to remove the ink completely. Accordingly, to print one set, the ink-removal operation was repeated four to five times.

One proof-printing machine produced about two sets of four-color prints per hour, and thus, the blanket was cleaned eight to 10 times. Because the actual working hours was 10 hours, the total number of cleaning operation reached 160–200 times for the two machines.

White gasoline was used as the blanket cleaner from 1971 to 1973 and from 1975 to around 1986. Subsequently, 95–100% 1,2-DCP (cleaning agent I) was used until 1998. The amount of blanket cleaner used was about 9 liters (half an 18-liter square can) per day. Workers used plastic gloves while cleaning, but they were not provided with any respiratory protection. No working environment measurements had been conducted.

3) Estimation of exposure level of 1,2-DCP

The installed ventilators had a blade diameter of 30 cm, a voltage of 100 V and electric power consumption of 46 W. According to an electronics manufacturer catalog, a ventilator with these specifications generates 1,300–2,000 m\(^2\)/hour of air flow; therefore, three ventilators generate 3,900–6,000 m\(^2\)/hour. However, as there was no outside air intake, the actual amount of ventilation was unclear. Assuming that the amount of blanket cleaner used over the course of 10 hours was 10 kg (9 liters), and that the air volume of the printing room was 210 m\(^3\), the 1,2-DCP concentration was estimated to be 5,200 ppm as a shift time-weighted average with no ventilation at all. If the room was ventilated with fresh air at 6,000 m\(^2\)/hour, the 1,2-DCP concentration was estimated to be 36 ppm as a steady state level, based on the complete mixing model\(^6\). However, exposure concentrations for workers near the source would be actually higher. According to the results of a reproductive experiment at the offset proof-printing company in Osaka, the concentrations of 1,2-DCP and DCM in the breathing zone were approximately twice those of the workroom environmental concentrations\(^6\). Thus, the exposure concentration for the worker was estimated to be 72 ppm. These calculations suggest that the exposure concentration was between 72 and 5,200 ppm. Given that two of the three ventilators were operating during winter, by similar estimation, the exposure concentration of 1,2-DCP was between 110 and 5,200 ppm.

Case 2

1) Patient characteristics and occupational and medical histories

The patient was a man born in November 1963. He drank a can of beer (350 ml) two or three times a week and smoked four cigarettes a day from 20 to 30
years old.
He worked at a restaurant for one year from 1982. He then worked in a termite extermination company for about one month, going under the floors of standard homes to spray termicide (component unknown). From 1984 to 1995, he worked for a general offset printing company (non proof-printing) in Nagoya, Japan, and engaged in printing operations. From 1995 up to the present, he has been working for a semiconductor manufacturing company. He served as a clean-room operator for the first two years, but no chemical use was involved. He has been engaged in computer-based work since then.

In January 2006, abnormal liver function (γ-GTP, 1,150 IU/l; ALP, 773 IU/l; AST, 52 IU/l; ALT, 113 IU/l) was observed in a periodic health examination at the semiconductor manufacturing company. He received treatment with oral medication at a nearby clinic, but as there was no sign of improvement, he visited a municipal hospital in March 2007. Abdominal CT and magnetic resonance cholangiopancreatography revealed a neoplastic lesion at the anterior segmental branch of the bile duct. In April 2007, he received a definitive diagnosis of hilar cholangiocarcinoma (adenocarcinoma) by liver biopsy. Tests for hepatitis B and for hepatitis C were negative. He received ion beam radiotherapy for one month starting in May 2007 at an ion beam medical center.

In January 2010, an increase in the level of tumor marker C19-9 was noted, and as the follow-up examination revealed lymph node metastasis, he was started on chemotherapy. In June 2012, with relapse of lymph node metastasis, he underwent lymph node resection. At present, he receives regular follow-up.

2) Operations at the offset printing company

The printing room was about 17 m × 14 m with a ceiling height of about 3 m and was located in the first floor of the building; 3 four-color sheet-fed offset press machines and 2 one-color sheet-fed offset press machines were located in the room. The windows in the room were always closed, and two or three ventilators installed in the room were used. For each of the four-color press machines, two printing workers were allocated, totaling 6 or 7 workers for the entire room, including those who were allocated to one-color press machines that were not always in use. Prints included flyers, catalogs and brochures.

The printing procedure was as follows: 1) Sheets of paper and a plate were set on the machine. 2) Four color inks were placed in each ink fountain, and the ink roller was rotated to roll-in the inks. 3) While feeding about 30 sheets of papers, the supplied amounts of ink and dampening solution and the position of the plate were adjusted. 4) Once adjustment was complete, the blanket was wiped off with a cloth soaked in kerosene and then with a cloth soaked in a mixture of 50% DCM and 50% 1,1,1-trichloroethane (1,1,1-TCE) (cleaning agent II). 5) Final printing was then performed. 6) The blanket was cleaned every printing about 3,000 sheets.

