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Case Report

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False-Positive Ethanol Level in Urine and Plasma Samples of a Resuscitated Infant

B. Lefrère[1,*], D. Wohrer[2], C. Godefroy[1], M. Soichot[3], A. Mihoubi[3], V. Nivet-Antoine[1,4], M. Oualha[2,5] and P. Houzé[1,3,6]

[1]Laboratoire de Toxicologie Biologique, Hôpital Universitaire Necker-Enfants Malades, Assistance Publique-Hôpitaux de Paris (AP-HP), 149 rue de Sèvres, Paris 75015, France; [2]Service de réanimation et surveillance continue médico-chirurgicale, Hôpital Universitaire Necker Enfants-Malades, Assistance Publique-Hôpitaux de Paris (AP-HP), 149 rue de Sèvres, Paris 75015, France; [3]Laboratoire de toxicologie, Hôpital Lariboisière, Assistance Publique-Hôpitaux de Paris (AP-HP), 2 rue Ambroise Paré, Paris 75010, France; [4]INSERM UMRS-1140, Faculté de Pharmacie, Université de Paris, 4 avenue de l'Observatoire, Paris 75006, France; [5]EA7323, Évaluation des thérapeutiques et pharmacologie périnatale et pédiatrique, Université Paris Descartes, 27 rue du Faubourg Saint Jacques, Paris 75014, France and [6]CNRS UMR 8258-U1022, Faculté de Pharmacie Paris Descartes, Unité de Technologies Chimiques et Biologiques pour la Santé (UTCBS), 4 avenue de l'Observatoire, Paris 75006, France

*Author to whom correspondence should be addressed. Email: bertrand.lefrere@aphp.fr

Abstract

We report the case of an 11-month-old male infant with a complex congenital heart disease who was admitted in the intensive care unit following cardiorespiratory arrest at home. Toxicological urine screening reported an ethanol concentration of 0.65 g/L using an enzymatic assay, without suspicion of alcohol intake; a significant amount of ethanol concentration was found in two plasma samples using the same enzymatic assay. Plasma and urine ethanol concentrations were below the limit of quantification (LOQ) when tested using a gas chromatography method. Urine ethanol level was also below the LOQ when tested by enzymatic assay after an initial urine ultrafiltration. These results confirmed our suspicion of matrix interference due to elevated lactate and lactate dehydrogenase levels interfering in the enzymatic assay. This analytical interference, well-known in postmortem samples, extensively studied *in vitro*, has been rarely reported *in vivo*, especially in children. To the best of our knowledge, this case is only the sixth one reported in an infant's plasma and the first initially discovered from urine. Indeed, as for ethanol, this last matrix has not been studied in the context of this artifact that may induce false-positive ethanol results while seeking a diagnosis in life-threatening or fatal situations that are potentially subject to forensic scrutiny. In parallel to a synthetic literature review, we propose a simple, informative decision tree, in order to help health professionals suspecting a false-positive result when performing an ethanol assay.

Case History

The following case highlights the importance of controlling an unexpected analytical interference, in the context of an enzymatic ethanol assay performed on an emergency basis, revealed in particular by clinical inconsistency.

An 11-month-old male infant, born at gestation week 38 with a complex congenital heart disease, was admitted to the intensive care unit following cardiorespiratory arrest at home. The parents mentioned the administration of an indeterminate dose of paracetamol syrup to their son in order to treat a fever. Fifteen minutes later, the infant was breastfed. The mother reported agitation and sudden hypotonia—prompting a call to the emergency medical services. When the medical team arrived, the child was in cardiac arrest. The cardiopulmonary resuscitation lasted for 30 minutes.

The patient was given adrenaline and physiological saline solution.

