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The strong ion gap does not have prognostic value in critically ill patients in a mixed medical/surgical adult ICU

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Abstract *Objective:* To examine whether the strong ion gap (SIG) or standard base excess corrected for abnormalities of serum chloride and albumin (BE_{UA}) can predict outcome and to compare the prognostic abilities of these variables with standard base excess (SBE), anion gap (AG), pH, and lactate, the more traditional markers of acid-base disturbance. *Design:* Prospective, observational study. *Setting:* University teaching hospital, general adult ICU. *Patients:* One hundred consecutive patients on admission to the ICU. *Measurements and results:* The anion gap (AG) was calculated and corrected for abnormal serum albumin ($AG_{corrected}$). Serum lactate was measured and SBE, BE_{UA}, SIG, and APACHE II scores calculated for each patient. 28-day survival was recorded. There was a significant difference between the mean APACHE II (P<0.001), SBE (P<0.001), lactate (P=0.008), AG (P=0.007), pH (P<0.001), and BE_{UA} (P=0.009) of survivors and non-survivors. There was no significant difference between the mean SIG (P=0.088), SIDeff (P=0.025), and SID app (P=0.254) between survivors and non-survivors. The pH and SBE demonstrated the best ability of the acid-base variables to predict outcome (AUROC curves 0.72 and 0.71, respectively). Neither of these were as good as the APACHE II score (AUROC 0.76) *Conclusion:* Traditional indices of SBE, $BE_{UA,}$ lactate, pH, AG, and APACHE II all discriminated well between survivors and non-survivors. In this group of patients the SIG, SIDeff, and SIGapp appear to offer no advantage in prediction of outcome and their use as prognostic markers can therefore not be advocated.

Keywords Strong ion gap · Standard base excess · Prognostic indicators · Acid-base disturbance

Introduction

The critically ill frequently exhibit complex acid-base disturbances often with mixed respiratory and metabolic derangements. The arterial partial pressure of CO_2 ($PaCO_2$) gives some indication of the respiratory component, however, quantification of the metabolic component is more complex.

Traditional measures may help in the understanding of the metabolic component of acid-base dysfunction. These include the anion gap (AG), standard bicarbonate, and standard base excess (SBE) [1, 2]. All of these measures give an insight into the derangement, but they give little information as to the source of the problem. The significance of these variables in quantifying the degree of acid-base disturbance is dependent upon normal plasma composition [3, 4, 5, 6]. When electrolyte and protein abnormalities are present, simplistic clinical interpretation of acid-base derangements may be misleading. Abnormalities of these plasma components are common

in critically ill patients and thus the validity of these measures in this population may be questioned.

Recently, alternative methods of assessing acid-base disturbance have been described by Stewart [7]. These techniques are posited as being more sensitive indicators of metabolic disturbance by estimating unmeasured anion concentrations: encompassing the contribution of the respiratory status ($PaCO_2$) and electrolytes and plasma protein abnormalities to the acid-base imbalance.

The mathematical model of plasma properties based on physico-chemical principles [7] described by Stewart and modified by Figge [3, 8] proposes three independent variables determining acid-base imbalance: (i) the strong ion difference (difference between fully dissociated anions and cations); (ii) $PaCO_2$; and (iii) the total weak acid concentration (consisting mainly of albumin and phosphate). Fencl [9] demonstrated the clinical application of these principles which resulted in the introduction of the term strong ion gap (SIG) by Kellum [10].

Gilfix [6] developed alternative equations to correct the base excess for the common abnormalities in plasma albumin, chloride, and sodium seen in critically ill patients. This variable is known as the standard base excess corrected to account for unmeasured anions (BE_{UA}). If SBE measured is equal to BE_{UA} no unmeasured anions/cations are present, a difference between the two indicates the presence of unaccounted anions/cations. The use of SIG and BE_{UA} in the critically ill has shown these alternative indices may better identify the presence and origin of acid-base derangements than the traditional indices of AG and SBE [6, 10].

Measures of metabolic disturbance have in the past been used to predict patient outcome on admission to the intensive care unit [11, 12]. A recent study in paediatric patients has demonstrated that elevated unmeasured anions identified by determining BE_{UA} were more strongly associated with mortality than either SBE, AG or lactate [13]. This study attempts to assess whether BE_{UA} or SIG could improve outcome prediction of patients being admitted to an adult intensive care unit in comparison to SBE, AG, and lactate.

Methods

This observational study took place in a single, mixed medical and surgical adult intensive care unit in a university teaching hospital. The data from 100 consecutive patients were collected prospectively in patients who had blood gas analysis and serum electrolytes and proteins measured on a single blood sample on admission to the adult intensive care unit. APACHE II data was collected for each patient for the first 24 h after admission [14]. As the blood tests and data collected in this study were all standard clinical practice, the Local Research and Ethics Committee waived informed consent.

