Correction of the anion gap for albumin in order to detect occult tissue anions in shock

M Hatherill, Z Waggie, L Purves, L Reynolds, A Argent

Background: It is believed that hypoalbuminaemia confounds interpretation of the anion gap (AG) unless corrected for serum albumin in critically ill children with shock.

Aim: To compare the ability of the AG and the albumin corrected anion gap (CAG) to detect the presence of occult tissue anions.

Methods: Prospective observational study in children with shock in a 22 bed multidisciplinary paediatric intensive care unit of a university children’s hospital. Blood was sampled at admission and at 24 hours, for acid-base parameters, serum albumin, and electrolytes. Occult tissue anions (lactate + truly “unmeasured” anions) were calculated from the strong ion gap. The anion gap (\((Na + K) - (Cl + bicarbonate)\)) was corrected for serum albumin using the equation of Figge: \(AG + (0.25 \times (44 - \text{albumin}))\). Occult tissue anions (TA) predicted by the anion gap were calculated by (anion gap – 15 mEq/l). Optimal cut off values of anion gap were compared by means of receiver operating characteristic (ROC) curves. Ninety three sets of data from 55 children (median age 7 months, median weight 4.9 kg) were analysed. Data are expressed as mean (SD), and mean bias (limits of agreement).

Results: The incidence of hypoalbuminaemia was 76% (n = 42/55). Mean serum albumin was 25 g/l (SD 8). Mean AG was 15.0 mEq/l (SD 6.1), compared to the CAG of 19.9 mEq/l (SD 6.6). Mean TA was 10.2 mmol/l (SD 6.3). The AG underestimated TA with mean bias 10.2 mmol/l (4.1–16.1), compared to the CAG, mean bias 5.3 mmol/l (0.4–10.2). A clinically significant increase of TA >5 mmol/l was present in 83% (n = 77/93) of samples, of which the AG detected 48% (n = 36/77), and the CAG 87% (n = 67/77). Post hoc ROC analysis revealed optimal cut off values for detection of TA >5 mmol/l to be AG >10 mEq/l, and CAG >15.5 mEq/l.

Conclusion: Hypoalbuminaemia is common in critically ill children with shock, and is associated with a low observed anion gap that may fail to detect clinically significant amounts of lactate and other occult tissue anions. We suggest that the albumin corrected anion gap should be calculated to screen for occult tissue anions in these children.

Methods

This prospective observational study was set in the 22 bed multidisciplinary paediatric intensive care unit (PICU) of a university children’s hospital. Children admitted to the PICU...
with shock requiring either additional fluid resuscitation or inotropic support, were eligible for enrollment with the informed consent of their parents. Shock was defined as hypotension (blood pressure lower than 2 standard deviations from the age appropriate mean), or poor peripheral perfusion (absent peripheral pulses or capillary refill time > 4 seconds). \(^{15}\) Children admitted following trauma, cardiac surgery, or with an inherited metabolic disease were excluded. The institutional research ethics committee approved the study protocol.

Ringer’s lactate is the routine resuscitation fluid for children with hypovolaemia and shock at this institution, in preference to albumin based solutions, normal (0.9 %) saline, or synthetic colloid. It is not routine practice to correct hypoalbuminaemia by infusion of a concentrated albumin solution.

Blood was sampled on admission to PICU, 24 hours after admission, and at intervals determined by the patient’s clinical condition, for determination of: arterial pH, base excess (BE), standard bicarbonate (SB), serum lactate, serum albumin, and serum electrolytes. A maximum of two samples per patient were included for analysis. Acid-base parameters were measured and derived using a Radiometer ABL 520 blood gas analyser (Copenhagen, Denmark). Serum electrolytes were measured by a Beckman Syncron CX5 analyser, using ion specific electrodes (Berlin, Germany). Serum albumin and lactate were measured by a Beckman Syncron CX5 analyser, using the enzymatic method (Berlin, Germany).

Hypoalbuminaemia was defined as <33 g/l. \(^{15}\) Protein energy malnutrition was defined as weight below 60% of expected weight for age, or weight below 3rd centile for age with the presence of oedema. Liver dysfunction was defined as an increase of hepatic enzymes, or international normalised ratio (INR) in the absence of a disseminated intravascular coagulopathy, of more than twice the upper limit of normal.

