

# Challenges of managing toxic alcohol poisoning in a resource-limited setting

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Accepted 21 May 2013

## ABSTRACT

We present a series of patients with profound metabolic acidosis admitted to the Role 3 Medical Treatment Facility, Camp Bastion, Afghanistan, in 2012. A police service breath alcohol analyser, calculation of the osmolar gap and urine microscopy assisted in diagnosing methanol poisoning. The challenge of diagnosing and managing toxic alcohol poisoning in this resource-limited setting is discussed. We believe this is the first description of using a breath alcohol analyser to assist a diagnosis of methanol poisoning.

## INTRODUCTION

It is unusual to encounter methanol poisoning in the UK—only 11 cases were discussed with the National Poisons Information Service in 2008.<sup>1</sup> However, large outbreaks of toxic alcohol poisonings are regularly described in other developed and developing countries.<sup>2–3</sup> In March 2013, news agencies reported over 300 poisonings and 50 deaths attributed to methanol in Tripoli, Libya.<sup>4</sup>

Toxic alcohol poisoning has been previously managed by deployed UK clinicians.<sup>5–6</sup> However, this clinical scenario is not included in Clinical Guidelines for Operations<sup>7</sup> and clinicians are unlikely to have significant experience of managing toxic alcohol poisoning in their UK practice.

## Background

Methanol is a clear, sweet and colourless liquid present in numerous household products: anti-freeze, lighter fluid and as a denaturant added to ethanol to discourage abuse (methylated spirits). Once ingested, methanol is initially metabolised to formaldehyde by alcohol dehydrogenase and then to formic acid by aldehyde dehydrogenase.<sup>8</sup> Formic acid causes a metabolic acidosis and directly inhibits mitochondrial cytochrome oxidase leading to cellular hypoxia and hyperlactataemia, further exacerbating the acidosis.<sup>9</sup>

Treatment of methanol poisoning is aimed at:<sup>8–10–11</sup>

- Managing the acidosis
- Preventing further metabolism of methanol
- Enhancing the metabolism of formic acid
- Enhancing the elimination of methanol, formaldehyde and formic acid.

The acidosis is managed with high-dose intravenous sodium bicarbonate and, when available, continuous veno-venous haemodiafiltration (CVVHDF).

Ethanol and fomepizole (4-methylpyrrole) are competitive inhibitors of alcohol dehydrogenase and are used to prevent further metabolism of methanol, which is then excreted unchanged via the kidneys and lungs.<sup>10–11</sup> Intravenous and enteral ethanol have been successfully used to manage

## Key messages

- ▶ Calculation of the osmolar gap is useful in the differentiation of metabolic acidosis (particularly in the absence of a chloride concentration).
- ▶ A police service breath alcohol analyser may support a diagnosis of toxic alcohol poisoning.
- ▶ Contribution of different alcohols to the osmolar gap can be easily calculated.
- ▶ Adaptability and improvisation are important skills for a military doctor.

toxic alcohol poisoning;<sup>12–13</sup> however, ethanol causes central nervous system depression (thereby confounding neurological assessment) and requires regular blood level monitoring. Additionally, enteral ethanol has unpredictable bioavailability. Conversely, intravenous fomepizole has predictable bioavailability, is safe, effective, does not affect neurological function and may obviate the need for CVVHDF in less severe poisoning.<sup>14–15</sup> Fomepizole is recommended by both the American Academy of Clinical Toxicology<sup>8</sup> and the UK College of Emergency Medicine<sup>16</sup> as a first-line treatment for methanol poisoning.

Formic acid is slowly converted in humans to water and carbon dioxide by 10-formyl tetrahydrofolate synthetase. This enzyme is folic acid dependent and its reduced (active) form, folinic acid, is recommended as an adjunct to methanol poisoning.<sup>11</sup> The only human study examining the benefit of folinic acid did not demonstrate improved outcome and its clinical benefit is therefore questionable.<sup>2</sup>

CVVHDF is required to enhance the elimination of methanol, formaldehyde and formic acid while also independently correcting the acidosis.<sup>11</sup>

The Role 3 Medical Treatment Facility (R3MTF) has a stock of intravenous sodium bicarbonate, but does not routinely have a CVVHDF capability, ethanol (either intravenous or enteral), the ability to measure serum concentrations of alcohols (either ethanol or methanol), fomepizole, folinic acid or the ability to measure serum chloride concentration (required to calculate the anion gap). Investigation and management of methanol poisoning in this environment therefore requires improvisation and adaptation of standard practice.

