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CASE REPORT

Falsely elevated lactate in severe ethylene glycol intoxication

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ABSTRACT

A 29-year-old male presented at the emergency department of our hospital in a confused state. He had a history of psychoses and substance abuse. Physical examination revealed hyperventilation and abdominal tenderness. Blood gas analysis in the emergency department using an ABL 725 Radiometer analyser showed a severe metabolic acidosis with massive lactate elevation. Lactate acidosis due to mesenteric ischaemia was suspected. However, toxicology screening demonstrated ethylene glycol intoxication. Treatment with ethanol infusion and acute haemodialysis was started.
Repeated laboratory measurements using a clinical chemistry analyser showed minimal plasma lactate elevation. Falsely elevated lactate measurement is a little known phenomenon that can occur in ethylene glycol intoxication and can cause serious delay in diagnosis.
Therefore, elevated lactate concentrations measured on intensive care unit and emergency department blood gas analysers should be confirmed by a clinical chemistry analyser in the main laboratory in case of suspected ethylene glycol intoxication.

KEYWORDS

Ethylene glycol intoxication, lactate, blood gas analyser

What was known on this topic?
Ethylene glycol metabolites, especially glycolic acid and glyoxylic acid, can cause falsely elevated lactate levels and was described for the first time in 1999.

What does this add?
This case together with the additional experiments show that analytical interference of glycolic acid occurs on different instruments in many Dutch hospitals. The majority of blood gas analysis machines demonstrate falsely elevated lactate levels and all Radiometer blood gas analysis instruments are affected.

INTRODUCTION

Ethylene glycol is a colourless and odourless fluid that has a sweet taste. It is a component of antifreeze fluid, which is the major source of exposure in poisonings. Poisoning with ethylene glycol can occur through attempted inebriation, intentional self-harm, or unintentional ingestion. The signs and symptoms of ethylene glycol intoxication generally develop in three distinct stages. Stage 1 (30 min to 12 hours after ingestion)[1]: gastrointestinal and nervous system involvement; stage 2 (12 to 24 hours after ingestion): cardiopulmonary dysfunction with profound metabolic acidosis; stage 3 (24 to 72 hours after ingestion): acute renal failure which can be oliguric or anuric. The mortality of ethylene glycol intoxication is variable, ranging from 1 to 22%.[1]
Ethylene glycol metabolites are structurally similar to lactate and can cause artificial elevation of lactate concentration. This is especially the case when using blood gas machines in the emergency department and intensive care unit.[2-4] We present a case of ethylene glycol intoxication and demonstrate the substantial potential for misdiagnosis.

CASE REPORT

A 29-year-old man with a history of psychoses and substance abuse presented at the emergency department of our hospital in a confused state. His medication was

penfluridol with unknown dose. On examination his temperature was 36.1°C, the pulse 110 beats/min, the blood pressure 180/100 mmHg, and a score of 11 on the Glasgow Coma Scale (possible range, 3 to 15, with higher scores indicating better status). The respiratory rate was 50 breaths/min, and the oxygen saturation 100%. His pupils were equal, round, and reactive to light. Further physical examination revealed a diffusely tender abdomen and hypoactive bowel sounds. Testing of arterial blood in the emergency department using the ABL 725 blood gas analyser (Radiometer Medical, Denmark) indicated severe metabolic acidosis with a lactate concentration of 24 mmol/l. Full laboratory investigations showed an elevated creatinine, an anion gap of 25 mmol/l and osmolal gap of 6 mOsmol/kg (*table 1*). Both a chest radiograph and computed tomography (CT) scan of the head were normal and because of physical exhaustion mechanical ventilation was started. A normal CT scan of the abdomen ruled out that the lactate elevation was caused by mesenteric ischaemia. Urine toxicological screening indicated cannabinoid use. The urine sediment showed calcium oxalate crystals. Toxicological screening of serum at the time of admission showed an ethylene glycol level of 640 mg/l (10.3 mmol/l) and was negative for ethanol and methanol. Remarkably, a second plasma lactate level measured on an DxC-800 automated chemistry analyser (Beckman Coulter) in the hospital's main laboratory was only 4.7 mmol/l. Ethanol infusion, bicarbonate infusion and haemodialysis were initiated immediately and the patient was admitted to the intensive care unit. Shortly afterwards, he could be extubated. The renal failure has completely recovered.

PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

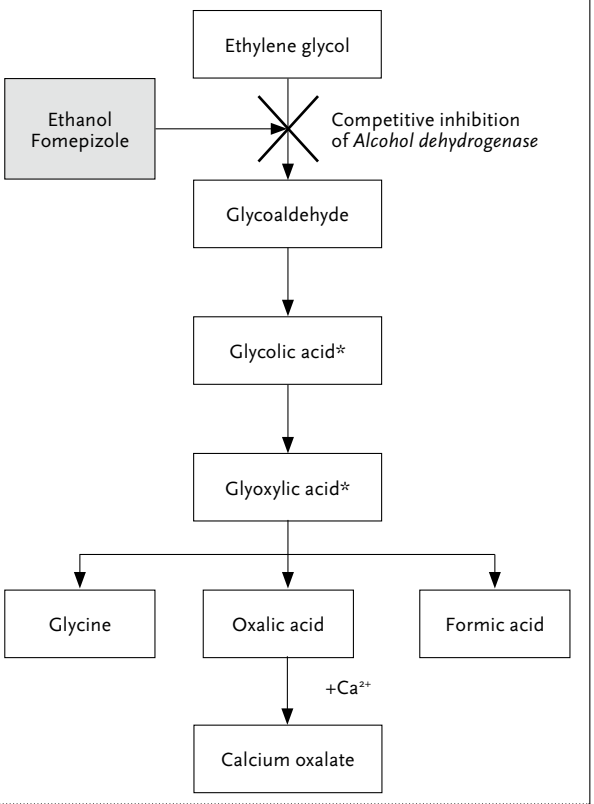
Ethylene glycol itself is relatively nontoxic, but it is metabolised by successive oxidations to toxic metabolites such as glycolic acid, glyoxylic acid and oxalic acid (*figure 1*).[5] The prominent metabolic acidosis and organ failure are caused by circulating glycolic acid. Oxalic acid may combine with ionised calcium in the plasma to form calcium oxalate crystals. Calcium oxalate precipitates in the renal tubules and is thought to cause renal failure.[6,7] Detection of typical calcium oxalate crystals in the urine supports the diagnosis of ethylene glycol intoxication but is a late and non-specific finding. The increased anion gap is attributable to ethylene glycol and its metabolites, the osmolal gap is only increased shortly after ethylene glycol ingestion.[8] The time span between ingestion and presentation in our case was more than 12 hours and explains the normal osmolal gap at presentation.

Table 1. *Results of laboratory tests*

Measurement		Time			
		13.00	16.00	17.00	20.00
Sodium	mmol/l	145	151	149	147
Potassium	mmol/l	5.1	4.7	4.0	4.1
Urea	mmol/l	6.1	7.1	-	8.4
Creatinine	µmol/l	135	160	-	187
Chloride	mmol/l	118	112	115	113
Calcium	mmol/l	2.37	2.23	-	-
Glucose	mmol/l	11.9	10.6	10.0	-
pH		7.11	7.09	7.11	7.45
pCO_2	kPa	0.8	7.2	4.7	2.7
pO_2	kPa	19.2	56.7	59.1	22.7
Bicarbonate	mmol/l	1.9	15.7	10.8	18.8
Oxygen saturation		98	99	100	99
Lactate dehydrogenase	U/l	983	-	-	547
Creatinine kinase	U/l	1515	-	-	763
Anion gap[1]	mmol/l	25	23	23	15
Osmolal gap[2]	mOsmol/kg	6	-	-	-
Lactate (POCT)[3]	mmol/l	24	23	23	
Lactate (Chemistry analyser)	mmol/l	4.7	4.3	2.6	3.2
Ethylene glycol	mg/l	640	-	-	234
Ethanol	g/l	0	-	-	0.9

[1]Anion gap = $[Na^+]$- ($[Cl^-]$+$[HCO_3^-]$); [2]Osmolal gap = measured osmolality- (2x $[Na^+]$ + [glucose] + [urea]); [3]POCT = point-of-care test; – = not done.

