Acid-base disorders in critical care

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INTRODUCTION

Metabolic acidosis is a common component of critical illness. Evaluation of this component can aid diagnosis, assess severity (and likely outcome) and allow the clinician to determine whether current treatments are working.

Summary

Disorders in acid-base balance are commonly found in critically ill patients. Clinicians responsible for these patients need a clear understanding of acid-base pathophysiology in order to provide effective treatment for these disorders. This article concentrates on aspects of metabolic acidosis often seen in intensive care, including poisoning with the alcohols (ethanol, methanol and ethylene glycol).

CASE EXAMPLES

Case 1

A known diabetic patient presented with severe diabetic ketoacidosis. He was drowsy, exhibited classical Kussmaul respiration and proceeded to have a respiratory arrest whilst being admitted to the ICU. After immediate intubation the trainee ventilated the patient with the ventilator's default settings (rate 12, tidal volume 500ml, PEEP 5, FiO_2 0.5) and attempted to secure arterial and central venous access. Shortly after intubation the patient became asystolic and could not be resuscitated.

- Why did this patient have a respiratory arrest?

- Why did he deteriorate after intubation?

Case 2

A young woman was admitted to the surgical ward with a history of severe vomiting and increasing right iliac fossa abdominal pain. On examination she was found to have a rigid abdomen, with visible sub-diaphragmatic gas on chest Xray. She was cardiovascularly unstable and her admission bloods showed Hb 17.4, WCC 24.6, Plt 79, Na^+ 125, K^+ 4.3, Cl^- 93, urea 20.4, creatinine 310 (mcmol.L^{-1}) and blood gas analysis showed:

pH	7.10
$PaCO_2$	5.2kPa
PaO_2	29.3kPa
HCO_3^-	14.3mmol.L^{-1}

- Interpret these results. What is the likely cause of her acidosis?

- How do you interpret her chloride level?

- Is her compensation adequate/maximal?

Case 3

An elderly lady was admitted from a care home with a one week history of severe diarrhoea. She was dehydrated and hypotensive. Admission bloods revealed Na^+ 134, K^+ 2.5, Cl^- 122, urea 15.4, creatinine 280, and blood gas analysis revealed:

pH	7.21
$PaCO_2$	2.9 kPa
PaO_2	19.5 kPa
HCO_3^-	6.4mmol.L^{-1}

- Describe the acid-base disorder present. What is the likely cause?

- Is her compensation adequate?

Case 4

A man was brought in to the emergency room heavily intoxicated. He was known to be alcohol dependent and attended regularly. Blood analysis confirmed normal biochemistry apart from a borderline low glucose (3.8mmol.l^{-1}) and arterial gas analysis showed pH 7.43, $PaCO_2$ 4.8, PaO_2 15.7, HCO_3^- 20. He was placed into an observation bed overnight with a diagnosis of alcohol intoxication but later became tachypnoeic and hypotensive. Repeat gas analysis showed pH 7.0, $PaCO_2$ 4.2, PaO_2 24, and HCO_3^- 9.

- What is the cause of his deterioration?

- What other information would be useful?

Case 5

The same man re-presented a month later, again heavily intoxicated. Blood analysis confirmed normal biochemistry and arterial gas analysis showed pH 7.43, $PaCO_2$ 4.8, PaO_2 15.7, and HCO_3^- 20. Toxicology was requested and minimal ethanol was measured and no methanol found. Urinalysis revealed ketones but no blood or protein. He became more deeply unconscious and on intubation his arterial gases showed pH 7.1, $PaCO_2$ 9.5, PaO_2 21, HCO_3^- 27. Serum osmolarity was measured at 336 (calculated 284).

- What is the cause of his deterioration?

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DEFINITIONS

An **acid** is a substance that has the ability to give up a proton (H^+ - a positively charged hydrogen ion), and so when in an aqueous solution they have a low pH.

pH is a format used to describe the proton concentration in a solution. It is the negative logarithm$_{10}$ of the H^+ concentration, so when the blood pH is normal (7.40) the H^+ concentration in the blood is 40nmol.L^{-1}. For every ten-fold increase in H^+ concentration the pH goes down by 1 unit.

A **base** is a substance that has the ability to accept a proton and has a high pH in solution.

Metabolic acidosis (a low pH in the tissue) exists when there is an excess level of fixed or exogenous acids in the body. Fixed acids include hydrochloric acid, sulphuric acid, phosphoric acid, ketoacids and lactic acid. Examples of exogenous acids are salicylate and methanol. Metabolic acidosis is accompanied by a drop in plasma bicarbonate concentration (relative to the bicarbonate concentration present prior to the onset of the acidosis). This drop in bicarbonate can either be caused by bicarbonate loss or by the presence of extra acid.

The body can accommodate significant alterations in acid levels through buffering. The primary buffer in the blood is bicarbonate, which combines with excess acid (hydrogen ions) to make carbon dioxide, which decreases the effect of the acid on the blood pH. Buffering means that metabolic acidosis (a low tissue pH) does not always lead to the presence of metabolic acidaemia (a low blood pH). Blood pH only falls appreciably when the buffering capacity of the blood becomes overwhelmed.