## CASE REPORTS

Three Afghan men, all approximately 25-years-old, presented to the R3MTF in Afghanistan. One was

**To cite:** Barnard E, Baladurai S, Badh T, et al. *J R Army Med Corps* Published Online First: [please include Day Month Year] doi:10.1136/jramc-2013-000117

## Case report

**Table 1** Initial blood analysis, osmolar gap, breathalyser results and doses of sodium bicarbonate administered to three patients with methanol poisoning

	Patient A (venous)	Patient B (arterial)	Patient C (arterial)
pH	6.58	6.75	6.77
pCO <sub>2</sub> (kPa)	12.8	4.6	1.72
pO <sub>2</sub> (kPa)	1.73	8.0	28.1
SaO <sub>2</sub>	95%	95%	93%
SvO <sub>2</sub>	84%	61%	30%
SaO <sub>2</sub> to SvO <sub>2</sub>	0.88	0.64	0.32
Base deficit	29	>30*	>30*
NaHCO <sub>3</sub> (mmol/L)	9.2	4.9	1.9
Lactate (mmol/L)	15.0	16.0	16.9
Sodium (mmol/L)	150	142	147
Potassium (mmol/L)	8.2	10.2	6.6
Urea (g/dL)	4.4	3.8	3.8
Glucose (mmol/L)	9.8	12	18.2
Calculated osmolarity	330.6	320.2	329.2
Serum osmolality	486	401	408
Osmolar gap	155.4	80.8	78.8
Breathalyser	Positive	Positive	Positive
NaHCO <sub>3</sub> administered in the first 24 h	8×50 ml vials 8.4% and 1.5 L 1.26% NaHCO <sub>3</sub>	7×50 ml vials 8.4% and 1.5 L 1.26% NaHCO <sub>3</sub>	14×50 ml vials 8.4% and 1.5 L 1.26% NaHCO <sub>3</sub>

\*30 is the upper limit of the iSTAT machine.

in asystolic cardiac arrest (Patient A) and two were in peri-arrest with profound hypotension, reduced consciousness and hypothermia. A limited history of prior nausea and abdominal pain was described.

The patient in cardiac arrest had a return of spontaneous circulation after 6 min of cardiopulmonary resuscitation and 2 mg of adrenaline. Point-of-care blood analysis (iSTAT, Abbott Laboratories, Illinois, USA) demonstrated profound acidosis, hyperkalaemia, hyperlactataemia and high venous oxygen saturations (Table 1). The ECGs of all patients were consistent with hyperkalaemia (Figure 1) and all had mydriatic pupils, a divergent gaze and Glasgow Coma Scale scores of between 3 and 8. All had Kussmaul respiration with no detectable breath odour. In the emergency department, they underwent rapid sequence induction of anaesthesia, tracheal intubation and

ventilation, intravenous sodium bicarbonate (Table 1) and standard therapy to manage hyperkalaemia (calcium chloride, insulin and dextrose).

### Management in the intensive care unit

Methanol poisoning was suspected after exclusion of other causes of metabolic acidosis by: laboratory assays (absence of elevated blood lipids, calculation of the osmolar gap), urine analysis (absence of calcium oxalate crystals associated with ethylene glycol poisoning), rapid fall of high venous oxygen saturations (excluding cyanide) and the use of a police service breath alcohol analyser (which identified the presence of an alcohol) (Table 1). The day after admission, methanol poisoning was confirmed by the discovery of an empty bottle of methanol at the patients' accommodation (Figure 2).

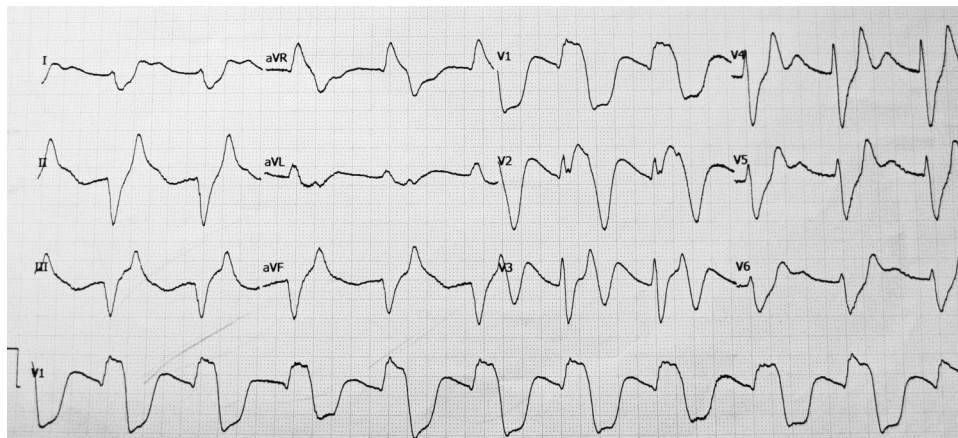
Fortuitously, the R3MTF pharmacy held stock of commercial ethanol that had been obtained the previous year to manage a toxic alcohol poisoning. All patients were commenced on treatment with enteral ethanol in accordance with guidance from the National Poisons Information Service (Figure 3).<sup>11</sup> This strategy involved a loading dose of 800 mg/kg followed by 200 mg/kg/h (non-habitual alcohol drinker on dialysis). We estimated a weight of 80 kg and each patient received a double measure (50 mL) of 40% ethanol per hour (via nasogastric tube).

