

CASE REPORT

Toxicology

Trending of a falsely elevated serum creatinine after a pediatric nitromethane ingestion: A case report

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Abstract

Introduction: Nitromethane is a primary nitroalkane used as a solvent and a fuel that may be toxic by ingestion, inhalation, or contact. Its presence can be detected in serum of exposed persons, but levels are not readily available to guide patient care. Nitromethane has been shown to falsely elevate serum creatinine when clinical laboratories use Jaffe assays to measure creatinine; enzymatic assays are not affected. Ex vivo experiments have demonstrated a linear relationship between serum nitromethane and the elevation in Jaffe assay creatinine. This case report demonstrates an elevation of creatinine measured by Jaffe assay with normal creatinine measurement by enzymatic assay after exposure to nitromethane.

Case report: A 21-month-old girl ingested an unmeasured quantity of a hobby fuel, a fuel containing methanol, nitromethane (20%), and lubricants used in miniature internal combustion engines, such as remote-controlled cars. She was initially evaluated at a community hospital, treated empirically for methanol toxicity with fomepizole and folic acid, and transferred to a university hospital for further management. By 19 hours after ingestion, methanol was below detection, but a serum creatinine of 2.63 mg/dl raised concern for kidney injury. Toxicology consultation recognized that the creatinine had been measured using a Jaffe assay and recommended a repeat creatinine using an enzymatic assay, which was within normal limits. The patient remained an inpatient for further evaluation, which permitted trending of her Jaffe assay creatinine over a 3-day period. The Jaffe assay creatinine demonstrated a gradual decline; repeat enzymatic assay creatinine remained within normal limits.

Discussion: The decline in this pediatric patient's Jaffe assay creatinine is consistent with first-order clearance of nitromethane, which has been previously described in adult exposures. This case demonstrates how Jaffe assay-derived serum creatinine may be useful in the pediatric population to establish, quantify, and trend nitromethane exposure with essential concurrent use of an enzymatic assay to determine actual creatinine.

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KEYWORDS

creatinine, enzymatic assay, falsely elevated creatinine, ingestion, Jaffe assay, nitromethane, pediatric

1 | INTRODUCTION

Nitromethane (CH_3NO_2) is a primary nitroalkane that is used as an organic solvent, in industrial organic synthesis, and as a fuel and fuel additive (often in combination with methanol) in motorsports and miniature internal combustible engines, such as remote-controlled cars.^{1,2} Potential routes of exposure include ingestion, inhalation, and absorption (skin contact); exposures may be accidental or intentional.³ Significant nitromethane exposures may occur in industry, at race tracks, and in the home. Nitromethane is a skin, eye, and respiratory tract irritant. It has been detected in the serum of exposed persons.⁴ Nitromethane exposures have been associated with nausea and vomiting, headache, somnolence, unconsciousness, seizures, and methemoglobinemia.⁵ Treatment for acute nitromethane exposures is primarily supportive, with decontamination when indicated, such as using methylene blue for symptomatic methemoglobinemia and hemodialysis in severe cases. Based on animal studies and human case reports, nitromethane is probably carcinogenic, may be toxic to the liver and kidneys, and may induce contact dermatitis.¹⁻⁴

Nitromethane has been shown to interfere with the measurement of serum creatinine (an indicator of renal function), resulting in falsely elevated creatinine when clinical laboratories use Jaffe assays to measure creatinine.⁶ In the Jaffe assay, the addition of picrate to the serum sample causes formation of a creatinine-picrate complex. The concentration of this orange-colored complex, and thus the creatinine, is determined from optical absorbance analysis at an appropriate wavelength.⁷ Nitromethane is believed to interact with picrate in such a way as to produce similar optical absorbance.⁶ Other substances known to interfere with the Jaffe assay include cephalosporins, streptomycin, metimazole, aspirin, and acetaminophen.⁸ Serum creatinine may alternatively be measured by enzymatic assays in which the serum creatinine undergoes ≥ 1 enzymatically driven reactions, with quantitative measurement of the end product, which is produced in proportion to the creatinine.⁷ Nitromethane does not interfere with enzymatic assays,^{3-4,6} which can be used to determine true creatinine when nitromethane is present in the serum. Enzymatic assays are not as prone to interference from chromogens.