A drop in bicarbonate concentration is the hallmark of metabolic acidosis

EVALUATION

When evaluating a critically ill patient with a metabolic acidosis it is necessary to determine the type of acidosis in order to identify the cause of the acidosis. To classify metabolic acidosis it is useful to calculate the anion gap and, if present, the size of the osmolar gap. These concepts are explained below.

The role of the anion gap

The anion gap is defined as the concentration difference between the major measured cations (ions which are positively charged) and anions (ions which are negatively charged) within the plasma and is normally 12 to 18 mmol.l^{-1}.[2] Anionic proteins, phosphate, sulphate and low levels of organic acids, which are not measured, account for the difference (i.e. the 'gap'). When examining the cause of a metabolic acidosis it is useful to calculate the anion gap.

Anion gap = $[Na^+ + K^+] - [HCO_3^- + Cl^-]$ = $15(\pm3)$mmol.L^{-1}

A normal anion gap implies that an acidosis is due to primary bicarbonate loss:

- Plasma bicarbonate is low (the hallmark of acidosis) and chloride concentration is raised.

- This bicarbonate loss may be:
  - gastrointestinal (diarrhoea, fistula)
  - renal (renal tubular acidosis, drug effect).

- Also occurs with rapid intravenous infusion of normal saline (excess chloride) or intravenous nutrition rich in cationic amino acids (e.g. arginine).

An increased anion gap implies that fixed acids are being retained or an abnormal organic acid is present.
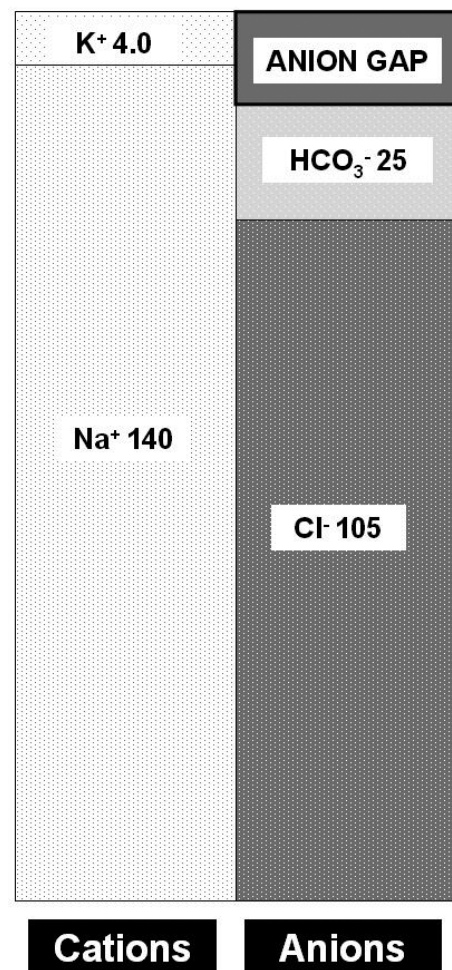
Figure 1. *Illustration of the anion gap (all figures are mmol.L^{-1})*

- Plasma bicarbonate is low and chloride concentration is normal.
- Fixed acids may be retained in:
    - uraemia
    - ketoacidosis (diabetic, alcoholic)
    - lactic acidosis.
- If fixed acids are normal, exogenous acids should be considered:
    - salicylate (aspirin) poisoning
    - methanol poisoning
    - ethylene glycol poisoning.

Limitations of the anion gap

While the anion gap is useful in evaluating metabolic acidosis, it is not sensitive. The normal range is quoted as 12 to 18 mmol.L^{-1} which means it is possible for a patient with a normal anion gap of 12 to acquire a severe lactic acidosis (plasma lactate greater than 5mmol.L^{-1}) without generating an anion gap outside the normal range. The anion gap is also affected by plasma albumin (an important unmeasured anion) and low albumin levels can significantly offset an anticipated rise in anion gap.

Role of the osmolar gap

The osmolar gap represents the difference between a sample's measured osmolality (number of osmoles of solute per kilogram of solvent) and its calculated osmolarity (number of osmoles of solute per litre of solution). It is a useful calculation to perform if alcohol poisoning is suspected (see later in this article).

Osmolality is measured in the laboratory with an osmometer that either assesses the depression of a sample's freezing point or the depression of its vapour pressure. It is preferable to use the former as any volatile alcohols in the sample will evaporate as the sample is heated and the results from this method will be inaccurate.

Osmolarity can be calculated using various formulae. One such formula is:

$$\text{Calculated osmolarity} = 2\,[Na^+] + \text{urea} + \text{glucose}$$

Osmolality and osmolarity differ according to whether the number of osmotically active particles is dissolved in a kilogram or a litre of solvent respectively. The calculated osmolarity utilises the plasma concentration of sodium, glucose and urea. Even though sodium and chloride represent the most important determinants of osmolarity in plasma, chloride concentration is not commonly available. The formula is simplified by taking into account the incomplete dissociation of sodium chloride in plasma.

