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CASE REPORT

Factors Influencing Hippuric acid as a Biomonitor for Toluene Exposure

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ABSTRACT

A 36 years old technicianworking in a special laboratory for the analysis of crude oil had been found with high urine level of hippuric acid. Hippuric acid urine levels can be used as a biological monitor to detect toluene toxicity but there are other natural and unnatural causes of hippuric acid production.Before taking samples for analysis, precautions should be taken concerning the type of food, drinking tea or coffee, and smoking as these factors may affect the levels of hippuric acid in the urine.

Key Words: *Toluene, Hippuric Acid, Urine, Biomonitor*

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CASE REPORT

A 36 years old male technicianis working inthe laboratory for the analysis of crude oil fora period of 10 years. He is smoker (15-20 cigarettes/day) and drinking tea and coffee. During his work he is exposed to toluene, for which hippuric acid is used as a biomonitor. Hehad been found withelevated levelof hippuric acid(1.8 g/L)in his urine during a routine physical and laboratory checkup.A second sample had been taken after stopping tea and coffee as well as stopping smoking and a dietary restriction for foods and drinks containing benzoic acid. The second result was within normal limits (0.6 g/L).

DISCUSSION

Crude oil is a complex mixture of aliphatic and aromatic hydrocarbons. Toluene is an aromatic hydrocarbon, occurring naturally in crude oil. Toluene has numerous commercial and industrial applications and is a solvent in paints, lacquers, thinners, glues, nail polish remover, and is used in the printing and leather tanning processes, and as a by-product in the manufacture of styrene. Toluene is the most popular solvent used in industry[1].

Occupational exposure to toluene may lead to adverse health problems. Chronic effects on CNS include neuropsychosis, cerebral and cerebellar degeneration, seizures, choreoathetosis, optic and peripheral neuropathies, decreased cognitive ability, optic atrophy, blindness, ototoxicity, and deafness. Toluene effects on the heart include direct negative effects on cardiac automaticity and conduction and can sensitize the myocardium to circulating catecholamines. "Sudden sniffing death" secondary to cardiac arrhythmias has been reported. Hepatotoxicity may occur after prolonged

toluene exposure. A rare form of hepatitis (hepatic reticuloendothelial failure) has been reported with toluene exposure. Reported renal toxicity from toluene exposure includes renal tubular acidosis, hypokalemia, hypophosphatemia, hyperchloremia, azotemia, sterile pyuria, hematuria, and proteinuria. Hematologic consequences of exposure may include lymphocytosis, macrocytosis, eosinophilia, hypochromia, and basophilic stippling, and in severe cases, aplastic anemia.

Hippuric acid level in urine is used as biomonitor to detect degree of toluene exposure.Hippuric acidis an organic acidcalled by this name because it was firstly found in the urine of hippos. Hippuric acid does not accumulate and is rapidly excreted in urine where about 97% may be excreted in the first 4 hours[2].

In humans, hippuric acid appears as an excretory product from natural sourcessignaling metabolic dietary sources of hippuric acid[3]. The metabolic sources include the dietary proteins and quinic acid in colored foodstuffs[3]. The normal excretory level of hippuric in the urine is up to 1 g/L according to Biosentia Labs (Germany) where analysis had been done and the same level had been approved by Japanese Regulation and Prevention of Organic Solvent Poisoning[4].

Hippuric acid is still the most used indicator in the bio monitoring of toluene-exposed workers because it shows a good correlation with the exposure levels[5].Hippuric acid appears in the urine as a metabolite of toluene; it is metabolized to benzoic acid, which conjugates with glycine in the liver to yield hippuric acid[6]. Severity of chronic toluene toxicity increases among toluene abusers "glue sniffers", or from environmental contamination[7].

There are many factors, other than toluene exposure, that could influence the urinary excretion of hippuric acid. These factors should be kept in consideration before taking urine for the determination of hippuric acid level.

