

# Between analyser differences in chloride measurements and thus anion gap cause different interpretations of the acid-base balance.

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## Letter to the Editor

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# Between analyser differences in chloride measurements and thus anion gap cause different interpretations of the acid-base balance

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**Keywords:** acidosis; anion gap; chloride; overestimation.

To the Editor,

The physiological approach is a serviceable method for interpreting acid-base disorders [1, 2]. The anion gap can be helpful in narrowing the differential diagnosis in a patient with metabolic acidosis. Metabolic acidosis due to the presence of an additional acid (endogenous or exogenous) usually results in an increased anion gap, whereas

loss of bicarbonate typically results in a hyperchloremic metabolic acidosis, with a normal anion gap. Traditionally, the anion gap has been calculated from plasma values obtained on routine chemistry analysers in the laboratory [3]. With the availability of (bedside) electrolyte measurement in arterial blood gases (ABG), clinicians can evaluate metabolic acidosis rapidly by calculation of the anion gap from the ABG sample. Recently, we noticed that there were substantial differences between the anion gap obtained by ABG (ABL835, Radiometer), compared to the laboratory anion gap, calculated with concentrations obtained in plasma on the routine chemistry analyser (Cobas C-modules, Roche DX).

To assess the extent of the observed differences, electrolyte measurements and resulting anion gaps

**Table 1:** Comparison of mean electrolyte concentrations and the anion gap in arterial blood gas and venous plasma.

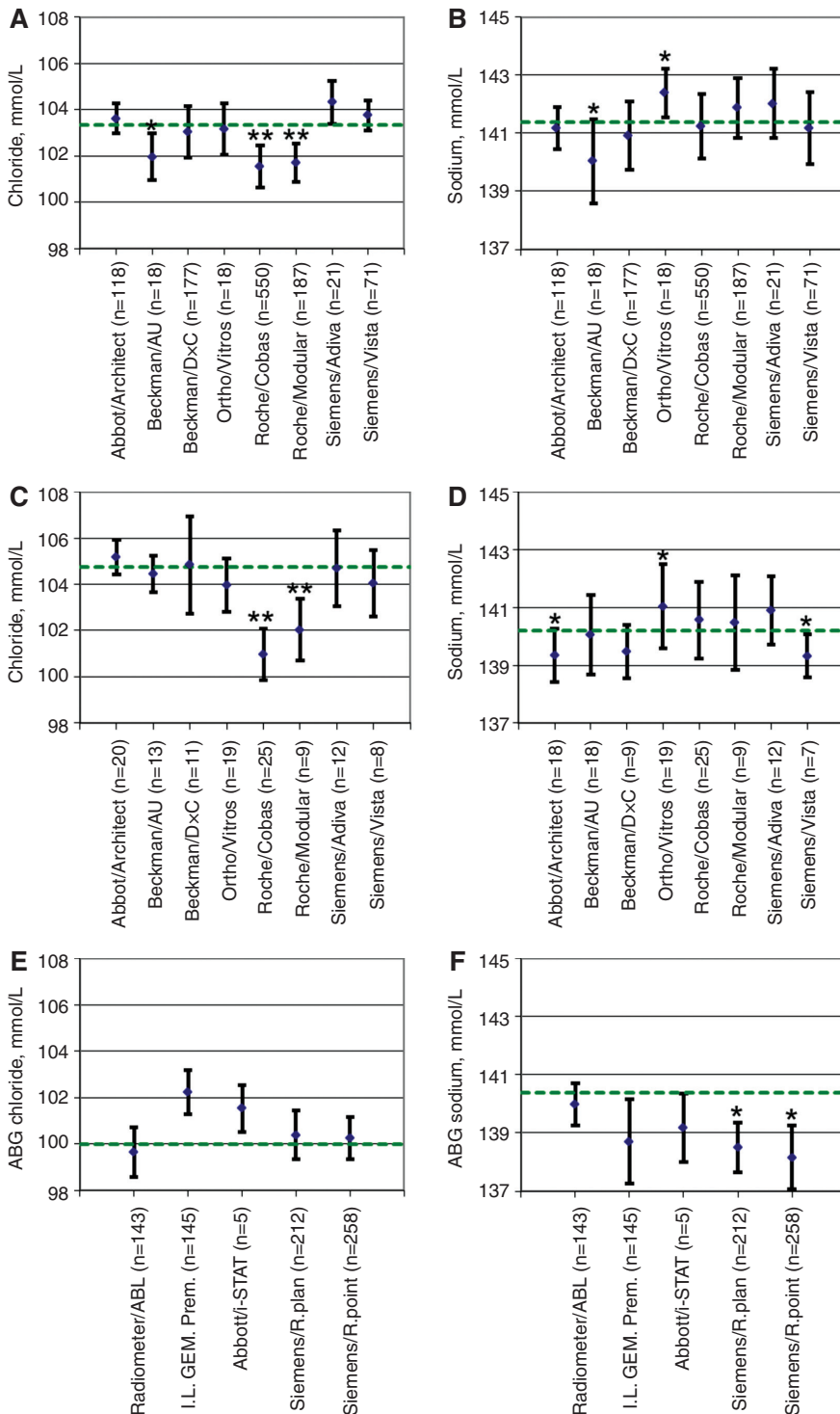
	ABG (whole blood)	Venous plasma	$\Delta$ Mean	95% LoA	ICC agreement
Sodium, mmol/L	138.1±5.6	137.6±5.2	0.51	-4.24; 5.28	0.945
Potassium, mmol/L	4.3±1.0	4.3±1.1	-0.03	-0.74; 0.68	0.968
Chloride, mmol/L	105.1±6.0	101.1±6.2	3.99	-2.63; 10.61	0.821
Anion gap, mmol/L	15.9±5.6	19.4±6.3	-3.47	-11.1; 4.2	0.806
Bicarbonate, mmol/L	17.1±4.8	-	-	-	-

