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Low sensitivity of the anion gap as a screen to detect hyperlactatemia in critically ill patients

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The anion gap is commonly used as a screening test for the presence of lactic acidosis. Analysis of the distribution of anion gaps for 56 adult surgical ICU patients with peak blood lactate levels ≥2.5 mmol/L showed the anion gap to be an insensitive screen for elevated lactate in a critically ill, hospitalized population. All patients (11/11) with a peak lactate ≥10 mmol/L had an anion gap ≥16 mmol/L; however, 50% (6/12) of patients with lactates between 5.0 and 9.9 mmol/L and 79% (26/33) of those with lactates between 2.5 and 4.9 mmol/L had anion gaps <16 mmol/L. Hyperlactatemia was associated with considerable mortality at all levels: 100% among patients with lactate levels ≥10 mmol/L, 75% between 5.0 and 9.9 mmol/L, and 36.4% between 2.5 and 4.9 mmol/L. Acidosis (pH <7.30) did not significantly alter mortality by lactate level. The observation that, for 57% of patients in this study, an elevated lactate level was not accompanied by an elevated anion gap suggests that hyperlactatemia should be included in the differential diagnosis of nonanion gap acidosis. (Crit Care Med 1990; 18:275)

Blood lactate levels in critically ill patients provide an assessment of tissue oxygenation, the effectiveness of therapy, and patient prognosis. Lactic acidosis has traditionally been predicated on an elevated anion gap, the standard screening test for organic acidoses (1, 2). However, clinical observation of patients in the surgical ICU (SICU) who have hyperlactatemia without an elevated anion gap challenges the validity of this approach.

We reviewed the medical records of SICU patients with elevated blood lactate levels to determine the frequency with which elevated blood lactate is accompanied by high anion gap, the relationship between pHa and hyperlactatemia, and the hospital survival of SICU patients with hyperlactatemia.

PATIENTS AND METHODS

Patient Characteristics

The study was carried out in the SICU at the Mount Sinai Medical Center. The SICU admits approximately 650 adult, noncardiac, and non-neurosurgical patients per year. The SICU population primarily is comprised of patients undergoing general and vascular surgery.

All patients admitted to the SICU in the 29-month period from August 12, 1985 to January 4, 1988, who had at least one recorded blood lactate level ≥2.5 mmol/L were identified from the SICU register. SICU staff have standing orders to obtain lactate levels for all patients meeting at least one of the following criteria: a total CO_2 content (C_{CO_2}) <20 mmol/L, a decrease in total C_{CO_2} of 4 mmol/L regardless of level, mean arterial pressure (MAP) <70 mm Hg, suspected sepsis, suspected low cardiac output, or a pH <7.35.

Two hundred four patients (13.2% of admissions) with elevated blood lactate levels were identified; their medical records were requested. Fifty-six charts could be retrieved from medical records that met both criteria for inclusion in the study: a) blood specimens for measurement of peak lactate levels had clearly been drawn at the same time as those for electrolyte determinations, and b) laboratory data were sufficient to permit calculation of the anion gap. Among study subjects, lactate levels and electrolytes were determined from simultaneously drawn arterial blood samples.

Given that the particular set of 56 individuals included in this study did not constitute a random sample of all patients known to have had elevated lactate levels, we used data from the SICU register to determine whether there were systematic differences between individuals included in the study and the remaining 148 patients with elevated lactate levels. Study subjects comprise a representative sample with regard to age, sex, and survival to SICU discharge. On average, however, study subjects have lower peak lactate levels (Table 1).

Measurements of Lactate and Anion Gap

All lactate levels were determined using a lactate analyzer (Yellow Springs Instruments, Yellow Springs, OH). The analyses reported here are based on the highest lactate reading recorded for each patient, and the corresponding electrolyte and pH measurements. For purposes of this study, lactic acidosis was defined as a blood lactate level >2.5 mmol/L and a pHa <7.3. The anion gap was calculated as $Na^+ - (Cl^- + HCO_3^-)$.

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TABLE 1. Comparison of selected characteristics of study subjects and other SICU patients with elevated blood lactate levels

Variable	Study Subjects (n = 56)	Others (n = 148)	p-Value
Median age	69.0	67.0	NS
Age	68.6 ± 13.6[a]	66.0 ± 15.5	NS
% male	44.6	47.3	NS
% survival (discharge from SICU)	57.1	48.0	NS
Median of highest recorded lactate level	4.6	6.0	<.02
Highest recorded lactate levels	7.3 ± 7.0[a]	8.9 ± 6.6	NS

[a] Mean ± SD values.

Statistical Methods

Continuous variables were compared by the Wilcoxon rank-sum test. Chi-square statistics were used to test differences in proportions; the Mantel-Haenszel chi-square statistic was used to test the significance of trends in the data. All analyses were performed using the SAS program.

RESULTS

The anion gap was not a sensitive indicator of blood lactate levels in the study population (Table 2). If an anion gap of 16 mmol/L is taken as the upper limit of normal (2), 57.1 ± 6.6 (SE) % of the individuals with elevated lactate levels in this study had normal gaps. If the upper bound of normal is lowered to 12 mmol/L, 44.6 ± 7.4% of all study subjects had normal gaps.

The sensitivity of the anion gap as an indicator of elevated blood lactate improves with increasing levels of lactate (Table 2). All subjects with lactates ≥10 mmol/L had an anion gap ≥16 mmol/L; however, using 16 mmol/L as the cutoff, 50% of the subjects with lactate levels between 5.0 and 9.9 mmol/L, and 79% of those with lactates between 2.5 and 4.9 mmol/L would not be identified.

