Comparisons of Complete Blood Counts and Urinary Benzene Metabolites After Exposure to Benzene

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Background. The effects of low level benzene exposure are still controversial. The aim of our study was to clarify the relationship of the hematological effects of low level benzene exposure.

Methods. We conducted a cross-sectional study in which 334 workers with different degrees of exposure to benzene were enrolled. According to the levels of urinary benzene metabolites concentrations, markers of benzene exposure that were determined by high performance liquid chromatography. The participants were divided into three groups: high exposure workers (n = 107), low exposure workers (n = 182), and non-exposed workers which made up the control group (n = 45). Complete blood count was measured using an automatic cell counter to determine outcomes of benzene exposure.

Results. Means of urinary concentrations of hydroquinon, t,t-muconic acid, and cathecol were 0.51 ± 0.43 mg/g cre, 0.39 ± 0.33 mg/g cre, 1.04 ± 0.76 mg/g cre. No significant differences among groups were found. The white blood cell (WBC), lymphocyte, monocyte, eosinophil counts and hemoglobin (Hgb) levels were significantly higher in the high exposure group than in the low exposure group or control group (ANOVA, all $p < 0.05$). After adjusting for age, sex, and habits of tobacco use and alcohol consumption, the benzene exposure significantly correlated with the Hgb level ($\beta = 0.46$, $p < 0.05$). Tobacco use significantly correlated with WBC count and Hgb level (both $\beta = 0.01$, $p < 0.05$).

Conclusions. Our study suggests that low levels of benzene exposure (< 5 ppm) may increase hemoglobin levels. Although of No. clinical significance, it may reflect an early hematological effect. Further longitudinal studies are needed to confirm the relationship. **(Mid Taiwan J Med 2000;5:235-42)**

Key words

benzene, complete blood counts, hematotoxicity

INTRODUCTION

Benzene, a widely used chemical in numerous industrial facilities, is derived primarily through the refinement and fractionation of crude petroleum. The International Agency for Research on Cancer classified benzene as a group I human carcinogen [1]. The limit for exposure to benzene has decreased over time from 100 ppm in 1946, to 10 ppm in 1977 and finally to 0.5 ppm in 1998 by the American Conference of Governmental Industrial Hygienists [2]. The hematopoietic system has been shown to be a major target site in long-term benzene exposure. It has been well documented that relatively high levels of benzene exposure can cause decreases in white blood cell (WBC)

Received : June 22, 2000. Revised : August 2, 2000.
Accepted : August 10, 2000.
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counts and red blood cell (RBC) counts, hemoglobin (Hgb) levels, and platelet counts in humans and mice [3-5]. It has also been shown that the mean corpuscular volume (MCV) values increased with benzene exposure [3]. The hematological effects of low levels of benzene exposure are still controversial. Townsend et al [6] and Ward et al [7] found hematologic suppression effects after low level benzene exposure (< 5 ppm). Khuder et al [8] found that with the exception of WBC, all other complete blood count (CBC) values were significantly reduced. Whereas, Tsai et al [9] and Hancock et al [10] reported no differences in RBC counts, WBC counts, Hgb levels, or platelet counts after low level benzene exposure. Collins et al [11,12] concluded that low-level benzene exposure did not appear to result in abnormal CBC results. It should be noted that each of the studies differed in the classification of "low-level" exposure, blood parameters measured, and study design.

Benzene is metabolized by the hepatic microsomal enzymes, dehydrogenase and oxidation to form phenol (PH), s-phenyl-mercapturic acid (SPMA), catechol (CAT), hydroquinon (HQ) and t,t-muconic acid (MA) [13]. Snyder and other researchers proposed that HQ, CAT, MA and SPMA were more sensitive biological markers than phenol [14]. Hotz reported that urinary phenol and HQ were less suitable biomarkers than MA [15].

We conducted this study to clarify the relationship between low level benzene exposure and the hematological effects in a petrochemical plant in Taiwan.

