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ORIGINAL ARTICLE

The effect of exposure to a mixture of organic solvents on liver enzymes in an auto manufacturing plant

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Abstract
Aim Organic solvents are widely used in industry. Hepatotoxicity of halogenated hydrocarbons has been confirmed in many studies. However, there are few studies about the association between exposure to aromatic solvents and hepatic toxicity. The objective of this study was to assess the effects of long-term exposure to a mixture of aromatic hydrocarbons at above permissible levels on the hepatic system.
Subjects and methods In this study, two groups of workers in an auto manufacturing plant were selected, workers in the painting room as the case group and workers in the assembly room as the control group. A questionnaire including demographic data was filled out for all 349 workers. After considering inclusion and exclusion criteria, 163 and 186 workers were entered into the case and control group, respectively, and were compared for plasma levels of ALT, AST and ALP.
Results The mean plasma ALP level in the case group was significantly higher than in the control group ($P<0.001$). The plasma level of ALT and AST was higher in the case group as well, but was not statistically significant. An increase in ALP had a significant association with BMI ($P<0.001$) and smoking ($P=0.007$).
Conclusion Results of this study show that exposure to non-permissible levels of a mixture of aromatic solvents can cause mild cholestatic hepatic dysfunction. Therefore, using liver function tests (especially ALP), which are inexpensive, simple and non-aggressive, can be recommended as a screening method for early diagnosis of hepatic dysfunction.

Keywords Liver enzyme · Organic solvent · Occupational exposure

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Background

Organic solvents are widely used in industry. They are used in many industries and workplaces, such as those having to do with printing, rubber, plastics, dyes, toys, photographic film and adhesives (Fiedler and Lerman 2007). According to NIOSH (National Institute of Occupational Safety and Health), 9.8 million workers in the US were exposed to organic solvents in the first half of the 1970s. In the 1980s, about 400,000 workers (15% of the work force) in Denmark were exposed to solvents. In 1984, more than 49 million tons of different kinds of organic solvents were produced in the US (Lundberg et al. 2005). Therefore, exposure to organic solvents is common and comprises one of the most common chemical exposures in workers. Organic solvents are classified into different groups according to their chemical structure, i.e., aliphatic, aromatic, halogenated, etc. (Lundberg et al. 2005). Many halogenated solvents, e.g., carbon tetrachloride, chloroform and vinyl chloride, are known to be hepatotoxins (Attarchi et al. 2007). Many epidemiologic studies have been

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conducted to determine the effect of long-term exposure to halogenated solvents on the hepatobilliary system. Most of these studies are cross sectional and have assessed the effects of solvents on hepatic transaminases and bile acids (Lundberg et al. 2005). Some recent studies have shown a positive association between exposure to halogenated solvents and fatty liver (Lundgvist et al. 1999). However, there are few studies about the association between exposure to aromatic solvents and hepatic toxicity. Benzene, toluene, xylene and styrene are among the most highly used aromatic solvents and the most important industrial solvents used in the production of dyes, adhesives and pesticides. According to NIOSH, 4.8 million workers are exposed to tolouene, and 140,000 workers are exposed to xylene (Rosenberg and Katz 2007). Tolouene is one of the most common solvents used in industry and is a known hepatotoxin in animals (Lundberg et al. 2005). Increased levels of serum transaminases and gama glutamyl transpeptidase (GGT) have been shown in workers in the printing industry exposed to toluene via the respiratory route. Liver biopsy in these workers has shown fatty liver following non-specific mild inflammation (Kinght et al. 1991).

Studies on the workers exposed to organic solvents have shown increased levels of liver transaminases and GGT, which indicate hepatic necrosis and cholestasis (Ann et al. 2001; Hussein et al. 2008). Two cross-sectional studies in workers exposed to lower levels of styrene have shown increased levels of direct bilirubin and alkaline phosphatase compared with the control groups, but no increase in transaminases, which shows mild metabolic disorder without significant hepatic parenchymal necrosis (Brodkin et al. 2001).

In general, exposure to mixed organic solvents is more common than to a particular solvent. Some studies have shown increased levels of liver enzymes in painters and workers in the printing industry exposed to a mixture of aromatic solvents (Lundberg et al. 2005).