The factors are:

1. **Benzoic Acid Intake**: benzoic acid is an importantsource for hippuric acid production. Most of the benzoic acid is derived from dietarycomponents, whereas a smaller part is excreted as aresult of intermediate amino acid metabolism[8]. Benzoates are used as preservatives for several foods because of their antimicrobial effect that is related to their activity against yeasts and moulds, and to a lesser extent against bacteria, examples of foods with benzoates include fruit juice, lemonade, ketchup andmustard[8].Benzoic acid is rapidly absorbed and thereafter rapidly and completely excreted as hippuric acid in the urine[8].Szadkowski et al.[9] have shown that a meal of food containing benzoic acid caused a threefoldincrease of hippuric acid excretion. Other than benzoic acid, some aromatic phenolic acidsfrom ingested edible fruits such as blueberry, cherry, raspberry, melon, and blackberry leaded to increased concentrations of excreted hippuric acid[10], the same increase was found after the consumption of grapes, apples, peach and plums[11].

2. **Alcohol Consumption**: Alcohol interacts with toluene metabolism, and could havedifferent effects on its metabolism; chronic consumption causes stimulating effects while acute consumption leads to inhibiting effects[12,13]. This is a possible explanation for the controversial effects of alcohol consumption on urinary excretion of hippuric acid in humans exposed to toluene, reported by different studies. Dossing et al.[14] and Baelum et al.[15] recorded a reduction in hippuric acid urine levels after alcohol consumption in comparison to Bavazzano et al.[16]who recorded an increase in the elimination of hippuric acid into urine.An interesting study by Hjelm et al.[17] found that the excretion of hippuric acid in urine is reduced when alcoholic drinks are combined with a carbohydrate restricted diet.Siqueira andPaiva[1]had found that alcohol consumption does not affect urine levels of hippuric acid among individuals who are not exposed to toluene.

3. **Cigarette-Smoking**: according to Inoue etal.[18], the combination of alcohol and cigarettes reduceshippuric acid in the urine of workers exposed to toluene. Siqueira and Paiva[1] did not find significant differences in hippuric acid excretion between subgroups of smokers/non- smokers and alcohol drinkers and non-drinkers were observed.

4. Black tea consumption was found to increase hippuric acidexcretion[19].Inanother study the consumption of black or green tea was found to increase hippuric acidexcretion[20].

5. Coffee consumption may result in increased levels of hippuric acid in the urine[4].

CONCLUSION

In our case study; the first result of hippuric acid urine level is 1.8 g/L, which is slightly higher than the normal level (up to 1g/L). The first sample was taken without precautions ofthe above-mentioned factors.A second sample was taken after stopping smoking, drinking tea and coffee, and avoidance of all possible foods and drinks that may contain benzoic acid. There is no history of alcohol consumption. The result of second sample was 0.6 g/L i.e. within normal limits.

For optimal accuracy when using hippuric acid level as a biomonitor for toluene exposure, the following precautions should be taken before taking the urine sample:

1. Diet restrictions during the sampling day and on the day before samplingshould be used to avoid the intake of benzoic acid and therefore to avoid changes in hippuric acid levels.The foods and drinks that contain benzoates include any of the following permitted preservatives according to the European Union (E numbers 210-219).

E210 or Benzoic acid
E211 or Sodium benzoate
E212 or Potassium benzoate
E213 or Calcium benzoate
E214 or Ethyl 4-hydroxybenzoate or Ethyl para-hydroxybenzoate
E215 or Ethyl 4-hydroxybenzoate, sodium salt or sodium ethyl para-hydroxy-benzoate
E216 or Propyl 4-hydroxybenzoate or Propyl para-hydroxybenzoate
E217 or Propyl 4-hydroxybenzoate, sodium salt or sodium propyl parahydroxybenzoate
E218 or Methyl 4-hydroxybenzoate or Methyl para-hydroxybenzoate
E219 or Methyl 4-hydroxybenzoate, sodium salt or Sodium methyl parahydroxybenzoate.

2. Tea and coffee drinks should not be taken at least 24 hours before taking the sample.
3. Smoking and alcohol consumption should be stopped for optimal results without possible false positive results.

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