ORIGINAL ARTICLE

Correcting the anion gap for hypoalbuminaemia does not improve detection of hyperlactataemia

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Background: An elevated lactate level reflects impaired tissue oxygenation and is a predictor of mortality. Studies have shown that the anion gap is inadequate as a screen for hyperlactataemia, particularly in critically ill and trauma patients. A proposed explanation for the anion gap's poor sensitivity and specificity in detecting hyperlactataemia is that the serum albumin is frequently low. This study therefore, sought to compare the predictive values of the anion gap and the anion gap corrected for albumin (cAG) as an indicator of hyperlactataemia as defined by a lactate ≥ 2.5 mmol/l.

Methods: A retrospective review of 639 sets of laboratory values from a tertiary care hospital. Patients' laboratory results were included in the study if serum chemistries and lactate were drawn consecutively. The sensitivity, specificity, and predictive values were obtained. A receiver operator characteristics curve (ROC) was drawn and the area under the curve (AUC) was calculated.

Results: An anion gap ≥ 12 provided a sensitivity, specificity, positive predictive value, and negative predictive value of 39%, 89%, 79%, and 58%, respectively, and a cAG ≥ 12 provided a sensitivity, specificity, positive predictive value, and negative predictive value of 75%, 59%, 66%, and 69%, respectively. The ROC curves between anion gap and cAG as a predictor of hyperlactataemia were almost identical. The AUC was 0.757 and 0.750, respectively.

Conclusions: The sensitivities, specificities, and predictive values of the anion gap and cAG were inadequate in predicting the presence of hyperlactataemia. The cAG provides no additional advantage over the anion gap in the detection of hyperlactataemia.

An elevated lactate level reflects impaired tissue oxygenation and is a predictor of mortality.^{1,2} Lactate levels are usually not ordered on initial laboratory tests. Measurement of lactate requires a fresh sample of blood that is collected in a tube containing sodium fluoride and potassium oxalate. Ideally, no tourniquet should be applied while obtaining the sample, and the sample should be chilled in ice and processed immediately (preferably within 30 minutes of collection). Having to redraw blood specifically for lactate levels often times can delay the diagnosis and treatment of hyperlactataemia, especially in emergency situations. As the anion gap is easily calculated from routine chemistries, it is often used as a screen for metabolic acidosis, particularly hyperlactataemia. Although it is possible to directly measure lactate from venous blood, this laboratory test is not routinely ordered. However, several studies have shown that the anion gap is inadequate as a screen for hyperlactataemia, particularly in critically ill and trauma patients.^{2–4} A proposed explanation for the anion gap's poor sensitivity and specificity in detecting hyperlactataemia is that albumin is frequently low in critically ill patients. Variations in albumin, an unmeasured anion, can affect the anion gap as described by the following equation:

Anion gap (mmol/l) = unmeasured anions – unmeasured cations [Equation 1].

In critically ill patients with low baseline albumin, the anion gap will also be low at baseline. When metabolic acidosis and resulting hyperlactataemia are present in a patient with low albumin, the anion gap may underestimate the presence of the acidosis.⁵ Some authors have proposed that the corrected anion gap (cAG)—anion gap corrected for albumin—be used in all critically ill patients.⁶ The cAG as

proposed by Figge *et al* is calculated as follows:⁵

cAG (mmol/l) = anion gap + 0.25 × (normal albumin – measured albumin) (albumin is measured in g/l) [Equation 2].

Although studies have shown the anion gap to be an unreliable indicator of hyperlactataemia, no studies have compared anion gap with cAG in detecting hyperlactataemia.^{2–4} This study was therefore conducted to compare the sensitivity, specificity, and predictive values of cAG and anion gap as an indicator of hyperlactataemia.

METHODS

We retrospectively reviewed 639 sets of laboratory values from 356 patients admitted to the Queen's Medical Center, a tertiary care hospital, between 30 October 2000 and 30 November 2001. The Queen's Medical Center Research and Institutional Review Committee waived the need for informed consent. Patients' laboratory results were included in the study if serum chemistries (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, and creatinine) and lactate were drawn consecutively. Blood samples were collected in heparinised tubes and laboratory values were obtained using the Beckman Synchron LX 20 (Beckman Coulter, Inc, Fullerton, California), an ion-selective electrode analyser. The normal reference range for the anion gap for the Beckman Synchron LX 20 was 5–12 mmol/l. The anion gap was defined as: anion gap = sodium (Na) – chloride (Cl) – bicarbonate (HCO₃). The bromocresol purple colorimetric method was used to measure the serum albumin

Abbreviations: AUC, area under the curve; cAG, corrected anion gap; ROC, receiver operator characteristics

concentration. The cAG was defined as anion gap + $0.25 \times$ (normal albumin – measured albumin). Albumin in this case is measured in g/l. No clinical or outcome data were obtained in the study.

