CASE REPORT

Methanol Poisoning: A Diagnostic Challenge in High Anion Gap Metabolic Acidosis

*Yin Ye Lai[1,2], Chee Hoe Lim[2], Subashini C. Thambiah[1], Intan Nureslyna Samsudin[1]

[1] Department of Pathology, Faculty of Medicine & Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia.
[2] Department of Pathology, Hospital Kuala Lumpur, Ministry of Health Malaysia.

ABSTRACT

A 47-year-old gentleman was admitted with decreased responsiveness and vomiting. Clinically, he had altered mental status, pupils sluggish to light and laboured breathing. Thoracoabdominal examination and computed tomography of the brain were normal. Preliminary laboratory testing revealed high anion gap metabolic acidosis (HAGMA). Blood acetaminophen and urine paraquat were negative. Serum salicylate was not measured however respiratory alkalosis typical of salicylate intoxication was absent. Normoketonaemia and normoglycaemia rendered diabetic ketoacidosis improbable, whilst uraemia was ruled out as renal profile was only moderately impaired. Raised plasma lactate was inadequate to account for the magnitude of HAGMA, leading to a suspicion of ethylene glycol or methanol poisoning. Despite early treatment with intravenous ethanol, the patient died at day three of admission. Blood methanol concentration which was obtained on admission and reported three days later by the referral toxicology lab affirmed the diagnosis of methanol poisoning. Methanol poisoning can be challenging in situations where patient is obtunded and methanol analysis not widely available.
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Corresponding Author:
Lai Yin Ye, MPath
Email: laiyinye@upm.edu.my
Tel: +603-97692375

INTRODUCTION

Methanol is a highly toxic substance widely used as a solvent in cleaning solutions, anti-freeze and dyes (1). Methanol intoxication occurs usually from unintended consumption of products containing methanol (2). Even though rare, methanol toxicity carries a lethal risk of mortality and morbidity (2).

CASE REPORT

A 47-year-old gentleman with no comorbid was brought to the hospital with altered behaviour, generalised abdominal discomfort and persistent vomiting. Upon admission, his Glasgow Coma Score was 4 and he had deep laboured breathing. He was afebrile, but hypotensive, tachycardic and tachypneic. Pupils appeared equal, however was mydriatic and sluggish to light response. Clinical examinations of the cardiovascular, respiratory and gastrointestinal systems were unremarkable. An immediate arterial blood gas showed high anion gap metabolic acidosis (HAGMA) with further laboratory investigations performed to determine the underlying cause (Table I). Blood methanol was sent to a referral laboratory for analysis and results were not immediately available. A bedside echocardiogram, lung and abdominal ultrasound were normal while urgent computed tomography (CT) brain ruled out cerebrovascular accident. This patient was intubated, ventilated, and started on intravenous ethanol for suspected methanol poisoning. Despite early treatment, he died at day three of admission. Blood methanol concentration reported by the referral laboratory on the same day of patient's death revealed a concentration of 24.1 mg/dL, hence affirming the diagnosis of methanol toxicity.

DISCUSSION

Upon oral consumption, methanol which has a volume of distribution similar to body water is swiftly absorbed, leading to maximal serum concentration within an hour (1). Alcohol dehydrogenase (ADH) enzyme metabolises methanol to formaldehyde and later to its major toxic metabolite- formate and formic acid (1). Elimination of formate follows zero-order kinetics and accumulates rapidly in the absence of treatment. Depending on the absorbed dose, a latent period between 6-24 hours may happen before the initial phase of methanol toxicity is identified. The first phase is characterised by generalised weakness,

Table I : Baseline blood and urine investigation results

Parameter	Blood results on admission	Reference Interval
Full blood count		
Hb, g/dL	16.0	13.0-17.0
WBC, 10^9 /L	18.3	4.0-10.0
Platelet, 10^9/L	283	150-450
Renal Profile		
Urea, mmol/L	8.1	2.8-8.1
Sodium, mmol/L	136	136-145
Potassium, mmol/L	8.2	3.4-4.5
Chloride, mmol/L	103	98-107
Creatinine, µmol/L	215	44-80
eGFR (2009 CKD-EPI) (ml/min/1.73 m^2)	32	>90
Liver function test		
Total protein, g/L	99	66-87
Albumin, g/L	50	35-52
Globulin, g/L	49	20-36
Albumin Globulin ratio	1.0	0.8-2.0
Total bilirubin, umol/L	6	<21
Alanine Aminotransferase, U/L	24	10-35
Alkaline Phosphatase, U/L	161	35-104
Arterial blood gas		
pH	6.718	7.35-7.45
pCO2, mmHg	47.7	35-45
pO2, mmHg	47.3	75-100
HCO3, mmol/L	6.5	22-28
BE, mmol/L	-29.7	-2 - +2
Other investigations		
Total Calcium, mmol/L	2.33	2.20-2.55
Magnesium, mmol/L	1.44	0.66-0.99
Phosphate, mmol/L	4.14	0.81-1.45
Lactate, mmol/L	12.8	0.5-2.2
Blood ketone, mmol/L	0.3	<0.5
Blood glucose, mmol/L	8.8	3.0-6.1
Serum Acetaminophen level, ug/ml	<5.0	<5.0
Urine for Paraquat	Not detected	Not detected
Urine for Amphetamine, Methamphetamine, Morphine, Benzodiazepine, Cannabinoids	Not detected	Not detected

nausea, inebriation and dizziness (1). These CNS effects indicate central nervous system depression, mediated through enhanced gamma-aminobutyric acid (GABA) action and retardation of N-Methyl-D-Aspartic acid (NMDA) glutamate receptors (3). Development of HAGMA, Kussmaul breathing, mydriasis and loss of photomotor reflex observed in our patient implies that accumulation of formate has occurred, placing him in the second phase of methanol toxicity (1). Lastly, neuronal injury, optic nerve damage, retinal necrosis and basal ganglia haemorrhage are seen in the final phase of methanol toxicity (1).

