Disturbances of water, electrolyte and acid-base metabolism in acute poisoning

Disturbances of water, electrolyte and acid-base metabolism may develop as a result of a direct effect of poisons on metabolic systems, or indirectly as a result of an effect of the poison on cardiorespiratory, gastrointestinal, hepatic, or renal function.

ACID-BASE DISORDERS[1]

A low pH is referred to as acidaemia, and for practical purposes severe acidaemia may be defined as a pH < 7.2 (normal range: 7.35 - 7.45).

Acidaemia causes potassium to leave cells, resulting in hyperkalaemia. Brain metabolism and the regulation of its volume are impaired, resulting in progressive central nervous system depression and coma.

Metabolic acidosis

Metabolic acidosis is a condition characterised by a low arterial pH and a reduced plasma HCO_3^- concentration, and is usually accompanied by compensatory alveolar hyperventilation, resulting in a decreased $PaCO_2$. Severe metabolic acidosis also implies a plasma bicarbonate concentration of 8 mmol/l or lower. Major adverse consequences of severe acidaemia include decreased cardiac output, decreased arterial blood pressure, reduction in the threshold for cardiac dysrhythmias, and a decrease in hepatic and renal blood flow. Acidaemia causes potassium to leave cells, resulting in hyperkalaemia. Brain metabolism and the regulation of its volume are impaired, resulting in progressive central nervous system depression and coma.[1]

The anion gap (unmeasured anions) is a valuable calculation in the differential diagnosis of metabolic acidosis. This gap (something of a misnomer) refers to the difference between the concentration of cations other than Na^+, and the concentration of anions other than Cl^- and HCO_3^-, in the plasma. Usually, the unmeasured anions exceed the unmeasured cations. The normal anion gap is -8 - 16 mmol/l (since the pH of the serum is 7.4). It is increased when the plasma concentration of organic anions, such as lactate or foreign ions, accumulates in blood. The anion gap is increased in cases of ketoacidosis, lactic acidosis, and other forms of acidosis in which organic anions are increased.

The anion gap can be calculated as follows:[2]

Anion gap = $[Na^+] - ([HCO_3^-] + [Cl^-])$

Normal range: 8 to 16 mmol/l

E.g.: Anion gap = 140 - (26 + 106) = 8 mmol/l

(Note: Clinicians should consult their particular laboratory's reference ranges when assessing the anion gap, as some may include the $[K^+]$ in the above formula.)

Causes of a high anion gap metabolic acidosis[3,4]

- Renal failure.
- Diabetic ketoacidosis and alcoholic ketoacidosis.
- Profuse fluid losses leading to loss of bicarbonate from the digestive tract (as in severe diarrhoea).
- Lactic acidosis. Two types are recognised, i.e. type A, where there is evidence of impaired tissue oxygenation, and type B, where no such evidence is apparent. Most cases of type A lactic acidosis are caused by tissue hypoxia arising from circulatory failure. In poisoned patients type A lactic acidosis may occur nonspecifically owing to impairment of cardiorespira-

tory function (e.g. as a result of seizures), or more specifically where the oxygen-carrying capacity of blood is impaired (e.g. as in carboxyhaemoglobinaemia or methaemoglobinaemia). Type B lactic acidosis occurs with poisons that directly inhibit mitochondrial enzymes (as in cyanide poisoning). Therapy should focus primarily on securing adequate tissue oxygenation and on identifying and treating the underlying cause. Improvement of tissue oxygenation may require ventilatory support, maintenance of a high inspired oxygen fraction, repletion of extracellular fluid, afterload reducing agents and inotropic support. In severe acidaemia (pH < 7.2 and/or base excess > -12), the abovementioned measures may be supplemented by cautious administration of intravenous sodium bicarbonate, initially at doses of no more than 1 - 2 mmol/kg of body weight (see information below).