Naturally, the additive effect of a mixture of organic solvents causes increased hepatotoxicity. Another study has shown that the oxidative metabolism in human liver changes with exposure to a mixture of organic solvents containing toluene. This may explain various hepatic toxicities seen with exposure to a mixture of organic solvents (Warnes et al. 2000; Xiao and Levin 2000).

In Chen et al.'s study, after adjusting for non-occupational factors, increased activity of GGT was related to the intensity of exposure to a mixture of organic solvents. In this study, xylene and toluene were the most common contaminants in the air samples (Chen et al. 1991). However, in another study on workers exposed to a mixture of organic solvents in shoe repair work, there were no differences in the hepatic enzyme levels between the two groups (Uuksulainen et al. 2002).

In Pool and Orono's study among workers occupationally exposed to mixed organic solvents in the petrochemical industry, there were no statistically significant differences in the levels of hepatic enzymes compared to the control group (Pool and Orono 2001).

Todd et al.'s study did not show toxic effects of mixed organic solvents on liver (Todd et al. 2008). There is also some evidence that long-term exposure to organic solvents, e.g., toluene and xylene, may contribute to hepatic carcinoma (Porru et al. 2007).

In the painting rooms of auto manufacturing plants, many workers are exposed to a mixture of aromatic solvents, and few studies have been performed to show the association between aromatic solvents and hepatic toxicity, so we decided to design a study to assess this relationship and evaluate the predictive value of screening hepatic injury by measurement of plasma levels of liver enzymes in workers exposed to a mixture of aromatic solvents.

Methods

Study population and design

This study was performed in a large auto manufacturing plant in Iran in 2009. Cases (exposed to organic solvents) and controls (not exposed to organic solvents) were selected from painting rooms and assembly rooms, respectively. All persons in the case and control groups were male workers, working around 8 h a day.

All persons with at least 6 months of employment in the painting or assembly rooms were included in the study, and those persons with active hepatic disease, alcohol consumption (even recreational), consumption of hepatotoxic drugs, systemic diseases (i.e., diabetes and thyroid dysfunction) and history of blood transfusion in the last 3 months were excluded from the study. Five workers were excluded because of alcohol consumption (three men in the case group and two in the control group); also eight workers were excluded because of diabetes mellitus (three persons in the case group and five persons in the control group). In order to rule out infectious hepatitidis, serum HBsAg, HBcAb and HCVAb were evaluated in the entire study population, and 12 persons were excluded from the study because of positive tests (4 HBsAg positive and 1 HBcAb positive person in the case group and 5 HBsAg positive, 1 HBcAb positive and 1 HCVAb positive persons in the control group).

All necessary data, i.e., age, weight, stature, duration of employment, alcohol consumption, drug consumption and history of diseases, were obtained and recorded in a questionnaire.

After considering inclusion and exclusion criteria, 163 persons were included in the case group and 186 in the

control group. Then alanine amino transferase (ALT), aspartate amino transferase (AST) and alkaline phosphatase (ALP) were measured for both groups before the first shift of the work week (after 40 h abstinence from exposure to organic solvents) in fasting condition. All laboratory technicians were blind to the case and control groups. All workers participated voluntarily in this study and gave informed consent (written consent was obtained in Persian).

Exposure evaluation

All solvents in the workplace were measured by an industrial hygiene team working in the plant, and the details are as follows:

Organic solvents used in the painting room were benzene, toluene, xylene and tetrachloroethylene. These solvents have similar and sometimes synergistic effects on the body, so in order to evaluate the level of exposure to the mixture of organic solvents, we used the following formula (Cohen 2007) and considered the ACGIH-TLVs (American Conference of Governmental Industrial Hygienists Threshold Limit Values, which are standard values established annually for chemical substances and physical agents) as the standard for permissible levels:

$$E_m = C_1/L_1 + C_2/L_2 + \ldots + C_n/L_n$$

in which Em, C and L stand for equivalent concentrations of the mixture of the organic solvents, mean concentration of organic solvents in the workplace air and permissible levels of exposure to organic solvents, respectively.