Upon admission to the intensive care unit, the patient had a body temperature of 35.4°C, a Glasgow Coma Scale of 3 and weighed 7 kg. The patient presented with severe lactic acidosis (pH 6.78, bicarbonates 6.5 mmol/L, pCO_2 46 mmHg and lactates 16 mmol/L) with an elevated plasma anion gap at 34.7 mmol/L, hypoglycemia (1 mmol/L), shock liver (ASAT 3,064 UI/L and ALAT 1,485 UI/L) and oliguric acute kidney failure (serum creatinine at 83 mmol/L). During the intensive care unit stay, the patient received glucose solution, bicarbonate, cefotaxime, adrenaline, paracetamol, pantoprazole, ketamine and vitamin K. Measurements of urinary ethanol concentration and toxicological screening were performed using an Architect cSystems c16000 clinical chemistry analyzer with Abbott Diagnostics reagent kits (Rungis, France). As emphasized in Table I, ethanol in urine was measured at 0.65 g/L by enzymatic assay. Immuno-screening was negative for amphetamines, barbiturates, benzodiazepine, methylenedioxymethamphetamine, cocaine, cannabis, opiates, methadone and dextropropoxyphene. For two plasma samples, collected ∼1.5 hours before and ∼3 hours after urination, the enzymatic assay allowed to quantify ethanol concentrations of 0.39 and 0.25 g/L, respectively (Table I). When using a gas chromatography system equipped with a flame ionization detector (GC–FID), plasma and urine ethanol concentrations were systematically below the limit of quantification (LOQ) (0.1 and 0.06 g/L, respectively). We also performed a urinary ultrafiltration prior to the enzymatic assay, which resulted in the urine specimen having an ethanol concentration below the LOQ.

During the intensive care unit stay, the patient's condition was degrading rapidly. He developed a post-anoxic encephalopathy and a pulmonary arterial hypertension with a fatal outcome. Therefore, the identification of an analytical interference, described in detail further in this work, enabled us to conclude that the ethanol result was a false positive. In addition, the autopsy conclusions retained pulmonary hypertension as the main mechanism of the cardiac arrest, which as a result ruled out a medico-legal alert.

Discussion

Enzymatic ethanol assays are widely used in hospital laboratories for practical reasons such as the absence of sample pre-processing, high throughput and ease of automation. If required, the samples can be sent to a dedicated laboratory able to perform GC–FID assay, a more reliable, accurate and robust analytical method, which can also detect other alcohols, but which involves a slightly longer analysis time and requires specifically trained personnel. GC–FID remains the standard alcohol analysis method, which is selective and virtually without interference, except for a possible rare exception of some anesthetics (not administered here) for ethanol assay (1), for which coelution can be excluded, thanks to a dual polarity column. In contrast, possible artifacts may occur when using enzymatic assay, and a dialogue between the medical biologist and the clinician is essential in order to avoid any bias or delay. Thus, in the present case, the observed urine ethanol concentration measured using enzymatic assay was not consistent with the clinical context.

First, with regard to the pre-analytical step, we considered whether a false-positive ethanol level could result from the microbial fermentation of a poorly stored sample (2,3). In the present case, despite the absence of NaF 1% (4)—and the presence of glycosuria (1.14 mmol/L)—a microbiological ethanol generation *in vitro* can be reasonably ruled out considering (i) the very short storage time between the sample collection and the assay in addition to (ii) the absence of proven urinary infection or colonization. A microbial generation *in vivo*, a microbial fermentation *in vivo*, the extremely rare urinary or bladder auto-brewery syndrome, with a false positive of urinary ethanol evidenced (5), could reasonably be ruled out, as the patient was not diabetic.

We also considered the hypothetical possibility that ethanol could have been present in the breast milk ingested by the infant (6). Theoretical calculation of infant's ethanolemia after breastfeeding yielded a very low level in literature (6), below the LOD of our enzymatic assay, which was 0.01 g/L of ethanol according to the manufacturer. The hypothesis of intoxication by breastfeeding was therefore rapidly excluded based on the mother's statement (which was considered to be reliable), as well as the ethanol concentrations which have been thought to be significant initially in the infant samples. In the same vein, an inhalation coming from ethanol-based sanitizers (7) can be ruled out as the patient was not an isolette. Using the urine/blood ratio of ethanol was not possible, as (i) we did not have a urine sample concomitant to a plasma sample for this oliguric patient and (ii) ratio interpretation is only valid during the elimination phase. We could not determine for sure that this was the case (8).

