Original Article

Early Liver and Kidney Dysfunction Associated with Occupational Exposure to Sub-Threshold Limit Value Levels of Benzene, Toluene, and Xylenes in Unleaded Petrol

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A R T I C L E   I N F O

Article history:
Received 21 April 2015
Received in revised form 29 June 2015
Accepted 21 July 2015
Available online 5 August 2015

Keywords:
blood biochemical tests
benzene, toluene, and xylenes
hepatotoxicity
nephrotoxicity
unleaded petrol

A B S T R A C T

Background: Unleaded petrol contains significant amounts of monocyclic aromatic hydrocarbons such as benzene, toluene, and xylenes (BTX). Toxic responses following occupational exposure to unleaded petrol have been evaluated only in limited studies. The main purpose of this study was to ascertain whether (or not) exposure to unleaded petrol, under normal working conditions, is associated with any hepatotoxic or nephrotoxic response.

Methods: This was a cross-sectional study in which 200 employees of Shiraz petrol stations with current exposure to unleaded petrol, as well as 200 unexposed employees, were investigated. Atmospheric concentrations of BTX were measured using standard methods. Additionally, urine and fasting blood samples were taken from individuals for urinalysis and routine biochemical tests of kidney and liver function.

Results: The geometric means of airborne concentrations of BTX were found to be 0.8 mg m⁻³, 1.4 mg m⁻³, and 2.8 mg m⁻³, respectively. Additionally, means of direct bilirubin, alanine aminotransferase, aspartate aminotransferase, blood urea and plasma creatinine were significantly higher in exposed individuals than in unexposed employees. Conversely, serum albumin, total protein, and serum concentrations of calcium and sodium were significantly lower in petrol station workers than in their unexposed counterparts.

Conclusion: The average exposure of petrol station workers to BTX did not exceed the current threshold limit values (TLVs) for these chemicals. However, evidence of subtle, subclinical and prepathologic early liver and kidney dysfunction was evident in exposed individuals.

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1. Introduction

Unleaded petrol contains significant amounts of aromatic hydrocarbons [1]. Among aromatic compounds, benzene, toluene, and xylenes (BTX) are the most dangerous elements of petrol [2,3]. The risk of acute or chronic toxicity in humans exists during production, distribution, and use of petrol [4].

Hepatotoxicity and nephrotoxicity have been reported following human and animal exposure to unleaded petrol [2,3,5]. For instance, kidney adenoma [5], elevated serum activity of liver enzymes [6,7], urea, creatinine, and potassium, and decreased chloride and sodium have been reported in laboratory animals [8]. Similarly, proteinuria, elevated serum activity of liver enzymes (aspartate aminotransferase, alkaline phosphatase, alanine aminotransferase), and total bilirubin and fatty liver changes have been reported in drivers and workers following exposure to unleaded petrol [9–12]. Furthermore, xylene and toluene have been reported to cause renal and liver damage and toxicity in humans [13–15]. Kidney effects including renal tubular acidosis, hypokalemia, hypophosphatemia, azotemia, hematuria, proteinuria, and pyuria

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after exposure to toluene have also been reported [16]. Additionally, exposure to benzene and alkyl benzene has been associated with kidney and liver injury and kidney cancer [17,18]. Moreover, xylene has been reported to cause liver and kidney damage in laboratory animals [14,19].

Conversely, some studies have failed to demonstrate any renal and liver injuries following exposure to BTX [20,21].

Although the issue of nephrotoxic and hepatotoxic potentials of petrol components has been considered individually, these effects from petrol as a complex of hydrocarbons have not been thoroughly investigated, and little information exists in this regard. This study was, therefore, undertaken to address this issue and in response to the concerns raised by the public regarding the safety of newly introduced unleaded petrol.

2. Materials and methods

This was a cross-sectional study in which the hepatotoxic and nephrotoxic potentials of occupational exposure to unleaded petrol were assessed in a group of workers employed in Shiraz private petrol stations.

The criteria of workers’ selection were: (1) a history of at least 1 year occupational exposure to unleaded petrol; and (2) lack of history of exposure to other known nephrotoxic and hepatotoxic agents and no job history of exposure to other chemical materials.