After measuring the mean concentration of each solvent and using the formula, Em>1 was considered as exposure to more than permissible levels of a mixture of organic solvents in the workplace. In this study, Em was 2.52, i.e., the concentration of the mixture of organic solvents in the painting room of this factory was higher than the permissible level. The concentration of organic solvents in the assembly room was measured as well, which was near zero, and it could be ignored.

Therefore, in this study the case and control groups were composed of workers exposed to a mixture of organic solvents at more than permissible levels (in the painting room) and workers without any sizeable exposure to these solvents (in the assembly room), respectively.

Environmental measurement of organic solvents present in the workplace was performed at the breathing zone. Air samples were collected on charcoal tubes with constant flow (100 ml/min) pumps (SKC 226-01) in seven stations designed for the painting room and nine stations designed for the assembly room. Air monitoring was performed continuously during all working hours (8 h). Subsequently, gas chromatography was used to analyze the samples, and the average concentration of each solvent was identified.

This study was approved by the Ethics Committee of Iran University of Medical Sciences.

Statistical analysis

For statistical analysis, the mean, standard deviation and range were measured for quantitative variables, and they were compared using a t-test. In order to compare qualitative variables, we used the chi-square test. In order to adjust the confounding factors and more precisely evaluate the relationship between exposure to the mixture of organic solvents and change in plasma levels of liver enzymes, we used the linear regression method. All calculations were done using SPSS (version 15). P values less than 0.05 were considered statistically significant.

Results

In this study all individuals in both the case and control groups were male. The mean age was 34.63 (range: 24–57) years and 33.53 (range: 23–55) years in the case and control groups, respectively. Mean employment duration was 9.61 (range: 0.5–30) years and 8.84 (range: 2–26) years in the case and control groups, respectively. Individuals in the case group had a mean BMI (body mass index) of 22.86 (range: 19–34.29) kg/m^2, and this variable was 22.60 (range: 19–29) kg/m^2 in the control group. There were 41 (25.15%) and 35 (18.81%) smokers in the case and control groups, respectively. There was no statistically significant difference between the two groups regarding age (P=0.095), employment duration (P=0.112), BMI (P=0.285) and smoking (P=0.156).

The mean concentration of organic solvents is shown in Table 1.

Table 1 Mean concentration of organic solvents in the workplace air in the painting room

Solvent	Mean concentration (ppm)[I]	ACGIH-TLV[II] (ppm)
Benzene	0.62	0.5
Toluene	8.10	50
Xylene	88	100
Tetrachloroethylene	6	25

[I] Part per million

[II] American Conference of Governmental Industrial Hygienists Threshold Limit Value

Table 2 Comparison of liver function tests in both groups

Significance	Control group Mean (SEM)	Case group Mean (SEM[I])	Liver function test
NS[II]	28.01 (0.099)	28.49 (1.254)	ALT (IU/ml)
NS	21.39 (0.113)	21.93 (0.497)	AST (IU/ml)
<0.001	172.23 (0.392)	201.87 (3.839)	ALP (IU/ml)

[I] Standard error of mean

[II] Not significant

As mentioned earlier, the total concentration of the mixture of organic solvents was higher than permissible levels.

Table 2 shows the mean value of the liver function tests in both groups.

According to this table, in the case group ALP was significantly higher than in the control group ($P<0.001$). The absolute level of ALT and AST was also higher in the case group than in the control group, but the difference was not statistically significant.

After adjustment for age, smoking, BMI and employment duration, there was again a statistically significant difference in ALP level between the two groups using linear regression analysis (Table 3).

According to Table 3, there was no significant relationship between age and duration of exposure and increase in ALP level ($P=0.175$ and $p=0.615$, respectively). But the increase in ALP had a significant relationship with BMI and smoking ($P<0.001$ and $P=0.007$, respectively).

Discussion

In this study the results of liver function tests in workers exposed to a mixture of organic solvents at a level above the permissible limit was evaluated. Because mixtures of organic solvents are used extensively in industries, we studied the effects of a mixture of aromatic solvents. Previous studies have mostly focused on one type of solvent and especially halogenated solvents. Another characteristic of this study is the adjustment of such confounding factors as age, BMI, alcohol consumption, drug consumption and active hepatic diseases (hepatitis B and C).