Mean Cl levels were 102 ± 0.9 (SE) mmol/L for patients with an elevated anion gap and 110 ± 0.9 mmol/L for patients with a normal anion gap. Mean HCO_3 levels were 13.9 ± 0.47 (SE) mmol/L for patients with an anion gap ≥16 and 19 ± 0.48 mmol/L for patients with a normal anion gap.

Elevated lactate levels are associated with high mortality rates. Overall mortality (Fig. 1) among study subjects was 57.1 ± 6.6%. Mortality increased significantly with increasing levels of lactate ($p < .01$). Twelve (36%) of the 33 patients whose highest blood lactate level was between 2.5 and 4.9 mmol/L died, as did 75% (9/12) of those with lactate levels between 5.0 and 9.9 mmol/L and 100% (11/11) of patients with blood lactates ≥10 mmol/L.

TABLE 2. Number and percent of false-negatives resulting from use of the anion gap as an indicator of elevated blood lactate, for specific cutoffs and by lactate level

mmol/L	Highest Lactate Reading (mmol/L)							
	2.5–4.9		5.0–9.9		10.0+		Total	
	No.	%	No.	%	No.	%	No.	%
<16	26	78.8	6	50.0	0	—	32	57.1
<15	25	75.8	6	50.0	0	—	31	55.4
<14	23	69.7	6	50.0	0	—	29	51.8
<12	19	57.6	6	50.0	0	—	25	44.6

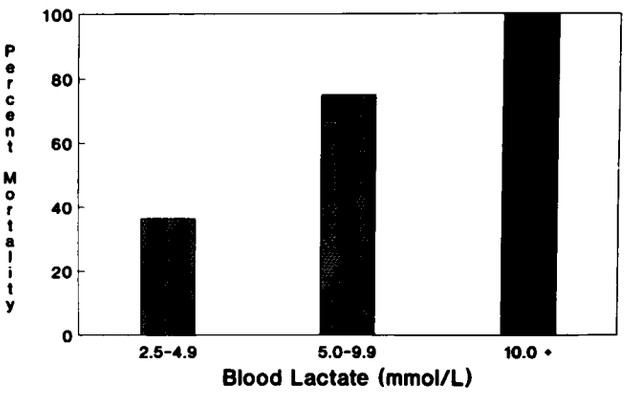

FIG. 1. Inhospital mortality by lactate level.

TABLE 3. Number and percent of false-negatives resulting from use of low pH as an indicator of elevated blood lactate, for specific cutoffs and by lactate level

pH	Highest Lactate Reading (mmol/L)							
	2.5–4.9		5.0–9.9		10.0+		Total	
	No.	%	No.	%	No.	%	No.	%
7.35	18	54.5	3	25.0	0	—	21	37.5
7.30	24	72.7	8	66.7	2	18.2	34	60.7
7.25	31	93.9	9	75.0	4	36.4	44	78.6

The pHa (Table 3) is as insensitive a marker of elevated blood lactate as the anion gap. Even using a pH ≤7.35 as the criterion for acidosis, 37.5 ± 6.5% of the subjects with elevated lactate levels would not be identified. As is the case with the anion gap, the sensitivity of this measure increases with increasing lactate levels.

DISCUSSION

The present study suggests that the mortality currently associated with hyperlactatemia and lactic acidosis has changed remarkably little over the past 20 yr (3–5). It also confirms the importance of differentiating among mild (2.5 to 4.9 mmol/L), moderate (5.0 to 9.9 mmol/L), and high (≥10 mmol/L) elevations in blood lactate (3, 5–7). Prognosis varies significantly by level; while 64% of the patients with mild hyperlactatemia survived, no patient survived with a level ≥10 mmol/

L. Furthermore, hyperlactatemia, regardless of the presence of acidosis, had a high associated mortality.

Given the above factors, it is important to be able to determine which patients are hyperlactatemic. Current medical teaching stresses that organic acidoses, including lactic acidosis, should be suspected whenever an elevated anion gap is observed. Lactic acidosis is usually not included in the differential diagnosis of nonanion-gap metabolic acidosis (2, 8, 9). However, our finding that nearly 60% of SICU patients with elevated lactate levels did not have an anion gap >16 mmol/L and the comparable findings of Mehta et al. (10) indicate the low sensitivity of this measurement as a screen for hyperlactatemia among critically ill, hospitalized patients.

Possible explanations for the finding of hyperlactatemia despite normal anion gaps include: a) the presence of hyperchloremia from high Cl resucitation fluids or free water deficits, b) hypoalbuminemia, and c) presence of a mixed acid-base disorder. The first situation is frequent in our population, as shown by the mean serum Cl concentration of 110 mmol/L in hyperlactatemic patients with a normal anion gap.

In the population studied, pHa was not a useful alternative to the anion gap as a screen for hyperlactatemia. Normalization of pH in critically ill patients is common as a result of respiratory compensation (intrinsic or via mechanical ventilation), a coexisting metabolic alkalosis, and/or a concurrent primary metabolic alkalosis.

The selective nature of the study sample limits the conclusions that can be drawn from it. Data were collected exclusively on patients known to have elevated blood lactate levels. There is no information available on patients for whom lactates were not ordered, some of whom may have had blood lactate levels ≥2.5 mmol/L, nor is information available on those with lactate levels <2.5 mmol/L. As a result, our estimates of mortality must be interpreted cautiously, particularly those for mild and moderate lactate elevations. In addition, neither the positive (elevated gap) nor negative (normal gap) predictive value of the anion gap as a screening test for lactic acidosis and hyperlactatemia could be calculated from study data.

Despite these constraints, the study provides strong evidence that the anion gap is not a sensitive method of detecting elevated blood lactate levels. While an elevated anion gap often signals a high blood lactate level, the inverse does not hold in the SICU population; a normal gap does not rule out elevated blood lactate.

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