An unconscious patient with extreme anion gap metabolic acidosis and an uneventful recovery

A Koopmans, M Hilkens, JG van der Hoeven

Department of Intensive Care, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Abstract. An unconscious patient was treated in our Intensive Care Unit for severe metabolic acidosis (pH 6.76 despite hyperventilation) due to presumed parent alcohol intoxication. The first calculated osmolar and anion gaps were 27 mOsm/kg and 48 mmol/l. She was mechanically ventilated and treated with sodium bicarbonate. Folic acid and thiamine were given intravenously. Ethanol infusion was administered immediately to inhibit alcohol dehydrogenase thus preventing toxic metabolite formation from the parent alcohols. Haemodialysis was started. High serum ethylene glycol and urine oxalate levels were subsequently confirmed. The patient recovered completely without any deleterious effects. Ethylene glycol intoxication can be life-threatening and needs immediate treatment. We discuss the initial diagnosis, pathophysiology, and treatment options.

Introduction

Metabolic acidosis with increased anion gap is commonly encountered in the emergency room. The main causes are lactic acidosis, ketoadicosis, acute renal failure and ingested toxins [1-3]. A thorough history, minute physical examination and appropriate laboratory evaluation are important for an immediate presumptive diagnosis. In some conditions, therapy has to be started before a final diagnosis is made [3-6]. We present a case report that underlines these important principles.

Case Report

A 51-year-old comatose woman was brought to the emergency department. The day before admission she went to bed early complaining of nausea. Her previous medical history was positive for alcohol and ethyl alcohol abuse and she was taking paroxetine for a depressive mood disorder. Physical examination showed a comatose patient (Glasgow Coma Scale 3) breathing spontaneously 25 times per minute, with a mean arterial pressure of 135 mmHg and a heart rate of 120 bpm. Her pupils were reactive and isocore with absent corneal reflexes. The rest of the physical examination and electrocardiogram showed no abnormalities.

The patient was intubated and mechanically ventilated. An arterial blood sample showed the following: pH 6.76, PaO\textsubscript{2} 44.1 kPa, PaCO\textsubscript{2} 3.4 kPa, bicarbonate 3.5 mmol/l, base excess -32.1 mmol/l, sodium 151 mmol/l, potassium 5.3 mmol/l, chloride 105 mmol/l, ionized calcium 1.22 mmol/l, magnesium 1.21 mmol/l, phosphate 3.84 mmol/l, lactate 3.7 mmol/l, glucose 14.5 mmol/l, urea 6.0 mmol/l, creatinine 159 mmol/l, albumin 43 g/l, haemoglobin 10.2 mmol/l, ethanol < 0.1 g/l. A computer tomography scan showed no intracranial abnormalities.

The patient was admitted to our Intensive Care Unit (ICU) for further diagnostics and treatment. As the increase in lactate level and the degree of renal failure did not explain the severity of the metabolic acidosis, another diagnosis was pursued. Urine sediment showed no calcium oxalate crystals, although later on the urine oxalic acid concentration appeared to be increased (3.3 mmol/24 hours – reference 0.6 mmol/24 hours). Funduscopy showed no optic disc hyperaemia or oedema.

The first calculated anion gap was 48 mmol/l ([Na\textsuperscript{+}] + [K\textsuperscript{+}] – [Cl\textsuperscript{–}] – (HCO\textsubscript{3}\textsuperscript{–})), no correction needed for a normal plasma concentration of albumin), and the first osmolar gap was 27 mOsm/kg (measured serum osmolality – 2 x [Na\textsuperscript{+}] – [urea] – [glucose]), at 30 and 120 minutes after presentation (Table 1). Her husband suspected alcohol abuse and acknowledged the presence of a large amount of antifreeze at home. These findings suggested an auto-intoxication with parent alcohols (methanol, ethylene glycol). While waiting for confirmation, we treated the patient for presumed parent alcohol intoxication by means of ethanol infusion, haemodialysis, sodium bicarbonate, folic acid and thiamine. Haemodialysis was started within four hours after presentation and was stopped after eight hours of dialysis when the anion gap and pH were normalized.

The measured blood concentration of ethylene glycol was 0.6 g/l. Acetone, methanol and salicylic acid were not present.

The next day the patient awakened slowly. She was extubated on day 2 after admission and transferred to the ward. As a result of acute renal failure she needed several sessions of intermittent haemodialysis. After two weeks, she was discharged with no neurological deficits and near normal renal function.

