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Strong ions, weak acids and base excess: a simplified Fencl–Stewart approach to clinical acid–base disorders†

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Background. The Fencl–Stewart approach to acid–base disorders uses five equations of varying complexity to estimate the base excess effects of the important components: the strong ion difference (sodium and chloride), the total weak acid concentration (albumin) and unmeasured ions. Although this approach is straightforward, most people would need a calculator to use the equations. We proposed four simpler equations that require only mental arithmetic and tested the hypothesis that these simpler equations would have good agreement with more complex Fencl–Stewart equations.

Methods. We reduced two complex equations for the sodium–chloride effect on base excess to one simple equation: sodium–chloride effect (meq litre^{-1})=[Na^+]–[Cl^-]–38. We simplified the equation of the albumin effect on base excess to an equation with two constants: albumin effect (meq litre^{-1})=0.25×(42–[albumin]g litre^{-1}). Using 300 blood samples from critically ill patients, we examined the agreement between the more complex Fencl–Stewart equations and our simplified versions with Bland–Altman analyses.

Results. The estimates of the sodium–chloride effect on base excess agreed well, with no bias and limits of agreement of –0.5 to 0.5 meq litre^{-1}. The albumin effect estimates required log transformation. The simplified estimate was, on average, 90% of the Fencl–Stewart estimate. The limits of agreement for this percentage were 82–98%.

Conclusions. The simplified equations agree well with the previous, more complex equations. Our findings suggest a useful, simple way to use the Fencl–Stewart approach to analyse acid–base disorders in clinical practice.

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A challenge in clinical acid–base assessment is to analyse the size of the acid–base change and the underlying physiological mechanisms.[1 2] Base excess is a single variable used to quantify the metabolic (non-respiratory) component of a patient's acid–base status. Several research groups[3–5] have combined the base excess approach with the Stewart approach to acid–base physiology.[6] To combine these approaches,[5] these groups examined the base excess effects of two of Stewart's independent variables: the strong ion difference and the total weak acid concentration. Balasubramanyan and colleagues[5] called this approach to base excess the Fencl–Stewart approach.

Gilfix and colleagues[4] used the work of Figge and colleagues[7] and Fencl's unpublished work[8] to derive five equations to estimate the base excess effects of the strong ion difference and the total weak acid concentration. In plasma, sodium and chloride are the principal components of the extracellular strong ion difference,[6] and albumin is the principal extracellular weak acid.[9] While this approach is reasonably simple, most people would need a calculator to use the five equations.

We believe that these equations, used to estimate the sodium–chloride effect on base excess, can be simplified. Balasubramanyan and colleagues[5] simplified the Fencl–

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Stewart albumin equation. Work by Figge's group[9] has further modified the Fencl–Stewart equation for the base excess effect of albumin.[8] This equation can also be simplified in the same way that Balasubramanyan simplified the older equation.[5] We proposed four simpler equations that require only simple mental arithmetic for clinical use.

We tested the hypothesis that the simplified estimates of the base excess effects of the plasma sodium–chloride concentration and the plasma albumin concentration have sufficiently strong agreement with the Fencl–Stewart estimates[3 4] to be used clinically. We used blood samples from critically ill adults to test this hypothesis.

Methods

Data were collected from intensive care unit records at the Austin and Repatriation Medical Centre, a tertiary referral hospital affiliated with the University of Melbourne. All samples were taken from arterial cannulae in patients requiring intensive care. No additional sampling was required. The Austin and Repatriation Medical Centre Human Research Ethics Committee waived the need for informed consent.

Arterial blood samples were collected in heparinized blood-gas syringes (Rapidlyte; Chiron Diagnostics, East Walpole, MA, USA) and analysed in the intensive care unit blood-gas analyser (Ciba Corning 865; Ciba Corning Diagnostics, Medfield, MA, USA). The analyser made measurements at 37°C. Nursing staff from the intensive care unit who had been taught to use the machine by support staff performed the analysis. Samples were not stored on ice. We collected data on the pH, partial pressure of carbon dioxide and the standard base excess.

For each data set, a further sample was drawn at the same time from the same arterial cannula using a vacuum technique with lithium heparin tubes or clot-activating tubes (Vacuette; Greiner Labortechnik, Kremsmunster, Austria). These samples were sent to the hospital core laboratory in the Division of Laboratory Medicine. Plasma and serum underwent multicomponent analysis (Hitachi 747; Roche Diagnostics, Sydney, Australia). Scientific staff from the hospital clinical chemistry department analysed the samples. Samples were not stored on ice. We collected data on the plasma or serum concentrations of sodium, chloride and albumin.