- Acute poisonings. These include methanol, ethylene glycol, and salicylate poisoning. Both methanol and ethylene glycol are substrates for hepatic alcohol dehydrogenase and are metabolised to formic and glycolic acids, respectively. Exposure to toluene, by sniffing glue, may also cause severe metabolic acidosis resulting from the stepwise metabolism of toluene to benzoic and hippuric acid. Other poisons known to cause metabolic acidosis include ethanol, iron, isoniazid and strychnine.

Management of the abovementioned acute poisonings may require large amounts of sodium bicarbonate to combat severe acidaemia. The role of sodium bicarbonate in the management of high anion gap acidaemia, however, is controversial. Bicarbonate given in large quantities may lead to sodium and fluid overload, to hypokalaemia, and to 'alkalosis overshoot'. Regardless of whether or not sodium bicarbonate is given, the underlying cause of the acidaemia must be identified and treated where possible (e.g. management of ethylene glycol or methanol poisoning with fomepizole or ethanol, etc.).

Despite the above reservations, most experts still recommend the judicious use of intravenous $NaHCO_3$ in the management of severe metabolic acidosis (pH < 7.2).

In salicylate poisoning $NaHCO_3$ is given to alkalinise the urine to enhance excretion of salicylate (ion trapping) and is usually not administered to correct the acidosis. Although alkaline diuresis increases the elimination of salicylates and phenobarbitone, it is clinically difficult to achieve a urinary pH above 8 with $NaHCO_3$. In phenobarbitone poisoning parenteral acetazolamide (Diamox) has been recommended to alkalinise the urine. Administration of 250 - 500 mg of acetazolamide increases both urinary pH and urine flow. Urine pH values may increase to 7.8. This procedure is, however, not recommended in salicylate poisoning, since it may worsen the central nervous system effects of poisoning. In tricyclic antidepressant overdose, $NaHCO_3$ is given pri-

Using sodium bicarbonate in severe metabolic acidosis

$NaHCO_3$ may be given undiluted as a 4.2% solution. However, some prefer diluting it in 5% dextrose in water or hypotonic (0.45%) saline solution, depending on the clinical setting. The goal of bicarbonate therapy is to raise the blood pH to 7.3 and the plasma bicarbonate to 12 - 15 mmol/l. The amount necessary can be calculated using the formula: base excess x 0.3 x body weight (kg), expressed in mmol bicarbonate. (One ml 8.5 % $NaHCO_3$ = 1 mmol, or 1 ml of 4.2% = 0.5 mmol.) It is wise to give only two-thirds of the calculated amount initially, and then reassess the situation. To raise the plasma bicarbonate concentration from 4 to 8 mmol/l in a 70 kg patient, one should administer 4 x 70 x 0.5, or 140 mmol of sodium bicarbonate. An average dose is 1 - 2 mmol/kg (2 - 4 ml) of a 4.2% solution over 15 minutes. (Several formulae exist to calculate the dose of $NaHCO_3$.) If acid-base data are not available 1 - 2 mmol/kg body weight may be given. About 30 minutes must elapse after the administration of $NaHCO_3$ before its effect can be judged. It is important to consider the serum calcium level when treating metabolic acidosis, especially in children. Metabolic acidosis increases the ionised fraction of total calcium. Treatment of acidosis decreases the amount of ionised calcium, an effect which may precipitate tetany and/or seizures. The administration of calcium gluconate, therefore, is sometimes indicated.[1,3,5,6]

marily to prevent the development of cardiac dysrhythmias.

Respiratory acidosis

Respiratory acidosis is a condition caused by decreased ventilation, resulting in a low arterial pH, an elevated $PaCO_2$ and, usually, a compensatory increase in plasma HCO_3^- concentration. Causes include upper or lower airway obstruction, status asthmaticus, severe alveolar defects, ventilatory restriction, central nervous system depression and neuromuscular impairment. The two last-mentioned entities are often complications of overdoses with sedative-hypnotics (e.g. barbiturates), opioids, tricyclic antidepressants, botulism and paralytic mussel poisoning, to mention a few. In patients breathing room air a rise in $PaCO_2$ will cause a fall in PaO_2, which in severe cases, may cause hypoxia. Concomitant hypoxaemia results in type A lactic acidosis. Management is directed towards oxygenation, respiratory support and removing the underlying cause.[4]