As for an analytical artifact, three possible reasons for an interference in urine can be envisaged in view of the enzymatic ethanol assay process: (i) substrate competition; (ii) cross detection and (iii) excessively high reduced cofactor concentrations. The assay is based on kinetic measurements of the optical absorbance (340 nm) of the reduced cofactor NADH (Nicotinamide Adenine Dinucleotide, reduced), obeying Beer–Lambert law, generated from the oxidation of ethanol, the substrate, into acetaldehyde, the product, by ADH (Alcohol Dehydrogenase, E.C 1.1.1.1.) (Figure 1). The enzymatic activity of ADH, and thus the blood or urine ethanol level, is pro-

Table I. Patient Biochemical Relevant Parameters to Determine the Analytical Interference

	Plasma 1	Urine	Plasma 2	Plasma 3	Post-ultrafiltration urine
Sample collection	08:00 pm	9:30 pm	12:10 pm	12:30 pm	A posteriori
Lactates (mmol/L)	16	51	/	10.2	/
LDH (U/L)	/	5,784	7,733	/	69 UI/L
Ethanol (g/L)	0.39	0.65 g/L[a]	0.25	/	<0.1 g/L
Enzymatic assay					
Ethanol (g/L) GC–FID	<0.1	<0.06	<0.1	/	/
ASAT (U/L)	3,064	/	/	/	/
ALAT (U/L)	1,485	/	/	/	/
Hemolysis index	0	/	0	0	/

[a]First ethanol assay performed. The others have been performed after the urine screening.

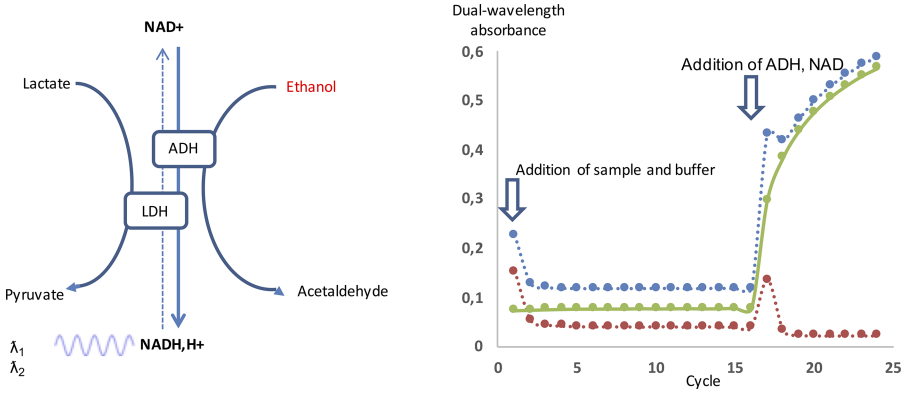

Figure 1. Schematic representation of the enzymatic assay implemented for the quantification of ethanol in biological samples. Ethanol is assayed after the addition of reactants: first, Tris buffer; then, ADH and NAD reagents, added at the 16th revolution cycle. The reaction curve integrates the change over time in the dual-wavelength detection of the difference (green) between a primary absorbance (blue) and a secondary absorbance (red). The concentration in the sample is finally determined from a three-point calibration curve.

portional, apart from a concentration factor, to the concentration of NADH ($\Delta A_{NADH}/\varepsilon_{NADH}.l.$) generated over a certain time (Δt). The factor A refers to the absorbance, ε refers to the molar extinction coefficient and l refers to the spectrophotometer cuvette's width. As illustrated in Figure 1, the reaction curve did not demonstrate any irregularities, which indicates normal performances of the enzymatic test reagents and instrumentation.