The measured and calculated values should lie within 10mmol.L^{-1} of each other (the difference being created by the inaccuracy of the calculation and the inaccuracy of the osmometer) and if the gap is larger it suggests the presence of unmeasured osmotically active species.

It is important to realise that the osmolar gap also has significant limitations. When considering alcohol poisoning the osmolar gap is only present as an early feature and returns towards normal as the alcohol is metabolised and the associated metabolic acidosis develops. Similarly the osmolar gap is not sensitive in ethylene glycol poisoning as the large molecular weight of this substance determines the mortality, only causing a small rise in osmolar gap.

COMPENSATION FOR METABOLIC ACIDOSIS

When treating critically ill patients with metabolic acidosis, it is important to consider the adequacy of their ventilatory response to acidosis when deciding on treatment priorities. Buffering provides the main means of accommodating a metabolic acidosis. As buffering capacity is exceeded, acidaemia develops. Once this rise in hydrogen ion concentration has reached the CSF, it is detected by chemoreceptors and compensation occurs by reducing carbon dioxide levels through hyperventilation (first described by Kussmaul). Detection of low pH in CSF rather than blood explains the delay in this compensation; rapid onset acidosis (for example during convulsions) tends not to stimulate respiration in spite of a low blood pH.

Even though respiratory compensation occurs relatively quickly, it can take up to twelve hours to reach maximal capacity. This maximal capacity can be calculated:

$$PaCO_2 \text{ (maximal change, in kPa)} = 0.2\,[HCO_3^-] + 1$$

If the patient's PaCO$_2$ lies within 0.5kPa of this calculated value, then the respiratory response is appropriate to the level of metabolic acidosis. If the PaCO$_2$ is higher, then the compensation is in a very early stage or the patient has a superimposed respiratory acidosis. If this is the case then earlier intervention with respiratory support is indicated.

When providing respiratory support in patients with a metabolic acidosis it is important to remember that respiratory compensation causes an increased minute volume. If you instigate controlled ventilation with a normal minute volume, then the PaCO$_2$ level will rise rapidly towards normal, the acidaemia will worsen, and the patient will become acutely unstable. Young fit patients with severe diabetic ketoacidosis can generate huge minute volumes (20-30 l.min^{-1}) and drop their PaCO$_2$ to below 2kPa.

PITFALLS IN ASSESSING METABOLIC ACIDOSIS

It is impossible to interpret arterial gases accurately without considering the history and presentation first. Consider the following arterial gas:

pH	7.1
PaCO$_2$	10.5kPa
PaO$_2$	29.3kPa
HCO$_3^-$	24.3mmol.L^{-1}

The interpretation of this result will vary according to the clinical presentation:

- If the gas sample was taken from a young unconscious patient, admitted through the emergency room, with pinpoint pupils then you would interpret the gas as showing primary respiratory acidosis from opiate overdose.
- If the gas was taken from an elderly man with severe COPD presenting with sepsis, then the gas interpretation will be different.

Full compensation for a chronic respiratory acidosis should raise the bicarbonate by 3 x (PaCO$_2$ – 5.3). If the PaCO$_2$ level is chronically raised then you would expect the bicarbonate to be 36mmol.L^{-1}.

This bicarbonate is significantly lower and this suggests a metabolic acidosis superimposed on the background of a compensated respiratory acidosis.

This highlights the importance of basing gas interpretation on clinical assessment. Other pitfalls arise from failing to recognise the limitations of the anion gap and osmolar gap.

METABOLIC ACIDOSIS DUE TO ENDOGENOUS ACIDS

Lactic acidosis

Lactic acid is a weak acid that is present in the blood in low levels (1-2mmol.L^{-1}). It is produced from pyruvate, the end substrate in glycolysis, the process by which carbohydrates are broken down to produce energy. Since some tissues (such as skin) produce more pyruvate than their mitochondria can handle, excess pyruvate is converted to lactate, released into the blood and metabolised by the liver (60%, Cori cycle) or kidney (40%).

A rise in the lactate level in the blood suggests increased lactate production or decreased lactate metabolism. As the liver's capacity to metabolise lactate is large, a rise in blood lactate levels suggests that a degree of impaired liver lactate handling is present; however, increased lactate production is still the primary feature of lactic acidosis that is amenable to treatment. Lactic acidosis is categorised according to the state of oxygen delivery.

If oxygen delivery is inadequate (type A lactic acidosis), then aerobic metabolism is impaired, pyruvate accumulates and lactate is produced. We know oxygen delivery is a product of cardiac output and blood oxygen content, but in lactic acidosis low cardiac output is invariably the most important consideration. Oxygen content is rarely low enough to create a lactic acidosis in isolation – the haemoglobin would need to be less than 5g.dl^{-1} or the PaO$_2$ less than 4kPa.