Respiratory alkalosis

Respiratory alkalosis is a condition of hyperventilation resulting in an elevated arterial pH, a low $PaCO_2$ and usually a compensatory decrease in the plasma HCO_3^- concentration. Salicylate overdose is known to cause respiratory alkalosis, especially in adults. This is caused by direct stimulation of the respiratory centre by salicylates.[4,7]

WATER AND ELECTROLYTE/ OSMOLALITY DISTURBANCES

Poisons, such as digoxin and theophylline in overdose, may cause electrolyte disturbances directly by inducing shifts of electrolytes (especially K^+) across cell membranes. Poisons may also cause water and electrolyte disorders indirectly, for example by inducing vomiting and diarrhoea.

Plasma osmolarity

The osmolal concentration of a solution is called osmolality when the concentration is expressed as osmoles per kilogram of water; it is called osmolarity when it is expressed as osmoles per litre of solution.[8] The major intracellular cation is potassium, with a concentration range of 3.3 - 5.3 mmol/l. The major extracellular cation is sodium, with a concentration range of 135 - 147 mmol/l. Normally, the osmolarity of the extracellular fluid (280 - 295 mmol/l) approximates that of the intracellular fluid. Therefore, the plasma osmolarity is a convenient guide to intracellular osmolarity.

The body fluid or plasma osmolarity can be calculated from routine electrolyte measurements by the following formula:

Calculating body fluid or plasma osmolality

2 x [Na^+] + [urea] + [glucose] in mmol/l (calculated osmolarity)

The osmolal gap = measured osmolarity - calculated osmolarity. The normal range is 10 - 15 mmol/l

(A slightly modified formula includes the plasma potassium concentration:

2 x [$Na^+ + K^+$] + [urea] + [glucose]

For this formula a gap > 10 mmol/l indicates unmeasured osmotically active solute.)

A gap greater than 15 mmol/l indicates that an unmeasured osmotically active solute, e.g. an alcohol, is present. An elevated osmolal gap, together with a high anion gap metabolic acidosis, may indicate methanol or ethylene glycol poisoning.[9]

Hypokalaemia

Hypokalaemia (< 3 mmol/l) is often caused by excessive losses of K^+ from the gastrointestinal tract, as in diarrhoea. Hypokalaemia is almost invariably present in metabolic alkalosis. Hypokalaemia is also a complication of theophylline and $beta_2$-agonist poisoning. This is caused by the movement of potassium from the extracellular fluid into the cell.

Intravenous potassium should be given slowly, preferably through a central line, while monitoring the amplitude of the T-wave of the ECG (10 ml of a 15% KCl solution contains 1.5 g potassium chloride, or 20 mmol of KCl). The maximum concentration of KCl in an intravenous solution should generally not exceed 40 mmol/l. If higher concentrations are required, it should be administered in an ICU.

Correcting severe hypokalaemia

To correct severe hypokalaemia, adequate urine flow should be ensured, and then potassium should be administered by adding 30 mmol to each litre of fluid. The amount of potassium needed can also be calculated using the following formula:

(desired K^+ - measured K^+) x 0.3 x weight in kg

Hyperkalaemia

Hyperkalaemia (> 5.5 mmol/l) is particularly common in oliguric states (acute renal failure). It is also associated with rhabdomyolysis (often a complication of acute poisoning). Hyperkalaemia is also a major feature of severe metabolic acidosis (due to movement of potassium out of the cells to the extracellular fluid). Hyperkalaemia may also be associated with an

overdose of certain drugs that inhibit membrane ion pumps (Na^+/K^+ATPase), an effect which may lead to a shift of potassium from inside the cell to the extracellular fluid (e.g. digoxin). Other poisonous substances associated with hyperkalaemia include fluoride (opening of potassium channels), cyanide (depletion of adenosine triphosphate), ingestion of potassium salts and lithium (in cases where lithium produces renal tubular toxicity).