The four-color press machine was equipped with eight blankets for two-sided printing. Since two workers operated the machine, one person performed four ink removal operations each time. It took about four hours to print 10,000 sheets, and during this time, cleaning was usually performed four times (including cleaning at the end of printing); therefore, each worker performed 16 ink removal operations. Given that the actual working hours were 12 hours, the number of ink removal operations performed by one worker was 48. This means that in the printing room as a whole, the ink removal operation was repeated about 300 times.

The plate was cleaned using the same cleaner (cleaning agent II), sometimes simultaneously with the blanket, or only once at the end of printing. Moreover, at the end of daily operations, the ink roller and ink fountains were cleaned using cleaning agent II, and the whole press machine was also cleaned using kerosene and cleaning agent II.

About 54 liters of cleaning agent II was used each day for the entire printing room. Workers wore plastic gloves during cleaning, but they were not provided with any respiratory protection. No working environment measurements had been conducted.

3) Estimation of exposure level of DCM

The printing room was equipped with two or three ventilators; however, the specifications were unknown. Moreover, with no outside air intake, the actual ventilation effect is unclear. Assuming that the amount of blanket cleaner used over the course of 12 hours was about 60 kg (54 liters, 30 kg DCM and 30 kg 1,1,1-TCE) and that the air volume of the printing room was 710 m³, DCM concentration was estimated to be 6,100 ppm as a shift time-weighted average with no ventilation at all. If the room was ventilated with fresh air at 6,000 m³/hour (three ventilators, each at 2,000 m³/hour), the concentration of DCM was estimated to be 120 ppm as a steady state level, based on the complete mixing model\(^9\). The exposure concentration for a worker was estimated to be 240 ppm, assuming that the value was twice the workroom environmental concentration. Based on the above calculations, the exposure concentration of DCM was estimated to be between 240 and 6,100 ppm. This patient was simultaneously exposed to similar levels of 1,1,1-TCE.
Discussion

The two patients were younger than the peak age (50 years or older) of cholangiocarcinoma onset\cite{1,2}. The risk factors for cholangiocarcinoma include liver fluke infection, primary sclerosing cholangitis, biliary malformation, biliary stone, viral hepatitis, heavy drinking and smoking, and exposure to chemicals such as thorotrast\cite{3}. The two patients, however, did not have any of these risk factors. Therefore, no known risk factors applied to the patients, and thus, chemicals used at their work were possibly associated with the pathogenesis.

Case 1 was exposed to white gasoline and 1,2-DCP for 13 years and 12 years, respectively. Case 2 was exposed to both DCM and 1,1,1-TCE for 11 years. Of these chemicals, 1,2-DCP and DCM were also used in the color proof-printing company in Osaka at which 17 workers developed cholangiocarcinoma\cite{4}.

Both 1,2-DCP and DCM cause hepatocellular tumors in mice but not in rats\cite{5,6}. DCM metabolism proceeds through two pathways: a high-affinity/low capacity oxidation pathway catalyzed by cytochrome (CYP) P450 and a low affinity/high capacity conjugation pathway mediated by glutathione-S-transferase (GST)\cite{7}. DCM is mainly metabolized through the CYP pathway at low concentrations, and when this pathway becomes saturated, the GST pathway becomes active. Development of hepatocellular tumors is thought to be associated with S-chloroethylthylglutathione, a putative genotoxic intermediate of DCM, in the GST pathway\cite{8,9}. Because GST activity in the liver is much lower in rats than in mice\cite{10}, DCM might not be a likely cause of hepatocellular tumors in rats. The expression of GST T1-1, which plays the most important role in glutathione conjugation of DCM, is highest in the nucleus of hepatic cells in mice and the nucleus of bile duct epithelial cells in humans\cite{11}. It is therefore highly likely that workers exposed to high levels of DCM would develop cholangiocarcinoma. 1,2-DCP is also metabolized by CYP and GST\cite{12} and has a species difference in sensitivity to developing hepatocellular tumors similar to DCM, which suggests that hepatocellular tumors may be related to an intermediate metabolite of 1,2-DCP in the GST pathway. If GST T1-1 plays the largest role in glutathione conjugation of 1,2-DCP, exposed workers would develop cholangiocarcinoma.

In humans, the exposure concentration at which saturation of the CYP pathway occurs is thought to be in the range of 400–500 ppm for DCM\cite{13}. The corresponding concentration for 1,2-DCP is thought to be in the range of 150–250 ppm\cite{14}, by analogizing from saturated concentration for 1,2-dichloroethane\cite{15}. The estimated 1,2-DCP exposure concentration in Case 1 is 72-5,200 ppm, and the estimated DCM exposure concentration in Case 2 is 240-6,100 ppm. These values indicate that the exposure concentrations for the two patients were possibly approaching levels high enough to saturate the CYP pathway.

This study suggests that the incident at the proof-printing company in Osaka was not a specific case, and it is certainly possible that long-term exposure to high concentrations of 1,2-DCP or DCM would lead to the development of cholangiocarcinoma. Consequently, occupational history should be examined for cholangiocarcinoma patients.

References