MATERIALS AND METHODS

Subjects

The 348 subjects in this study were selected from a petrochemical plant in central Taiwan. The plant has been in operation for over 20 years and the worker turnover rate is low. This plant uses benzene as a raw material for the production of ammonium sulfate and caprolactam. Airborne benzene concentrations within the plant are monitored periodically. Based on data of airborne benzene concentrations provided by the plant manager (the authors were not permitted to take air samples), the plant was divided into three areas: 3–4.67 ppm (manufacturing cyclohexane), 1–2 ppm (reaction area, water purification unit, maintenance) and non-detectable-0.5 ppm (administrative area). Study subjects were divided into three groups: high exposure, low exposure and reference group according to the airborne benzene exposure levels.

Clinical and Laboratory Data

All of the participants were required to complete a structured questionnaire. Information collected from the questionnaires included: demographic information, personal habits, medical history, occupational history and some clinical symptoms.

The workers fasted for more than 8 hours prior to taking blood samples. The blood samples were sent to the clinical laboratory of China Medical College Hospital within 4 hours for analysis. A Sysmex NE8000 automatic cell counter (Toa Electronic, Inc., Chicago, Illinois) was used to determine CBC and the differential count of WBC. All the laboratories participate in the College of American Pathologists' external quality control program for their automated analyses.

Exposure and Assays

A total of 314 workers provided spot urine samples at the end of their work shift or at the end of high exposure periods during their work shift. Samples were immediately aliquoted and frozen on dry ice, and transported to the laboratory for storage. The metabolites of benzene in urine were determined using high performance liquid chromatography (HPLC, Shimadzu, SCL-10A) with ultraviolet detector (Shimadzu, SPD-6A). The HPLC column was run at a flow rate of 1 ml/min and the injection volume was 15 μL. The detector was set at UV-278 nm. The mobile phase used was phosphate solution (5 mmol/l)-methanol (9:1) at pH = 3.4. Standard curves were consistently linear with $r^2 > 0.99$

Table 1. Characteristics of demographic data of the benzene exposed workers

	Reference group (n = 17)	Low exposure group (n = 162)	High exposure group (n = 83)	*p* value
Gender				
Male	11 (64.7)*	156 (96.3)	83 (100)	0.001
Female	6 (35.3)	6 (3.7)	0	
Age (years)†	49.8 ± 5.8	47.5 ± 7.3	46.5 ± 7.0	0.08
Employment years				
< 7	0	15 (9.3)	7 (8.4)	0.001
7–15	0	11 (6.8)	3 (3.6)	
16–24	10 (58.8)	125 (77.2)	68 (81.9)	
≥ 25	7 (8.4)	11 (6.8)	46 (56.1)	
Smoking				
No	13 (81.3)	95 (60.1)	95 (60.1)	NS
Yes	2 (12.5)	50 (31.7)	32 (39.0)	
Ex-smoker	1 (6.3)	13 (8.2)	4 (4.9)	
Drinking				
No	10 (62.5)	103 (65.6)	50 (61.0)	NS
Yes	6 (37.5)	50 (31.9)	32 (39.0)	
Abstained	0	4 (2.6)	0	

*Date in the parentheses represent percentoges.†Data are expressed as mean ± SD. NS = not significant.

Table 2. Urinary concentrations (mg/g creatinine) of benzene metabolites among different benzene exposed workers

	Reference group (n = 40)	Low exposure group (n = 168)	High exposure group (n = 104)	*p* value
Hydroquinone	0.48 ± 0.43*	0.52 ± 0.47	0.50 ± 0.40	NS
t,t-muconic acid	0.38 ± 0.30	0.36 ± 0.29	0.43 ± 0.41	NS
Catechol	1.23 ± 0.82	0.94 ± 0.72	1.13 ± 0.74	NS
Total	2.09 ± 1.16	1.81 ± 1.02	2.05 ± 1.08	NS

* Data are expressed as Mean ± SD. NS = not significant.

for all metabolites. Creatinine (cre) in the urine was determined using the alkaline picrate method (Hitachi 736-15 autoanalyzer). All of the urinary parameters were adjusted for creatinine content.