Management of hyperkalaemia according to serum levels and/or ECG changes, includes the following measures:

- Mild hyperkalaemia (6.0 mmol/l) may respond to diminished intake (1/2 Darrow's solution should be avoided in children). Sodium bicarbonate can be given if the patient is acidotic. The acid-base status should be monitored. A loop diuretic (furosemide 1 - 5 mg/kg) may also enhance renal potassium excretion. A plasma potassium level above 6.0 mmol/l requires the administration of sodium polystyrene sulfonate (Kexelate, formerly known as Kayexelate). The dose in adults is 15 - 30 g orally or 30 - 50 g by retention enema, repeated 6 hourly as needed, and in children 1 - 2 g/kg/dose. The oral route is more effective although some clinicians prefer a high-retention enema. The onset of action is usually within 30 - 60 minutes.
- More severe cases of hyperkalaemia (potassium ≥ 7mmol/l) require Kexelate as well as other more aggressive and rapid-acting measures, including:
  - **Insulin/glucose regimen**. The ratio is 1 U insulin per 2 g glucose. The average dose of insulin is 5 - 10 U of regular insulin given by intravenous push, combined with 20 - 40 ml of 50% glucose. The onset of action is usually within 30 minutes. This should be followed by 10% dextrose/H_2O at 50 ml/h to prevent hypoglycaemia. The recommended paediatric dose of 50% dextrose/water is 1 - 2 ml (0.5 - 1.0 g)/kg intravenously over 30 minutes (50 ml of a 50% ampoule contains 25 g dextrose). To this solution is added 1 U of soluble insulin per 5 gram dextrose, or 0.1 U to 1 ml (0.5 g) 50% dextrose. Blood glucose levels should be monitored regularly. (Some paediatricians use the glucose/insulin regimen only if other measures fail, or in cases where potassium levels are between 9 and 10 mmol/l.
  - **Raising the pH**, either with $NaHCO_3$ or by hyperventilation, where applicable. The effectiveness of empirical administration of $NaHCO_3$ for the treatment of life-threatening acute hyperkalaemia has recently been questioned.
  - **Salbutamol therapy**, by inhalation or the intravenous route. The inhalation (nebulisation) dose in adults is 10 - 20 mg (5 mg/ml solution) over 10 minutes. In children the recommended inhalation dose is 2.5 - 5 mg over 20 minutes by nebulisation. The intravenous dose is 4 µg/kg in both adults and children. The effect lasts for 2 - 4 hours. The use of salbutamol should only be implemented as adjunctive therapy to other more traditional treatment modalities. It appears to be a safe and reasonably effective means of treatment. It may be used as an interim measure while waiting for dialysis or other potassium-removing therapies to be instituted.
  - **Haemodialysis** should be considered if the above measures fail. It could take a few hours to start a dialysis procedure. Other treatment modalities, therefore, should be carried out even if dialysis is anticipated.
  - **Note.** The intravenous administration of 10 - 20 ml of 10% calcium gluconate (over 5 - 10 minutes, and under ECG control) should be reserved for the *management of the cardiodysrhythmic and cardioplegic effects* of hyperkalaemia. However, if the patient initially presents with cardiac dysrhythmias due to hyperkalaemia, the administration of calcium should be a priority. Paediatricians tend to administer calcium earlier, especially if the serum calcium is decreased. The recommended paediatric dose of 10% calcium gluconate solution is 0.5 - 1 ml/kg at a rate of 1.0 ml/min. Pulse rate is a useful parameter to guide the dose. Caution should be employed when giving calcium to patients on digoxin, because of the risk of precipitating hypokalaemia-related dysrhythmias.

Hypernatraemia and hyponatraemia are uncommon in acute poisoning/drug overdose.

Hypernatraemia and hyponatraemia

Hypernatraemia and hyponatraemia are uncommon in acute poisoning/drug overdose. Hyponatraemia (< 130 mmol/l), however, has been reported to occur in certain cases of snakebite (e.g. berg adder and other minor adder bites). The cause is not

known, but it is probably not due to excessive secretion of antidiuretic hormone. Severe hyponatraemia (< 120 mmol/l) may cause convulsions.