Figure 1. *Metabolic transformation of ethylene glycol*



***These metabolites can cause artificial lactate elevation using blood gas analysis machines.**

TREATMENT

The metabolism of ethylene glycol occurs primarily through alcohol dehydrogenase. Ethanol is a competitive substrate for alcohol dehydrogenase, which has greater affinity for ethanol than for ethylene glycol. Therefore ethanol is effective and inhibits the metabolism of ethylene glycol (*figure 1*). Although it is difficult to dose and has sedative and behavioural effects, ethanol is inexpensive and easily obtained. An alternative is fomepizole (4-methylpyrazole). It is also a competitive inhibitor of alcohol dehydrogenase and prevents the formation of toxic acid metabolites. It is easy to dose, easy to administer, and side effects are rare.[5] However it is expensive and not available in all hospitals. Haemodialysis is used to clear both ethylene glycol and its toxic metabolites more quickly.

DISCUSSION

A remarkable finding in our case was the discrepancy between the lactate level measured on a blood gas analyser in the emergency department and the plasma lactate level measured on a clinical chemistry analyser (*figure 2*). Slightly elevated lactate concentrations can be found in ethylene glycol intoxication,[9] but ethylene glycol does not cause excess lactate production.[4] Glycolic acid and glyoxylic acid can both cause artificial elevation of lactate.[2,10-13] Certain types of L-lactate oxidase allow cross reaction with these ethylene glycol metabolites. Especially blood gas analysers (using L-lactate oxidase) are affected,[2] while analysers using lactate dehydrogenase are free of interference. Measuring a 'lactate gap' using two different technologies (*figure 2*), only one of which is sensitive to glycolic acid, is suggested to be helpful in diagnosing advanced ethylene glycol poisoning.[2,12,14] However, when ethylene glycol intoxication is in the differential diagnosis, the ethylene glycol concentration should be directly measured.

We wished to gain insight into how widespread the problem of false lactate elevation due to glycolic acid interference is. Therefore samples were spiked with various concentrations of glycolic acid ([2.5 mmol/l] and [12.5 mmol/l]). The lactate values were determined in 30 Dutch hospitals using different clinical chemistry analysers and blood gas machines, including Radiometer ABL analysers (*figure 3*). The majority of measurements (81%) on blood gas analysers showed falsely elevated lactate levels. Radiometer blood gas analysers were available in 12 hospitals and were all affected. The chemistry

Figure 2. *Lactate gap*

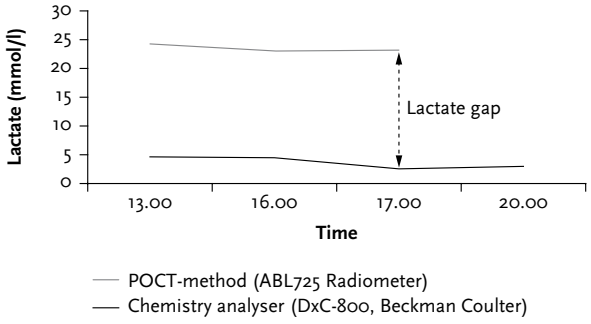
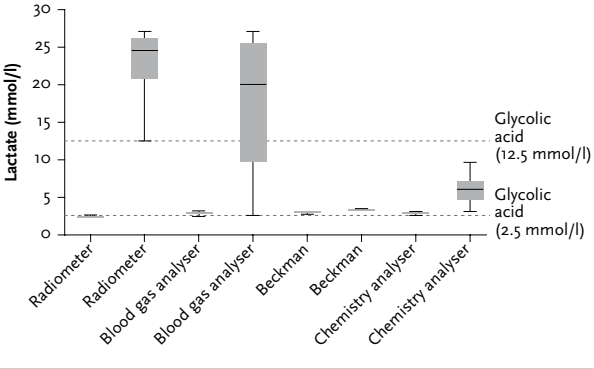


Figure 3. *The effect of glycolic acid upon blood lactate measurements using different analysers*



analysers demonstrated no or only minimally elevated lactate concentrations.

CONCLUSION

This case demonstrates the potential to misdiagnose ethylene glycol intoxication as a lactate acidosis due to falsely elevated lactate measurement. Although serum lactate elevations can be detected in patients with ethylene glycol intoxication, such elevations are usually minor. The falsely elevated lactate levels likely occur because of the incomplete specificity of L-lactate oxidase. Knowledge of this analytical interference is essential in every patient presenting with severe metabolic acidosis and massive lactate elevation. Elevated lactate concentrations on blood gas analysers should be confirmed by a chemistry analyser in case of suspected ethylene glycol poisoning. On the other hand, the lactate gap between measurements with different analysers can help in diagnosing a possible ethylene glycol poisoning.

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