We used simple linear regression analysis to compare the correlation between lactate versus anion gap and between lactate versus cAG. The partial correlation coefficient between creatinine (Cr) and anion gap adjusted for lactate concentration (the correlation between creatinine and anion gap while holding lactate constant) was derived using multiple linear regression. All regression analyses were performed using SPSS software (SPSS version 10, SPSS Inc, Chicago, Illinois). The sensitivity, specificity, and predictive values were obtained, with hyperlactataemia defined as a lactate ≥ 2.5 mmol/l. We used the software program Analyse-it (Analyse-it Software, Ltd, Leeds, England) to draw a receiver operator characteristics curve and calculate the area under the curve (AUC).

RESULTS

A total of 326 (51%) patient laboratory values had hyperlactataemia defined by a lactate ≥ 2.5 mmol/l, 321 (50%) had possible renal failure (Cr ≥ 141.4 μ mol (1.6 mg/dl)), and 182 (28%) had water excess (sodium < 136 mmol/l). The mean anion gap in the study group was 9.9 mmol/l (SD 5.4). Other patient laboratory characteristics are displayed in table 1. There was a significant correlation between anion gap versus lactate ($y = 0.99x + 6.17$; $r = 0.70$; $p < 0.001$). The slope of the regression line of anion gap versus lactate was approximately 1 mmol/l. Thus, a 1 mmol/l change in the lactate is associated with a 1 mmol/l change in the anion gap. The correlation between cAG versus lactate was similarly found to be significant ($y = 1.00x + 10.95$; $r = 0.71$; $p < 0.001$). The slope of the regression line between anion gap versus albumin was 0.12 mmol/l ($y = 0.12x + 7.08$; $r = 0.16$; $p < 0.001$).

Using the ROC curve (fig 1), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of a threshold anion gap and cAG were calculated and are given in table 2. The AUC of the cAG was almost identical to the anion gap (table 2).

The Hosmer-Lemeshow test for goodness of fit indicated adequate fit for separate models including uncorrected and corrected anion gap; however, as the screening characteristics described above indicate, there was little improvement in prediction of lactic acidosis when using the cAG. The partial correlation coefficient between serum creatinine and anion gap at a constant lactate was 0.51. In a subset of 318 laboratory values excluded for potential renal failure (Cr ≥ 141.4 μ mol), the results were not considerably different. The linear correlation between anion gap versus lactate ($r = 0.69$) and cAG versus lactate ($r = 0.71$) in this subset population were similar. The ROC curves for both anion gap

Figure 1 Receiver operator curves for anion gap (AG) and corrected anion gap as an indicator of hyperlactataemia (lactate ≥ 2.5 mmol/l).

Table 2 Sensitivities, specificities, and predictive values for anion gap (AG) and corrected anion gap (cAG) in detecting hyperlactataemia

	Hyperlactataemia (lactate ≥ 2.5 mmol/l)	
	AG (threshold 12)	cAG (threshold 12)
Spearman's correlation (r^2)*	0.49	0.50
ROC†	0.757	0.750
Sensitivity	39%	75%
Specificity	89%	59%
Positive predictive value	79%	66%
Negative predictive value	58%	69%

*Linear correlation between lactate versus anion gap, lactate versus cAG expressed as Spearman's correlation r^2 . All values were significant with $p < 0.001$.

†ROC, receiver operator characteristics. The value given is the area under the curve (AUC).

and cAG for the detection of hyperlactataemia in this subset population that excluded renal failure were nearly identical.

DISCUSSION

The sensitivity and specificity of the anion gap in detecting hyperlactataemia is similar to that reported in other studies.²⁻⁴ Although our patient population included all hospitalized patients and not just critically ill patients, the mean albumin level was low at 25 g/l (2.5 g/dl). This patient population was thus ideal for our study since the lower the albumin, the greater the theoretical benefit of using cAG over the anion gap. Using Figge's formula for the corrected anion gap (equation 2), the median cAG was 5 mmol/l higher than the median anion gap. This correction would theoretically unmask any organic acidosis which would not have been detected with the anion gap alone. Although the sensitivity of detecting hyperlactataemia is increased in cAG, the identical ROC curves suggest that cAG provides no additional advantage over anion gap in detecting hyperlactataemia.

