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Reliability of anion gap as an indicator of blood lactate in critically ill patients

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Abstract *Objective:* To evaluate the sensitivity, specificity, and predictive values of an elevated anion gap as an indicator of hyperlactatemia and to assess the contribution of blood lactate to the serum anion gap in critically ill patients.
Design: Prospective study.
Setting: General intensive care unit of a university hospital.
Patients: 498 patients, none with ketonuria, severe renal failure or aspirin, glycol, or methanol intoxication.
Measurements and results: The anion gap was calculated as $[Na^+] - [Cl^-] - [TCO_2]$. Hyperlactatemia was defined as a blood lactate concentration above 2.5 mmol/l. The mean blood lactate concentration was 3.7 ± 3.2 mmol/l and the mean serum anion gap was 14.3 ± 4.2 mEq/l. The sensitivity of an elevated anion gap to reveal hyperlactatemia was only 44 % [95 % confidence interval (CI) 38 to 50], whereas specificity was 91 % (CI 87 to 94) and the positive predictive value was 86 % (CI 79 to 90). As expected, the poor sensitivity of the anion gap increased with the lactate threshold value, whereas the specificity decreased [for a blood lactate cut-off of 5 mmol/l: sensitivity = 67 % (CI 58 to 75) and specificity = 83 % (CI 79 to 87)]. The correlation between the serum anion gap and blood lactate was broad ($r^2 = 0.41$, $p < 0.001$) and the slope of this relationship (0.48 ± 0.026) was less than 1 ($p < 0.001$). The serum chloride concentration in patients with a normal anion gap (99.1 ± 6.9 mmol/l) was comparable to that in patients with an elevated anion gap (98.8 ± 7.1 mmol/l).
Conclusions: An elevated anion gap is not a sensitive indicator of moderate hyperlactatemia, but it is quite specific, provided the other main causes of the elevated anion gap have been eliminated. Changes in blood lactate only account for about half of the changes in anion gap, and serum chloride does not seem to be an important factor in the determination of the serum anion gap.

Key words Acid-base equilibrium · Acid-base imbalance · Acidosis, lactic · Hemodynamics · Lactates · Severity of illness index

Introduction

Blood lactate measurement is an accessible method of estimating tissue oxygenation [1, 2] and therefore provides a reliable indicator of severity, prognosis, and the effectiveness of therapy in critically ill patients [3–7]. However, the determination of blood lactate is difficult and time consuming when an automated analyzer is not available [8, 9]. And prolonged storage of blood samples falsely increases the lactate concentration because of the release of lactate from erythrocytes [10]. Several clinicians have attempted to circumvent these problems

by using the anion gap as an indirect reflection of blood lactate, as the anion gap is directly linked to the blood concentration of organic acids [11–14]. But there have been few studies on the reliability of the anion gap as an indicator of hyperlactatemia in critically ill patients [15, 16]. Those that have been reported were performed on relatively small populations of hyperlactatemic patients, making it possible to estimate the sensitivity of an increase in the anion gap as a reflection of hyperlactatemia, but not its specificity.

Several papers have also shown that base excess is a reliable surrogate for lactate levels in acute trauma [17, 18]. These patients, unlike the others, are usually healthy before hospitalization, and it is therefore possible that the anion gap is more reliable in this population. This study was therefore conducted to evaluate the sensitivity, specificity, and predictive values of an elevated anion gap as an indicator of hyperlactatemia in different clinical situations and to quantify the contribution of blood lactate to the serum anion gap in critically ill patients.

Materials and methods

Study protocol

This study was approved by our Institutional Review Board and conducted according to the principles established in Helsinki. Informed consent was obtained from the patients or relatives, and all the patients admitted to our intensive care unit (ICU) over a 6-month period were included in the study. Arterial blood samples were taken from each patient by radial or femoral artery puncture and serum Na^+, Cl^-, total CO_2 (TCO_2), total proteins, lactate level, and blood gases were measured. Samples were immediately stored on ice, transported to our central laboratory, and measured within 15 min. Patients were subsequently excluded if they had a positive ketonuria (detected by color reaction to sodium nitroprusside), were intoxicated by products that increase the anion gap (aspirin, methanol, and glycol), or had severe renal failure (serum creatinine > 400 μmol/l and/or dialysis).