A referent group was composed of healthy individuals without current or past exposure to agents known to cause any hepatotoxic or nephrotoxic response. Collectively, 400 individuals (200 referent individuals and 200 exposed workers) entered the study. Exposed participants were the employees of all (20 active) private petrol stations in Shiraz. They were shift workers who used to work in rotating 8-hour shift schedules, morning shifts (5:00 AM to 1:00 PM), mid-day shifts (1:00 PM to 9:00 PM) and overnight shifts (9:00 PM to 5:00 AM).

All individuals signed an informed consent form before entering the study. The study was funded by the Vice Chancellor for Research and Technology of Shiraz University of Medical Sciences, Shiraz, Iran and it was approved by the university ethics committee. Fasting blood and urine samples were taken from all participants for urinalysis and biochemical tests of liver and kidney functions, which were performed by an automatic Italian made (Roma) auto analyzer (model BT 1500).

Sampling for BTX was conducted according to the National Institute for Occupational Safety and Health (NIOSH) method 1501 [22]. Using activated charcoal sorbent tubes, (model SKC No. 226-01, SKC, Philadelphia, PA, USA) and a sampling pump (model SKC 222-ML/count, SKC), with a flow rate of 0.1–0.02 L/minute, three personal air samples at the breathing zone of the employees of each petrol station (a total of 60 samples) were collected during different shifts and hours and the average was reported as daily environmental BTX concentration for each employee of that particular petrol station.

Similarly, from each administrative office, a typical 2-hour sample from the ambient air at the breathing zone height was collected (a total of 10 samples). The samples were transferred to the laboratory where they were analyzed by gas chromatography.

Absorbed BTX vapors were measured by the method recommended by NIOSH 1501, desorbing the activated charcoal with 1 mL carbon disulfide for 30 minutes. For quantifying the levels of BTX, 1 mL of sample was injected (split 1:50) into a Varian CP-3800 gas chromatograph (CP-3800, Varian Inc., Lake Forest, CA, USA) equipped with a flame ionization detector and a 30 m long × 0.25 mm diameter capillary column, packed with 100% dimethylpolysiloxane. The injector and detector temperatures were set at 250°C and 300°C, respectively. The initial oven temperature was 40°C for 10 minutes, followed by increases to 230°C at 10°C/minute. Helium gas was used as the carrier gas at a flow rate of 1 mL/minute. The detection limits were: 0.03 mg m⁻³ (0.01 ppm) for benzene and 0.04 mg m⁻³ (0.01 ppm) for toluene and xylene.

2.1. Statistics

The data were statistically analyzed using the Student t test or Welch’s alternate t test, when the F test showed that the standard deviations of two comparable variables were significantly different, and the Chi-square test or Fisher’s exact test, where applicable, with a preset probability of $p < 0.05$. When the direction of an effect caused by an independent variable was not predictable, a two-sided $p$ value was used for statistical analysis. To control the effects of confounders such as sex, age, body mass index, alcohol intake, or cigarette smoking on changes in blood parameters, multiple linear regression analysis was used. Statistical tests were conducted using SPSS version 16 (SPSS Inc., Chicago, IL, USA), released 2007.

3. Results

The average age and length of employment for the exposed group were $33.9 \pm 9.4$ years and $6.8 \pm 6.3$ years, respectively, and the corresponding values for the control group were $35 \pm 8.5$ years and $10.4 \pm 7.8$ years, respectively.

The length of employment was significantly higher for referent individuals. By contrast, a significantly higher proportion of exposed individuals were smokers, although the length of smoking was slightly higher for referent participants (Table 1).

The geometric and arithmetic mean atmospheric concentrations of BTX, as well as some other exposure data, are presented in Table 2. Threshold limit values (TLVs) for BTX have been set by ACGIH at 1.6 mg m⁻³, 75 mg m⁻³, and 434 mg m⁻³, respectively (ACGIH, 2013) [23].

Given the above, none of the mean values or maximum levels of exposure for these solvents in our study reached their current corresponding TLVs (Table 2).