(i) Along with the interference, one should consider the theoretical possibility of cross-reaction with the ADH's substrate. None of the xenobiotics taken by the patient, including paracetamol syrup—which notably contains *cis*-7 hexenol, propyleneglycol and benzylic alcohol—were likely to be metabolized by ADH, according to the manufacturer's indications and a French multicentric study concerning the analytical characteristics of ADH-based enzyme assays (9).

(ii) None of the drugs taken by our patient is known to significantly absorb light at the two wavelengths used to detect the cofactor. This allows us to conclude that no bias regarding the quantification of ethanol could be originating from the drugs administered to the patient during the intensive care unit stay. The possibility of cross detection with the drugs' metabolites has not been explored.

(iii) It is known that NAD (Nicotinamide Adenine Dinucleotide)/NADH is involved in reactions catalyzed by lactate dehydrogenase (LDH). *In vivo*, this reversible cytosolic enzyme can convert pyruvate into lactate by oxidizing NADH. However, in the present setting, with lactic acidosis following cardiorespiratory arrest, pyruvate would no longer enter the mitochondrion to be transformed into acetyl-CoA and thus would be primarily reduced to lactate. The hypothesis of an excess of lactates/LDH leading to an inappropriate NADH level has been thoroughly explored in laboratory studies but much less frequently *in vivo*, especially in children. To the best of our knowledge, only five cases in pediatrics have been reported, with only three living patients, all resuscitated (Table II). Some researchers have argued that few cases have been reported due to a recruitment bias. Indeed, such traumatic patients can be expected to present very high LDH/lactate levels, making these laboratory parameters less relevant (13). The two prospective *in vivo* studies comparing enzymatic and chromatographic methods were performed on adults: lactate and LDH levels were too low to generate a false-positive result (13,16). Pathological criteria reported in the literature due to analytical interference are detailed in Table II, which would help a medical biologist to critically appraise the assay result and assess the need for additional lactate/LDH assays. As highlighted in Table II, a few available data or established medical guidelines exist for suspicion of false-positive ethanol assays in the pediatric field. Based on conclusion regarding the excessive presence of LDH and lactate, we developed a simplified procedure for helping healthcare professionals facing a suspected analytical interference in an enzymatic ethanol assay (Figure 2).

Table II. Brief Literature Review on Alcohol Dehydrogenase Assay Interference

Study design	Patients plasma LDH/lactates (U/L/mmol/L)	Techniques	Key findings
Experimental study (10)	Postmortem plasma and vitreous humour samples from sudden infant death syndrome (SIDS) vs. non-SIDS.	Emit®-st™, Syva Co., Palo Alto, CA (homogenous NAD-enzyme immunoassay)	- First suspicion of an endogenous interferent with ADH. - Ethanol assay with special vials containing all the usual reagents except ADH was + - Another dehydrogenase, LDH, and its substrate, lactate, were present in high enough levels to convert NAD to NADH. The "enzyme level" increased with lactate and decreased with oxamide (an LDH inhibitor).