Fencl divided the effect of strong ion difference on base excess into sodium and chloride effects. This group calculated the base excess effects of changes in free water on the sodium concentration and changes in the chloride concentration:[4 5 8]

$$\text{sodium effect (meq litre}^{-1}) = 0.3 \times ([Na^+] - 140) \quad (1)$$

$$\text{chloride effect (meq litre}^{-1}) = 102 - ([Cl^-] \times 140/[Na^+]). \quad (2)$$

Sodium and chloride are the principal contributors to the strong ion difference.[6] The sum of the sodium and chloride effects will give the Fencl–Stewart estimate of the strong ion difference effect on base excess:

$$\text{sodium–chloride effect (meq litre}^{-1}) = 0.3 \times ([Na^+] - 140) + 102 - ([Cl^-] \times 140/[Na^+]). \quad (3)$$

Separately estimating the base excess effects of changes in free water and changes in chloride provides useful information. These separate effects, however, do not need to be quantified initially to determine the effect of the sodium–chloride component of the effect of strong ion difference on base excess. Changes in the difference in sodium and chloride can be used to calculate directly the major changes in the strong ion difference. As the strong ion difference is decreased the blood becomes more acidic.[6]

We proposed that the calculation of the strong ion difference effect on base excess could be simplified. From the reference range in our laboratory, the median value for sodium is 140 mmol litre^{-1} and that for chloride is 102 mmol litre^{-1}. Therefore the median difference is 38 mmol litre^{-1}. The measured sodium–chloride difference minus 38 mmol litre^{-1} will be an estimate of the change in the strong ion difference. For sodium and chloride, 1 millimole equals 1 milliequivalent.

A change in the sodium–chloride component of the strong ion difference will change the base excess directly. Therefore our simplified version of the equation for the sodium–chloride effect on base excess is:

$$\text{sodium–chloride effect (meq litre}^{-1}) = [Na^+] - [Cl^-] - 38. \quad (4)$$

Albumin is the principal contributor to the plasma total weak acid concentration. The effect of albumin on the base excess is due to the anionic effect of albumin. Figge and colleagues[9] developed a pH-dependent formula for the anionic effect of albumin:

$$\text{albumin anionic effect (meq litre}^{-1}) = (0.123 \times \text{pH} - 0.631) \times \text{albumin (g litre}^{-1}). \quad (5)$$

Changes in the concentration of albumin will cause changes in the anionic effect of albumin. Changes in the anionic effect of albumin will change the base excess. As the albumin concentration is decreased the blood becomes more alkaline. We calculated the Fencl–Stewart estimates for the base excess effects of albumin. We used the most recent estimates of the effects of albumin ionization:[8]

$$\text{albumin effect (meq litre}^{-1}) = (0.123 \times \text{pH} - 0.631) \times [42 - \text{albumin (g litre}^{-1})]. \quad (6)$$

We simplified this equation by using a single pH of 7.40:

$$\text{albumin effect (meq litre}^{-1}) = 0.28 \times [42 - \text{albumin (g litre}^{-1})]. \quad (7)$$

