lactic acidosis [created by Paul Young 15/12/07]

definitions & significance

- Definitions differ concerning the blood level at which a lactic acidosis is regarded as significant' but as a guide:
Hyperlactaemia: a level from 2 mmols/l to 5 mmol/l.
Severe Lactic Acidosis: when levels are greater than 5 mmols/l
- As levels rise above 5mmols/l, the associated mortality rate can become very high.
- The brief and often very high lactate levels that occur with severe exercise or generalised convulsions (eg up to 30 mmol/l) are associated with an extremely low mortality rate so the absolute lactate level (alone) is not a good predictor of outcome unless the cause of the high level is also considered.

physiology of lactate

Daily Production of Lactate
- Each day the body has an excess production of about 1500 mmols of lactate (about 20 mmols/kg/day) which enters the blood stream and is subsequently metabolised mostly in the liver. This internal cycling with production by the tissues and transport to and metabolism by the liver and kidney is known as the Cori cycle. This normal process does not represent any net fixed acid production which requires excretion from the body.
- All tissues can produce lactate under anaerobic conditions but tissues with active glycolysis produce excess lactate from glucose under normal conditions and this lactate tends to spill over into the blood.

Relationship of lactate to pyruvate
- Lactate is produced from pyruvate in a reaction catalysed by lactate dehydrogenase:
Pyruvate + NADH + H+ <=> Lactate + NAD+
- This reaction is so rapid that pyruvate and lactate can be considered to be always in an equilibrium situation. Normally the ratio of lactate to pyruvate in the cell is 10 to 1. The ratio [NADH]/[NAD+] by the Law of Mass Action determines the balance between lactate and pyruvate. This ratio is also used to denote the redox state within the cytoplasm. Lactic acid has a pK value of about 4 so it is fully dissociated into lactate and H+ at body pH. In the extracellular fluid, the H+ titrates bicarbonate on a one for one basis.

Tissues Producing Excess Lactate
- At rest, the tissues which normally produce excess lactate are:
(i) skin - 25% of production
(ii) red cells - 20%
(iii) brain - 20%
(iv) muscle - 25%
(v) gut - 10%
- During heavy exercise, the skeletal muscles contribute most of the much increased circulating lactate.
- During pregnancy, the placenta is an important producer of lactate which passes into both the maternal and the foetal circulations.

Lactate metabolism
- Lactate is metabolised predominantly in the liver (60%) and kidney (30%).
- Half is converted to glucose (gluconeogenesis) and half is further metabolised to CO2 and water in the citric acid cycle. The result is no net production of H+ (or of the lactate anion) for excretion from the body.
- Other tissues can use lactate as a substrate and oxidise it to CO2 and water but it is only the liver and kidney that have the enzymes that can convert lactate to glucose.
- The balance between release into the bloodstream and hepatorenal uptake maintains plasma lactate at about one mmol/l.
- The renal threshold for lactate is about 5 to 6 mmols/l so at normal plasma levels, no lactate is excreted into the urine. The small amount of lactate that is filtered (180mmol/day) is fully reabsorbed.

pathophysiology of lactic acidosis

- Lactic acidosis can occur due to:
(i) excessive tissue lactate production
(ii) impaired hepatic metabolism of lactate
- In most clinical cases it is probable that both processes are contributing to the development of the acidosis. The liver has a large capacity to metabolise lactate so increased peripheral production alone is unlikely to lead to other than transient acidosis.

- In situations where lactic acidosis is clearly due to excessive production alone (such as severe exercise or convulsions), the acidosis usually resolves (due to hepatic metabolism) within about an hour once the precipitating disorder is no longer present. In severe exercise, lactate levels can rise to very high levels eg up to 30 mmol/l.

- A continuing lactic acidosis means that there is continuing production of lactate that exceeds the liver's capacity to metabolise it. This may be due to clearly very excessive production (eg convulsions) with a normal liver at one extreme, or to increased production in associated with greatly impaired hepatic capacity to metabolise it (eg due to cirrhosis, sepsis, hypoperfusion due hypovolaemia or hypotension, hypothermia, or some combinations of adverse factors) at the other extreme.