Measurement techniques

Na^+, Cl^-, TCO_2, and total protein concentrations were measured with the Ektachem 700 analyzer (Johnson & Johnson, France). The normal serum chloride range was 100–109 mmol/l. The anion gap was calculated as $Na^+ - (Cl^- + TCO_2)$. Its normal value was 5–16 mEq/l (which is higher than that given by many modern analyzers, such as ASTRA analyzers, where the normal value is often 3–11 mEq/l [19, 20]). Blood gas was measured using a BGS 288 analyzer (Ciba-Corning, Cergy-Pontoise, France). The serum protein charge was evaluated according to the Van Leeuwen formula [21]:

$$\text{Proteinate (mmol/l)} = 10.3 \times (\text{pH} - 5.66) \times 0.1 \times \text{total protein (g/dl)}.$$

Blood lactate concentration was measured with the Ektachem 700 analyzer. The mean variation of lactate assay with this analyzer is about 1%, with a standard deviation of nearly 0.04 mmol/l. Hyperlactatemia was defined as a blood lactate concentration higher than 2.5 mmol/l.

Data analysis

Sensitivity was calculated as the percentage of hyperlactatemic patients with an elevated anion gap, specificity was the percentage of patients with a normal blood lactate level and a normal anion gap, the positive predictive value (PPV) was the percentage of patients with an elevated anion gap and hyperlactatemia, and the negative predictive value (NPV) was the percentage of patients with a normal anion gap and a normal blood lactate level. The resulting percentages for these parameters were rounded off to the nearest whole unit. The 95% CI were calculated after approximation of the binomial law to a normal distribution except for numbers below 30 and/or percentages below 5% or above 95%. When such was the case, the exact CI were taken from binomial distribution tables. The receiver operating characteristic (ROC) curve was used to evaluate the reliability of an elevated anion gap independently of the threshold value selected. Percentages were compared by Fisher's exact test.

Statistical correlation was calculated by linear regression analysis with the method of least squares, making it possible to calculate the r_{xy} correlation coefficient. Calculation of the partial correlation coefficient $r_{xy,z}$ from the three correlation coefficients r_{xy}, r_{yz}, and r_{xz} provided the theoretical relationship linking x and y for z constant. The slope of a relationship was compared to a theoretical value by Student's t-test. The means were compared by Student's t-test for unpaired data after logarithmic transformation in cases of log-normal distribution. A logistical regression analysis using the maximum likelihood method was performed to evaluate the probability of survival according to the initial blood lactate level. A value of $p < 0.05$ was considered to be significant.

Results

Patient characteristics

A total of 518 patients were included in the study. Subsequently, 20 patients with positive ketonuria ($n = 10$), aspirin ($n = 4$) or glycol ($n = 1$) intoxication, or severe renal failure ($n = 5$) were excluded. The characteristics of the remaining 498 patients are shown in Table 1. Over 70% of these patients were outpatients, and all the trauma patients came directly to the ICU from the trauma scene. Only 24 patients had a serum creatinine above 150 μmol/l (range: 165–246).

Population laboratory data

The mean lactate level of the patients was 3.7 ± 3.2 mmol/l (range: 0.6–22.9 mmol/l, median: 2.7 mmol/l) (Fig. 1). A total of 268 patients (53.8%) had a blood lactate above 2.5 mmol/l, 109 (21.9%) above 5 mmol/l, and 29 (5.8%) above 10 mmol/l. The mean anion gap was 14.3 ± 4.2 mEql (median: 13.9 mEq/l) with a range of − 0.5 to 31.5 mEql (Fig. 1). A total of 360 patients (72.3%) had a normal anion gap (below 16 mEq/l), and 138 (27.7%) and a wide gap. As expected, in-hospital mortality increased significantly with the initial blood lactate level (Fig. 2).

Table 1 Patients' characteristics

Reason for admission to ICU	No. of patients (%)	Age (years) (mean ± SD)	No. who died (%)
Postoperative	125 (25.1)	55 ± 18	34 (27.2)
Neurologic disorder	100 (20.1)	45 ± 22	45 (45)
Multiple trauma	80 (16.1)	38 ± 17	14 (17.5)
Acute respiratory failure	72 (14.4)	58 ± 17	12 (16.7)
Drug intoxication	47 (9.4)	45 ± 16	2 (4.3)
Other	74 (14.9)	57 ± 17	34 (45.9)
Total	498	52 ± 20 (13–97)	141 (28.3)