Data are expressed as mean±standard error of the mean. Anion gap=sodium-(chloride+bicarbonate), using the sodium and chloride concentrations of arterial whole blood and venous plasma, respectively. ABG, arterial blood gas; ICC, intraclass correlation coefficient; LoA, limits of agreement.

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**Figure 1:** External control and master comparison results on different platforms.

(A) Mean concentration of yearly external electrolyte quality control samples (SKML 2014, The Netherlands) as measured on different chemistry analysers (n=number of measurements). The dotted line is the SKML-assigned mean reference concentration: Chloride concentrations. (B) as A: Sodium concentrations. (C) Mean concentration of external quality assessment survey with 20 fresh frozen, single donation samples (Mastercomparison 2014 STT consulting/UGent). The dotted line is the all manufacturer trimmed mean concentration: Chloride concentrations. (D) As C: Sodium concentrations. (E) Mean concentration of yearly external electrolyte quality control samples (SKML 2014, The Netherlands) as measured on different blood gas analysers (n=number of measurements). The dotted line is the SKML-assigned mean reference concentration: Chloride concentrations. (F) as E: Sodium concentrations. Differences between assigned reference concentration and measured concentration are significant at  $p < 0.05$  (\*); at  $p < 0.01$  (\*\*). Error bars indicate standard errors of the mean.

were compared in simultaneously drawn arterial blood and venous plasma samples of 529 patients that had visited the emergency department during the last 3 years. On average the anion gap was  $-3.47$  mmol/L lower (95% LoA:  $-11.2$ ;  $4.1$ ) when calculated from ABG values compared to venous measurements (Table 1). A closer look at the electrolyte concentrations indicated that, especially the chloride concentrations are significantly lower when measured in venous plasma samples (Table 1).