Management of hyponatraemia includes the restriction of water and the administration of sodium if serum levels are < 130 mmol/l in cases of inappropriate ADH secretion.

Hypocalcaemia *(see block)*

Hypocalcaemia is a known complication of fluoride poisoning. It is also associated with ethylene glycol poisoning. (The normal total serum calcium is 2.05 - 2.56 mmol/l, the ionised calcium is 1.1 - 1.3 mmol/l and the protein-bound calcium is 0.9 - 1.1 mmol/l.) In severe cases intravenous calcium gluconate is indicated (see block).

The use of intravenous calcium gluconate in severe hypocalcaemia

In acute symptomatic hypocalcaemia the intravenous dose is 10 ml of a 10% calcium gluconate solution, at a rate not exceeding 5 ml/min, repeated once, if necessary. Thereafter, 10 ml of 10% calcium gluconate per litre of 5% dextrose/H_2O at a rate of 50 - 100 ml/h. The paediatric dose is one-half of the adult dose. Hypocalcaemia is common in children in acute renal failure, and calcium levels may decrease precipitously to very low levels in rhabdomyolysis (phosphate levels may at the same time be elevated).

Hypoglycaemia

Coma and convulsions resulting from hypoglycaemia occur occasionally in acute poisonings. (Normal random serum glucose is 4.1 - 11.1 mmol/l.) The sulphonylureas (oral antidiabetic agents), insulin and ethanol are implicated in most cases. Hypoglycaemia may also be a complication of severe paracetamol and *Amanita phalloides* poisoning due to liver failure. After correction of hypoglycaemia with 50% dextrose/H_2O, a continuous infusion of 20% glucose should be administered to prevent relapse.[4]

References available on request.

The amount of sodium needed to replace the deficit can be calculated (if 130 mmol is your aim) as follows:

(130 - measured Na^+) x 0.6 x weight in kg. This formula gives the deficit in mmol. The administration of 40 ml normal saline per kg should raise the serum sodium by 10 mmol/l. If fluid has to be restricted, a 5% NaCl solution may be used (1.17 ml of a 5% NaCl solution is equal to 1 mM). Hypertonic (5%, 850 mmol/l) saline should be administered by a central line. It is recommended to give half the calculated dose of sodium, and then according to follow-up levels. In the management of acute hyponatraemia it is advisable to administer sodium until the symptoms (convulsions) disappear and not until the serum sodium is normal. ($NaHCO_3$ solution (4.2%) may also be utilised as a source of sodium.) *Note:* As a general guideline it is recommended that the serum sodium not be allowed to increase by > 0.5 mmol/l/h in chronic hyponatraemia (not > 2 mmol/l in 4 hours), or > 1 mmol/l/h (not > 4 mmol/l in 4 hours) in acute hyponatraemia. (Hyponatraemia of more than 36 - 48 hours' duration is considered chronic.) Serum sodium levels should be monitored at least 4 hourly. Inappropriate rapid correction of serum sodium may produce central pontine myelinosis.

IN A NUTSHELL

Acid-base and potassium abnormalities are common in poisoning.

Poisoning should be excluded in cases of unexplained metabolic acidosis.

Major adverse consequences of severe acidaemia include decreased cardiac output, decreased arterial blood pressure, reduction in the threshold for cardiac dysrhythmias, and a decrease in hepatic and renal blood flow.

The anion gap is increased in cases of ketoacidosis, lactic acidosis, and other forms of acidosis in which organic anions are increased, as in methanol and ethylene glycol poisoning.

SINGLE SUTURE

A little of what you fancy ...

As drinking and abstinence behaviour changes over time, some view the conventional J-shaped mortality curve (which depicts abstainers and heavy drinkers as having a higher mortality risk than those who indulge moderately) with scepticism. When researchers prospectively studied the relation by using two measurement points, they found that risk for consistent abstainers was not raised, but for men who consistently drank heavily the all-cause mortality risk was higher. Abstainers who started drinking did not improve their survival rate; heavy drinkers who reduced consumption did.

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