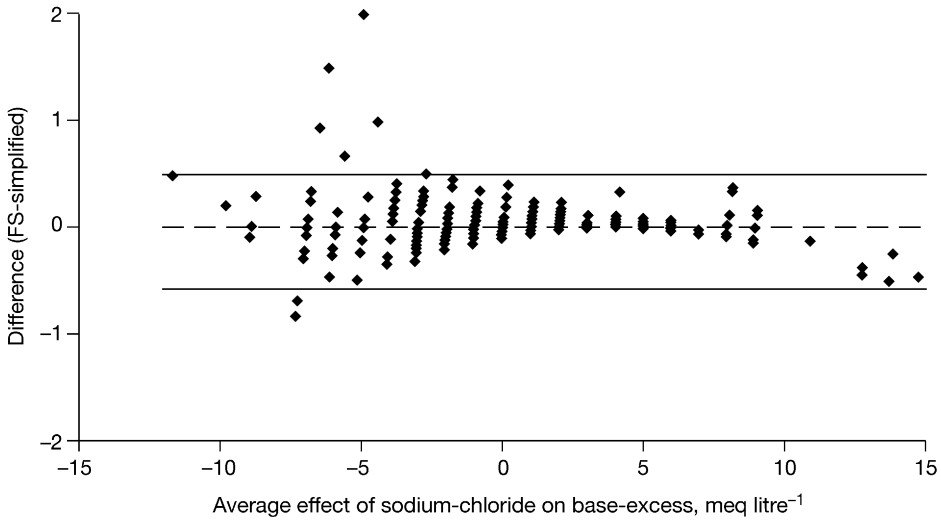

Fig 1 Bland–Altman plot, for 300 samples, of the differences in sodium–chloride effect on base excess between the Fencl–Stewart (FS) and simplified methods (*y* axis), and the average of the two methods: (Fencl–Stewart+simplified)/2. The full lines are the limits of agreement and the dashed line is the bias. The *y* axis represents our proposed upper limits of agreement of bias ±2 meq litre^{-1}.

To facilitate calculation at the bedside we further simplified the equation by using the constant of 0.25. This allows the simple mathematics of dividing the difference in albumin concentrations by 4. Therefore the simplified equation became:

$$\text{albumin effect (meq litre}^{-1}) = 0.25 \times [42 - \text{albumin (g litre}^{-1})]. \quad (8)$$

Statistical analysis

Data were collected from patient charts and the hospital computer system. Data were stored on a computer spreadsheet (Excel, Microsoft, Seattle, WA, USA). All statistical calculations were done with Statview software (Abacus Concepts, Berkeley, CA, USA).

We used the limits of agreement method of Bland and Altman[10 11] to determine the agreement between the Fencl–Stewart and simplified estimates of the albumin and strong ion difference effects on base excess. We proposed that a bias of ±1 meq litre^{-1} and limits of agreement of bias ±2 meq litre^{-1} were acceptable for clinical use of the simplified equations. That is, the greatest difference between two estimates would be 3 meq litre^{-1}. Data were analysed for the overall group and three subgroups: an acidaemic group (pH <7.35), a reference range group (pH 7.35–7.45) and an alkalaemic group (pH >7.45). We used these groups to examine the possibility that different acid–base states may affect the agreement.

Where the difference between the estimates varied with the average of the two estimates (heterodasticity), the relationship was analysed with correlation statistics. If the correlation were statistically significant, at a *P* value of <0.05, the data were log-transformed. The limits of agreement statistics were reported as proportions because a log minus a log is the ratio of the antilogs.[10]

We analysed the relative risk of death where the standard base excess, sodium–chloride effect or unmeasured ion effect was less than –5 meq litre^{-1}. The effect of albumin was almost always alkalinizing; therefore we calculated the relative risk of death of an albumin effect on base excess greater than 5 meq litre^{-1}. We assumed the increase in mortality risk was statistically significant if the 95% confidence interval for the risk ratio did not include 1. We used Confidence Interval Analysis software (BMJ Books).

Results

Three hundred pairs of data were collected from 300 adult patients. The median age of the patients was 65 yr (range 12–94 yr). The median Simplified Acute Physiology Score (SAPS II) score[12] was 17 (range 2–40). The median risk of death calculated from the SAPS II was 26% (range 0–96%).

The agreement between the Fencl–Stewart and simplified estimates was analysed for the entire set of 300 samples (Figs 1 and 2) and for the three subgroups: pH <7.35 (acidaemic), pH 7.35–7.45 (reference range) and pH >7.45 (alkalaemic) (Tables 1, 2 and 3).

There was strong agreement between the Fencl–Stewart and simplified estimates of the sodium–chloride effect. There was no bias and the limits of agreement were from –0.5 to 0.5 meq litre^{-1} (Fig. 1). There was an apparent pattern in the data points (Fig. 1); however, the cause and importance of this pattern are unclear. The agreement was similar in the three subgroups classified according to pH (Tables 2 and 3).