Ex vivo experiments in which chemical-grade nitromethane has been added to samples of human serum and creatinine of the resulting serum measured by Jaffe assay have demonstrated a linear relationship between serum nitromethane and the elevation in Jaffe assay creatinine, although there are significant discrepancies in the conversion factor^{3,6,9}; the etiology of this discrepancy is unclear. Cao et al demonstrated in an ex vivo assessment that the addition of nitromethane into a plasma sample did not interfere with the measurement of the anion gap or osmolar gap with Jaffe assay or point-of-care testing.⁹

2 | CASE REPORT

A 21-month-old girl ingested an unmeasured quantity of a fuel containing methanol, nitromethane (20%), and lubricants formulated for use in radio-controlled toys. A drinking straw was present in the fuel bottle to facilitate fueling. The patient was observed by family to sip from the straw, and the patient spit up fuel and vomited shortly thereafter. The patient presented to a community hospital and was evaluated in collaboration with poison control. Initially, the concern was for a hydrocarbon ingestion, and the patient was observed. However, after family brought in the fuel bottle, it was realized that the fuel contained methanol. The patient was evaluated for methanol toxicity and treated empirically with fomepizole and folic acid. Blood work obtained 10 hours after ingestion, at the outside hospital, included creatinine, 0.23 mg/dl; blood urea nitrogen (BUN), 13 mg/dl; potassium, 4.7 mmol/L; venous pH, 7.35; anion gap, 13; carbon dioxide, 29 mmol/L; osmolality, 285 mOsm/kg, with an osmolar gap of -12 ; and methemoglobin, 1.0. A methanol level was sent from the outside hospital, but the results were not provided during the patient's admission.

The patient was transferred to a tertiary care facility for further management. Blood work was obtained at about 19.5 hours after ingestion while the patient was being observed in the general pediatrics ward. A second methanol level was below detection, serum creatinine of 2.63 mg/dl raised concern for renal injury (BUN, 11 mg/dl; potassium, 4.1 mEq/L; anion gap, 11; bicarbonate, 22 mEq/L). Plans were made to transfer the patient to the pediatric intensive care unit, and toxicology was consulted. An investigation raised the possibility that the nitromethane coingestion was producing a falsely elevated creatinine. An inquiry to the laboratory confirmed their routine use of a Jaffe assay. The laboratory analyzed the patient's serum creatinine using an enzymatic assay (ABL837 analyzer), and the creatinine results were within normal limits. The patient remained in the hospital for further evaluation of non-specific laboratory abnormalities (resulting in the diagnosis of transient hyperphosphatasemia of infancy and early childhood and vitamin D deficiency), and electrolytes with renal function was repeated periodically. This permitted the trending of the patient's creatinine, as measured by the usual routine Jaffe assay. During the 3-day inpatient stay, a total of 7 creatinine levels were obtained using the Jaffe assay. Although the enzymatic assay creatinine remained within normal limits, the Jaffe assay creatinine demonstrated a gradual decline over time (Figure 1), representing the gradual decline in the patient's serum nitromethane as estimated using a previously determined conversion factor (apparent creatinine = $0.99[\text{nitromethane}] + 0.21$).⁶ The patient's stay was otherwise uncomplicated, and her last serum creatinine measured by Jaffe reaction before discharge was 0.82 mg/dl.

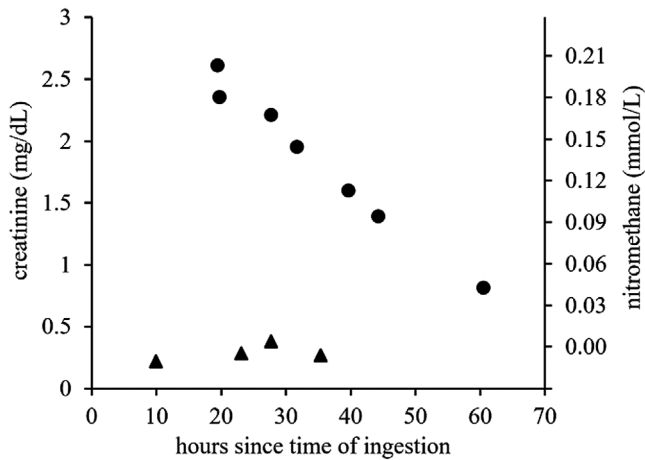


FIGURE 1 Serum creatinine (mg/dl) (left vertical axis) obtained using Jaffe assay (closed circles) and obtained using enzymatic assay (closed triangles) for the 21-month-old girl in this case report from time of ingestion of the hobby fuel with estimated corresponding serum nitromethane (right vertical axis) for the Jaffe assay creatinine (closed circles) based on a previously determined conversion factor⁵