Table II. Brief Literature Review on Alcohol Dehydrogenase Assay Interference

Study design	Patients plasma LDH/lactates (U/L/mmol/L)	Techniques	Key findings
Case report and experimental study (11)	- End-stage renal disease due to type II diabetes mellitus, received kidney transplant, necrotic colon, metabolic acidosis. LDH/lactate 27,000/15. - Myocardial infarction after carotid endarterectomy. LDH/lactate 24,623/5.6 *One postmortem sample	Emit®-st™, Syva Co., Palo Alto, CA vs. GC (Perkin-Elmer, Norwalk, CT, model 3920)	Complete elimination of the interference by preparing a protein-free ultrafiltrate from plasma, thanks to a filter (Centrifree Micropartition System, Amicon, Danvers, MA) and a special centrifugation protocol (20 minutes, 1,500 g) in order to remove LDH. The absence of a matrix effect when comparing an ethanol-supplemented ultrafiltrate with a serum sample.
Case report and experimental study (12)	- 4-month-old boy: extensive postnatal respiratory problems, resuscitated after cardiopulmonary arrest. - 2-month-old girl: resuscitated after cardiopulmonary arrest caused by accidental asphyxiation. Study: 17 postmortem samples; samples from two adults with (i) chronic liver failure, severe metabolic acidosis, kidney failure and (ii) end-stage liver disease	Emit®-st™, Syva Co., Palo Alto, CA Abbott REA assay (North Chicago, IL) Roche Assay (Nutley, NJ) vs. GC (Perkin-Elmer)	Comparison of lactate and LDH interference in three enzymatic assays: - Syva: false positive result for 15 of 17 autopsy samples and both of the samples from living and critically ill patients; Abbott: false-positive result for 2 of 17 autopsy samples; Roche: no false positives. - Correlation for the three kits between the false positive ethanol concentration and concomitant lactate/LDH levels, revealed by spiking sera with commercial stock solutions of LDH and lactate. - Thresholds for a combination of LDH and lactate: 682/14 (Syva), 26,339/26 (Abbott), 43,990/6 (Roche). - Apparent disappearance of interference in the Syva assay; possibly due to NAD depletion, confirmed when NAD was added (ethanol once again measurable).
Prospective study (13)	24 samples from living trauma patients	Dade Behring Dimension® vs. GC–FID (Perkin—Elmer 8310)	- No false positive in ethanol concentrations observed. - No significant difference values obtained between the two techniques.
Case report (14)	Three patients with marked hepatocellular necrosis due to acetaminophen intoxication.	Advia 1650® assay vs. GC	- Plasmatic osmolarity gap not fitted to ethanol level. Osmolality = $2[Na^+] + [urea] + [glucose] + 1.25\times[ethanol]$ (mmol/L). - Suspected interference by endogenous dehydrogenases other than LDH, because the concentrations of LDH/lactates were below the manufacturer's threshold. - Late diagnosis of paracetamol intoxication.
Medicolegal investigation (15)	33-year-old man—car accident	Roche Ethanol Gen.2	- Extrapolation of lactate and LDH (not measured) levels with, respectively, (i) the anion gap and (ii) ASAT, ALAT levels. Comparison between known levels of commercial ADH and theoretical lactate, and LDH concentrations. - No significant contribution to the ethanol reading in the essay due to lactate oxidation (no interference).
Prospective study (16)	46 sera from living patients who presented to the emergency department (mean age: 59 years), primarily with sepsis and metastatic cancer vs. 20 normal controls LDH/lactates range: 242–8,838/2.4–24.2	Roche Diagnostics (1776312 90) vs. GC–FID Agilent 6890	- No false-positive ethanol concentrations observed. - Obtaining theoretical concentrations of LDH, lactate that can trigger an artifact in a living patient would be very unlikely.
Case report (17)	85-year-old woman Unconscious collapse, with cardiopulmonary history, mild dementia LDH/lactates 294/not provided	DRI ethyl assay, Microgenics, Freemont CA vs GC Perkin Elmer Clarus 500/	Aspects of pharmacokinetics, ethanol stability and drug interference taken into consideration for highlighting this false positive.
Case report (18)	42-year-old female patient Lung cancer, liver and bone metastasis, progressive confusion, liver failure LDH/lactates: not provided/8–9	Enzymatic assay not provided vs. GC Agilent Technology 7890A, Santa Clara, California, USA	Enzymatic interference revealed in a living and critically ill adult.