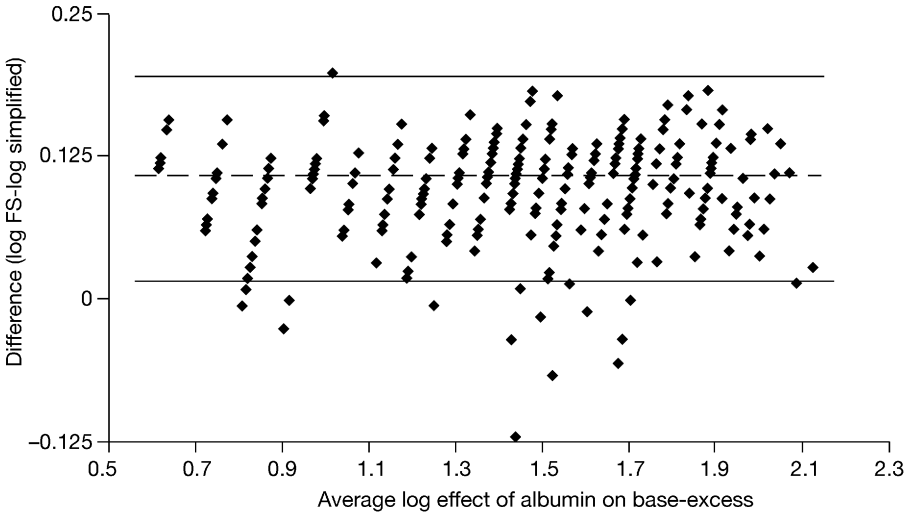

Fig 2 Bland–Altman plot, for 300 samples after log transformation, of the differences in estimates of the albumin effect on base excess between the Fencl–Stewart (FS) and simplified methods (y axis), and the average of the two methods: (Fencl–Stewart+simplified)/2. The full lines are the limits of agreement and the dashed line is the bias.

Table 1 Plasma acid–base variables for three subgroups. Median (range)

Variable	Group		
	Acidaemic	**Reference range**	**Alkalaemic**
Number	105	136	59
pH	7.29 (6.93 to 7.34)	7.40 (7.35 to 7.45)	7.49 (7.46 to 7.61)
Carbon dioxide (kPa)	6.4 (1.5 to 12.9)	5.6 (3.2 to 9.3)	4.7 (2.7 to 7.3)
Base excess (meq litre^{-1})	–4.8 (–24.8 to 19.0)	0.1 (–10.8 to 12.5)	4.1 (–9.4 to 23.4)
Bicarbonate (mmol litre^{-1})	22.1 (4.7 to 44.8)	24.9 (14.2 to 37.8)	27.0 (14.2 to 46.0)
Lactate (mmol litre^{-1})	2.6 (0.3 to 18.8)	1.6 (0.1 to 8.6)	1.7 (0.38 to 11.9)
Phosphate (mmol litre^{-1})	1.53 (0.24 to 3.60)	1.14 (0.10 to 2.58)	1.10 (0.28 to 3.45)

Table 2 Subgroup analysis for sodium–chloride and albumin effects on base excess. Median (range)

Variable	Group		
	Acidaemic (pH <7.35)	**Reference range (pH 7.35–7.45)**	**Alkalaemic (pH >7.45)**
Sodium (meq litre^{-1})	141 (113 to 161)	140 (119 to 162)	140 (121 to 152)
Chloride (meq litre^{-1})	103 (78 to 128)	103 (81 to 119)	100 (86 to 113)
Fencl–Stewart sodium–chloride effect on base excess (meq litre^{-1})	–1.1 (–9.8 to 13.8)	–0.9 (–11.5 to 14.5)	2.0 (–7.9 to 13.5)
Simplified sodium–chloride effect on base excess (meq litre^{-1})	–1.0 (–10 to 14)	–1.0 (–12 to 15)	2.0 (–7 to 14)
Albumin (g litre^{-1})	25 (9 to 42)	27 (12 to 50)	26 (13 to 44)
Fencl–Stewart albumin effect on base excess (meq litre^{-1})	4.3 (0 to 8.5)	4.2 (–2.2 to 8.4)	4.8 (–0.6 to 8.3)
Simplified albumin effect on base excess (meq litre^{-1})	4.3 (0 to 8.3)	3.8 (–2.0 to 7.5)	4.1 (–0.5 to 7.3)

The agreement between the Fencl–Stewart and the simplified estimates of the albumin effect varied with the average effect. This correlation had an R^2 of 0.47 and a P value of <0.001. The data were log-transformed and analysed again. The log transformation removed the correlation between the difference of the estimates and the average value (Fig. 2). After log transformation there was good agreement between the Fencl and simplified estimates of the albumin effect. The simplified estimate was, on average, 90% of the Fencl estimate. The limits of agreement for this percentage were 82–98%. The results were similar in the three pH subgroups, with the best agreement in the acidaemic group (Tables 2 and 3).