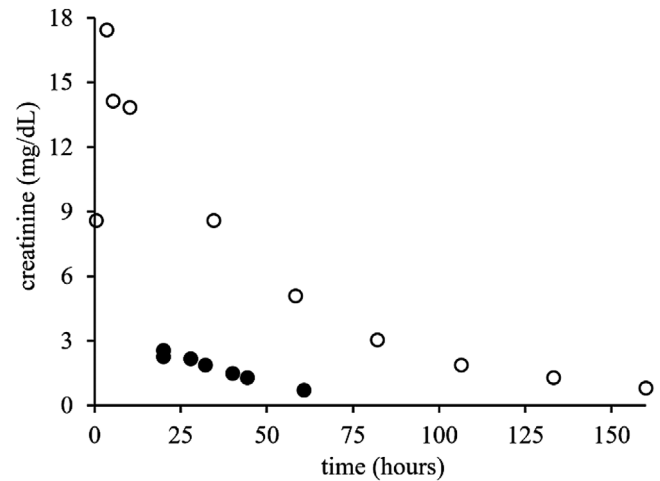


FIGURE 2 Comparison over time of Jaffe assay serum creatinine (mg/dl) (closed circles) obtained from the 21-month-old girl in this case report with Jaffe assay serum creatinine (mg/dl) (open circles) obtained from a previously reported case³ involving a 25-year-old male patient who sustained a nitromethane exposure (by contact and likely inhalation)

3 | DISCUSSION

This case demonstrates a falsely elevated Jaffe assay–measured creatinine but a normal-range enzymatic assay creatinine in the context of a pediatric nitromethane exposure, occurring with the ingestion of a hobby fuel. The ability of serum nitromethane to falsely elevate Jaffe assay creatinine in direct proportion to the concentration of the nitromethane in serum has been previously documented in multiple case reports.^{3–6} The circumstances of this case permitted quantification of the effect of nitromethane on the Jaffe assay creatinine in a pediatric patient in vivo and over time. The variation in Jaffe assay creatinine with time (representing nitromethane clearance) in the 21-month-old girl in this case report was compared with that of a previously reported case³ involving a 25-year-old man who sustained a nitromethane exposure resulting from a high-speed drag-racing crash that saturated his jumpsuit and underclothing with fuel containing 95%–98% nitromethane, with possible concomitant inhalation of the fuel (Figure 2). For both patients, the natural log of the Jaffe assay creatinine revealed a linear relationship consistent with first-order clearance of nitromethane (Figure 3). The half-life of serum nitromethane was calculated as 35 hours for the adult male patient and 26 hours for the pediatric female patient. Although the decline in the Jaffe assay creatinine of the pediatric patient in this case report may be described as linear (Figure 1), which would represent zero-order clearance, the literature supports first-order clearance of nitromethane,^{3,4} and the data for the pediatric patient in this case report are consistent with first-order clearance (Figure 3).

Although the Jaffe assay is the more common method of measuring creatinine for central laboratories, it is more susceptible to interferences from various pharmaceuticals and endogenous substances such as bilirubin, glucose, ketones, and proteins.^{8,10} The Jaffe method

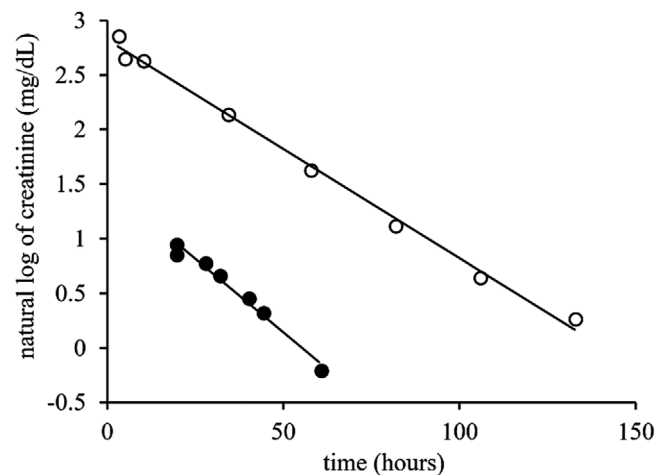


FIGURE 3 Natural log of the Jaffe assay serum creatinine of the 21-month-old girl in this case report (closed circles) and of the 25-year-old male patient (open circles)³ over time, demonstrating the linearity expected of first-order clearance of nitromethane. Calculated half-life is 26 hours for the 21-month-old girl and 35 hours for the 25-year-old male patient