The benzene metabolites were readily separated using HPLC, with little interference. The detection limits of the methods were 2.46 ng/mL for HQ, 0.13 ng/mL for MA, 2.34 ng/mL for CAT, and 9.69 ng/mL for PH. Reproducibility of the methods was assessed by measuring all urine samples in duplicate and calculating the means of the percentage differences. The means of the percentage differences of the measurements at low concentrations were: HQ = 5.1% MA = 2.9%, CAT = 2.0%, and PH = 8.2%.

Statistical Analyses

Comparisons among group means were based on the analysis of variance (ANOVA) for independent samples. Categorical variables were analyzed using Fisher's exact test. Correlation among variables was assessed using Pearson's coefficients. The exposure level and other possible confounding factors were considered in the final multiple linear regression model. Statistical analyses were performed with the aid of an SAS package (Version 6.12, SAS Institute Inc., Cary, North Carolina).

RESULTS

Characteristics of high exposure workers, low exposure workers, and reference group are summarized in Table 1. There were no significant differences among the subjects in the groups with respect to age, tobacco use, and alcohol consumption. Duration of employment was slightly longer in the reference group (high exposure group: 18.8 ± 5.9 years, low exposure group: 19.1 ± 6.7 years,

Table 3. Comparisons of complete blood count variables among different benzene exposed workers

Variables	Reference group (n = 45)	Low exposure group (n = 182)	High exposure group (n = 107)	*p* value
Red blood cell ($\times 10^6$/ μL)	5.0 ± 0.5*	5.1 ± 0.5	5.6 ± 4.2	NS
Hemoglobin (gm/dL)	14.3 ± 1.3	14.7 ± 1.2	14.8 ± 1.2	0.03
Hematocrite (%)	44.0 ± 3.7	44.9 ± 3.3	44.9 ± 4.6	NS
MCV (fl)	88.2 ± 7.9	88.3 ± 7.5	87.6 ± 10.5	NS
MCH (pg/cell)	28.7 ± 2.9	28.9 ± 2.9	29.0 ± 2.9	NS
MCHC (gm/dL)	32.5 ± 0.9	32.8 ± 1.2	32.8 ± 1.1	NS
Platelet ($\times 10^3$/ μL)	235.5 ± 44.9	244.0 ± 57.7	242.3 ± 61.8	NS
White blood cell ($\times 10^3$/ μL)	6.2 ± 1.5	6.5 ± 1.8	6.9 ± 1.7	0.01
Neutrophil	3527.2 ± 1053.4	3402.7 ± 1117.8	3636.3 ± 1244.8	NS
Lymphocyte	2136.6 ± 549.3	2296.6 ± 641.8	2456.3 ± 809.6	0.02
Monocyte	449.8 ± 145.1	657.5 ± 266.7	680.9 ± 241.6	0.001
Eosinophil	134.1 ± 75.8	163.7 ± 125.2	189.2 ± 128.4	0.03
Basophil	46.1 ± 21.4	43.5 ± 22.7	37.4 ± 15.4	0.02

*Data are expressed as Mean ± SD. NS = not significant; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration.

Table 4. Correlation between complete blood count variables and urinary benzene metabolite concentrations

Variables	Hydroquinone	t,t-muconic acid	Catechol	Total
Red blood cell ($\times 10^6$)	−0.14*	0.09	−0.05	0.08
Hemoglobin (gm/dl)	−0.10	−0.09	−0.14*	−0.15*
Hematocrite (%)	−0.09	−0.02	−0.10	−0.09
MCV (fl)	0.05	−0.12*	−0.06	−0.03
MCH	0.05	−0.13*	−0.06	−0.04
MCHC	0.02	−0.09	−0.04	−0.04
Platelet ($\times 10^3$)	−0.02	0.03	−0.01	0.002
White blood cell ($\times 10^3$)	0.07	0.10	0.15†	0.17†
Neutrophil	0.06	0.08	0.11	0.13*
Lymphocyte	0.01	0.05	0.02	0.03
Monocyte	0.01	0.0004	0.03	0.04
Eosinophil	0.10	−0.01	0.11*	0.08
Basophil	−0.05	−0.07	−0.08	−0.10

MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration. *$p < 0.05$, †$p < 0.01$.

reference group: 23.2 ± 4.2 years, $p = 0.08$). Male subjects were predominant in the high exposure group. None of the subjects reported a regular use of solvents at home.

Comparisons of urinary concentrations of benzene metabolites are shown in Table 2. Means and ranges of urinary concentrations of benzene metabolites were HQ: 0.51 (0.1–3.46) mg/g cre., MA: 0.39 (0.03–2.51) mg/g cre., and CAT: 1.04 (0.12–3.68) mg/g cre. No significant differences among groups were found.

The results of comparison of CBC are shown in Table 3. The WBC count, Hgb, lymphocyte count, monocyte count, and eosinophil count were significantly higher in the high exposure group than in the low exposure group or the reference group (all $p < 0.05$). The basophil count was significantly lower in the high exposure group than in the low exposure group or the reference group ($p < 0.05$).

The correlation between CBC parameters and urinary benzene metabolites are weak and summarized in Table 4. Urinary HQ concentration negatively correlated with RBC count ($r = -0.14$, $p < 0.05$). Urinary MA

Table 5. Comparisons of complete blood count variables among different concentrations of urinary benzene metabolite

Variables	Low concentration* (n = 104)	Intermediate concentration (n = 153)	High concentration (n = 77)	*p* values
Red blood cell ($\times 10^6$/ μL)	5.1 ± 0.4†	5.1 ± 0.5	5.0 ± 0.6	NS
Hemoglobin (gm/dL)	14.7 ± 1.4	14.8 ± 1.2	14.4 ± 1.3	NS
Hematocrite (%)	44.7 ± 5.0	45.2 ± 3.0	44.0 ± 3.6	NS
MCV (fl)	88.1 ± 7.7	88.5 ± 7.2	88.0 ± 7.7	NS
MCH (pg/cell)	28.9 ± 3.0	29.0 ± 2.8	28.9 ± 3.0	NS
MCHC (gm/dL)	32.7 ± 1.1	32.8 ± 1.1	32.8 ± 1.1	NS
Platelet ($\times 10^3$/ μL)	246.2 ± 57.3	239.4 ± 57.0	242.9 ± 58.8	NS
White blood cell ($\times 10^3$/ μL)	6.5 ± 1.8	6.5 ± 1.6	7.0 ± 1.9	0.04
Neutrophil	3279.3 ± 1176.4	3415.9 ± 1125.0	3613.8 ± 1139.1	NS
Lymphocyte	2386.9 ± 682.2	2221.0 ± 665.1	2421.6 ± 709.0	NS
Monocyte	627.0 ± 272.8	637.8 ± 228.2	646.9 ± 292.2	NS
Eosinophil	167.5 ± 129.8	174.0 ± 124.7	168.3 ± 129.0	NS
Basophil	43.7 ± 19.6	42.9 ± 22.3	40.0 ± 19.1	NS

*Low concentration indicates < 1.11 mg/g creatinine; intermediate concentration indicates 11.1–2.41 mg/g creatinine; high concentration indicates > 2.41 mg/g creatinine. †Data are expressed as mean ± SD. NS = not significant; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration.

concentration negatively correlated with MCV and MCH (r = –0.12 and –0.13 respectively, both $p < 0.05$). Urinary CAT concentration positively correlated with WBC count and eosinophil count (r = 0.15 and 0.11 respectively, both $p < 0.05$), but negatively correlated with Hgb (r = –0.14, $p < 0.05$). Comparisons of CBC parameters among different benzene metabolite concentrations are shown in Table 5. The WBC count was significantly higher in subjects with high urinary benzene metabolite concentration than those with intermediate or low concentrations ($p < 0.05$). Other CBC parameters were not significantly different among the different metabolite concentration groups.

