**Blue acid blues**

**Introduction**

Anion gap metabolic acidosis is always a medical emergency and requires diagnosis with therapeutic decisions within 30 min. The holidays commonly are associated with anion gap metabolic acidosis for various reasons. One such reason is the fact that not everyone is celebrating; rather, for some, holidays contribute to personal loneliness and depression termed 'the blues'. During the Christmas holidays, depression is particularly common. We encountered two patients with sudden, severe metabolic acidosis and Kussmaul’s respiration during the last Christmas holidays. Comparisons and contrasts between the two patients were particularly revealing.

**Cases**

**Case 1**

A 50-year-old woman was admitted after developing depressed consciousness. She had never been ill before but was known to enjoy a ‘drop or two’ and had been tipsy (German slang *blau*) on previous occasions. On physical examination, she was cooperative but appeared intoxicated. She could not perform serial-seven subtractions and was not oriented to time and place. Her physical examination revealed a deep respiratory rate of 24/min. Her heart rate was 100/min and her blood pressure was 140/90 mmHg. Otherwise, there were no localizing neurological findings or remarkable physical findings.

Her haemoglobin and haematocrit were normal. She had a leukocytosis and her serum creatinine was 69 µmol/l. Her PaO₂ was 106 mmHg, PaCO₂ 16 mmHg, HCO₃ 6 mmol/l and pH 7.13. Furthermore, Na was 140 mmol/l, K 5.8 mmol/l and Cl 111 mmol/l. Her lactate level was <1 mmol/l. The blood sugar was 6 mmol/l while the urea concentration was 9 mmol/l. The anion gap was 18 mmol/l. Thus, the increase in the anion gap of 18 mmol/l was quite similar to the 18 mmol/l decrease in the HCO₃ concentration. Serum osmolality was 348 mOsm/kg H₂O. No ethanol was identified in her plasma. A urine specimen was obtained and microscopic needle-like and envelope-shaped crystals were identified. Ethanol was given intravenously sufficient to raise the serum concentration to 100 mg/dl. Dialysis was promptly instituted. Her husband found a suspicious bottle in the home that had previously resided in the trunk of his car. The clinical pathologist confirmed the diagnosis and the patient recovered after two haemodialysis treatments.

**Case 2**

A 36-year-old chemistry laboratory technician was brought into the emergency department in a coma. The time of admission was shortly after 12.00. His mother had visited him earlier that morning at 09.00. At that time, he was well. The mother related that other than attempted suicide 3 years earlier, her son had been medically well. The deep respiratory rate was 32/min, the heart rate was 100/min and the blood pressure was 120/60 mmHg. Other than coma with fairly wide-spaced pupils, there were no localizing neurological findings. The oculovestibular reflexes appeared intact, the neck was supple and the plantar responses were flexor. Corneal reflexes were present, but the patient did not respond to pain. The chest was clear. Other than tachycardia, the heart was unremarkable and the abdominal examination was negative. No needle marks were seen and no strange odours were perceived.

The PaO₂ was 120 mmHg, PaCO₂ 19 mmHg and pH 6.96. The haemoglobin and haematocrit were normal while the white count was 32 000 µl⁻¹. The HCO₃ was 3.8 mmol/l, Na 145 mmol/l, K 3.0 mmol/l and Cl 107 mmol/l. The creatinine was 97 µmol/l, urea 5 mmol/l and glucose 10 mmol/l. The anion gap was 35 mmol/l. The lactate level was 20 mmol/l. The serum osmolality was 326 mOsm/kg H₂O. Searches for ethylene glycol, ethanol, acetylsalicylic acid and methanol were negative. The urinary sediment was unremarkable. Analyses for a host of other drug ingestions were negative. The patient’s anion gap increase fitted well with his HCO₃ decrease. His lactate increase also corresponded well with his HCO₃ decrease and accounted for the increase in the anion gap. The mystery for the clinicians was to
determine how the patient developed a sudden, severe, lactic acidosis without being in shock. A diagnostic gastric aspirate was obtained and activated charcoal was given. The patient received sufficient NaHCO₃ intravenously to increase his serum HCO₃ to >10 mmol/l. After 9 h, the patient regained consciousness without specific therapy and was able to give a history of what had transpired.

**Questions**

- What did each of these patients have and what was the mechanism of the anion gap metabolic acidosis?
- Why did each patient have a fairly normal or low serum potassium concentration in spite of the severe acidosis?
Answer to the quiz on the preceding page

Astute clinicians will make the diagnosis of metabolic acidosis on the basis of history and physical signs alone. Kussmaul drew attention to the typical respiratory pattern almost 150 years ago. Both patients had markedly increased alveolar ventilation, as shown by a low PaCO₂. The increased anion gap immediately draws attention to the differential diagnosis that can be drawn from Kussmaul’s name (ketoadiposis, uraemia, salicylic acid (säure in German), methanol, ethylene glycol (ae in German), uraemia (twice for beginners) and lactate). Failure to act on an anion gap metabolic acidosis may have fatal consequences for the patient [1]. Also important is to determine whether or not the increase in the anion gap accounts for all of the decrease in the bicarbonate concentration. If this is not the case, a non-anion gap-related mechanism is contributing to the metabolic acidosis.