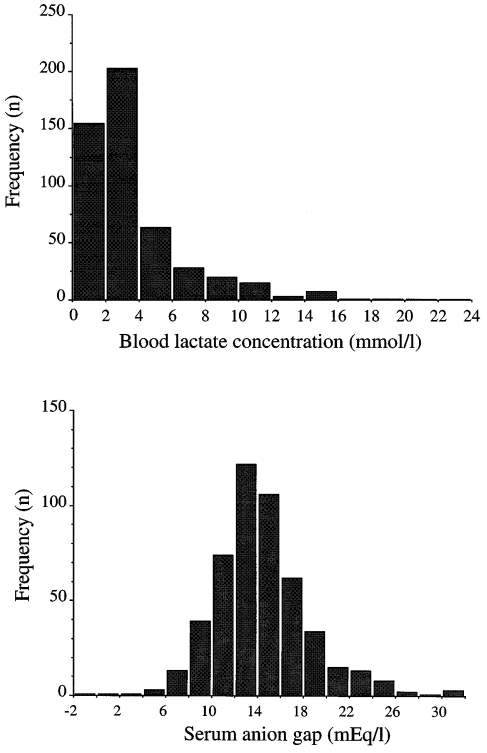

Fig. 1 Distribution frequency of blood lactate concentration *top* and serum anion gap *bottom* in 498 critically ill patients. The data distribution is log-normal for blood lactate (mean = 3.7 mmol/l; median = 2.7 mmol/l) and normal for anion gap (mean = 14.3 mEq/l; median = 13.9 mEq/l)

Sensitivity and specificity of the anion gap

The principal results are shown in Table 2. The anion gap did not prove to be a very sensitive indicator of hyperlactatemia, since only 44% (CI 38 to 50) of patients with a lactate level above 2.5 mmol/l had an elevated anion gap. But it was specific, since 91% (CI 87 to 94) of the patients with normal lactate levels had a normal anion gap. In this population, 86% (CI 79 to 90) of the patients with a wide anion gap had hyperlactatemia (PPV), whereas only 58% (CI 53 to 63) of the patients with a normal anion gap had normal blood lactate levels (NPV). An anion gap wider than 25 mEq/l was always accompanied by hyperlactatemia (PPV: 100%). The area under the ROC curve for anion gap was 0.79, and it showed that the best compromise between sensitivity and specificity was obtained using a threshold anion gap value of 14 mEq/l (Fig. 3). As expected, sensitivity increased with the threshold lactate value, whereas the specificity, and especially the PPV, decreased (Table 2). An increased anion gap was no better an indicator of hyperlactatemia in trauma patients than in the other patients (Table 3).

Composition of the anion gap

There was a significant ($p < 0.001$) but broad ($r = 0.64$) correlation between the serum anion gap and the blood lactate concentration (Fig. 4). The slope of the regression line was 0.483 ± 0.026 (significantly less than 1, $p < 0.0001$). The slope of the regression line correlating the anion gap with TCO_2 was 0.81 ± 0.035 (significantly less than 1, $p < 0.001$). The partial correlation coefficient indicated that there remained a very significant correlation between the anion gap and TCO_2 for a constant lactate level ($r = 0.57$, $p < 0.001$).

There was a significant correlation ($p < 0.001$) between proteinate concentration and the anion gap but it was a negative one ($r = -0.377$). Blood lactate was significantly lower in patients with protein concentrations above 5.5 g/dl (3.3 ± 3 mmol/l) than in the other patients (4 ± 3.3 mmol/l, $p < 0.01$). The serum chloride concentration in patients with a normal anion gap (99.1 ± 6.9 mmol/l) was similar to that in patients with an elevated anion gap (98.8 ± 7.1 mmol/l).

Discussion

This study confirms that initial hyperlactatemia is associated with a high mortality but than an elevated anion gap is a poor indicator of hyperlactatemia. More than half our patients with hyperlactatemia had a normal anion gap. But the anion gap is a specific indicator under the conditions of our study protocol, since fewer than

Table 2 Sensitivity, specificity, and positive *PPV* and negative *NPV* predictive values of an elevated anion gap as an indicator of hyperlactatemia for different lactate concentration threshold values. Results are proportions (95% CI)

	Threshold lactate concentration (mmol/l)		
	2.5	5	10
Sensitivity (%)	44 (38 to 50)	67 (58 to 75)	93 (78 to 98)
Specificity (%)	91 (87 to 94)	83 (79 to 87)	76 (72 to 80)
PPV (%)	86 (79 to 90)	53 (44 to 61)	20 (14 to 27)
NPV (%)	58 (53 to 63)	90 (86 to 93)	99 (98 to 100)

Table 3 Reliability of an increased anion gap as an indicator of hyperlactatemia in trauma and non-trauma patients. Values are proportions (95% CI) (*PPV* positive predictive values, *NPV* negative predictive value)

	Trauma patients ($n = 80$)	Non-trauma patients ($n = 418$)	p value
Sensitivity (%)	46 (40 to 53)	35 (22 to 51)	0.23
Specificity (%)	91 (86 to 94)	93 (80 to 98)	> 0.99
PPV (%)	86 (79 to 91)	82 (58 to 94)	0.71
NPV (%)	58 (52 to 64)	59 (46 to 70)	> 0.99

10% of the patients with a normal blood lactate concentration had an elevated anion gap. The positive predictive value of an elevated anion gap was quite good in this population, since 86% of the patients with an elevated anion gap had hyperlactatemia.