No detectable concentration of these solvents was found in the working atmosphere of referent individuals.

Tables 3 and 4 illustrate the association of unleaded petrol with Liver Function Test and Kidney Function Test (LFT and KFT indices) using univariate analysis.

As shown, significant statistical differences were noted between both groups for a number of parameters of kidney and liver function. Serum albumin, serum protein, and calcium levels were significantly lower in the exposed group than in the control group. By contrast, blood urea nitrogen, serum creatinine, and alanine

| Table 1 | Demographic characteristics of the study participants |
|---------|-----------------------------------------------|
| Variable | Unexposed group (n = 200) | Exposed group (n = 200) | $p$ |
| Male | 194 | 194 | |
| Female | 6 | 6 | |
| Age (y) | $35 \pm 8.5$ | $33.9 \pm 9.4$ | 0.23* |
| Length of exposure or employment (y) | $10.4 \pm 7.8$ | $6.75 \pm 6.32$ | <0.001* |
| Body mass index (kg m⁻²) | $25.4 \pm 3.9$ | $24.2 \pm 3.9$ | 0.007* |
| Number of smokers (%) | 27 (13.5) | 49 (24.3) | <0.001* |
| Length of smoking (y) | 11 ± 6 | 10.5 ± 8.6 | 0.7* |

* Independent sample t test.
† Chi-square test.
SD, standard deviation.
aminotransferase (ALT), aspartate aminotransferase (AST), and direct bilirubin levels were significantly higher in the exposed group than in the control group.

Using multiple linear regression analysis, the effects of confounding variables of age, cigarette smoking, and body mass index on the parameters of liver and kidney function were adjusted and controlled (Table 5).

Results showed that after adjusting for these confounders, significant negative associations exist between exposure to unleaded petrol and albumin, total protein, serum sodium, and calcium levels and positive associations with direct bilirubin, AST, ALT, urea, and creatinine levels.

4. Discussion

This study aimed to evaluate nephrotoxic and hepatotoxic potentials of unleaded petrol.

The geometric mean concentrations of BTX in petrol stations were estimated to be 0.8 mg m\(^{-3}\), 1.4 mg m\(^{-3}\), and 2.8 mg m\(^{-3}\), respectively. Although these values are lower than their corresponding TLV values (ACGIH, 2013)\(^{[23]}\), no information exists as to the average concentrations of these chemicals to which individuals in the previous years had been exposed. However, given the fact that the process has not changed over time, it would be reasonable to assume that the exposure scenario in the past has not been different from that of the present time. Therefore, one might tentatively conclude that individuals during the course of their employment have been exposed to sub-TLV levels of these solvents.

Our findings showed that serum albumin, serum protein, sodium, and calcium levels were significantly lower in the exposed group than in referent participants. By contrast, blood urea nitrogen, plasma creatinine, AST, ALT, and direct bilirubin were significantly higher in the exposed group than in the unexposed employees.

Increased serum aminotransferase (ALT and AST) generally reflects acute liver cell injuries [24]. Similarly, proteinuria, albuminuria, and increased serum creatinine are the primary markers of renal disorders. Changes in serum electrolytes are also indicators of renal effects [24–26].

The observation of significantly elevated levels of ALT and AST in exposed individuals in this study is in line with the findings of Akintonwa and Oladele [10], Nwanjo and Ojiako [12], Saadat and Ansari-Lari [27], and Michailova et al [28].

In 1998, Michailova et al [28] reported significant increases in the serum activity of ALT and AST in oil industry workers. Similar results were reported in 2003 by Akintonwa and Oladele [10] in workers of pump stations. Likewise, in 2004, Saadat and Ansari-Lari, in a study on 56 workers of Shiraz pump stations, reported significantly elevated plasma levels of creatinine, and serum activity of ALT and AST, as well as significantly decreased albumin and protein values in the exposed group as compared to a control group.

In 2007, Nwanjo and Ojiako [12], in a study of 20 gasoline station workers with a history of 6–10 years exposure to gasoline and 20 control individuals, reported significant increases in Alkaline Phosphatase (ALP), ALT, AST, urea, and creatinine of exposed individuals.