Figge's equation implies that the expected slope between anion gap versus albumin should be 0.25 mmol/l. However, our data showed that the anion gap increased by only 0.12 mmol/l for every 1 g/l increase in albumin. There are several explanations for the discrepancy in the expected changes in the anion gap using Figge's equation and the values observed in this study. In Figge's study the anion gap was calculated controlling for the effects of pH. Although we did not measure pH, changes in the pH produce only small

Table 1 Patients' laboratory characteristics

	Study group (n = 639) Mean (SD)	Normal reference range
Sodium (mmol/l)	138 (5.9)	136–146
Potassium (mmol/l)	4.2 (0.7)	3.6–5.0
Chloride (mmol/l)	107 (7.5)	97–110
Bicarbonate (mmol/l)	22 (5.1)	23–29
Albumin (g/l)	24 (7)	34–50
Blood urea nitrogen (mmol/l)	14.3 (10.6)	2.1–6.8
Creatinine (μ mol/l)	152.5 (122)	45.8–114.4
Lactate (mmol/l)	3.8 (3.8)	0.5–2.2
Anion gap (mmol/l)	9.9 (5.4)	5–12
Corrected anion gap for albumin (mmol/l)	14.8 (5.4)	

changes in the electronegative charge of albumin. Increases in unidentified anions with hypoalbuminaemia may have a larger impact on the anion gap. Using linear regression analysis, the unidentified anions (XA) (as calculated by the equation below) increases by 1 mmol/l per 1 g/l decrease in albumin.

$$XA = Na + K + Mg + Ca - Cl - HCO_3 - 1.86 \times \text{phosphate} - 0.28 \times \text{Alb} - \text{lactate [Equation 3]}$$

(phosphate is measured in mmol/l and albumin is measured in g/l).

The loss of negative charge from hypoalbuminaemia is thus counteracted by a considerable gain in negative charge from elevations in unidentified anions. The result is that severe hypoalbuminaemia causes only a small decrease in the anion gap. In Figge's study, gapped anions (gapped anions = unidentified anions + inorganic phosphate), were held constant, such that [anion gap - (gapped anions -)] versus albumin resulted in a slope of 0.25. In this study, we compared anion gap versus albumin to derive at a slope of 0.12. Our findings suggest that the calculation of the slope using this method is more clinically applicable.

The composition of unidentified anions is unclear, but probably consists largely of anions which are unidentifiable by current analysers. In Levraut *et al*'s study of critically ill patients, hyperlactataemia (lactate ≥ 2.5 mmol/l) was identified in 54% of the patients enrolled in the study, whereas other identifiable anions including keto-anions, salicylate, and glycol were identified in less than 3% of the 518 patients.⁴ Gabow attempted to quantitate the composition of the increments of the anion gap in 22 patients with elevated anion gap. Despite measurements of serum chemistries, lactate, pyruvate, 3-hydroxybutyrate, acetoacetate, and citrate, 23% of the change in the anion gap was undetermined and presumed to be from unidentifiable anions.⁷ Unidentifiable anions have also been proposed to contribute significantly to the elevation of the anion gap in both septic animals and humans. In patients with severe sepsis, the increase in the anion gap could not be explained by the contributions of lactate, phosphate, urate, and total serum proteins.⁸ In sepsis in rats induced by cecal perforation, measurement of lactate, pyruvate, β -hydroxybutyrate, acetoacetate, citrate, and amino acids also could not completely explain the elevation in the anion gap.⁹ Figge *et al* determined that in normal human plasma, albumin is the only protein which contributes an electronegative charge, suggesting that these unidentified anions are anions other than proteins.¹⁰ Unidentified anions are known to be present in patients with renal failure. This was supported in our data showing that serum creatinine and the anion gap had a significant partial correlation of 0.51 at a constant lactate. However, exclusion of patients with potential renal failure (Cr ≥ 141.4 μ mol) did not significantly change our results.

Both the ROC curves for anion gap and cAG in detecting hyperlactataemia, and the linear correlations between anion gap versus lactate and cAG versus lactate were all similar. The focus of our study was to compare the sensitivity, specificity, and predictive values of cAG and anion gap as an indicator of hyperlactataemia. As such, we did not collect outcome data and cannot make inferences on patient care and outcomes. Our findings are similar to previous studies showing the limitations of the anion gap in the diagnosis of hyperlactataemia.^{11, 12}

A limitation to our study is that serum lactate levels were obtained from venous blood. The concentration of lactate in venous blood may be greater compared with arterial blood in decreased perfusion states. However, venous blood gases may more accurately reflect tissue pH. In a prospective study, venous blood was more accurate than arterial blood in reflecting the acid-base state during cardiopulmonary resuscitation.¹³

In summary, in the present study, the sensitivities, specificities, and predictive values of the anion gap and cAG were inadequate in predicting the presence of hyperlactataemia. The ROC curves of the anion gap and cAG in the detection of hyperlactataemia were almost identical. Therefore clinically, correcting the AG for hypoalbuminaemia provides no advantage over the anion gap itself for the detection of hyperlactataemia.

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