Upon encountering our patient who was severely obtunded with a non-specific clinical presentation, laboratory investigations became the beacon of light to our team of clinicians in guiding them to the final diagnosis. The most striking initial biochemical result was metabolic acidosis. Both hypermagnesaemia and hyperphosphataemia were likely contributed by metabolic acidosis as the increase in hydrogen ions within the systemic circulation causes influx of magnesium and phosphate ions from the intracellular to extracellular compartment (4). Because the metabolic acidosis was of high anion gap type, the provisional diagnosis was narrowed down based on subsequent laboratory findings. Pyroglutamate acidosis was ruled out when blood acetaminophen was not detected. Serum salicylate was not measured however respiratory alkalosis typical of salicylate intoxication was absent. Urine for paraquat was negative, so were the screening tests for common drugs of abuse such as amphetamine, methamphetamine, morphine, benzodiazepine and cannabinoids, hence excluding these potential causes of HAGMA. The presence of normoglycaemia and normoketonaemia rendered diabetic ketoacidosis unlikely. Uraemic acidosis was improbable in the setting of an acute kidney impairment with normal plasma urea and moderately raised plasma creatinine. Plasma lactate was elevated but lactic acidosis alone could not account for the magnitude of HAGMA (Anion gap: 35 mmol/L), making ethylene glycol or methanol intoxication a highly possible aetiology.

While most of these differentials of HAGMA can be ruled out from physical examination and routine biochemical tests, methanol and ethylene glycol intoxication often have similar clinical manifestations (neurologic abnormalities, cardiopulmonary and renal dysfunction) (5) and are difficult to distinguish apart especially when blood osmolality and methanol analysis are unavailable. There are however two important differentiating points. Clinically, retinal damage with blindness is only seen in methanol intoxication due to the accumulation of its metabolite-formate. Biochemically, hypocalcaemia and the pathognomonic urine calcium oxalate crystals are only perceivable in ethylene glycol poisoning due to breakdown of its metabolite -glycolic acid into oxalic acid, which then binds calcium to form insoluble crystals in urine (5). In the case of our patient, upon ruling out the other potential causes of HAGMA as described, the findings of reduced papillary response to light as well as absence of hypocalcaemia favoured methanol rather than ethylene glycol intoxication.

Osmolal gap, known as the difference between measured and calculated osmolality, rests on the initial osmolality and the rise in osmolality generated by osmotically active substances in systemic circulation at time of sampling (2). Normal osmolal gap is defined as less than 10 mOsm/kg/H_2O (5). Osmolal gap although not measured in our case, is postulated to be raised due to the accumulation of osmotically active methanol in the blood. It is interesting to note that despite a good association between methanol concentration and osmolal gap, the osmolal gap may remain normal if the methanol has been completely metabolised in delayed blood sampling, or when baseline osmolal gap is negative (5).

Gas or liquid chromatography is the current gold standard for determination of blood methanol concentration (5). Because this method is labour-intensive, time-consuming, expensive and only available in a few specialised toxicology laboratories in the country, blood methanol samples need to be outsourced and are usually not immediately available.

Bedside dispstick impregnated with alcohol oxidase that allows detection of not only methanol, but ethanol and ethylene glycol; as well as an enzymatic method using formate dehydrogenase and nicotinamide adenine dinucleotide to indirectly estimate methanol concentration by measuring serum formate have been described in the literature (5). These methods nevertheless require extensive validation and are yet to be available for clinical use (5). Unavailable blood methanol and osmolality analysis is not unusual in smaller laboratories with limited financial and human resources like to ours. This implies that doctors must have a high index of suspicion and rely on clinical examination or other laboratory investigations to make a diagnosis of methanol toxicity.

General supportive care with mechanical ventilation, intravenous fluids, vasopressors and correction of acidosis are important measures in methanol toxicity (1). Dialysis is the most effective method to promptly remove lethal metabolites in severe intoxication cases especially when pH seems refractory to base treatment or when there is evidence of end organ damage (3). Administration of fomepizole or ethanol

such as in our case aims to delay or inhibit toxic metabolite generation when most methanol remains in the unmetabolised state (5). Although Fomepizole is preferred as an antidote because of its higher affinity (500-1000 times superior affinity for ADH enzyme) and longer duration of action (1), ethanol is used in our centre due to its cheaper cost and easy accessibility (5).

CONCLUSION

Methanol poisoning can be challenging in situations where patient history is incomplete and toxic alcohol levels are not widely available. Blood methanol measured using gas chromatography in reference laboratories are often delayed. In these circumstances, routine biochemical investigations such as HAGMA is pertinent to guide further investigations. Early treatment with alcohol dehydrogenase enzyme inhibitors is crucial to reduce the degree of irreversible destruction by formate.

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