Multiple linear regression models were used to examine the variance in CBC parameters (Table 6). Factors such as age, gender, duration of employment, alcohol consumption, and urinary metabolite concentration were not found to be associated with CBC parameters. After adjusting for age, gender, tobacco use and alcohol consumption, the benzene exposure was significantly associated with the Hgb level (β = 0.46, $p < 0.05$). Tobacco use was significantly associated with WBC count and Hgb level (both β = 0.01, $p < 0.05$).

DISCUSSION

Most benzene-related hematological effects in humans have been observed in populations exposed to relatively high concentrations of benzene due to their occupation [3-5]. Although hematological toxicity has been reported in workers after long-term exposure to benzene at concentrations as low as 20 ppm [7], the meaning of these relatively low exposure levels remain questionable due to the inadequate monitoring of affected individuals. Whether chronic low levels of benzene exposure can also damage the human hematological system cannot be stated conclusively at this time, however, the results of this study reveal no clinically significant effects of benzene exposure on the hematopoietic system.

Cumulative data suggest that chronic benzene exposure may result in leukemia. Moreover, Vigliani and Forni [16] suggested

Table 6. Multiple linear regression analyses of complete blood count variables in benzene exposed

Variables	White blood cell	Red blood cell	Hemoglobin	Hematocrite	Mean corpuscular volume
Gender (male = 0)	−0.27 (0.85)*	0.85 (1.73)	−0.03 (0.66)	0.38 (2.28)	−1.28 (5.25)
Benzene exposure (no = 0)	−0.04 (0.25)	0.46 (0.50)	0.46 (0.19)†	1.04 (0.66)	0.50 (1.53)
Age (year)	−0.04 (0.03)	−0.04 (0.06)	0.02 (0.02)	0.09 (0.08)	0.19 (0.18)
Employment (year)	0.06 (0.03)	−0.08 (0.07)	−0.03 (0.03)	−0.09 (0.09)	0.04 (0.21)
Urinary metabolite (mg/g cre)	0.07 (0.13)	−0.39 (0.26)	−0.18 (0.10)	−0.26 (0.34)	0.24 (0.78)
Tobacco use (piece-year)	0.01 (0.00)‡	0.00 (0.00)	0.01 (0.00)†	−0.00 (0.00)	0.00 (0.00)
Alcohol consumption (no = 0)	0.16 (0.26)	−0.41 (0.53)	0.14 (0.20)	0.74 (0.70)	2.28 (1.60)
R^2	0.10†	0.09†	0.08	0.03	0.05

* regression coefficient (standard error); †$p < 0.05$, ‡$p < 0.01$.

that leukemia associated with benzene exposure was often preceded by pancytopenia (i.e., depressed production of WBC, RBC, and platelet by the bone marrow). On the contrary, the workers of high exposure group in this study seem to have higher Hgb levels than those of lower levels of exposure and referents. This result may be because female workers with lower Hgb levels were in the reference group. Also, it may reflect an early effect of low level benzene exposure. The trends of increasing MCV values and decreasing WBC and lymphocyte count were similar to previous report, however, they were not of statistical significance. The reasons for such phenomenon might come from individual susceptibility to benzene exposure.

Age, gender, tobacco use and other personal habits were found to be very important determinants for many hematological outcomes [17]. Surprisingly, we found a strong effect of tobacco use on many CBC measures. Tobacco use was a significant factor in increasing Hgb levels and WBC count. There have been some indications that smokers have higher concentrations of benzene in the blood [18]. It is important to consider the confounding effects of smoking while evaluating the CBC outcomes from occupational factors.