Iberti et al. [15], working with a smaller population, also reported the poor sensitivity of the anion gap (57.1%), although it was slightly higher than ours. This poor sensitivity may be due to the fact that critically ill patients are often complex patients, whose blood profile is altered by previous treatments. However, we were unable to show any difference between the trauma and the non-trauma patients, which does not support this explanation, as trauma patients are usually healthy before hospitalization. The sensitivity of the anion gap for detecting hyperlactatemia is probably low because the normal blood lactate concentration varies little (0.5–2.5 mmol/l), whereas the anion gap is much wider (5–16 mEq/l). As a result, a patient with an anion gap that increases by less than 3 mmol/l will probably remain within the normal range, since, statistically, more than 50% of normal patients have an anion gap of 5–12 mEq/l. Conversely, this explains the good specificity of the anion gap for detecting moderate hyperlactatemia: a patient whose blood lactate does not rise above 2.5 mmol/l will maintain a normal anion gap, if it is initially smaller than 14 mEq/l. Statistically, this represents over 90% of cases. Obviously, this is only true after the other common causes of a wide anion gap (ketosis, glycol or aspirin intoxication, and severe renal failure) have been eliminated.

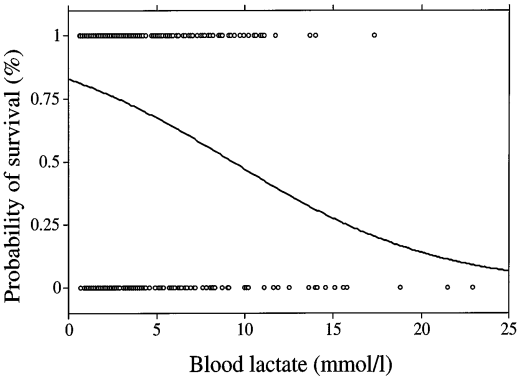

Fig. 2 Probability of survival depending on the blood lactate concentration at the time of admission to the ICU. The data points at the top indicate the blood lactate concentrations of patients who survived ($n = 357$) and those at the bottom indicate the blood lactate concentrations of patients who died ($n = 141$). The explained variance is about 74%

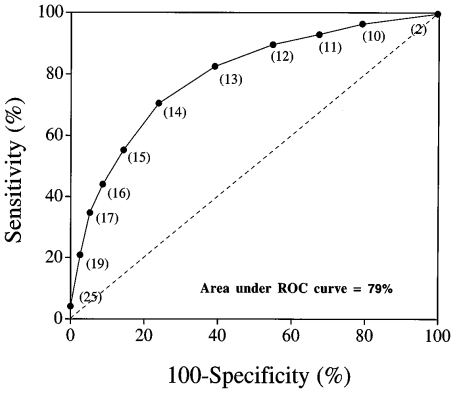

Fig. 3 ROC curve for anion gap as an indicator of hyperlactatemia (blood lactate concentration > 2.5 mmol/l) in 498 critically ill patients. Numbers in parentheses are anion gap threshold values

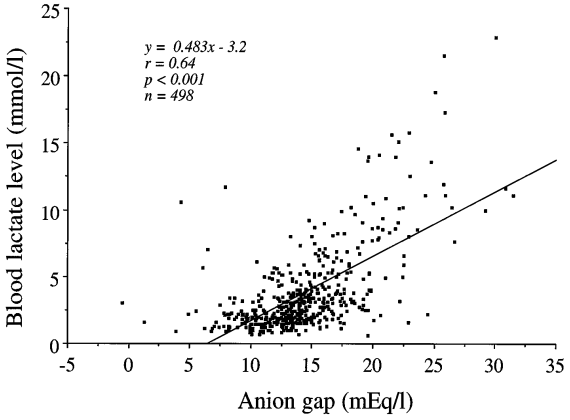

Fig. 4 Relationship between the serum anion gap and blood lactate concentration in 498 patients admitted to an ICU. The 95% CI of the slope is 0.43 to 0.53. About 60% of the observed variance in anion gap is not explained by that of blood lactate

The mean blood lactate concentration was high in this patient population (3.7 mmol/l). This is probably due to two factors. First, the frequency distribution of blood lactate concentrations was log-normal. This shifts the mean of the population toward the high values. This was demonstrated by the median value of the population, which was only 2.7 mmol/l. Second, most of the patients were first admitted to the ICU during a period of acute injury.