In this study, no significant difference was noted between mean values of serum activity of alkaline phosphatase of exposed and referent individuals. This observation is also in accord with the findings of Saadat and Ansari-Lari [27].

However, it is inconsistent with the findings of Nwanjo and Ojiako [12] and Dogru et al [29], who showed that alkaline phosphatase was high in children who inhaled high doses of gasoline vapors.

Akinosun et al [30], in a study on a small population (29 workers exposed to gasoline and 22 unexposed employees) in Nigeria, reported that except for ALP which was significantly lower in exposed individuals, other parameters such as AST, ALT total protein, total bilirubin, and albumin were the same in exposed and control groups.

The exact reason(s) for these discrepancies and inconsistencies are not known. However, differences in exposure concentrations, sample size, confounders, statistical analyses (univariate or multivariate)

### Table 2

Mean atmospheric concentrations of benzene, toluene, and xylene (BTX) (mg m\(^{-3}\)) for exposed individuals (n = 60)

| Chemicals               | GM     | Arithmetic mean | Median | Minimum | Maximum | SD   | Variance | CV   |
|-------------------------|--------|----------------|--------|---------|---------|------|----------|------|
| Benzene\(^*\)           | 0.8    | 0.79           | 0.77   | 0.06    | 1.25    | 0.268| 0.072    | 0.34 |
| Toluene\(^\dagger\)     | 1.4    | 1.47           | 1.43   | 0.53    | 3.09    | 0.521| 0.271    | 0.35 |
| Xylene\(^\ddagger\)     | 2.8    | 3              | 2.98   | 1       | 6.69    | 1.26 | 1.58     | 0.42 |

- \(^*\) TLV = 1.6 mg m\(^{-3}\).
- \(^\dagger\) TLV = 75 mg m\(^{-3}\).
- \(^\ddagger\) TLV = 434 mg m\(^{-3}\).

CV, coefficient of variation; GM, geometric mean; SD, standard deviation; TLV, threshold limit value.

### Table 3

Comparison of Liver Function Test (LFT) indices between exposed and unexposed groups

| Indices (units)       | Exposed group (n = 200) (Mean ± SD) | Unexposed group (n = 200) (Mean ± SD) | p     |
|-----------------------|-------------------------------------|--------------------------------------|-------|
| Serum albumin (mg/dL) | 4.5 ± 0.5                           | 4.8 ± 0.4                            | <0.001* |
| Total proteins (mg/dL)| 7.36 ± 0.8                          | 8.2 ± 0.7                            | <0.001* |
| Alkaline phosphatase (u/L) | 207 ± 58.5                      | 217 ± 56.7                          | 0.09  |
| Direct bilirubin (mg/dL) | 0.19 ± 0.14                      | 0.15 ± 0.06                        | <0.001* |
| Total bilirubin (mg/dL) | 0.7 ± 0.26                       | 0.7 ± 0.24                        | 0.6   |
| Aspartate aminotransferase (units/L) | 24.14 ± 9.2               | 22.3 ± 8.7                        | 0.04  |
| Alanine aminotransferase (units/L) | 23.1 ± 13.9            | 19.4 ± 10.4                       | 0.018 |

- * LFT, Significantly different (independent sample t test, p < 0.05).
- SD, standard deviation.

### Table 4

Comparison of Kidney Function Test (KFT) indices between exposed and unexposed groups

| Indices (units)       | Exposed group (n = 200) (Mean ± SD) | Unexposed group (n = 200) (Mean ± SD) | p     |
|-----------------------|-------------------------------------|--------------------------------------|-------|
| Urea (mg/dL)          | 36 ± 5.4                            | 34 ± 8.2                             | <0.001* |
| Serum creatinine (mg/dL) | 1.1 ± 0.3                   | 1.05 ± 0.14                          | 0.05  |
| Calcium (mg/dL)       | 9.2 ± 0.7                           | 9.7 ± 0.6                            | <0.001* |
| Sodium (mEq/L)        | 139 ± 2.6                           | 140 ± 2.6                            | 0.008* |
| Potassium (mEq/L)     | 4.3 ± 0.38                          | 4.3 ± 0.39                           | 0.3   |

- * Independent sample t test.
- KFT, Significantly different (p < 0.05).
- SD, standard deviation.
regression analysis), or personal protective equipment, may explain, at least in part, these differences.