Table II. Brief Literature Review on Alcohol Dehydrogenase Assay Interference

Study design	Patients plasma LDH/lactates (U/L/mmol/L)	Techniques	Key findings
Case report (19)	- 6-year-old male resuscitated after drowning. Premortem plasma samples: LDH/lactates: not measured/>20. ASAT 18,798 U/L, ALAT 9,179 U/L. Urine sample: non-detailed. - 2-year-old female with severe sepsis. Premortem plasma sample: LDH/lactate not provided. ALAT: 1,404 UI/L ASAT 2,333 U/L	SYNCHRON Systems ETOH Alcohol - Beckman Coulter vs. GC Agilent 7890A/FID fitted with an Agilent 7697A Headspace Sample. Dual column	Enzymatic interference in two pediatric premortem samples.

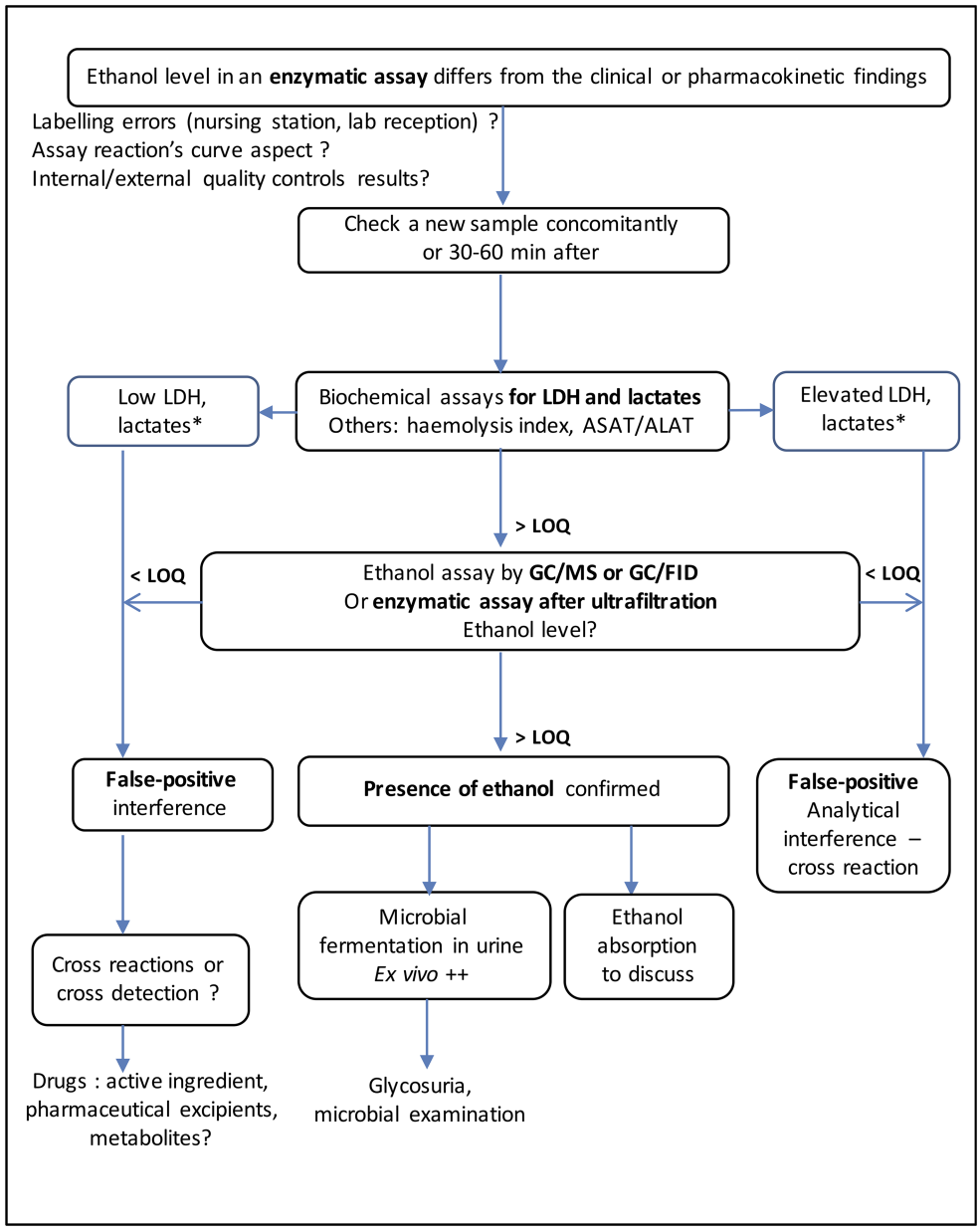

Figure 2. Proposition of a decision-tree procedure implemented to identify potential interferences for ethanol quantification. *Assay-specific threshold. LOQ: limit of quantification.

It should be noted that our samples were collected after resuscitation following cardiorespiratory arrest, 10 hours before death. In fact, most of the samples analyzed in other studies were collected at or after the moment of death, and one must be very cautious about extrapolating these results to a living patient, considering the possible consequences of a forensic/police inquiry.

Along with the liver, the kidney plays a major role in lactate uptake and metabolism (20). Contrary to blood LDH, which represents a tetrameric protein of 135 kDa (21), blood lactates are fully filtered and almost completely reabsorbed by the proximal tubule (20). In the physiological context, urinary lactates may not rise to levels capable of producing this type of enzymatic interference, although this matrix has not been reported or studied in this context. In order to probe possible interference with the urine ethanol level, we determined the lactate concentration and LDH activity in the urine sample of the child. Results showed unexpected values: 51 mmol/L of lactate and 5,784 UI/L of LDH. This marked increase in urinary excretion might have been related to an extreme decrease in renal perfusion (20). The patient experienced acute kidney failure with acquired tubulopathy, in the context of his lactic acidosis due to the cardiac arrest. His severe metabolic acidosis could also have stimulated the renal uptake of lactate, despite reduction in renal blood flow (20).