Liver dysfunction was defined as an incidence of liver dysfunction, or international normalised ratio (INR) in the absence of a disseminated intravascular coagulopathy, of more than twice the upper limit of normal. The AG was calculated using the formula (Na + K) – (Cl + HCO\(_3\)), whereby potassium was considered a “measured”, rather than “unmeasured” cation. \(^{11,13}\) The upper limit of normal of the AG calculated by this formula was defined as 15 mEq/l, based on 2 standard deviations from the mean in studies of “normal” populations which used modern ion specific electrode techniques for the measurement of sodium and chloride, and including an upward adjustment of 4 mEq/l for potassium where necessary. \(^{15,22}\) It should be noted that this limit is lower than that historically derived by flame photometry and colorimetry. \(^{16,17,22-24}\) The CAG was calculated using the formula of Figge. \(^{15}\)

The strong ion difference (SID) and strong ion gap (SIG) were calculated using the standard formulae reported previously. “Unmeasured” anions were derived from the SIG. Occult tissue anions predicted by the SIG were calculated from the serum lactate plus “unmeasured” anions. \(^{15}\) See Appendix 1 for formulae.

Hypolactataemia was defined as serum lactate <2 mmol/l. \(^{11,25}\) Raised “unmeasured” anions were defined as >3 mmol/l. \(^{12}\) A clinically significant increase of occult tissue anions was defined as >5 mmol/l. \(^{12}\)

Occult tissue anions predicted by the anion gap (both AG and CAG) were calculated from the anion gap minus 15 mEq/l. This method assumes that no lactate or “unmeasured” anions occurred in the serum of the “normal” populations from whom this upper limit of 15 mEq/l was obtained. Since the serum lactate of normal individuals may vary between zero and 2 mmol/l, and unmeasured anions between zero and 3 mmol/l, there is inherent potential for underestimation of occult tissue anions, but importantly, this effect is common to both the AG and CAG. \(^{12,25}\)

In order to further define the optimal cut off value of anion gap that should be used for detection of clinically significant occult tissue anions in this study population, post hoc analysis of receiver operating characteristic (ROC) curves was performed for the AG, and CAG, for TA >5 mmol/l.

Non-parametric demographic data were reported as median (range), and analysed using the Mann-Whitney test for continuous data. Parametric data were reported as mean (SD) for continuous data, and analysed using the \(t\) test for categorical data. Differences between techniques were reported as mean bias and limits of agreement (2 SD).

Complete data for calculation of tissue anions from the strong ion difference were available in 55 children, median age 7 months (range 0.1–144), weight 4.9 kg (range 1.8–30). Thirty eight children (69%) had blood sampled both at admission and at 24 hours, such that 93 samples were available for analysis.

### RESULTS

Forty four of the 55 children (80%) were admitted with shock associated with local or systemic sepsis. Other diagnoses included viral myocarditis (\(n = 4\)), meningococcal sepsis (\(n = 2\), as well as iron poisoning, hepatitis, aortic stenosis, hypoplastic left heart syndrome, and near drowning (all \(n = 1\)).

The incidence of hypoalbuminaemia was 76% (\(n = 42/55\)). The incidence of liver dysfunction was 22% (\(n = 12/55\)), and the incidence of protein energy malnutrition was 7% (\(n = 4/55\)). The serum albumin concentration was lower in children with liver dysfunction, median 23 g/l (range 9–33) compared to 25 g/l (range 7–42), and in children with protein energy malnutrition, median 17 g/l (range 15–22) compared to 25 g/l (7–42) (both \(p < 0.001\)).

Table 1 shows acid-base, albumin, tissue anion, and anion gap data. The mean AG was 15.0 (SD 6.1) mEq/l, compared to the CAG of 19.9 (SD 6.6) mEq/l (mean bias 4.9 mEq/l, limits of agreement 0.9–8.8 mEq/l).

Occult tissue anions predicted by the AG were 0.0 (SD 6.1) mmol/l, compared to 4.9 (SD 6.6) mmol/l predicted by the CAG (mean bias and limits of agreement the same as for anion gap above).

### Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{pH})</td>
<td>7.25</td>
<td>0.20</td>
<td>6.70 to 7.62</td>
</tr>
<tr>
<td>BE (mmol/l)</td>
<td>−11.4</td>
<td>8.4</td>
<td>−30 to 5.3</td>
</tr>
<tr>
<td>SB (mmol/l)</td>
<td>15.6</td>
<td>6.3</td>
<td>2.6 to 28.1</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>25</td>
<td>8.0</td>
<td>7 to 42</td>
</tr>
<tr>
<td>Lactate (mmol/l)</td>
<td>5.2</td>
<td>4.8</td>
<td>0.4 to 20.1</td>
</tr>
<tr>
<td>“Unmeasured” anions (mmol/l)</td>
<td>5.0</td>
<td>3.6</td>
<td>−1.1 to 14.5</td>
</tr>
<tr>
<td>SIG calculated TA (mmol/l)</td>
<td>10.2</td>
<td>6.3</td>
<td>0.8 to 32.5</td>
</tr>
<tr>
<td>AG (mEq/l)</td>
<td>15.0</td>
<td>6.1</td>
<td>5.8 to 37.3</td>
</tr>
<tr>
<td>CAG (mEq/l)</td>
<td>19.9</td>
<td>6.6</td>
<td>9.0 to 42.8</td>
</tr>
<tr>
<td>AG predicted TA (mmol/l)</td>
<td>0.0</td>
<td>6.1</td>
<td>−9.2 to 22.3</td>
</tr>
<tr>
<td>CAG predicted TA (mmol/l)</td>
<td>4.9</td>
<td>6.6</td>
<td>−6.0 to 27.8</td>
</tr>
</tbody>
</table>

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\(\text{CAG}\) predicted TA (mean bias and limits of agreement the same as for anion gap above).
Occult tissue anions calculated from the SIG were 10.2 (SD 6.3) mmol/l. It follows that the AG under predicted the amount of tissue anions with mean bias 10.2 mmol/l (limits of agreement 4.1–16.1 mmol/l). The CAG also under predicted tissue anions, with mean bias 5.3 mmol/l (limits of agreement of 0.4–10.2 mmol/l).

Table 2 shows the relations between an increased (>15 mEq/l) AG, CAG, and occult tissue anion concentrations of <2 mmol/l, 2–5 mmol/l, and >5 mmol/l respectively.

<table>
<thead>
<tr>
<th>TA &lt;2 mmol/l</th>
<th>TA 2–5 mmol/l</th>
<th>TA &gt;5 mmol/l</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>AG &lt;15 mEq/l</td>
<td>5 (100%)</td>
<td>11 (100%)</td>
<td>40 (52%)</td>
</tr>
<tr>
<td>AG &gt;15 mEq/l</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>37 (48%)</td>
</tr>
<tr>
<td>CAG &lt;15 mEq/l</td>
<td>5 (100%)</td>
<td>7 (64%)</td>
<td>10 (13%)</td>
</tr>
<tr>
<td>CAG &gt;15 mEq/l</td>
<td>0 (0%)</td>
<td>4 (36%)</td>
<td>67 (87%)</td>
</tr>
<tr>
<td>Total</td>
<td>5 (5%)</td>
<td>11 (12%)</td>
<td>77 (83%)</td>
</tr>
</tbody>
</table>

DISCUSSION

We have shown that in this population of critically ill children with shock, metabolic acidosis, and hyperlactataemia, the incidence of hypoalbuminaemia is greater than 75%. This finding lends support to the hypothesis that critically ill children are likely to have both increased tissue anions and hypoalbuminaemia simultaneously. In other words, a factor that confounds interpretation of the anion gap is present in the very group of patients in whom we most wish to apply it.

Furthermore, the anion gap underpredicted the amount of occult tissue anions by 10 mmol/l, and failed to detect the presence of a clinically significant increase of tissue anions >5 mmol/l in more than 50% of cases. Since both lactate and "unmeasured" anions have been associated with severity of illness and increased mortality, failure to detect such an increase of occult tissue anions might have adverse consequences for the patient.

However, it is gratifying that correction of the anion gap for albumin underestimated occult tissue anions to a lesser degree, and revealed clinically significant increase of these anions in more than 80% of cases. This finding is of clinical importance, since calculation of the albumin corrected anion gap (anion gap + [0.25 × (44 – albumin)]) is relatively simple, and may be performed at the bedside.