Treatment aims concentrate on restoring correct distribution of cardiac output and, to a lesser extent, ensuring adequate blood oxygen content (this is one situation where the low transfusion threshold of 7g.dl^{-1} for the critically ill should not apply).

Type B lactic acidosis occurs when oxygen delivery is normal and a problem in carbohydrate metabolism is present. Causes of type B acidosis are subdivided as follows:

B1   Underlying disease, also called 'stress lactate' (ketoacidosis, haematological malignancy)

B2   Drug or toxin effect (e.g. salbutamol)

B3   Inborn error of metabolism

Treatment in this situation depends on determining the cause from the history and clinical signs and addressing the root cause, rather than attempting to correct the acidosis directly.

Ketoacidosis

Ketone bodies include β-hydroxybutyrate, acetoacetate and acetone. When lipids are metabolised by β–oxidation, acetyl co-enzyme A is produced (as the central conversion molecule of cellular metabolism). Acetyl coA normally binds to oxaloacetate (OAA) to enter the citric acid cycle and generate high energy substrates. However if inadequate levels of OAA are present, then acetyl coA is converted into acetoacetate. If adequate levels of NAD$^+$ are present, then acetoacetate is subsequently converted into β–hydroxybutyrate. Ketones can be used as energy sources by the brain and the heart.

The main causes of ketoacidosis include:

• Starvation ketoacidosis

• Alcoholic ketoacidosis

• Diabetic ketoacidosis.

Starvation ketoacidosis

This occurs when glycogen levels in the liver have become exhausted and the liver attempts to make more glucose via the gluconeogenesis pathway. Gluconeogenesis requires OAA and the subsequent drop in OAA levels limits the ability of the citric acid cycle to utilise acetyl coA provided by lipid metabolism. The excess acetyl coA is converted into ketone bodies and ketoacidosis develops. The acidosis tends to be within buffering capacity and the anion gap rise is small. The situation is resolved by supplying glucose in a controlled fashion and allowing the liver to revert back to the usual metabolic pathways.

Alcoholic ketoacidosis

This condition develops when ethanol is taken without enough calories. The starvation response is now complicated by the liver's effort to metabolise ethanol. The conversion of ethanol into acetaldehyde requires NAD$^+$ (a proton carrier with a vital role in the generation of the fuel molecule, ATP) and the excess NADH generated inhibits gluconeogenesis. This exacerbates the glucose deficiency and the corresponding drop in insulin levels stimulates lipid metabolism and ketoacidosis.

The anion gap in this instance will be raised and the acidosis more severe (pH approaches 7.0). Analysis of the acid-base balance can be complicated by an appropriate compensatory respiratory alkalosis and a metabolic alkalosis if the patient has been vomiting. If significant dehydration is present these patients can also get a lactic acidosis, amplified by the relative excess of NADH.

Treatment involves restoration of adequate circulating volume and the administration of both insulin and glucose. With prompt treatment the acidosis should resolve rapidly.

Diabetic ketoacidosis

Diabetic ketoacidosis develops when inadequate amounts of insulin are available. The insulin deficit reduces available intracellular glucose and increases fat breakdown and free fatty acid levels. The liver responds, as if in a starving state, by increasing lipid metabolism (further encouraged by increased levels of 'stress' hormones) and, as gluconeogenesis depletes available oxaloacetate, the acetyl CoA generated is converted into ketone bodies. Acetoacetic acid and β-hydroxybutyric acid dissociate and the H$^+$ ion released is buffered by bicarbonate. An increased anion gap acidosis develops.

This acid-base picture may be complicated by various factors. Patients are often severely dehydrated and this can cause lactic acidosis due to inadequate tissue perfusion. Ketoacidosis causes vomiting and the resulting loss of acid can cause the calculated anion gap to under-represent the severity of the acidosis. In addition, initial resuscitation with chloride rich solutions (0.9% saline) will increase chloride levels and further decrease the anion gap.

Renal acidosis

The kidney's ability to regulate acid-base balance can be adversely influenced in numerous ways. It is useful to categorise these conditions according to their effect on glomerular filtration.

Acidosis associated with decreased glomerular filtration

The most common forms of renal acidosis seen in intensive care are associated with a profound drop in glomerular filtration. Acute kidney injury (commonly due to acute tubular necrosis), and acute exacerbation of chronic kidney disease, both cause a metabolic acidosis because the kidney is unable to excrete fixed acids.

The acidosis is exacerbated by the associated tubule damage. This damage prevents bicarbonate production from CO_2, and ammonia excretion and buffering capacity is reduced as a result. Bicarbonate levels drop and chloride tends to remain stable and as a result the anion gap rises. Treatment involves correction of the precipitating factors and supporting renal function (with renal replacement therapy if required).

