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Teaching Point
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Where is the gap?

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Introduction

In 1960, John F. Kennedy ran against Richard Nixon in an extremely close US presidential election. Kennedy, an adroit politician if ever there were one, made the 'missile gap' into his major campaign issue. After his successful election, this disingenuous issue was never heard from again; the gap was suddenly gone. We were recently confronted with a gap of a different nature or rather lack of one. Our riddle lay in figuring out, 'where is the gap'.

Case

A 17-year-old girl presented herself in our emergency department in the morning after suicidal ingestion of 250–300, 325 mg acetylsalicylic acid (Aspirin®). She announced that she had ingested the tablets on the previous evening. She developed vomiting and tinnitus prior to admission. She was 167 cm tall and weighed 52 kg. Her blood pressure was 132/74 mmHg, heart rate 110/min and the respiratory rate 26/min. She was alert, her pupillary response slightly delayed, she had mild epigastric tenderness and the bowel sounds were diminished. Her blood values were as following: pH 7.51, pO_2 121 mmHg (16.1 kPa), pCO_2 18 mmHg (2.38 kPa), HCO_3^- 14 mmol/L, lactate 0.8 mmol/L, sodium 142 mmol/L, potassium 3.2 mmol/L, chloride 123 mmol/L, ionized calcium 0.98 mmol/L, creatinine 72 μmol/L (0.81 mg/dL). The serum salicylate concentration was 6.4 mmol/L (88 mg/dL).

We administered 100 mL sodium bicarbonate 8.4%, 40 mmol potassium, 2 mg tropisetron and 80 mg esomeprazole intravenously. Furthermore, a central venous catheter was introduced into the internal jugular vein and haemodialysis was begun. Haemodialysis was continued until the salicylate levels decreased sufficiently. The clinical course was uneventful and we transferred her to our psychiatric department.

Discussion

Our patient presented with alkalaemia, pCO_2 18 mmHg and a HCO_3 concentration of 14 mmol/L. Thus, she had respiratory alkalosis. Her pCO_2 was reduced from normal by 22 mmHg, so we would have expected compensation of her HCO_3 from 24 to about 19 mmol/L. However, her HCO_3 level was lower than anticipated for appropriate [1]. We reasoned that a clandestine metabolic acidosis had to be concomitantly present. The next step would be to check the anion gap. However, her anion gap was [142 − (14 + 123)] 5 mmol/L. The gap was low rather than high. Just like John Kennedy's missile gap, our anion gap was gone. Fortunately, we knew the diagnosis and enjoyed excellent laboratory support. We measured salicylate directly and did not have to add ferric chloride to her urine as earlier generations of clinicians once did. None of us could recall ever having seen a chloride of 123 mmol/L in a patient with serum sodium 142 mmol/L. Low anion gaps are generally related to hypoalbuminaemia, which was not present in our patient. The possibility of positively charged IgG proteins also appeared remote [2]. But then, our patient required care and we directed our attention elsewhere.

We gave our patient a bicarbonate infusion because alkalinizing the urine should increase salicylate elimination. The conventional view is that ionization of a weak acid is increased in an alkaline environment. However, as salicylic acid is almost completely ionized within physiological pH limits, alkalinization of the urine could not possibly further increase the extent of ionization [3]. Sacred cows indeed resist killing. Fortunately, dialysis is helpful in removing this small water-soluble compound. Our patient's salicylate concentrations were 88 mg/dL. The therapeutic serum level of salicylate is 1.1–2.2 mmol/L (15–30 mg/dL). Levels >30 mg/dL are associated with toxic symptoms [4]. We decided to err on the safe side [5].

Pilots are taught, 'believe your instruments; they are better than you are'. Most low or negative anion gaps are related to errors in the measurement of one of the electrolytes. Ion-selective electrodes have largely circumvented this problem. Bromide and iodide can confound chloride measurements, but our patient was not exposed to these halides. Interference of salicylates with ion-selective electrodes is less known, although a few cases have been described in the literature [6–8].

We measured chloride with a different method (P-Modular; Roche Diagnostics, Rotkreuz, Switzerland), which

is unsusceptible to salicylate interference, and amazingly, the new measured chloride concentration was 108 mmol/L (instead of 123 mmol/L as measured initially with the blood gas analyzer ABL™ 725 (Radiometer Medical ApS, Brønshøj, Denmark)). We checked the reference manual of the ABL 700 series, and we found the puzzle's solution: a description of acetylsalicylic acid and salicylic acid interference on the chloride electrode. Acetylsalicylic acid at 3.0 mmol/L increases chloride by 2 mmol/L and salicylic acid at 4.0 mmol/L even increases chloride by 7 mmol/L.

Our gap was thus restored. With this adjustment, we now had an elevated anion gap of 20 mmol/L and the world was in order again. What if John Kennedy would have lost that 1960 election and Richard Nixon had assumed command 8 years earlier? Would there have been that 18-min gap in tapes underneath his desk? We underscore the importance of gaps, particularly those that are not readily explained.

Teaching points

(1) A low anion gap is caused by either a decrease in unmeasured anions or an increase of unmeasured cations.

(2) Trust the numbers, but if they make no sense, seek other alternatives.

(3) Modern equipment is terrific but not fail proof.

Conflict of interest statement. None declared.

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