The GC–FID analyses of urine and plasma samples for ethanol and other alcohols (like methanol) were systematically below the LOQ, enabling us to confirm that the enzymatic assay gave a false-positive result. We did not measure the urinary osmolality, which would have provided more support for the hypothesis of a false positive if the osmolarity gap did not match our ethanol values. On the basis of a plasmatic ultrafiltration protocol (10), we *a posteriori* filtrated 500 µL of the patient's urine with an Amicon Ultra 0.5 Centrifugal 100 K Filter (Merck, Darmstadt, Germany) adjusted to the molecular weight of LDH (21). After centrifugation (10 minutes, 14,000 g), the eluate was negative for ethanol when tested by the enzymatic assay method. This fast pre-treatment, requiring only about 15 minutes, led to a filtrate containing very little concentrations of LDH (69 U/L), as lactate alone cannot generate the artifact. This technique, which needs to be validated, could help the biologists in the case where a GC–FID testing system is not quickly available. The limitations evoked do not compromise the identification of excessive concentrations of LDH and lactate in the urine sample as the source of important biases in ethanol quantification using the enzymatic assay. For these patients, such analytical interference should be taken into consideration to critically appraise other enzymatic dosages requested that are based on the detection of NADH (22).

Conclusion

Acquired tubulopathy may have caused a urinary elevation of lactate and LDH leading to a false-positive ethanol concentration when using an enzymatic assay. For the first time in the literature, we highlight a new case of interference concerning ethanol quantification by enzymatic assay, in urine taken from a living but critically ill infant. We resolved this interference by using GC–FID and also by using an original urine ultrafiltration test before the enzymatic assay. Based on this case study, we propose a procedure that could be implemented to help identify the occurrence of false-positive ethanol concentrations. This procedure, which does not rely on additional experiments, could be used to assist the diagnostic process and prevent a medical error. Further studies would be of interest in order to establish the specific thresholds of urinary LDH/lactate concentrations that trigger the artifact and validate a urinary ultrafiltration protocol.

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Conflict of interest

None.

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