Of the 529 included patients, 269 (51%) had a metabolic acidosis (pH  $<7.35$ ; bicarbonate  $<22$  mmol/L). The differences in anion gap were large enough to be clinically relevant. Twenty-five patients with a metabolic acidosis (9%) had a normal anion gap according to ABG measurements, but an increased anion gap with plasma electrolytes. This could potentially result in a different differential diagnosis, and thus treatment. It should be noted that for both anion gaps ABG bicarbonate was used. While venous plasma bicarbonate is usually higher (approx. 1 mmol/L), calculating the anion gap with venous measurements exclusively will result in slightly lower anion gaps than reported here.

Ideally, the platform or chemistry analyser used, should not influence the measurement of electrolytes. In practice, even differences are found when the (average) concentrations of external quality control samples, measured on different platforms, are compared (Figure 1). Figure 1A indicates that both Roche-Cobas and Roche-Modular find significantly lower chloride concentrations than assigned (dotted line). The other analysers listed, besides Beckman/AU, do not show this deviation. The deviation of Beckman/AU may be due to the limited number of results. The observed difference of approximately 1.5 mmol/L in the external quality control does not fully explain the observed difference in the anion gap. However, when a comparison is made with 20 patient samples (Figure 1C) instead of control samples, the differences between Cobas modules and other platforms become more pronounced. The average difference of approximately 3.5 mmol/L is in agreement with the observed discrepancy in the anion gap. Figure 1B and D show that a similar difference in control or patient samples is not observed for sodium; the average concentrations measured on Cobas modules agree well with the assigned (reference) values (dotted line). Figure 1E and F indicate that the blood gas analyser used (Radiometer; ABL835) measures chloride and sodium accurately.

Due to known difference between direct and indirect electrolyte measurements, it is recommended to adjust

blood gas analyser results to make these comparable with direct measurements [4]. However, here the low chloride concentrations measured by the Cobas C-modules lead to higher anion gaps compared to ABG-anion gaps. In other words, even chemistry platforms (only indirect measurements) measure different chloride concentrations. For now, a correction factor is implemented to increase the chloride concentrations found on the routine chemistry analyser to a more factual concentration.

In conclusion, we describe a situation where the anion gaps, and thus clinical conclusions, depend on the analyser used. We are not the first to note differences in electrolyte concentration between ABG whole blood samples compared to venous plasma. Differences in sodium as well as chloride concentrations have been reported [5]. In this study, the observed difference could be traced back to consistently lower chloride concentrations in venous plasma samples compared to ABG and external quality control reference concentrations. For now, a practical solution to obtain a workable situation was chosen: a correction factor for chloride concentrations measured on the chemistry analysers has been implemented. However, this is neither desirable nor necessary, as others have reported similar problems >10 years ago [5]. Standardisation of sodium has been largely accomplished, it is now time for diagnostic companies to standardise chloride measurements as well.

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## References

1. Berend K, De Vries AP, Gans RO. Physiological approach to assessment of acid-base disturbances. *N Engl J Med* 2014;371:1434–45.
2. Adrogue HJ, Gennari FJ, Galla JH, Madias NE. Assessing acid-base disorders. *Kidney Int* 2009;76:1239–47.
3. Kraut JA, Madias NE. Serum anion gap: its uses and limitations in clinical medicine. *Clin J Am Soc Nephrol* 2007;2:162–74.
4. Ben Rayana MC, Burnett RW, Covington AK, D’Orazio P, Fogh-Andersen N, Jacobs E, et al. Recommendation for measuring

and reporting chloride by ISEs in undiluted serum, plasma or blood. International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). IFCC Scientific Division, Committee on Point of Care Testing and Working Group on Selective Electrodes. Clin Chem Lab Med 2006;44:346–52.

5. Morimatsu H, Rocktaschel J, Bellomo R, Uchino S, Goldsmith D, Gutteridge G. Comparison of point-of-care versus central laboratory measurement of electrolyte concentrations on calculations of the anion gap and the strong ion difference. Anesthesiology 2003;98:1077–84.