Clinical application of the anion gap hinges on three key issues. Firstly, the upper limit of normal depends on whether potassium concentrations are readily obtainable. Ultimately, it does not matter which equation is used, provided that the reference limit is adjusted accordingly for the inclusion, or exclusion, of the charge on potassium.

Secondly, the reference limit should be compatible with the technique used to measure serum electrolytes in that laboratory. Historically, the upper reference limit still quoted by some current texts is that of 16 mEq/l using (Na – (Cl + HCO3)). However, these reference ranges were obtained during the 1970s using flame photometry and colorimetry techniques, which underestimate chloride compared to the modern ion specific electrode techniques that have superseded them. Therefore, since the reference range for serum chloride has risen, the upper limit of the anion gap (mean + 2SD) has fallen correspondingly, to an average of 11 mEq/l excluding potassium or 15 mEq/l including potassium.

Thirdly, the anion gap should be interpreted in the context of other pathophysiological derangements in the individual patient. We have shown that children with shock are frequently hypoalbuminaemic, and that this results in a lowered anion gap that severely underestimates the presence of occult tissue anions. We have shown that in order to detect the presence of tissue anions in children with shock, either the upper limit of "normal" might be lowered to 10 mEq/l, or the anion gap should be corrected for the serum albumin concentration.

It would appear from the ROC analysis that a CAG of 17–20 mEq/l (including potassium) would be the optimal value—that is, the best combination of sensitivity and specificity, to detect occult tissue anions. Yet the negative predictive value of a CAG >15 mEq/l was only 55%. It follows that many shocked children with a normal CAG may still have clinically significant tissue anions, since even the corrected anion gap underestimated the total amount of tissue anions by a considerable margin.

This finding may be due partly to the inherent underestimation of the technique, in that occult tissue anions present “within” the normal anion gap are not accounted for. Interpretation of the anion gap, and the strong ion gap, may also be confounded by the presence of excess “unmeasured” cations, such as paraproteins and cationic drugs, which decrease the observed anion gap. We should also consider the influence of pH. While correction of the anion gap for albumin takes into account the charge on protein at that pH, the equation makes use of the linear relation between albumin and charge shown in critically ill adults whose pH ranged from 7.09 to 7.65. However, at the extremes of metabolic acidoses seen in these children with shock, the relation between pH and charge on protein may not be linear.

Our study population had a higher incidence of protein energy malnutrition (7%) than might be expected in most “developed world” intensive care units. Although these children had a lower albumin concentration than children without evidence of malnutrition, the high incidence of protein energy malnutrition...
hypoalbuminaemia in the entire study group suggests that this finding is a function of critical illness, rather than nutritional status, as has been found previously in both children and adults. These findings should therefore be applicable to all critically ill children.

We suggest that the albumin concentration should be measured in all critically ill children with shock. In centres where the serum lactate is not routinely measured, the albumin corrected anion gap should be calculated to screen for the presence of lactate and other occult tissue anions. Correction of the anion gap for serum albumin will reveal a clinically significant increase of these anions in the majority of cases.

**APPENDIX 1: FORMULAE**

Strong ion difference (apparent) (SIDa) = (Na + K + Mg + Ca) – (Cl + lactate)

Strong ion difference (effective) (SIDe) = (1000 × 2.46E–11 × pCO2 /10) + [albumin × (0.123 × pH – 0.631)] + [PO2 × (0.309 × pH – 0.469)]

Strong ion gap (SIG) = “unmeasured” anions (UA) = SIDa – SIDe

Uncorrected anion gap (AG) = (Na + K) – (Cl + HCO3–)

Albumin corrected anion gap (CAG) = AG + [0.25 × (44 – albumin)]

Tissue anions (TA) = lactate + UA

**Authors’ affiliations**

M Hatherill, Z Wagie, L Reynolds, A Argent, Paediatric Intensive Care Unit, School of Child & Adolescent Health, University of Cape Town, and Red Cross War Memorial Children’s Hospital, Cape Town, South Africa

L Purves, Department of Chemical Pathology, School of Child & Adolescent Health, University of Cape Town, and Red Cross War Memorial Children’s Hospital

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