In this study, urea and creatinine levels were significantly higher in the exposed group than in the referent individuals. These findings are also in line with the findings of Nwanjo and Ojiako [12], and Abdel Aziz et al [31].

Serum levels of calcium and sodium were significantly different in the exposed group compared to their unexposed counterparts. Several factors can cause calcium loss, including vitamin D deficiency, chronic renal failure, exposure to organic and inorganic acids such as hydrofluoric acid (hydrogen fluoride), and exposure to ethanol and toluene [16,24,32,33]. Furthermore, reduced plasma sodium levels have been reported in laboratory animals exposed to gasoline [8] and in oil industry workers exposed to chemicals [34].

Results of urinalysis were not significantly different between both groups. Nwanjo and Ojiako [12] reported proteinuria in workers exposed to gasoline for 6–10 years. However, Yin et al [35] did not find any significant differences in the results of urinalysis of workers exposed to 75 mg m⁻³ toluene and xylene as compared with a group of control individuals.

Kidney and liver effects resulting from exposure to gasoline in studies by Abdel Aziz et al [31] and Pranji et al [36] are also similar to the findings of the present study.

It is believed that chronic exposure to low concentrations of solvents in occupational settings may cause damage to the kidney and liver of exposed individuals which is difficult to identify [37,38].

Uchida et al [21] did not observe any changes in kidney and liver function tests (protein, bilirubin, AST, ALT, and creatinine) of workers exposed to 91.2 mg m⁻³ xylene. Chen et al [20] also did not observe any significant changes in AST and ALT levels of paint manufacturers exposed to a mixture of solvents including 0–1585 mg m⁻³ xylene, 0–2035 mg m⁻³ toluene, and 0–64 mg m⁻³ benzene [20].

Therefore, in the light of these findings, the observation of a significant association between exposure to sub-TLV levels of BTX and significant alterations in the parameters of kidney and liver function may seem unusual. However, it has to be noted that these findings are not peculiar to this study. Authors have already shown that exposure of dentists to sub-TLV levels of mercury was also associated with subclinical symptoms of intoxication, casting doubt on the usefulness of TLV and BEI of this toxic metal, per se, as sensitive predictors and biological markers of mercury-induced neuropsychological disorders [39].

Inherent limitations of cross-sectional studies, such as the present study, prevent one from establishing cause and effect relationships. Therefore, it may be argued that findings of this study may not necessarily be linked with exposure to BTX. While true, the following lines of circumstantial evidence indicate that these are very likely to be the direct consequences of exposure to these chemicals. These include: (1) the exposed group had no medical or family history of kidney and liver diseases; (2) exposed individuals did not have any exposure to other hepatotoxic or nephrotoxic chemicals that can cause liver or renal dysfunction during the course of their employment; and (3) after adjusting for important confounders, significant associations were observed between exposure to BTX and changes in LFT, and KFT.

Occupational exposure to sub-TLV levels of BTX is associated with subtle, sub-clinical, prepathologic changes in the parameters of kidney and liver function.

Additional case-control, longitudinal epidemiological studies with larger sample sizes, sufficient follow-ups, and longer duration of exposure are clearly required to further substantiate these findings and to assess long term consequence and ramifications of these changes.

Conflicts of interest

There is no conflicts of interest.

Acknowledgments

Funding through the Shiraz University of Medical Sciences, Iran (89-5199). Vice Chancellor for research and technology, contract no. 89-5199, partially supported these investigations. The authors also wish to sincerely thank Mr Bonyani and Ms Keshavarz for their technical assistance. We are grateful to the employers and employees of Shiraz petrol stations for their cooperation. This manuscript has been emanated from the materials embodied in the thesis of Mr Hosseinzadeh, MSc student of occupational health, the second author of this paper, who carried out his research project under the supervision of Dr Neghab.

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