A single CVVHDF machine with limited dialysate was available from the Royal Air Force Critical Care Air Support Team. Patient A was not responding favourably to initial management and a decision was made to optimise the management of Patients B and C by alternating the single CVVHDF between them every 4 h.

### Further management and clinical outcomes

Over the first 24 h, Patient A's physiology continued to deteriorate despite increasing doses of inotrope and vasopressor therapy. After a multi-disciplinary team meeting (MDT) and a discussion with the patient's family, the treatment focus shifted to palliative care and he died shortly afterwards.

In a period of 48 h after commencement of intravenous ethanol therapy, a US lab near Kabul was able to provide us with a measurement of blood ethanol levels. This gave vital assurance of achieving a therapeutic ethanol level (100–150 mg/dL) and also allowed estimation of the concentration of methanol (and its osmolar-active metabolites) remaining in each patient by calculating the osmolar gap not due to ethanol (Table 2). Consequently, we were able to determine when to



**Figure 1** Patient A's ECG demonstrating changes of hyperkalaemia.

**Figure 2** The label from the bottle of Iranian methanol. A rough translation reads 'if you drink this you will die'. Note the faint 'skull and cross bones' figure on the background of label.



consider stopping enteral ethanol therapy, that is, when the calculated methanol concentration fell below a harmful level (20 mg/dL).

Prior to respiratory weaning, the patients underwent CT scanning of the head (Figures 4A and B). Both scans demonstrated classical changes of methanol poisoning with putaminal

haemorrhagic necrosis and subcortical white matter lesions.<sup>18 19</sup> Patient B's scan demonstrated such severe changes that, coupled with minimal neurological recovery off sedation, the chance of recovery was remote. After a further MDT and discussion with his family, the focus changed to palliation and he died 4 h after cessation of active management. The CT changes in Patient C

**Figure 3** Commercial ethanol ready to be administered enterally to patients on ICU.



## Case report

**Table 2** A summary of characteristics of alcohol poisonings

	pH	Anion gap	Glucose	Osmolar gap	Contribution to osmolar gap*
Ethanol	N	N	N	High	(Ethanol)/3.8
Isopropanolol	N	N	N	High	(Isopropanolol)/6.0
Methanol	Low	High	N/high	High	(Methanol)/3.2
Ethylene glycol	Low	High	N	High	(Ethylene glycol)/6.2

\*The contribution to the osmolar gap is estimated by taking the plasma concentration of the alcohol (mg/dL) and dividing by the number indicated. For example, a serum ethanol concentration of 80 mg/dL will contribute 21 to the osmolar gap (as 80 mg/dL divided by 3.8=21). The metabolites of some alcohols also contribute to the osmolar gap and are unmeasured.<sup>17</sup>

were less severe and he was successfully weaned from the ventilator. Despite an initially slow neurological recovery he was ambulant 72 h later with no demonstrable motor dysfunction. He did however have severe visual impairment that was limited to light/dark perception and visualisation of large structures. He was discharged to an Afghan hospital in Kabul, using a military physician-led aeromedical flight, 7 days after admission to the R3MTF. Further outcome information is not available.