Discussion

Parental intoxications are known to cause accidental and intentional intoxications in humans. These alcohols are frequently found in automotive antifreeze, de-icing solutions and other industrial products [1, 3-5, 7, 8]. Ethylene glycol is a sweet taste, is highly intoxicating and is therefore sometimes used as a cheap substitute for alcohol, as was the case in our patient. Ingesting even relatively small amounts of methanol and ethylene glycol can produce significant toxicity such as blindness, impaired renal function and even death [3-5, 7]. An important predictor of acute renal failure and mortality in ethylene glycol intoxication is the time that elapses between ingestion and recognition of this intoxication. The mortality of ethylene glycol intoxication ranges from 1 to 22% and is highest in patients with either a blood pH < 7.1 or
Three classical stages are described in ethylene glycol intoxication. The first neurological stage is characterized by depression of the central nervous system (CNS) and lasts for 0.5 to 12 hours. Clinical features are slurred speech, ataxia, lethargy, somnolence, nausea and vomiting. In stage 2, metabolic acidosis causes cardiopulmonary depression. This lasts for 12 to 72 hours and its clinical signs are hyperventilation, pulmonary infiltrates, tachycardia, hypertension and congestive heart failure. Hypocalcaemia may cause hyperreflexia, muscle spasms and QT interval prolongation. Acute renal injury heralds the gestive heart failure. Hypocalcaemia may cause hyperreflexia, muscle

in patients where treatment is delayed by > 10 hours. Several reports clearly show that treatment is often initiated too late [9-11].

Ethylene glycol is readily absorbed after ingestion with peak serum concentrations after 1 to 4 hours. It is water-soluble, not protein-bound and is metabolized by the liver. Without treatment, the elimination half-life of ethylene glycol is 3-8 hours. The unmetabolized portion is the main cause of the osmolar gap, whereas the toxic metabolites cause the anion gap. Patients who present late after ingestion may have a normal osmolar gap as a result of ethylene glycol metabolism [3, 4]. Our patient presented approximately 18 hours after ingestion. The greatly increased osmolar gap of 27 mOsm/kg and anion gap of 46 mmol/l, point to a much higher level of ingestion than the measured serum concentration of 0.6 g/l would suggest.

Approximately 20% of ethylene glycol is excreted unchanged by the kidneys. The remainder is oxidized by alcohol dehydrogenase into glycoaldehyde, glycolic acid, glyoxylic acid and finally into oxalic acid. Because of the rate-limiting conversion of glycolic to glyoxylic acid, glycolic acid is responsible for the metabolic acidosis. The reduction of nicotamide adenine dinucleotide (NAD) to dihydronicotinamide adenine dinucleotide (NADH) leads to a high NAD to NAD ratio, which facilitates the conversion of pyruvate to lactate (Figure 1) [3, 4]. The metabolism of glycolic acid to oxalic acid may exacerbate the toxic effects. Oxalic acid is deposited perivascularly as calcium oxalate crystals in almost every tissue. This also explains the hypocalcaemia. The exact toxic mechanism is not known. Renal tubular injury may be caused by accumulation of calcium oxalate crystals. These crystals are present in 50% of ethylene glycol intoxications. However, the amount of necrosis correlates poorly with the amount of oxalate crystal deposit. This suggests another mechanism of renal injury. Our patient also showed an increased concentration of oxalic acid in her urine, but ultimately had no significant loss of renal function. [3, 7].

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At first, treatment is supportive and includes airway protection, circulatory support, correction of metabolic disturbances and control of seizures. Hydration and sodium bicarbonate can be used both to correct metabolic acidosis if the pH is below 7.3, and to promote excretion of ethylene glycol and glycolic acid by alkalization of the urine. Deprotonation of the acidic metabolites prevents these metabolites from penetrating and injuring end-organ tissues [1, 3, 4]. Hypocalcaemia should only be corrected in symptomatic patients as calcium suppletion may increase the formation of calcium oxalate crystals [4]. Ethylene glycol is rapidly absorbed from the gastrointestinal tract and therefore, induced emesis, lavage of gastric contents and administration of activated charcoal are not recommended. The latter two measures may only be implemented immediately (within 1 hour) after ingestion, or if the presence of a co-ingestant is suspected [3, 4].

Thiamine and pyridoxine can be used to convert glycolytic acid to a non-toxic metabolite instead of formation of oxalic acid. Thiamic acid should be given intravenously four times a day at a dose of 100 mg until serum concentrations of ethylene glycol are no longer measurable. Pyridoxine should be given intravenously four times a day at a dose of 50 mg for no longer than 24 hours, as pyridoxine may induce a toxic sensory peripheral neuropathy at higher concentrations [1, 3, 4, 7].