The relative risk of death was greater when either the standard base excess or the unmeasured ion effect was less than –5 meq litre^{-1}. A sodium–chloride effect on base

Table 3 Limits of agreement between the Fencl–Stewart and simplified estimates for three subgroups

	Group		
	Acidaemic (pH <7.35)	**Reference (pH 7.35–7.45)**	**Alkalaemic (pH >7.45)**
Sodium–chloride effect (Fencl–Stewart estimate compared with simplified estimate)			
Bias (meq litre^{-1})	0.1	0.0	0.0
Limits of agreement (meq litre^{-1})	–0.5 to 0.7	–0.4 to 0.4	–0.4 to 0.4
Albumin effect (simplified estimate as % of Fencl–Stewart estimate)			
Average (%)	94	90	86
Limits of agreement (%)	88 to 101	87 to 92	84 to 89

Table 4 Relative risk of death. *Compared with patients with a base excess or base excess effect equal to or greater than –5 meq litre^{-1}; **compared with patients with an albumin base excess effect of equal to or less than 5 meq litre^{-1}

	Relative risk of death	**95% Confidence interval**
Standard base excess less than –5 meq litre^{-1}*	1.97	1.38 to 2.80
Sodium–chloride effect less than –5 meq litre^{-1}*	0.86	0.41 to 1.81
Albumin effect greater than 5 meq litre^{-1}**	1.26	0.84 to 1.81
Unmeasured ion effect less than –5 meq litre^{-1}*	1.50	1.05 to 2.16

excess less than –5 meq litre^{-1} or an albumin effect greater than 5 meq litre^{-1} was not associated with an increased risk of death (Table 4).

Discussion

We studied 300 blood samples from 300 critically ill adults. When analysing the acid–base status of these samples we used sodium–chloride as the principal component of the plasma strong ion difference[6] and albumin as the principal component of the plasma total weak acid concentration.[9] We found that the simplified equations to estimate the base excess effects of plasma sodium–chloride concentration and plasma albumin concentration agreed well with more complex equations used in other studies.[4 5 8] Furthermore, we found good agreement in the three subgroups classified according to pH.

Balasubramanyan and colleagues[5] simplified an earlier version of the equation for the albumin effect.[4] These researchers, however, did not examine the agreement of the simplified equation with the more complex Fencl–Stewart version.[4] One strength of our study is that we used the most recent versions of the Fencl equations.[8] Furthermore, we used a large number of samples from different patients with a wide range of acid–base disorders, including some with increased plasma lactate (another strong ion)[5] or increased plasma phosphate (another important weak acid).[9] Another strength is that we avoided overestimating the strength of agreement attributable to mathematical linking.[13] We avoided this problem by using the limits of agreement approach of Bland and Altman.[10 11]

In unpublished work, Fencl[8] proposed a method of combining base excess and the Stewart approach[6] to acid–base physiology and disease. This approach was designed to facilitate clinical application of the Stewart approach. We suggest the following simplified version of the Fencl method.[4 5]

Four variables are determined (standard base excess and the base excess effects of sodium–chloride, albumin and unmeasured ions) using the following four equations:

$$\text{standard base excess (mmol litre}^{-1}\text{=meq litre}^{-1}\text{) from a blood gas machine;}$$

$$\text{sodium–chloride effect (meq litre}^{-1}\text{)}=[Na^+]-[Cl^-]-38; \quad (4)$$

$$\text{albumin effect (meq litre}^{-1}\text{)}=0.25\times[42-\text{albumin (g litre}^{-1}\text{)}]; \quad (8)$$

$$\text{unmeasured ion effect (meq litre}^{-1}\text{)=standard base excess–sodium–chloride effect–albumin effect.} \quad (9)$$

These four variables, with the partial pressure of carbon dioxide, allow physicians to examine the base excess effects of the principal components of Stewart's independent factors: carbon dioxide, strong ion difference (sodium–chloride) and total weak acid concentration (albumin). The strong ion difference effect can be further analysed with the separate Fencl–Stewart equations for sodium and chloride.[4] The unmeasured ions may be strong ions, such as sulphate and acetate,[14] or weak acids, such as phosphate and polygeline.[15]