is more time intensive than the enzymatic assay but currently less expensive.¹¹ In the acute care setting, point-of-care devices and blood gas analyzers use the enzymatic assay for creatinine measurement.¹² The enzymatic method employs the enzymes creatinine amidohydrolase to metabolize creatinine to creatine, and then creatine amidohydrolase metabolizes creatine to sarcosine and urea. Sarcosine oxidase converts sarcosine to glycine, formaldehyde, and hydrogen peroxide. The ABL837 analyzer uses a 2-electrode system, where 1 electrode measures creatinine and creatine, and the other measures creatine.

One electrode contains all 3 enzymes in its inner membrane, and the other electrode contains the last 2 enzymes. The amount of creatinine is calculated by subtracting the signals between the 2 electrodes.¹³ The analyzer for this case, ABL837, uses amperometric measuring principles: a potential is applied to the electrodes resulting in the oxidation of hydrogen peroxide to produce an electrical current that is proportional to the amount of hydrogen peroxide, which in turn is directly related to the amount of creatinine and creatine in 1 electrode and creatine in another electrode.¹³

Interference with serum assays is not the only cause of a falsely elevated creatinine: increased creatinine production and decreased creatinine secretion results in an inaccurate elevation. A history of dietary supplementation with creatine, vigorous exercise, and a carnivorous diet leads to an increase production of creatinine and inaccurate elevation of creatinine.¹⁴ Trimethoprim, H₂-blockers, and salicylates can decrease the secretion of creatinine in urine, giving rise to an inaccurate elevation of serum creatinine.¹⁴ BUN is an imperfect marker of renal function, but in the setting of an acutely poisoned patient with possible acute kidney injury, a normal BUN would not be expected. Interpretation of BUN must include preexisting comorbidities such as chronic liver disease, nutritional status, catabolic status, volume status, and steroid use.¹⁵ In the poisoned patient with an acute elevation of creatinine, other laboratory abnormalities such as metabolic acidosis, an elevated lactic acid and anion gap, proteinuria, or the presence of an increased serum osmolar gap would be expected.

A limitation of this case report was the inability to obtain a nitromethane level. Many medical centers either are unable to obtain a level or it is sent out to an external laboratory, with a turnaround time that is not beneficial in the acute care of the patient. Another consideration is the undetectable methanol level: results of the first methanol-level test at the outside hospital were not provided, and levels in the second test were undetectable after 19.5 hours. Methanol is quickly absorbed from the gastric mucosa but has a substantive half-life 30 to 85 hours.¹⁶ As methanol is fairly volatile, there is a possibility that the methanol was exposed to air and partially evaporated, as the patient's parents reported she drank from the container with a straw. Even if methanol was detectable, end-organ dysfunction, such as renal failure, is unlikely to present as an isolated finding in methanol toxicity in the absence of prolonged metabolic acidosis and other neurologic sequelae as coma, central nervous system (CNS) and respiratory depression, and visual impairment.¹⁶ Nitroalkanes are derivatives of hydrocarbons, and typically most exposures to hydrocarbons cause respiratory, CNS, arrhythmia, and gastrointestinal symptoms but not isolated nephrotoxicity.¹⁷ There are a few exceptions, such as toluene, which can cause a renal tubular acidosis, hyperchloremia, and hypokalemia, with an increasing anion gap with metabolism of toluene.¹⁸

The primary contribution of this case report is the confirmation of first-order clearance of nitromethane in a pediatric patient. This case demonstrates how Jaffe assay-derived serum creatinine may be useful in the pediatric population to establish, indirectly quantify,

and trend nitromethane exposure, with essential concurrent use of an enzymatic assay to determine actual creatinine, for example, in confirming normal-range creatinine and when managing coexposures such as methanol. Nitromethane levels may be inferred from the difference between Jaffe assay creatinine and enzymatic assay creatinine. This case also highlights the clinical value of toxicological research on nitromethane. Based on convincing evidence from prior studies that nitromethane can falsely elevate serum creatinine, the pediatric patient in this case report was spared an unnecessary trip to the pediatric intensive care unit, unnecessary tests, and unnecessary and potentially harmful interventions.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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