Table 3 Results of the linear regression analysis for an association between ALP level and study variables

Variable	β	Standard error	Significance
Age	0.071	0.313	0.175
Exposure to solvent	0.389	1.769	<0.001
Smoking	0.136	4.414	0.007
Employment duration	0.026	0.442	0.615
BMI	0.209	0.803	<0.001

In this study, we found a significant relationship between ALP level and exposure to a mixture of organic solvents, indicating mild cholestatic hepatic injury. We couldn't find such a relationship for other hepatic enzymes (i.e., ALT and AST), although the level of these enzymes was higher in the case group than in the control group. In some other studies, e.g., that of Nijem et al., the relationship between the occupational exposure to organic solvents and toxic hepatic injury was propounded (Nijem et al. 2001).

In another study performed in a petrochemical plant by Perez et al., the level of liver transaminases was significantly higher in the case than in the control group (Perez et al. 2006). In our study there was a significant relationship between BMI and an increase in ALP level as well. Two other studies also showed a significant relationship between BMI and an increase in transaminase level and the incidence of non-alcoholic fatty liver (Church et al. 2006; Luo et al. 2001). In the study of Sia et al., BMI>25 was introduced as a risk factor for fatty liver (Sia et al. 2002). In our study, we did not observe a significant relationship between age and employment duration and an increase in ALP level, which was consistent with the study of Brautbara and Williams (2002). Chen et al. did not observe a significant relationship between age and employment duration and GGT level (Chen et al. 1991). In another study on workers exposed to organic solvents, there was no relationship between employment duration and ALP level (Sia et al. 2002). Although the results of the study of Michailova and Kuneva was not consistent with ours, there was a significant relationship between employment duration of more than 10 years and hepatic injury (Michailova and Kuneva 1998).

In general, the difference between various studies could be due to the difference in sample size, study method, type of the solvent studied, exposure intensity and liver tests studied. One study has proposed exposure intensity or the sensitivity of the test used for assessing liver function as the factors causing different results in the studies (Kaukiainen et al. 2004; Pratt and Kaplan 2000). Some studies have shown the higher sensitivity of serum bile acids than liver transaminases for diagnosis of liver dysfunction in persons exposed to organic solvents (Nunes and Pereira 2005).

Although liver function tests (AST, ALT and ALP) are not sensitive for the early diagnosis of early stages of liver dysfunction due to occupational exposures, the results of our study showed mild cholestatic liver injury in the

population exposed to a mixture of organic solvents; it can be expected that assessing the trend of the increase in the level of liver enzymes may be helpful in this regard.

Ultimately, according to the results of this study and the properties of liver function tests (ALT, AST and especially ALP), which are inexpensive, accessible and non-aggressive, these tests can be used in the screening of workers exposed to a mixture of organic solvents in order to diagnose liver injury early.

Finally, a probable defect in the recorded data and lack of personal monitoring data for aromatic organic solvents are the most important limitations of this study.

However, to express a precise opinion, longitudinal prospective studies with larger sample sizes and using more sensitive tests are required.

Conflict of interest We have no competing interests.

References

Ann C, Lee K, Park J, Jang J, Kim M (2001) The Association of Exposure to Organic Solvents with liver function. Korean J Occup Environ Med 13:64–74

Attarchi MS, Aminian O, Dolati M, Mazaheri M (2007) Evaluation of liver enzyme levels in workers exposed to vinyl chloride vapors in a petrochemical complex. J Occup Med Toxicol 2:6

Brautbara N, Williams J (2002) Industrial solvents and liver toxicity: risk assessment, risk factors and mechanisms. Int J Hyg Environ Health 205:479–491

Brodkin C, Moon J, Camp J, Echeverria D, Redlich C, Checkoway H (2001) Serum hepatic biochemical activity in two populations of styrene-exposed workers. Occup Environ Med 58:95–102

Chen J, Wang j, Jang J, Chen Y (1991) Exposure to mixtures of solvents among paint workers and biochemical alteration of liver function. Br J Ind Med 48:696–701