These equations require four input variables: the base excess and the plasma concentrations of sodium, chloride and albumin. By using the plasma sodium and chloride concentrations and the simplified sodium–chloride equation we can estimate the base excess effects of electrolyte changes from i.v. fluid therapies.[16 17] For example, Scheingraber and colleagues[16] studied acid–base changes during major gynaecological surgery. Patients received 0.9% saline or lactated Ringer's solution. The saline group had a greater metabolic acidosis, as shown by a more

Table 5 Clinical example of the simplified Fencl–Stewart approach. An acid–base assessment of a patient after anaesthetic induction and after 2 h of major gynaecological surgery. Normal saline was used as the intraoperative fluid. Data are the average values from Scheingrabber *et al.*[16] In this patient, after 2 h of surgery most of the metabolic acidosis can be explained by a decrease in the strong ion difference secondary to an increase in plasma chloride. This is partly offset by a decrease in the total weak acid concentration (albumin). Unmeasured ions are unimportant in this acidaemia. These changes follow the infusion of about 6 litres of 0.9% sodium chloride. *Sodium–chloride effect on base excess (meq litre^{-1})=[Na^+]–[Cl^-]–38; **albumin effect on base excess (meq litre^{-1})=0.25×(42–[albumin] g litre^{-1}); ***unmeasured ion effect (meq litre^{-1})=standard base excess–(sodium–chloride effect)–albumin effect

	After induction	After 2 h
pH	7.41	7.28
Carbon dioxide (kPa)	5.3	5.3
Sodium (meq litre^{-1})	140	142
Chloride (meq litre^{-1})	104	115
Albumin (g litre^{-1})	40	28
Base excess (meq litre^{-1})	–0.4	–6.7
Sodium–chloride effect (meq litre^{-1})*	–2	–11
Albumin effect (meq litre^{-1})**	0.5	3.5
Unmeasured ion effect (meq litre^{-1})***	1.1	0.8

negative base excess. One cause of this acidosis was a decreased strong ion difference. The Scheingraber group showed that these changes in base excess and strong ion difference occurred in parallel but they did not quantify the effect. The method described in our study allows easy quantification of the effects of changes in plasma sodium and chloride (strong ion difference) on base excess (Table 5).

Analysis of the fourth variable, plasma albumin concentration, is useful in the intensive care unit and in the perioperative setting. In addition to the acidifying effects of saline, Scheingraber and colleagues also found an intraoperative decrease in plasma albumin concentration in both their groups.[16] They speculated that this decrease in albumin would affect the base excess, but did not quantify the effect. Decreased plasma albumin leads to a decreased total weak acid concentration that produces a metabolic alkalosis.[3] Using a different method, Figge and colleagues[18] developed the same constant (0.25) to quantify the effect of changes in plasma albumin on the anion gap, as we did for the effects on base excess. Our work supports this finding because the physiology is the same: changes in the anionic effect of albumin will alter both the base excess and the anion gap.[19] Decreased plasma albumin concentration is common in critically ill patients.[20] The method described in our study allows easy quantification of the effects of changes in plasma albumin (total weak acid concentration) on base excess (Table 5).

Using an approach similar to ours, Balasubramanyan's group[5] studied critically ill children. In a subgroup of 66 children, they found that a base excess effect of unmeasured ions more negative than –5 meq litre^{-1} was an important predictor of mortality. Our approach simplifies estimation of the unmeasured ion effect on base excess by simplifying the calculations for the effects of the strong ion difference and the total weak acid concentration. Among 300 patients, we found that an unmeasured ion effect on base excess less than –5 meq litre^{-1} increased the risk of death by 50%. The risk of death with a standard base excess less than –5 meq litre^{-1} was increased by 100%. There was, however, considerable overlap in the 95% confidence intervals for the relative risk of death for the unmeasured ion effect and the standard base excess. Furthermore, similar changes in the base excess effects of sodium–chloride and albumin did not increase the relative risk of death. These findings suggest that it is the unmeasured ion component of the base excess that is the important clinical marker for mortality.

We have reduced five Fencl–Stewart equations to four simpler equations. We have maintained good agreement with the previous, more complex equations. These simple equations may allow easy, direct application of Stewart's independent factors to clinical work both inside and outside the operating room. We propose these equations as bedside clinical tools rather than as tools for detailed physiological research. Future studies should examine the importance of each of the base excess effects on patient outcome.

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