Acidosis associated with preserved glomerular filtration

This is renal tubular acidosis (RTA), which is less common in the critically ill and usually associated with either inherited disorders or pre-existing renal disease. While the glomerular filtration rate may be depressed, the acidosis is disproportionate to this minor reduction and tends to exhibit a normal anion gap.

Renal tubular acidosis (RTA) is subdivided according the site of the tubular defect:

Type 1	Distal tubular defect
Type 2	Proximal tubular defect
Type 4	Distal tubular resistance to aldosterone (or aldosterone deficiency)

Type 1 RTA is the most common form and is caused by the distal convoluted tubule failing to excrete hydrogen ions when attempting to reabsorb sodium. A metabolic acidosis develops as a consequence and the urine fails to acidify. Potassium excretion is unaffected and potassium loss in the urine may be increased as a result. This type of RTA has numerous causes including drug induced damage (amphotericin), autoimmune disorders (lupus) and nephrocalcinosis. It is diagnosed by confirming a high urine pH (greater than 5.5) in the presence of a severe metabolic acidosis. The underlying disorder should be addressed and the episodes of acidosis prevented by giving adequate dietary bicarbonate.

Type 2 RTA is much less common and is caused by a defect in the proximal convoluted tubule that prevents bicarbonate reabsorption. It can be inherited or associate with Fanconi syndrome (generalised defect of tubular amino acid reabsorption.) Urinary bicarbonate loss

is increased and the urine pH is raised. However, as the proportion of bicarbonate filtered by the kidney is proportional to the plasma bicarbonate concentration, the acidosis is less severe than with type 1 RTA. The condition tends to be self-limiting and the bicarbonate tends not to drop below 15mmol.L^{-1}. Potassium loss is less marked than with distal RTA but can be a problem if bicarbonate supplements are given to correct the acidosis. Any supplements need to include both bicarbonate and potassium.

Type 4 RTA is also rare and tends to occur while aldosterone is deficient or the distal tubule becomes resistant (papillary necrosis). Both acid and potassium secretion are reduced and the urine remains relatively alkali whilst a metabolic acidosis develops in the presence of raised potassium. If severe this condition can be treated with oral fludrocortisone (0.1mg.day^{-1}).

Other causes of normal anion gap acidosis

Normal anion gap acidosis occurs due to primary bicarbonate loss and this can occur through the kidney or the gut.

Renal loss occurs with renal tubular acidosis as discussed above but can also occur as a drug effect (acetalozamide) or when the ureters are diverted to the bowel (ureterosigmoidostomy). The latter causes a problematic acidosis that responds poorly to dietary supplements and can be difficult to treat.

Gut losses occur with severe diarrhoea or via nasogastric aspirates in patients with small bowel obstruction. Pancreatic fistulae, biliary drains and some bowel tumours also lose bicarbonate and cause a hyperchloraemic normal anion gap acidosis.
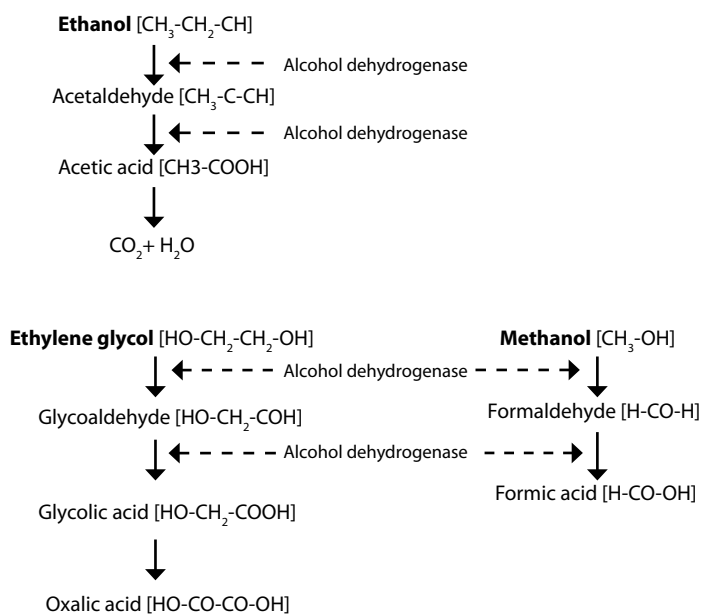
METABOLIC ACIDOSIS DUE TO EXOGENOUS ACIDS

Alcohol poisoning

Ethanol, methanol, ethylene glycol and isopropanol represent the main alcohols encountered in poisoning. Ethanol is by far the most common cause of alcohol poisoning. Specialist laboratories are able to measure plasma alcohols but this is often not immediately available, therefore the diagnosis of alcohol poisoning can be helped by estimation of the osmolar gap. In order to understand the patterns seen in alcohol poisoning it is necessary to discuss how the various alcohols are metabolised.

Metabolism of alcohol (methanol, ethanol and ethylene glycol)

Ethanol, methanol and ethylene glycol are metabolised by the same enzyme systems, but produce different metabolites. Collectively they are termed alcohols.