The slope of the regression line correlating the anion gap and TCO_2 was less than 1, which shows that the anion gap increased more rapidly than bicarbonate decreased. This goes against the principle that the change in the anion gap is equal to that of bicarbonate during organic metabolic acidosis [11, 12, 22]. There are several possible explanations for this. First, the contribution of non-bicarbonate buffer systems, and especially intracellular buffer systems, must be taken into account. It has been shown in experimental studies that the non-bicarbonate buffers play a greater role when the acid load is high [23]. Hyperventilation also modifies considerably the contribution of intracellular non-bicarbonate buffer systems [24]. All of these factors could contribute to the discrepancy between the change in TCO_2 and the change in anion gap. Second, the distribution volume of organic acids may be smaller than that of bicarbonate [25], resulting in an increase in the anion gap that is greater than the decrease in blood bicarbonates. Third, it has been reported that dyschloremia could give rise to changes in the anion gap that are independent of acid-base disturbances [15, 20]. This was not confirmed in our study, since the serum chloride concentrations of patients with a wide anion gap were very similar to those of patients with normal anion gaps. Lastly, an error in determining bicarbonate can lead to errors in calculating the anion gap. This is most often linked to prolonged exposure of the sample to air [26, 27]. Our measurements were performed within 15 min of sampling.

The slope of the regression line correlating the anion gap and blood lactate concentration was less than 1, which shows that the anion gap increased more rapidly than lactate. This has been described by others [28–30] and suggests that other anions contribute to the anion gap. This was confirmed by the relatively low value of the correlation coefficient between the anion gap and blood lactate ($r^2 = 0.41$), which shows that nearly 60 % of the change in the anion gap cannot be explained by the change in blood lactate. Gabow et al. [29] studied 57 hospitalized patients and found that lactate (and keto-anions) accounted for only 62 % of the increases in anion gap. These authors were also unable to identify the anions responsible, despite measurement of many ions. The nature of the other organic acids that increase the anion gap in our study is difficult to determine. Proteinates normally make up two-thirds of the anion gap [13, 31]. The Van Leeuwen formula used in this study assumes that the abumin/globulin ratio is normal. This was probably true, since changes in protein were mainly linked to hemodilution depending on the quantity of aqueous solutions perfused before admission to the ICU. Paradoxically, there was a negative correlation between the plasma proteins and the serum anion gap. This could be because most hemodiluted patients required great volume expansion because they were hypovolemic, while the indicator was a more elevated blood lactate concentration in such patients. This was the origin of an artificial, negative correlation between proteins and lactatemia and therefore, indirectly, between proteins and the anion gap. The absence of ketonuria, according to the nitroprusside test, means there was no acetoacetate, but betahydroxybutyrate could still have been present [32]. Hyperketonemia therefore cannot be absolutely eliminated, especially in hyperlactatemic patients with hypoxia, in whom there is a shift from acetoacetate toward hydroxybutyrate [32]. Other anions, such as phosphate, urate, and citrate in transfused patients, contribute to the composition of the anion gap, but their low concentrations cannot, in our opinion, account for more than 4 mEq/l of the anion gap. Toxicologic assays were not performed in all the patients and we cannot exclude the presence of anions like salicylates in some patients. Some antibiotics, including those derived from penicillin, can artificially increase the anion gap [13, 14]. All the patients admitted to the ICU for postoperative care were given perioperative antibiotic therapy, which may partly explain the widened anion gap in some cases. D-Lactate, which is not taken into account in standard lactate measurements, could be involved. However, it has been found in humans only under certain conditions, such as the short bowel syndrome [33, 34]. There have also been reports of moderately elevated blood D-lactate levels during the perioperative period in patients given lactate solutions [35]. This probably explains part of the change in the anion gap in our patients, since some had been given lactate solutions before admission to the ICU.

To conclude, this study confirms that the anion gap is not a sensitive way of measuring moderate increases in blood lactate concentration. But its specificity is good, provided that other common causes of a widened anion gap have first been eliminated, and, under these conditions, an elevated anion gap is a good indicator of hyperlactatemia. Nevertheless, calculation of the anion gap remains an imprecise tool, and lactate levels should be directly determined.

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