- lactic acidosis in sepsis has been attributed to:
(i) impaired regional microvascular blood flow & autoregulation
(ii) mitochondrial dysfunction with impaired pyruvate oxidation
(iii) excess catecholamines may impair hepatic lactate extraction (by reducing regional hepatic blood flow)
(iv) lactate clearance is decreased because pyruvate dehydrogenase activity is reduced in both skeletal muscle and liver.
NB:
- tissue hypoxia may not be a major mechanism & NMR spectroscopy suggests that hyperlactaemia may occur without tissue hypoxia
- net lactate production from the hepatosplanchnic bed is uncommon in sepsis

causes (Cohen & Woods classification)

Type A Lactic Acidosis : Clinical Evidence of Inadequate Tissue Oxygen Delivery
(i)Anaerobic muscular activity (eg sprinting, generalised convulsions)
(ii)Tissue hypoperfusion (eg shock -septic, cardiogenic or hypovolaemic; hypotension; cardiac arrest; acute heart failure; regional hypoperfusion esp mesenteric ischaemia)
(iii) Reduced tissue oxygen delivery or utilisation (eg hypoxaemia, CO poisoning, severe anaemia)
- If hypoxaemia is the only factor present, it needs to be severe (eg paO2 < 35mmHg) to precipitate lactic acidosis because of the protection afforded by the body's compensatory mechanisms which increase tissue blood flow. Similarly anaemia needs to be severe (eg [Hb] <5g/dl) if present alone because tissue blood flow is increased in compensation.

Type B Lactic Acidosis: No Clinical Evidence of Inadequate Tissue Oxygen Delivery
- refers to situations in which there is no clinical evidence of reduction in tissue oxygen delivery. Carbohydrate metabolism is disordered for some reason and excess lactic acid is formed. Research using more sophisticated methods to assess tissue perfusion have now shown that occult tissue hypoperfusion is present in many cases of Type B acidosis.
(i) type B1 : Associated with underlying diseases
- LUKE leukaemia, lymphoma
- TIPS thiamine deficiency, infection, pancreatitis, short bowel syndrome
- FAILURES hepatic, renal , diabetic failures
(ii) type B2: Assoc with drugs & toxins (eg phenformin, cyanide, beta-agonists, methanol, adrenaline, salicylates, nitroprusside infusion, ethanol intoxication in chronic alcoholics, anti-retroviral drugs, paracetamol, salbutamol, biguanides, fructose, sorbitol, xylitol, isoniazid)
(iii) type B3: Assoc with inborn errors of metabolism (eg congenital forms of lactic acidosis with various enzyme defects eg pyruvate dehydrogenase deficiency)

diagnosis

- The condition is often suspected on the history and examination (eg shock, heart failure) and is easily confirmed and quantified by measuring the blood lactate level.
- It may be associated with other causes of a high anion gap acidosis (eg ketoacidosis, uraemic acidosis)
- Coexistent lactic acidosis and metabolic alkalosis may result in minimally altered plasma bicarbonate level. A high anion gap may be a clue in this later situation but the anion gap is not invariably elevated out of the reference range

management

- The principles of management of patients with lactic acidosis are:
(i) Diagnose and correct the underlying condition (if possible)
(ii) Restore adequate tissue oxygen delivery (esp restore adequate perfusion)
(iii) Ensure appropriate compensatory hyperventilation where possible

Use of bicarbonate:
- two randomised controlled studies of bicarbonate in lactic acidosis and shock found no beneficial effects on cardiac function or any other effects of pH correction
- potential adverse effects include:
(i) acute hypercapnia
(ii) ionised hypocalcaemia
(iii) intracellular acidosis due to CO2 crossing cell membranes rapidly
(iv) acute intravascular overload
(v) bicarbonate increases lactate production by increasing the activity of the rate limiting enzyme phosphofructokinase, shifts Hb-O2 dissociation curve, increased oxygen affinity of haemoglobin and thereby decreases oxygen delivery to tissues
- potential indications:
(i) patients with pulmonary hypertension in whom pulmonary vasoconstriction may be worsened by acidosis
(ii) patients with significant ischaemic heart disease in whom severe acidosis lowers the threshold for arrhythmia

Carbicarb:
- carbicarb is an equimolar combination of sodium bicarbonate & sodium carbonate which generates less CO2 than HCO3 & may have less adverse effects. It is not in clinical usage

Dichloroacetate:
- DCA stimulates the activity of phosphate dehydrogenase complex, the rate limiting enzyme that regulates entry of pyruvate into the TCA cycle. It increases intracellular pH and decreases lactate concentrations; however, a large multicentred study found no haemodynamic benefit or improvement in patient outcome in treatment of patients with lactic acidosis
- it is not commercially available

Tris / THAM
- Tris-hydroxymethyl aminomethane is a weak alkali which is rarely used because of concerns about side effects. Namely,
(i) hyperkalaemia
(ii) hypoglycaemia
(iii) extravasation necrosis
(iv) neonatal hepatic necrosis

Dialysis / haemofiltration:
- peritoneal dialysis is not useful in removing lactate when using bicarbonate buffered haemofiltration; it remains a useful marker of clinical disease progression in patients on bicarbonate buffered haemofiltration