

# Acute Inhaled Xylene Poisoning Confirmed by Methylhippuric Acid Urine Test

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## Abstract

Xylene is a commonly used toxic volatile organic solvent. Diagnosis of acute xylene poisoning is limited by the lack of a readily available analytic assay. Methylhippuric acid, a metabolite of xylene excreted in the urine, is used for biomonitoring occupational exposures to xylene. We report two cases of acute occupational poisoning from xylene inhalation suggested by determination of high urinary methylhippuric acid. Two 21 and 23 years old healthy male adults collapsed after inhaling an unknown paint thinner during painting. On admission to the emergency department, they were confused and agitated, without hemodynamic or respiratory impairment. Admission urinary methylhippuric acid determined by HPLC with UV detector were 2.57 and 2.68 g/g creatinine (Biologic Exposure Index, BEI, 1.5 g/g creatinine). Urinary hippuric acid was below the previously used BEI for toluene. Mild increases in alanine aminotransferase (80 U/L) and aspartate aminotransferase (71 U/L) were found 12 hours after exposure, returning to normal after 24 hours. The patients gradually regained full consciousness within 24 hours and discharged after 48 hours' observation without any sequelae. High urinary methylhippuric acid concentrations suggested the diagnosis of acute xylene poisoning following its inhalation. Diagnosis in previous reports of acute xylene poisonings relied on history and clinical manifestations. Urinary methylhippuric acid assay is specific and available in special laboratories. It is suggested to determine urinary methylhippuric acid together with metabolites of other widely available organic solvents (e.g., hippuric acid, trichloroacetic acid) whenever unintentional exposure or abuse of volatile organic compounds is suspected.

**Keywords:** Xylene; Poisoning; Inhalation; Methylhippuric acid; Urine

## Introduction

Xylene is an aromatic hydrocarbon commonly used as an industrial solvent for the manufacturing of pharmaceuticals, paints, and chemicals [1,2]. Acute xylene poisoning is difficult to confirm, as specific analytic assays are not readily available in the acute clinical setting. Methylhippuric acid is the main metabolite of xylene excreted in the urine, and is used for biomonitoring occupational exposure to xylene [1,2]. We report two patients with acute inhaled xylene poisoning whose exposure was confirmed by urinary methylhippuric acid measurement within hours from exposure.

## Case report

Two young healthy male adults aged 21 and 23 years were brought to the emergency department after being found unconscious at home. According to their employer, they had been painting a closed ~10 m<sup>2</sup> room for a few hours before collapsing. The original containers of the paint and thinner were not retrieved. En-route to the hospital their level of consciousness partially improved. On admission, they were confused and agitated, with pulse rates of 90 and 110/minute regular, blood pressures 120/78 and 142/80 mmHg, respiratory rate 20/minute, oxygen saturations 95 and 100% (room air), and mydriasis reactive to light. Electrocardiograms and chest x-rays were interpreted as normal.

Complete blood count, kidney and liver functions were within normal range. Urine for metabolites of aromatic organic solvents was collected on admission and analyzed 12 hour later; samples were kept refrigerated until analysis. Methylhippuric acid and hippuric acid (a toluene metabolite) were measured in the patients' urine by high-pressure liquid chromatography (HPLC) with an UV detector (AS-2057/2089 and UV-1570, Jasco Inc., Tokyo, Japan) using specific columns (Prodigy ODS-3 5 µm, Phenomenex®, Torrance, CA, USA). Urinary methylhippuric acid concentrations were 2.57 and 2.68 g/g creatinine (Biologic Exposure Index, BEI, 1.5 g/g creatinine) [3]. Urinary hippuric acid (a toluene metabolite) concentrations were 0.18 and 0.46 mg/g creatinine (BEI 1.6 mg/g creatinine) [4]. It should be noted that hippuric acid is not used anymore as a biomarker for exposure to toluene. The patients were admitted to the cardiac intensive care unit; vital signs and respiratory parameters were within normal limits and stable, and no arrhythmias were detected in continuous cardiac monitoring. Confusion and agitation resolved while drowsiness ensued. They regained full consciousness within 24 hours; at that time neurological examination was normal. Mild increases in alanine aminotransferase (80 U/L; normal value 10-40 U/L) and aspartate aminotransferase (71 U/L; normal values 10-40 U/L) were found 12 hours after exposure, returning to normal after 24 hours. The patients were discharged after 48 hours' observation with no neurological or psychiatric impairment.

## Discussion

We report two cases of unintentional exposure to paint thinner resulting in coma and mild liver enzyme abnormality. Both cases were diagnosed as xylene poisoning by high urinary methylhippuric acid concentrations, about 1.75 times higher than the BEI set by the American Conference of Governmental Industrial Hygienists (ACGIH) for occupational exposure to xylene [3].

Acute xylene poisoning is infrequently reported; most cases are industrial or occupational accidental exposures [5-9]. The clinical presentation of acute inhaled xylene toxicity includes neurological manifestations, mainly drowsiness and coma [5-9], similar to our reported patients.

Mortality after mix inhalation of volatile hydrocarbons including xylene was reported in several cases; xylene contribution to the fatalities was not assessed [5,8,9].

Diagnosis of xylene acute exposure usually relies on medical history and clinical presentation [5-9]. Analytic assays for xylene are not readily available in the acute clinical setting. Post-mortem analysis of xylene isomers using a chromatography-mass spectrometry (GC-MS) assay was reported in few cases [8,9]. GC-MS is a complex, expensive and time-consuming assay, not regularly available in hospital laboratories. Environmental monitoring of xylene can serve as an indirect confirmation of exposure [7], but is less available and less relevant to acute exposure.

The presence of high concentrations of urinary methylhippuric acid, higher than the BEI, suggested the diagnosis of acute xylene inhalation in our patients. Urinary hippuric acid concentrations within the previously used BEI for toluene did not support exposure to toluene.

Xylene elimination is characterized by two phases, a relatively rapid phase and a slow one, representing a multi-compartment kinetic model [2]. Xylene is mainly metabolized by oxidation to methylhippuric acid (95%), which is excreted in the urine [1,2]. Methylhippuric acid can be detected in the urine within 1-2 hours post exposure and for at least 24 hours later. Methylhippuric acid urinary excretion is not significantly influenced by variation in renal physiology, e.g., urine pH, rate of diuresis, and reabsorption [2]. The assay of urinary methylhippuric acid has no known interferences, and is considered specific [10]. All these make methylhippuric acid most suitable for biomonitoring occupational exposure to xylene. Analytic

tests for methylhippuric acid are available in laboratories certified for performing occupational biomonitoring tests. HPLC with UV detector is an acceptable assay for measuring urinary methylhippuric acid [10]. Although determination of urinary methylhippuric acid cannot affect treatment of xylene poisoning, it can serve as a reliable laboratory tool for establishing this diagnosis.

## Conclusion

Diagnosis of acute xylene poisoning following its inhalation was suggested in our cases by urinary methylhippuric acid. It is suggested to determine urinary methylhippuric acid together with other metabolites of organic solvents (e.g., hippuric acid, trichloroacetic acid) whenever acute unintentional exposure or abuse of volatile organic compounds is suspected.

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