## DISCUSSION

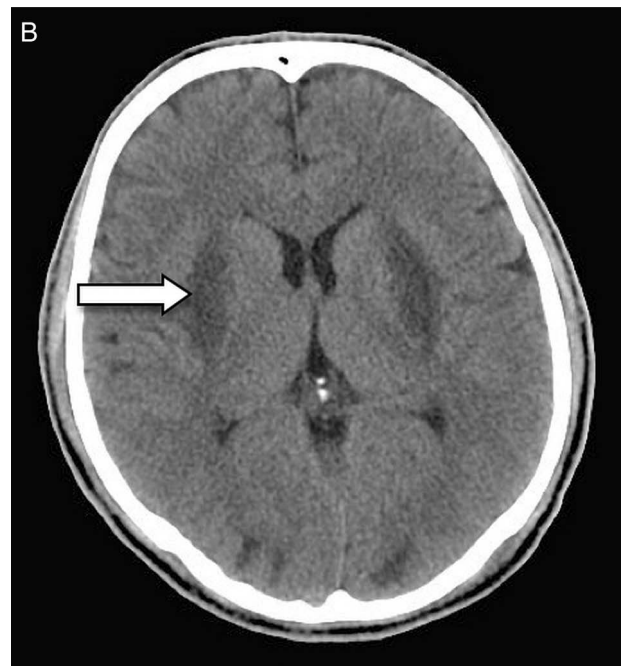
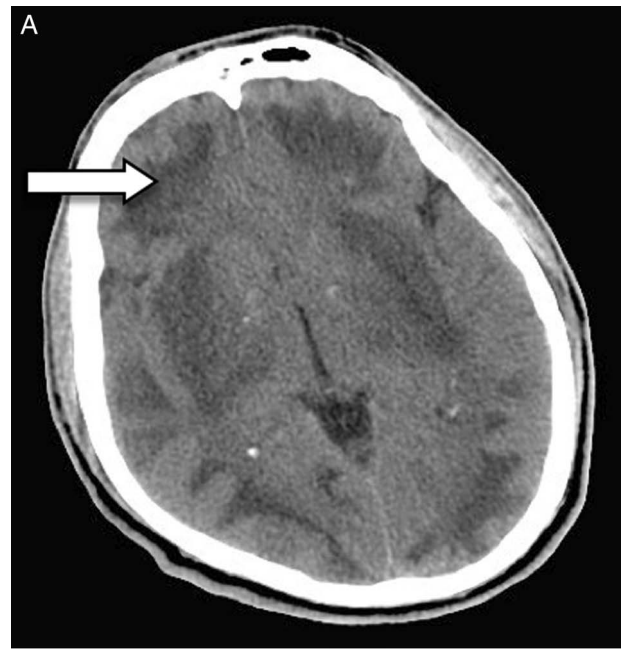
## Diagnostic challenge

On admission, the differential diagnosis included diabetic ketoacidosis, salicylate poisoning, acute kidney impairment, cyanide poisoning (which causes dilated pupils, metabolic acidosis, hyperlactataemia and high venous oxygen saturations) and toxic alcohol ingestion (including methanol and ethylene glycol). The initial high venous oxygen saturations (Table 1) rapidly fell which is inconsistent with cyanide poisoning. Diabetic ketoacidosis was felt to be extremely unlikely in three, simultaneous patients (despite the hyperglycaemia). Salicylate poisoning and renal impairment were excluded using standard laboratory assays.

The anion gap, calculated from the serum concentration of sodium, potassium, bicarbonate and chloride, may indicate the presence of unmeasured endogenous or exogenous anions (Table 3) and might assist the identification of the cause of a metabolic acidosis.<sup>21</sup> Neither of the iSTAT cartridges (EG7+ and CG4+) available at the R3MTF nor the laboratory analyser was capable of measuring chloride concentration. We therefore improvised and calculated the osmolar gap (Table 3), which was significantly raised (Table 1). The causes of a raised osmolar gap fall into four categories:<sup>22</sup>

- Sugars
- Lipids
- Proteins
- Alcohols (ethanol, methanol, ethylene glycol).

Toxic alcohol poisoning was most consistent with three simultaneous presentations (and the laboratory was able to exclude raised lipids and proteins, and the glucose was only moderately elevated). No laboratory assay to measure alcohol was available at the R3MTF. One clinician was aware that the military police had breath alcohol analysers and suggested using one to assist our diagnosis. The use of a breath alcohol analyser in methanol poisoning has been previously described, however, with the assumption that the positive test was due to ethanol.<sup>23</sup> After an inspiratory hold the analyser was placed next to the expired air tubing of our patients' ventilator circuits and positive 'alcohol' results were displayed (prior to administration of enteral ethanol).



**Figure 4** (A) Computed tomography scan of the head of Patient B demonstrating extensive areas of hypodensity throughout the basal ganglia, posterior limb of the internal capsules and bilateral external capsules. There is also extensive subcortical white matter hypodensity throughout the cerebral hemispheres (arrow). (B) Computed tomography scan of the head of Patient C demonstrating hypodensity within the lateral portions of the putamen with extension into the bilateral external capsules (arrow).