Blood gas analysis was performed using the ABL 625 blood gas analyser (Radiometer, Copenhagen) to measure pH and $PaCO_2$. Bicarbonate was calculated using the Henderson-Hasselbalch equation and the SBE using Siggaard-Andersen's formulae [15]. The analyser underwent daily calibration and quality control checks.

Blood was analysed for Na^+, K^+, Ca^{++}, Cl^-, and lactate by the ABL 625 analyser using potentiometry methods and sera analysed for Mg^{++}, PO_4^-, and albumin using a DAX72 analyser (first 30 patients only) (Bayer Diagnostics, Basingstoke, UK) and subsequently an ALEX 20 analyser (Beckman Instruments, High Wycombe, UK) according to manufacturers recommended methods.

The AG was calculated using the standard formula [1, 2] and corrected to compensate for abnormal albumin concentrations ($AG_{corrected}$) [16]. The SBE was corrected for abnormal sodium, chloride, and albumin using the equations of Gilfix [6] to give BE_{UA}. The strong ion gap (SIG) was calculated by subtracting the effective strong ion difference (SID_{eff}) from the apparent strong ion difference (SID_{app}) using previously described equations [7, 8].

SBE and BE_{UA} were considered to be normal if the measured /calculated values were between –4 and +4 mmol/l. An AG greater than 12 mmol/l was considered elevated. An SIG greater than zero represented the presence of unmeasured anions and was considered abnormal [10]. All patients were followed up to determine 28-day survival.

Data are presented as absolute values, percentages, or mean and standard deviations. All documented parameters approximated to normal distribution with the exception of lactate which underwent log transformation prior to analysis. A two-tailed *t*-test was used to assess which variables were related to outcome. Values of *P* less than 0.05 were considered significant. Variables that were significantly different between survivors and non-survivors had their prognostic ability tested for using simple logistic regression analysis and receiver operating characteristic (ROC) curve analysis. The greater the area under the ROC curve (AUROC) the better the prediction of outcome. All analyses were performed using STATA 5.0 (Stata, College Station, Tex., USA).

Table 1 Aetiology and outcome of patients in the study

Type of patient	Number	28-day mortality (%)
Medical		
Respiratory failure / COPD	17	8 (47)
Post-cardiac arrest	11	8 (72)
Complicated myocardial infarct	3	1 (33)
Meningitis/septic shock	4	2 (50)
Diabetic ketoacidosis	2	0
Gastrointestinal haemorrhage/ pancreatitis	4	1 (25)
Drug overdose	2	0
Miscellaneous	5	1 (20)
Surgical: elective		
Upper GI	0	
Lower GI	0	
Orthopaedic	2	0
Vascular	3	0
AAA repair	5	1 (20)
Urology	5	0
Plastics	5	0
Other	1	0
Surgical: emergency		
Lower GI	3	1 (33)
Perforated viscous	10	4 (40)
Trauma	8	1 (13)
AAA repair	5	3 (60)
Total	100	31 (31)

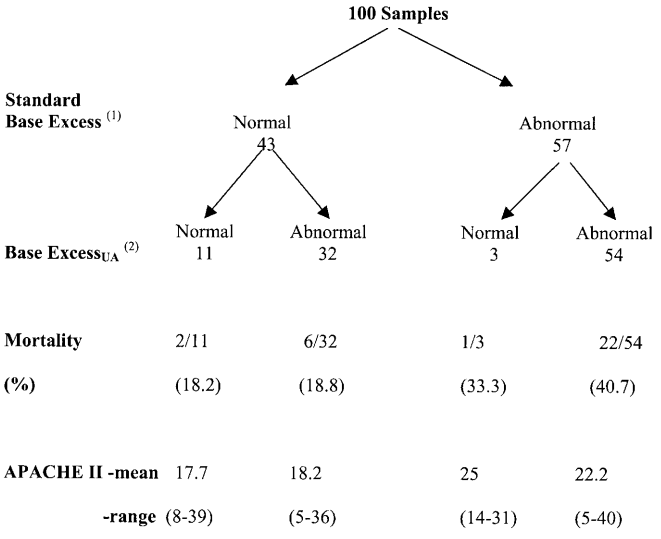

Fig. 1 Base excess adjusted to account for abnormalities of sodium, chloride, albumin, and free water (BE_{UA}) detected more patients with acid-base disturbance than the traditional base excess

Results

One hundred patients were enrolled into the study (Table 1). These patients were a diverse group of both medical and surgical patients with mean age of 61 years (range 19–93), a median APACHE II score of 21 (range 5–40), and a 31% 28-day mortality.