Two antidotes are currently used in the treatment of ethylene glycol intoxication. Ethanol and fomepizole are used separately to inhibit alcohol dehydrogenase (ADH). This inhibition blocks bioactivation of ethylene glycol to its toxic acid metabolites. Several indications for inhibition of alcohol dehydrogenase exist. These include a plasma concentration > 0.2 g/l, in combination with recent ingestion and an osmolar gap > 10 mOsm/kg. Another potential indication is a high degree of clinical suspicion and two of the following: pH < 7.3, serum bicarbonate < 20 mmol/l, osmolar gap > 10 mOsm/kg or the presence of urinary oxalate crystals [3, 4, 12-14]. A properly equipped toxicological laboratory is therefore essential in order to measure ethanol and other parent alcohol concentrations 24 hours after ingestion. Ethanol has a 100-fold higher affinity to ADH than ethylene glycol. Ethanol is given intravenously at a loading dose of 0.6 g/kg and at a constant infusion rate of 80 to 160 mg/kg/hour to maintain serum
levels of 1.0 g/l. Serum levels should be checked every 1 to 2 hours until steady state, and 2 to 4 hours thereafter. During haemodialysis, administration of ethanol should be increased by 2- to 3-fold [3-5, 15].

The affinity of fomepizole to ADH is 500- to 1000-fold higher than that of ethanol [16]. The intravenous loading dose is 15 mg/kg, followed by 10 mg/kg every 12 hours for 48 hours, and thereafter 15 mg/kg every 12 hours until serum ethylene glycol concentration < 0.2 g/l. The administration interval should be reduced to 4 hours during haemodialysis [3, 4, 8, 16].

Fomepizole has several advantages over ethanol in the treatment of ethylene glycol intoxication. Fomepizole has more predictable kinetics and there is no need for blood monitoring. It has minimal side effects, most commonly seen are dizziness, headache, nausea and unpleasant taste. It does not cause CNS depression, and some patients treated with fomepizole do not need to be observed in an ICU. The disadvantages of fomepizole are its high cost of about $1000 per gram and its relatively short shelf life of 3 years [3, 4, 17]. Although fomepizole costs about $4000 per case, it may also yield cost savings such as a reduction in the number of laboratory measurements and length of stay in the ICU, and a reduction in the need for haemodialysis [7, 8].

Ethylene glycol and its metabolites are very effectively cleared by haemodialysis. The half-life of the toxic metabolite glycolic acid is reduced by a factor of 6. Indications for haemodialysis include metabolic acidosis (pH < 7.3), respiratory failure, hypotension, acute renal failure and metabolic derangements unresponsive to conventional therapy. Ethylene glycol levels > 0.5 g/l are also an accepted indication for haemodialysis, but during treatment with fomepizole, even higher levels may be accepted without initiating haemodialysis. Several patients with normal renal function and no metabolic acidosis were successfully treated without haemodialysis [3, 4, 8, 12, 16, 18-20]. Due to the readily availability of ethanol and its unproven superiority, we did not use fomepizole in our patient. Until further evidence becomes available, we recommend ethanol infusion and haemodialysis as a valuable cost-effective therapy in hospitals where this mode of treatment is readily available [14, 21, 22].

In conclusion, ethylene glycol intoxication can result in serious sequelae and death. In suspected cases immediate treatment is indicated. A high anion gap in combination with an increased osmolar gap may give the physician the first important clue. Immediate treatment includes airway protection, circulatory support and correction of metabolic disturbances. Hydration and sodium bicarbonate infusions can be used to correct metabolic acidosis. Ethanol infusion must be considered to prevent formation of metabolic metabolites by inhibiting ADH. Haemodialysis is used to dialyse ethylene glycol and its toxic metabolites. Fomepizole may be considered as an alternative to ethanol in hospitals where haemodialysis is not available.

Our patient presented with an extreme metabolic acidosis but eventually left the hospital without any adverse sequelae. Presumably, immediate treatment while awaiting the results of the serum concentrations of parent alcohols played a role. With a high index of suspicion, patients with a presumed severe parent alcohol intoxication should be fully resuscitated and an immediate ethanol infusion started before the toxicology results return from the laboratory. We also suggest that the potential benefits of early haemodialysis in severe cases of intoxication outweigh the small risk that this diagnosis may not be confirmed.

References