With methanol and ethylene glycol poisoning, only the parent compounds and the first metabolites (formaldehyde and glycoaldehyde respectively) are osmotically active. The subsequent metabolites are weak acids that dissociate into electrically charged ions that become balanced by sodium, and so cease to exert an osmotic influence. In the initial stages, metabolism generates an osmolar gap with minimal acidosis, however, further metabolism produces formic and glycolic acid respectively. This is not the case with ethanol and accounts for the clinical progression seen in methanol and ethylene glycol poisoning. These metabolites generate a metabolic acidosis and as they are

Ethanol [CH_3-CH_2-CH]

↓ ← – – – Alcohol dehydrogenase

Acetaldehyde [CH_3-C-CH]

↓ ← – – – Alcohol dehydrogenase

Acetic acid [$CH3-COOH$]

↓

$CO_2 + H_2O$

Ethylene glycol [$HO-CH_2-CH_2-OH$]   **Methanol** [CH_3-OH]

↓ ← – – – Alcohol dehydrogenase – – – → ↓

Glycoaldehyde [$HO-CH_2-COH$]   Formaldehyde [$H-CO-H$]

↓ ← – – – Alcohol dehydrogenase – – – → ↓

Glycolic acid [$HO-CH_2-COOH$]   Formic acid [$H-CO-OH$]

↓

Oxalic acid [$HO-CO-CO-OH$]

Figure 2. *Metabolism of ethanol, ethylene glycol and methanol.*

produced the osmolar gap decreases. The enzyme responsible, alcohol dehydrogenase, metabolises both poisons at a lower rate than ethanol and this may result in toxicity being delayed for up to 30 hours for methanol, and twelve hours for ethylene glycol. Use of the osmolar gap may therefore be misleading.

When blood is taken for these tests it is impossible to determine which substance has been taken and how far the metabolism of the alcohol has progressed. If the osmolar gap is normal then either the alcohol metabolism is advanced or the patient has not ingested a large quantity. However, patients usually present to hospital with the onset of symptoms and this normally coincides with intermediate alcohol metabolism and a raised osmolar gap.

Methanol poisoning

Methanol is a potent poison and serious toxicity is seen after an intake of 10ml. Methylated spirits contains 5% methanol and ingestion of over 200ml is required before serious toxicity is encountered. This toxicity presents after a latent period of twelve hours or more. Patients report headache, breathlessness and visual symptoms ranging from blurring to complete blindness. Severe abdominal pain and nausea are common and patients may present with a rigid abdomen. The cardiovascular system is initially stable until a severe acidosis develops, then marked myocardial depression and bradycardia is encountered.

Treatment is directed at reducing the rate of organic acid production with intravenous ethanol and haemodialysis. Ethanol treatment consists of a 50g oral loading dose (125ml of spirits will suffice) followed by an intravenous infusion of 10-12g.h^{-1}. Treatment should aim to achieve a plasma concentration of 1-2g.L^{-1}. The indications for dialysis are not well defined but should be considered in the presence of a severe metabolic acidosis, marked visual or mental symptoms or in the presence of a high methanol plasma concentration (over 500mg.L^{-1}). Folinic acid can also be given intravenously to help prevent ocular toxicity (30mg IV 6 hourly).

Ethylene glycol poisoning

Ethylene glycol is less potent than methanol with 100ml ingestion representing a severe overdose. Toxicity initially presents with intoxication - slurring of speech, drowsiness and nausea. This can progress to marked cerebral depression and convulsions. Twelve hours after ingestion significant metabolism to glycoaldehyde has occurred causing cardiorespiratory depression and acidosis. Aldehydes inhibit oxidative phosphorylation, mechanisms for cellular respiration, glucose metabolism, protein synthesis, nucleic acid replication and synthesis. Myocardial depression can be significant and pulmonary oedema is commonly encountered.

Renal tenderness and oliguria may become evident as acute tubular necrosis becomes established. Metabolism of ethylene glycol to oxalic acid causes a demonstrable degree of oxalate crystalluria and accounts for the low plasma calcium seen (chelation to form calcium oxalate). Ethylene glycol poisoning is lethal with levels of 21mg.dl^{-1} but it must be remembered that this will only generate a late osmolality increase of 4mosm.L^{-1} (delayed presentation). The treatment approach is similar to methanol toxicity with emphasis on the early use of ethanol infusions and haemodiafiltration. These treatments should continue until ethylene glycol can no longer be detected in blood.

Isopropanol poisoning

Isopropanol should also be considered when patients present with alcohol toxicity. This alcohol forms a major component of rubbing alcohol and is used in windscreen cleaning preparations and de-icer. Unlike methanol or ethylene glycol, isopropanol is metabolised to acetone and excreted in the urine. Acetone is not metabolised further and organic acid production is minimal. Both the parent compounds and metabolites are osmotically active and significant osmolar gaps may be seen with ingestion. Isopropanol toxicity tends to present with intoxication, meiosis (small pupils), and brain stem depression with significant overdose. Isopropanol is irritant and causes marked gastritis, pancreatitis and, if aspirated, causes tracheitis and pulmonary oedema. It is rapidly absorbed from the stomach and gastric lavage is of little benefit. Ketosis is more marked with isopropanol ingestion and this can provide a useful clue to diagnosis. Treatment is supportive and no effort should be made to limit metabolism of isopropanol with ethanol infusions. Isopropanol is readily cleared by haemodiafiltration but this treatment is rarely required.