Albumin and electrolyte abnormalities were present in the majority of patients: on admission samples 93% of the patients had an albumin outside the normal range (35–48 g/l); 40% had an abnormal sodium concentration and 37% had an abnormal chloride measurements. These abnormalities had marked effects upon the AG and SBE values. Most patients (94/100) had an abnormal AG on admission and this increased to 100/100 when the AG was corrected for the abnormal albumin [16]. Similarly BE_{UA} identified a larger number of patients having a significant acid-base derangement as compared to SBE calculated by traditional methods (86 vs 57). Only 11 of the 43 patients with a 'normal' SBE, also had a normal $BE_{UA.}$ In contrast, of the 57 patients with an abnormal SBE, 54 also had an abnormal BE_{UA} (Fig. 1).

The following variables were significantly different between survivors and non-survivors; APACHE II, ionised calcium, lactate, pH, bicarbonate, SBE, BE_{UA}, AG, $AG_{corrected}$, and SID_{eff} (Table 2). In this series of patients the SIG was not significantly different between survivors and non-survivors (P=0.088). The AUROC for the variables are shown in Table 3. It can be seen that the APACHE II score has the best prognostic ability of the variables tested. Of the traditional markers of acid-base disturbance, pH and SBE have the best prognostic ability (AUROC 0.72 and 0.71, respectively). The SIG, BE_{UA} and $AG_{corrected}$ have little discriminating ability to predict outcome (AUROC 0.59, 0.65, and 0.62, respectively).

Discussion

AG and SBE are commonly used to assess acid-base disturbances [1, 2, 17]. It is, however, recognised that these techniques can fail to identify the complex metabolic disturbances seen in the critically ill [18]. The AG is influenced by plasma albumin [4, 16] and the SBE influenced by abnormalities of plasma sodium, chloride, and albumin [4, 6] – abnormalities that are nearly ubiquitous in critically ill patients.

Table 2 Measured and calculated admission parameters presented according to outcome

	Survivors		Non-survivors		P
	Mean	SD (+/–)	Mean	SD (+/–)	
Na^+ mmol/l	138	6.4	139	6.8	0.790
K^+ mmol/l	4.1	0.6	4.5	0.8	0.008
Ca^{++} mmol/l	1.0	0.12	1.2	0.47	0.010
Mg^{++} mmol/l	0.78	0.22	0.72	0.24	0.751
Phosphate mmol/l	1.4	0.74	1.7	0.82	0.060
Albumin g/l	21.6	7.7	21.7	8.6	0.966
Lactate	2.3	2.2	3.7	3.1	0.010
Cl^- mmol/l	102	6.9	103	8.5	0.489
pH	7.33	0.12	7.22	0.16	<0.001
HCO_3^-	22.3	5.9	18.6	6.5	0.006
SBE	–2.8	6.3	–8.1	7.9	<0.001
APACHE II	18.5	7.9	25.4	5.9	<0.001
BE_{UA}	–9.9	5.9	14.0	8.9	0.009
AG	18.5	4.9	21.8	7.0	0.007
$AG_{corrected}$	23.4	5.0	26.4	7.0	0.007
$SID_{apparent}$	42.1	5.5	40.6	6.2	0.254
$SID_{effective}$	30.8	6.6	27.5	6.8	0.025
SIG	11.2	4.6	13.1	5.9	0.088

Table 3 Predictors of mortality using LOGIT regression analysis

Variable	OR	*P* value	CI	Area under ROC Curve	CI
APACHE II	1.14	<0.001	1.06–1.22	0.76	0.66–0.86
pH	0.002	0.001	0.001–0.070	0.72	0.60–0.84
SBE	0.90	0.002	0.84–0.96	0.71	0.59–0.82
Lactate	1.23	0.018	1.04–1.46	0.65	0.52–0.78
HCO_3^-	0.91	0.011	0.84–0.98	0.66	0.55–0.78
AG	1.10	0.018	1.02–1.19	0.66	0.54–0.78
$AG_{corrected}$	1.09	0.027	1.01–1.17	0.62	0.50–0.74
BE_{UA}	0.93	0.017	0.88–0.99	0.65	0.52–0.76
SIG	1.06	0.096	0.98–1.16	0.59	0.48–0.71
SID_{eff}	0.93	0.03	0.87–0.99	0.62	0.50–0.74

Assessment of 'unmeasured anions', using the principles described by Stewart, may overcome these problems. The unmeasured anions present may be a variety of organic and inorganic compounds including lactate, salicylates, penicillin, methanol, and ethylene glycol. Better identification of the metabolic derangement, and improved understanding as to the pathophysiological cause of these disturbances may lead to more appropriately directed therapy. Work by Balasubramanyan in a paediatric intensive care suggested that the use of unmeasured anions results in improved mortality prediction compared with SBE, AG, and lactate [13].