Church T, Kulk J, Ross R, Priest E, Biltoft E, Blair S (2006) Association of cardiorespiratory fittness, body mass index, and waist circumference to nonalcoholic fatty liver disease. Gastroentrology 130:2023–2030

Cohen B (2007) Industrial hygiene measurement and control. In: Rom W (ed) Environmental and occupational medicine, 4th edn. Lippincott Williams & Wilkins, Philadelphia, p 1768

Fiedler N, Lerman S (2007) Organic solvents and fuels. In: Rom W (ed) Environmental and occupational medicine, 4th edn. Lippincott Williams & Wilkins, Philadelphia, p 1102

Hussein A, Abdalla M, Hussein J, Shousha W, Mohamed A (2008) Antioxidants in shoe-makers exposed to organic solvents. J Appl Sci Res 4:1107–1117

Kaukiainen A, Vehmas T, Rantala K, Nurminen M, Martikainen R, Taskinen H (2004) Results of common laboratory tests in solvent-exposed workers. Int Arch Occup Environ Health 77:39–46

Kinght A, Pawscy C, Aroney R (1991) Upholsteres glue associated with myocarditis, hepatitis, acute renal failure and lymphoma. Med J Aust 154:360–362

Lundberg I, Hogstedt C, Linden C, Nise G (2005) Organic solvents and related compounds. In: Rosenstock L, Cullen M (eds) Textbook of clinical occupational and environmental medicine, 2nd edn. Elsevier-Saunders Press, Philadelphia, p 991

Lundgvist G, Flodin U, Axelson O (1999) A case-control study of fatty liver disease and organic solvent exposure. Am J Ind Med 35:132–136

Luo J, Kuo H, Cheng T, Chang M (2001) Abnormal liver function associated with occupational exposure to dimethylformamide and hepatitis B virus. J Occup Environ Med 43:474–482

Michailova A, Kuneva T (1998) A comparative assessment of liver function in workers in the petroleum industry. Int Arch Occup Environ Health 71:546–549

Nijem K, Kristensen P, Thorud S, Al-Khatib A, Takrori F, Bjertness E (2001) Solvent exposures at shoe factories and workshops in Hebron City, West Bank. Int J Occup Environ Health 7:182–188

Nunes M, Pereira M (2005) Increased serum bile acids as a possible biomarker of hepatotoxicity in Brazilian workers exposed to solvents in car repainting shops. Biomarkers 10:456–463

Perez C, Bosia J, Cantore M, Chiera A, Cocozzella D, Adrover R (2006) Liver damage in workers exposed to hydrocarbons. Gastroenterol Hepatol 29:334–337

Pool F, Orono A (2001) Liver function of workers occupationally exposed to mixed organic solvents in a petrochemical industry. Invest Clin 42:87–106

Porru S, Placide D, Carta A, Gelatti U, Ribero M, Tagger A (2007) Pimary liver cancer and occupation in men: A case-control study in high incidence area in Northern Italy. Int J Cancer 94:878–883

Pratt D, Kaplan M (2000) Elevated liver enzymes in asymptomatic patients. N Engl J Med 343:662–663

Rosenberg J, Katz E (2007) Solvents. In: Ladou J (ed) Current occupational and environmental medicine, 4th edn. McGraw-Hill, USA, p 499

Sia H, Wang J, Huang CC, Huang Ch (2002) Prevalence and risk factors of chronic liver disease among oil refinery workers. J Occup Health 44:22–27

Todd L, Puangthongthub S, Mottus K, Mihlan G, Wing S (2008) Health survey of workers exposed to mixed solvent and ergonomic hazards in footwear and equipment factory workers in Thailand. Ann Occup Hyg 52:195–205

Uuksulainen S, Heikkila P, Olkinuora P, Kiilunen M (2002) Self-reported occupational health hazards and measured exposures to airborne impurities and noise in shoe repair work. Int J Occup Environ Health 8:320–327

Warnes T, Jain S, Smith A (2000) Hepatotoxic effects of workplace exposures. In: Baxter P, Adams P, Tar-Ching A (eds) Hunter diseases of occupations, 3rd edn. Arnold, London, p 501

Xiao J, Levin S (2000) The diagnosis and management of solvent-related disorders. Am J Ind Med 37:44–61