We were unaware at the time that the phenomenon of some breath alcohol analysers' sensitivity to other alcohols was limited to methanol and isopropanolol. We therefore asked the laboratory to perform microscopy of the patients' urine to look for calcium oxalate crystals, which are not infrequently seen in ethylene glycol poisoning.<sup>24</sup> No crystals were found and the management of methanol and ethylene glycol poisoning is, in the main, identical. We were therefore able to commence management for methanol poisoning.

**Table 3** 'MUDPILES' the causes of a metabolic acidosis

M	Methanol	Anion gap= $[\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-] - [\text{HCO}_3^-]$
U	Uraemia	Normal range=8–16 mmol/L <sup>20</sup>
D	Diabetic ketoacidosis	Osmolar gap is the difference between measured osmolality and calculated osmolality
P	Phenytoin	Calculated osmolality= $2([\text{Na}^+] + [\text{K}^+] + \text{urea} + \text{glucose})$ (difference >10 mmol/L is a raised osmolar gap) <sup>20</sup>
I	Iron, isoniazid	
L	Lactic acidosis	
E	Ethanol, ethylene glycol	
S	Salicylate	

Measurement of the anion and osmolar gap with reference ranges.

### Management challenge

The availability of fomepizole would have greatly simplified the treatment of these patients, particularly in the absence of alcohol assays. There is some evidence that in less severe poisonings (with normal pH), fomepizole can be used effectively as a sole treatment, negating the need for CVVHDF.<sup>14</sup>

We only had one CVVHDF machine with limited dialysate for three patients, all of whom required continuous treatment for optimal management. This, together with the knowledge that unconsciousness, severe metabolic acidosis and hyperglycaemia (>140 mg/dL) are independent predictors of mortality in methanol poisoning<sup>25–27</sup> assisted in making a difficult ethical decision to withhold haemodiafiltration from Patient A for the benefit of the other two patients.

Availability of alcohol assays (both ethanol and methanol) would have assisted with both the diagnosis and ongoing management of these cases. The US laboratory in Kabul was able to measure ethanol concentration and this was used to ensure a therapeutic ethanol level and to inform us when enteral ethanol could be stopped (by calculating the osmolar gap not due to ethanol (Table 2)). Without this assay, it would have been impossible to know how much enteral ethanol was being absorbed or indeed when it was appropriate to discontinue treatment (using the known ethanol level to back calculate the methanol concentration, represented by the osmolar gap not due to ethanol (Table 2)).

### The fourth patient

The following week, a patient presented to the same group of clinicians at the R3MTF. He had a Glasgow Coma Scale score of 8, a history of vomiting, an odour of alcohol and was hyperkalaemic. In the absence of a chloride concentration, the osmolar gap was calculated, which was significantly raised. He was treated with enteral ethanol and CVVHDF and made a full recovery. Subsequent analysis, as previously described, confirmed the presence of a toxic alcohol. It is conceivable that, with a normal blood gas and smelling of alcohol, this patient might have had a delayed diagnosis with fatal consequences had it not been for the recent experience and reflective practice.

### CONCLUSIONS

The primary function of the R3MTF is to manage military trauma. In this series of complex patients, the close working practices of a small number of clinicians (both physicians and trauma teams) undoubtedly assisted the rapid recognition, improvised investigation and management of these unusual cases.

A high index of suspicion for toxic alcohol poisonings in operational theatres must be maintained, even in 'dry' countries and deployed clinicians should be conversant with their typical

presentation. We would support the use of the osmolar gap to differentiate causes of a metabolic acidosis and cautiously advocate the use of a breath alcohol analyser to assist in the diagnosis of toxic alcohol poisonings.

Early administration of enteral ethanol from commercial spirits has been demonstrated to be an effective treatment. However, without the availability of a serum ethanol concentration neither a therapeutic level nor an appropriate time to discontinue treatment can be assured. Availability of fomepizole at the R3MTF would greatly simplify the management of this previously recognised deployed medical presentation.

**Acknowledgements** Lieutenant Colonel John Ritter US Army provided the CT head images (Figure 4A and B).

**Contributors** All authors managed the cases described. EN conceived the publication with input from TB. EB wrote the manuscript with input from SB and the oversight of EN.

**Competing interests** None.

**Patient consent** Written consent for journal publication was obtained from the family of all patients described in this article. The patients were unable to give their own written consent as two died and the one who recovered had severe visual impairment. Care has been taken to anonymise these cases.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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*J R Army Med Corps* published online July 2, 2013

doi: 10.1136/jramc-2013-000117

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