Salicylate poisoning

Aspirin (acetylsalicylic acid) poisoning causes over 200 deaths a year in the UK. Therapeutic doses of aspirin are absorbed rapidly and completely from the stomach and larger doses may be absorbed for up to 18 hours after ingestion as the tablets coalescence in the stomach.

Metabolism

Acetylsalicylic acid is hydrolysed to salicylic acid and further metabolised in one of three ways.

1. Conjugation with glycine to salicyluric acid

2. Hydroxylated to gentisic acid

3. Conjugation with glucuronic acid to either salicylacyl glucuronide or salicyl phenolic glucuronide.

Conjugation with glucuronic acid is saturable so that levels of non-protein bound salicylate rise disproportionately with increasing dose. The excretion of unchanged salicylate by the kidneys then becomes increasingly important and alkalisation of the urine will therefore maximise its excretion by ion trapping.

Drug effects

Central to the metabolic disturbances initiated by acetylsalicylic acid is the uncoupling of oxidative phosphorylation. The resulting increase in oxygen consumption and carbon dioxide production leads to a respiratory alkalosis that is worsened by direct stimulation of the respiratory centre. Bicarbonate excretion is enhanced and sodium, potassium and water loss also occurs. When this is combined with hyperpyrexia and sweating, then marked dehydration and electrolyte imbalance follow. Stimulation of the chemoreceptor trigger zone may induce vomiting and this will further exacerbate this imbalance.

Uncoupled oxidative phosphorylation enhances glycolysis and increases the peripheral demand for glucose. This occurs mainly in muscle and may provoke hypoglycaemia. The brain is particularly sensitive to this and neuroglycopenia may then lead to depression of the respiratory centre.

The metabolic acidosis seen in acetylsalicylic acid poisoning is caused by the stimulation of lipid metabolism (increasing the formation of ketoacids) and the inhibition of enzymes within the Krebs cycle (increasing levels of pyruvic and lactic acid). The acidosis is poorly tolerated due to the reduced buffering capacity following the initial respiratory alkalosis and bicarbonate excretion.

Clinical presentation

The clinical picture depends on the age of the patient and on the total dose ingested. Acute overdose in the setting of chronic use augments toxicity. Plasma salicylate levels 6 hours after ingestion can be classified as mild (300-$500mg.L^{-1}$), moderate (500-$750mg.L^{-1}$) and severe ($>750mg.L^{-1}$) poisoning. Below ten years of age respiratory alkalosis tends to be a transient feature with metabolic acidosis predominating. However, respiratory alkalosis is more marked in adults, where it helps to keep salicylate in the ionised form, preventing it from crossing cell membranes. The following features are usually present regardless of the severity: sweating, vomiting, pyrexia, tinnitus and epigastric pain. As the metabolic acidosis worsens more salicylate enters the central nervous system and tremor, delirium, convulsions and eventually coma ensues. Non-cardiogenic pulmonary oedema and acute renal failure are also features of acetylsalicylic acid toxicity.

Treatment involves vigorous gastric lavage to limit continued absorption. Dehydration and electrolyte disturbances (particularly hypokalaemia) should be corrected. Severe toxicity requires more than these basic manoeuvres and alkalisation of the urine should be performed. Urinary salicylate excretion is encouraged with intravenous infusions of bicarbonate, aiming to raise urinary pH >7.5 while avoiding a plasma pH >7.55. Haemodialysis has also been used to augment salicylate excretion.

CASE EXAMPLES - DISCUSSION

Case 1

The patient presented with a metabolic acidosis caused by loss of diabetic control, relative insulin deficiency and consequently ketoacidosis. Kussmaul respiration is seen in respiratory compensation through hyperventilation - the rise in minute volume can be substantial and maintaining this compensation is very strenuous. As time passes patients tire, the minute volume decreases and the acidosis worsens rapidly. Young patients in particular can maintain full respiratory compensation, almost to the point of respiratory arrest, as in this example. Elderly patients tend to tire earlier.

When taking over a patient's ventilation, in the setting of a metabolic acidosis, it is vital that the minute volume used is raised appropriately. If standard ventilation settings are applied, as in this case example, the drop in alveolar ventilation post-induction will remove the respiratory compensation and the acidosis will deteriorate dramatically. This is the likely cause of this patient's cardiovascular collapse.

Case 2

This patient, presenting with peritonitis, has a raised haemoglobin, urea and creatinine suggesting dehydration and a likely lactic acidosis due to inadequate tissue perfusion. The arterial gases confirm that acidaemia is present (low pH) and the low bicarbonate level implies that the acidosis is metabolic.