The inadequacy of this study was the lack of ambient monitoring of benzene exposure simultaneously due to lack of cooperation from the factory managers. The time-weighted average (TWA) of the benzene exposure provided by the factory in high exposure area were 3–4.67 ppm, and 1–2 ppm in low exposure area. All were under the threshold limit value (TLV) of 5 ppm of Taiwan. Urinary excretion of HQ, MA and CAT was used as a function of exposure level [19]. The biological monitoring of benzene metabolites in urine revealed that the average concentrations of HQ, MA, CAT and phenol were 0.94 mg/L, 0.66 mg/L, 1.87 mg/L, and 17.36 mg/L, respectively. The work environment in our study was under very low benzene level.

Another limitation of this study was the cross-sectional design. It was difficult to infer causality using such a design because exposure and clinical outcomes were mea-sured concurrently and at only one point in time. However, our data revealed some significant correlations between benzene exposure and CBC outcomes although most workers were exposed to legally allowable levels of benzene. We concluded that low levels of benzene exposure (< 5 ppm) may increase hemoglobin levels. Although not of clinical significance, it may reflect an early hematological effect. Further longitudinal studies are needed to confirm the relationship.

Table 6. Continued

Platelet	Neutrophil	Lymphocyte	Monocyte	Eosinophil	Basophil
31.76 (29.40)	108.68 (629.94)	341.83 (375.52)	59.43 (141.05)	−36.09 (67.65)	5.25 (11.26)
−2.97 (8.55)	118.28 (183.24)	−69.49 (109.23)	−15.23 (41.03)	19.85 (19.68)	−1.45 (3.28)
−0.44 (1.04)	8.73 (22.22)	−1.83 (13.25)	−0.09 (4.98)	0.57 (2.39)	0.32 (0.40)
−0.09 (1.18)	−7.37 (25.34)	7.30 (15.11)	−3.00 (5.67)	−0.14 (2.72)	−0.15 (0.45)
−4.26 (4.36)	160.76 (93.38)	2.33 (55.66)	−4.47 (20.91)	7.45 (10.03)	−1.79 (1.67)
0.01 (0.01)	0.11 (0.18)	0.06 (0.11)	0.06 (0.04)	0.00 (0.02)	0.00 (0.00)
−1.25 (8.97)	36.02 (192.22)	−46.49 (114.59)	−28.99 (43.04)	4.64 (20.64)	2.46 (3.44)
0.03	0.03	0.01	0.03	0.01	0.02

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石化業工人尿中苯代謝物濃度與全血球計數關係之研究

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背景　低濃度的苯暴露是否會造成健康危害仍有爭議。本研究之目的在探討低濃度苯暴露對血液學的影響。

方法　本研究是橫斷式之研究。收集台灣中部某石化廠334名員工將其分爲高暴露組(107人)、低暴露組(182人)、及對照組(45人)來比較。以尿中苯代謝濃度當作暴露指標，尿中苯代謝濃度是以高效能液態色層分析法分析。以全自動血球計數儀分析求得之全血球計數當作苯暴露之效應。

結果　尿中苯代謝物hydroquinon、t,t-muconic acid及catechol的平均濃度分別爲0.51 mg/g cre、0.39 mg/g cre及1.04 mg/g cre，在不同組別間並沒有統計上的差異。高暴露組在白血球、淋巴球、單核球、嗜伊紅球計數及血紅素濃度均較低暴露組及對照組高，達統計上之顯著差異($p < 0.05$)。在控制其他變項後，血色素濃度與苯暴露有顯著的相關($\beta = 0.46$，$p < 0.05$)，抽煙則與白血球數及血色素濃度有顯著的相關($\beta = 0.01$，$p < 0.05$)。

結論　我們的研究結果顯示在低濃度的苯暴露下會影響全血球計數，進一步長期追蹤研究將有助於釐清兩者之因果關係。（中台灣醫誌 **2000;5:235-42**）

關鍵詞

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收文日期：6/22/2000　　修改日期：8/2/2000

接受日期：8/10/2000