The first patient had ethylene glycol intoxication that was probably accidental rather than suicidal. Solutions of ethylene glycol are said to have a not unpleasant sweetish taste and persons seeking alcohol (ethanol) can drink sizeable quantities with apparent enjoyment. HOCH₂CH₂–OH has a molecular weight of 62 Da and is distributed within the total body water. One gram of the substance would provide 16 mmol. If we assume a total body water of 40 l, she must have ingested ~148 g of the toxin. This amount would equal 2368 mOsm. Distributed in 40 l, her osmolality should increase by ~60 mOsm/kg H₂O. She may have ingested more of the material, since some time had elapsed allowing metabolism to dialdehyde (glyoxal) and to glyoxylic acid via the enzyme alcohol dehydrogenase. Eventually, the compounds are metabolized to oxalate, which appears in the urine as oxalate monohydrate or oxalate dihydrate and is responsible for the characteristic crystals. The strategy is to block the metabolism with ethanol, since alcohol dehydrogenase by far prefers that substrate, and to remove the toxic compounds with haemodialysis. Ethanol (CH₃CH₂OH) has a molecular weight of 46 Da. The desired serum concentration is 100 mg/dl (or 0.1%). Assuming the patient’s total body water is ~40 l, ~40 g of ethanol would be necessary. This amount should raise her osmolality by ~20 mOsm/kg H₂O. The use of fomepizole to block alcohol dehydrogenase is preferable since the drug does not cause CNS depression, hypoglycaemia or acetaldehyde build up, all of which accompany ethanol therapy [2]. Drug-level maintenance with fomepizole is less of a problem. In the US where time is indeed money, calculations showed that with fomepizole and dialysis, the ethylene glycol-intoxicated patient could be discharged within 24 h [3]. We were obliged to use ethanol. Our patient recovered quickly and completely.

The second patient admitted to ingesting potassium cyanide with suicidal intent. Cyanide (hydrocyanic acid, prussic acid or blue acid, Blausäure in German) is one of the most rapidly acting poisons. Victims commonly die within minutes. Hydrogen cyanide gas is used to fumigate ships, buildings and to sterilize soil. In the household, cyanides are present in silver polish, insecticides, rodenticides and fruit seeds. Cyanide is also used for executions in so-called gas chambers and was used for more than 900 religious ‘suicide murders’ in Guyana some years ago. We were annoyed to learn that our patient had made contact with a ‘suicide’ website before his hospitalization. Oxidative phosphorylation can be inhibited at numerous places. Cyanide (CN⁻), azide (N₃⁻) and carbon monoxide (CO) can all block electron flow in cytochrome-c oxidase. Cyanide and azide react with the ferric (Fe³⁺) form of haem, whereas carbon monoxide inhibits the ferrous (Fe²⁺) form. Dimethylbiguanides are also associated with lactic acidosis. The mechanism is still being explored. Recent data suggest that the compounds inhibit cell respiration via an indirect effect on the respiratory chain complex I. Our patient had no type 2 diabetes and no reason to have ingested metformin. The risk of lactic acidosis caused by metformin, in any event, is remote [4].

We failed to make a speedy diagnosis in our patient, since we had no antecedent history. More importantly, we failed to initially recognize that oxidative uncoupling had undoubtedly occurred in our patient. The unexplained lactic acidosis should have tipped us onto this possibility immediately. Graham et al. [5] reported a similar case that they also initially missed. Their patient had ingested 600 mg potassium cyanide and presented with unexplained lactic acidosis and pulmonary oedema. They also relied on a gastric aspirate to make the diagnosis of potassium cyanide poisoning. We might have also measured mixed venous PvO₂, which is normally ~40 mmHg, representing an oxygen saturation of 40%. We would have undoubtedly learned that tissue oxygen delivery (DO₂) was normal in our patient, but that oxygen demand (VO₂) was impaired. Thus, the oxygen extraction was surely diminished in our patient.

Critical-care physicians are aware of smoke inhalation injuries causing cyanide, in addition to carbon monoxide poisoning. Shusterman and Hargis [6] drew attention to the close correlation between the anion gap and whole blood cyanide levels in smoke inhalation-induced cyanide poisoning. They show that the anion gap and arterial pH are excellent parameters of severity, in addition to being a valuable diagnostic clue. The treatment of cyanide poisoning, particularly in smoke inhalation, remains unsatisfactory. Nitrites result in methaemoglobin formation, which competes with cytochrome-c oxidase by virtue of its Fe³⁺ atom. The reaction favours methaemoglobin because of mass action. Cyanide is converted to less toxic thiocyanate by the enzyme transsulph하세요. To accelerate detoxification, thiosulphate is administered and the thiocyanate formed is excreted in the urine. Dialysis has...
been suggested to facilitate excretion of thiocyanate and various other potentially toxic products [7]. Hydroxycobalamin combines with cyanide to form cyanocobalamin. In a prospective study, hydroxycobalamin appeared safe in fire victims with or without cyanide poisoning. The only reported side effect was a red colouration of the skin and urine [8]. Five grams of hydroxycobalamin appears capable of binding all available cyanide ions for blood cyanide concentrations up to \( \sim 40 \mu \text{mol/l} \) [9].

Finally, why didn’t our two patients have hyperkalaemia accompanying their metabolic acidosis? Both had severe acidaemia. Most clinicians believe that acidosis causes hyperkalaemia because of shifts of potassium from the intracellular to the extracellular compartment. However, uncomplicated organic acidaemias do not produce hyperkalaemia [10]. In acidosis associated with mineral acids, such as end-stage uraemic acidosis, \( \text{NH}_4\text{Cl} \)- or \( \text{CaCl}_2 \)-induced acidosis, acidaemia per se, results in predictable increases in serum potassium concentration. In acidosis associated with non-mineral organic acids (such as diabetic and alcoholic acidosis, lactic acidosis, methanol and the less common forms of organic acidaemias secondary to methylmalonic and isovaleric acids, and ethylene glycol, paraldehyde and salicylate intoxications) serum potassium concentration usually remains within the normal range in uncomplicated cases.

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References

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