The anion gap is raised at 35 and this strongly suggests the presence of an increased anion gap acidosis. The vomiting that occurred in the days leading up to admission may have caused a metabolic alkalosis (loss of hydrogen ions and chloride) that has been masked by the superimposed lactic acidosis. Therefore a severely increased anion gap acidosis has only dropped the pH to 7.1, when you would expect the pH to be lower.

Using the bicarbonate level ($14.3mmol.L^{-1}$), the calculated $PaCO_2$ during maximal compensation would be 3.8kPa ($[14.3 \times 0.2]$ $+1$). The fact that her $PaCO_2$ is higher should serve as a warning of imminent fatigue and ventilation should be supported as quickly as possible in order to prevent cardiorespiratory collapse.

Case 3

This woman presented with a low pH and low bicarbonate, implying that a metabolic acidosis is present. The extent of the dehydration raises the possibility of a lactic acidosis, however this would create an increased anion gap. The anion gap in is low (8.5), and this strongly supports the presence of a normal anion gap acidosis secondary to bicarbonate loss from the gut.

With a bicarbonate level of 6.4 you would expect the patient to drop her $PaCO_2$ to 2.28 ([6.4 x 0.2] +1) and in this instance her respiratory compensation is appropriate.

Case 4

This patient was initially felt to be intoxicated with alcohol and the low blood glucose raised the possibility of alcoholic ketoacidosis. The initial arterial gas does not support this as a low bicarbonate and an increased anion gap would be expected. The subsequent deterioration however is typical of methanol poisoning.

Methanol metabolism is often delayed for 12 to 18 hours especially if taken with ethanol. The first stage in metabolism generates formaldehyde which is not an acidic species – metabolic acidosis will not feature at this stage. When the formaldehyde is metabolised into formic acid then the increased anion gap acidosis develops.

It would have been useful to determine whether there was an osmolar gap on initial presentation. If this was raised then it would have alerted the clinicians to the possibility of poisoning with an alcohol, and ethanol treatment would have prevented the deterioration.

Interestingly the subsequent arterial gas shows a severe metabolic acidosis but the $PaCO_2$ has only dropped minimally. The calculated $PaCO_2$ for maximal compensation suggests the $PaCO_2$ should have dropped to 3.0kPa. The relative respiratory acidosis arises from methanol induced respiratory depression and should prompt early ventilatory support.

Case 5

In this example the same patient re-presents with an intoxicated picture but ethanol and methanol are not detected on this admission. In spite of this, and the normal arterial gases on admission he became comatose with arterial gases suggesting a primary respiratory acidosis (low pH, raised $PaCO_2$). The rise in bicarbonate is appropriate for the rise in $PaCO_2$ (expected bicarbonate rise = 0.75 [$PaCO_2$ – 5.3] for an acute respiratory acidosis), so no metabolic effects are demonstrated.

This presentation is typical for isopropanol poisoning. Metabolic acidosis is not a feature of isopropanol poisoning; however the alcohol is heavily intoxicating and can easily cause respiratory depression as seen in this example. The key to aid diagnosis is the presence of the increased osmolar gap combined with the urine ketosis (from the metabolite, acetone). Treatment is supportive (the airway will need to be secured in this example and respiratory support provided) until the alcohol has been metabolised.

SUMMARY

Metabolic acidosis is commonly encountered in intensive care and correct management requires confirmation that an acidosis is present, determination of its nature and then determination of the probable cause. Identification of the root cause will then allow specific treatment with improved efficacy.

FURTHER READING

1. Cohen RD, Woods HF. Disturbances of acid-base homeostasis. In: Weatherall DJ, Ledingham JGG, Warrell DA, Eds. Oxford Textbook of Medicine. Oxford: *Oxford University Press*, 1987; **9**.174

2. Hoffman RS, Smilkstein MJ, Howland MA, Goldfrank LR. Osmol gaps revisited. Normal values and limitations. *Journal of Toxicology – Clinical Toxicology* 1993; **31**: 81-93.

3. Salem MM, Mujais SK. Gaps in the anion gap. *Archives of Internal Medicine* 1992; **152**: 1625-9.

4. Stewart PA. How to understand acid-base. A quantitative acid-base primer for biology and medicine. Available at: http://www.acidbase.org/

5. Vale JA, Meredith TJ Proudfoot AT. Poisoning by alcohols and glycols. In: Weatherall DJ, Ledingham JGG, Warrell DA, Eds. Oxford Textbook of Medicine. Oxford: *Oxford University Press*, 1987; 6.41-6.44.

6. Williams HE Alcoholic hypoglycaemia and ketoacidosis. *Medical Clinics of North America* 1984; **68**: 33-8.

7. Almaghamsi A, Yeung C. Osmolal gap in alcoholic ketoacidosis. *Clinical Nephrology* 1997; **48**:52-3.