In order for a variable to have discriminatory ability to predict outcome, the AUROC should be 0.8 or more [19]. In this group of patients the APACHE II score had an AUROC curve of 0.76. This is in keeping with previously published results for the APACHE II score but suggests that even this complex score does not discriminate well between survivors and non-survivors in datasets different to the original population [20]. Previous data from our ICU indicate that admission SBE and lactate can offer reasonable prognostic abilities from a single blood test [12]. A combination of these indices on admission had a sensitivity of 80.3% and specificity 58.7% for mortality [12]. Similar results were obtained for the patients in this study although in this group of patients the pH was as strong an indicator as the other variables. This ability of markers of acid-base dysfunction to predict outcome has been shown before. Plasma lactate concentration is associated with mortality in patients with shock [21, 22], trauma [23, 24, 25], and sepsis [26, 27]. The response of circulating lactate to resuscitation improves prediction of survivors and non-survivors [24, 28, 29], however, the predictive qualities have been questioned in patients without shock [30]. SBE has been shown to correlate with mortality in trauma [31, 32] shock [33, 34] and mixed groups of patients [12] although studies are conflicting [25].

Results of this study support the findings of others [18] that BE_{UA} identifies a greater number of patients with an acid-base derangements than SBE. The BE_{UA} in this study, however, is not a good predictor of outcome. This differs form Balasubramanyan's findings [13] in paediatric patients. The reasons behind these differences are speculative since clearly the two populations are very different and as such the underlying pathophysiology behind the acid-base derangements are unlikely to be similar. As such the groups cannot be compared since response to treatment and disease progression will differ. Although full details of his study are not yet published, Kaplan reported SIG, but not lactate, to be associated with survival in adult trauma patients on admission to ICU [35]; survival association of SBE was not reported. Others, however, have found lactate to be a good early predictor of morbidity and mortality in both trauma patients [36] and patients with septic shock [27]. The use of sequential measurements of lactate with both peak measurements and ability to clear lactate in response to treatment are thought to be best able to differentiate survivors and non-survivors [24, 29]; it is possible that sequential SIG measurements may similarly be more informative than individual measurements.

There are a number of potential reasons for the poor discriminative ability of SIG in this study. By compensating for abnormalities in electrolytes and albumin and taking lactate out of the equation, the abnormalities associated with an adverse outcome may be being removed, thus reducing the predictive power of the SIG. Second, the type of fluids used for resuscitation in our institution may have an adverse effect on the SIG and BE_{UA}. This effect has been described previously in both healthy volunteers and surgical patients [37, 38, 39]. Using the Fencl-Stewart method to examine the source of acidosis in post-bypass patients, Hayhoe found that the acidoses seen were predominantly iatrogenic. The majority of the acidosis (60%) seen was accounted for by the hyperchloraemia secondary to infusions of chloride rich solutions given to patients. The remaining 40% of acidoses were attributed to the use of polygeline, which acts as an acid resulting in increased unmeasured circulating anions [38]. Similarly, hetastarch infusions in healthy volunteers result in changes consistent with a metabolic acidosis [39]. The 'more physiological' solution of Ringer's lactate has been demonstrated to produce less of an acid-

base disturbance [37] and although readily available in this hospital, it is not routinely used in preference to gelatine based colloids or 0.9% saline in initial resuscitation. If part of the acidosis seen in our patients is iatrogenic due to the unmeasured anions in polygeline or starch, the effect will be an increase in SIG and therefore erroneously indicate a pathological acid-base disturbance with assumed associated adverse effect on outcome. As such, less ill patients are labelled as more severely ill due in part to changes from resuscitation fluids given and hence the prognostic value of these indices lost. It became apparent during the course of this study that fluid regimes at our institution – that is, the use of gelatin with its high anion content – may be influencing the SIG. Detailed data collection of fluid administration was under taken only after the first 26 patients entered into this study. It is a shortcoming of this study that we are unable to make adjustments according to the quantity of gelatin that these patients received. It is possible that this unaccounted factor could also be an explanation for the different results seen in this study compared to that of Balasubramanyan [13]. Since all patients admitted to our intensive care unit were enrolled into this study, a high proportion of the total (25/100) was post-elective surgery. This group differs from emergency admissions in two respects. First, they have a significantly lower mortality. Second, it is certain that the acid-base derangements seen in this group are at least, in part, iatrogenic due to intra-operative fluid administration. Any future studies need to accurately record the type and quantity of intravenous fluids administered to patients prior to ICU admission.

In summary this study agrees with previous work that BE_{UA}, $AG_{corrected}$, can identify more patients with acid-base disturbances, but fails to confirm their ability to act as prognostic markers. In future studies there is clearly a need to examine the measurement of unmeasured anions in relation to type of resuscitation fluids used. Once the degree of iatrogenic acid-base disturbance has been quantified, the prognostic value of assessing unmeasured anions using Stewart's principles could be re-examined.

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