Metabolic acidosis and strong ion gap: what is its real cause?

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In this issue of the Netherlands Journal of Critical Care, van Raalte et al. [1] describe an interesting case of severe metabolic acidosis in the ICU. It draws the attention of the clinician to a rarely recognized cause of high anion gap acidosis, namely pyroglutamic acidemia, which was at least partially caused by the chronic use of the counter drug acetaminophen.

Metabolic acidosis is the commonest form of acid-base disorder observed in critically ill patients. Interestingly, the interpretation and understanding of acid-base abnormalities was revisited several years ago. New quantitative approaches, mostly derived from Peter Stewart’s work in physical chemistry, are becoming more accepted in daily clinical practice.

In the presented case, the authors use a quantitative approach to describe the acid-base derangement in their patient. Using this approach, understanding that only three variables are important in determining pH, namely PCO₂, [SID] and [Atot], is essential. Furthermore, the physicochemical approach, described by Stewart to investigate the acid-base balance, includes the strong ion gap (SIG), a quantitative measure of “unmeasured” anions. The chemical nature of these anions is largely unknown.

Reading the case report, the first question that might arise is: do the calculations of the parameters SIDa, SIDe and SIG really help in the understanding and management of this case? Although the clinical applicability of Stewart’s quantitative approach is often debated by supporters of the more traditional Henderson-Hasselbalch approach, the most important advantage is to be able to specifically quantify the contribution of the individual components of a complex acid-base disorder.

The presented case nicely illustrates the usefulness of this approach in a complex clinical situation. In practice, after quantifying the metabolic component of an acidosis by calculating the standard base excess (SBE), the next appropriate step is to determine its aetiology. Because of the frequent occurrence of hypo-albuminemia, as in this case, calculation of the corrected anion gap (AGC) or the strong ion gap (SIG) is mandatory for the accurate detection and quantification of unmeasured anions. A high SIG, in most studies defined as >2 mEq/L, strongly correlates with the albumin and lactate corrected anion gap in ICU patients, and represents unmeasured anions other than lactate [3].

In the presented case, the SIG was 17.9 mEq/L, demonstrating that “unmeasured” anions were present that explain the metabolic acidosis. Thus, these anions contributed to the acidosis in this patient to a similar extent as the increased level of lactate (21.9 mEq/L).

The case report describes a high concentration of pyroglutamic acid in the patient. The pyroglutamic acidemia in this particular case is probably explained by multiple factors contributing to decreased glutathione reserve, which enhances acetaminophen toxicity. The second question that arises is how important the high level of pyroglutamic acid is in contributing to the acidosis in this patient. The quantitative approach allows us to answer this. The pyroglutamic acid level was measured and explains only 8% of the total SIG, thus contributing only partly to the metabolic acidosis.

So, the question of what other unmeasured anions cause the increased anion gap still remains. This issue in general, has been frequently addressed in the recent literature [3], but remains largely unresolved. Strong ion gap acidosis probably is a multi-causal entity. Both hepatic and renal dysfunction are known to impair anion clearance and result in the accumulation of unmeasured anions. Also, acute illness or injury, with or without sepsis, appears to result in an increased [SIG]. In the case presented, the hepatic failure probably was an important factor in contributing to unmeasured anions.

Recently, the presence of and contribution to the SIG of a large variety of compounds was explored in critically ill acidic patients [4]. By using several laboratory techniques such as ion-exchange column chromatography, reverse-phase high-performance liquid chromatography, gas chromatography and 1H-NMR mass spectrometry, amino acids, uric acid, and organic acids were measured. Using these methods, which are able to detect hundreds of different compounds, only 7.9% of the SIG could be explained. So, over 92% of the anions that are responsible for the increase in SIG represent an unclarified portion of the strong anion gap that remains to be explored. It is interesting to note that in this particular study, pyroglutamic acid levels in ICU patients with a high strong ion gap were much lower than those in the case presented in this issue of the NJCC, and explained only 0.2% of the SIG. Furthermore, no association between acetaminophen use and pyroglutamic acid levels was found [4].

The last question is whether the small contribution of pyroglutamic acid to the metabolic derangement in this patient justifies the use of renal replacement therapy to correct it. Pyroglutamic acid levels are expected to normalize after discontinuation of acetaminophen and the administration of N-acetyl-cysteine which replenishes glutathione stores. Although there is no clear evidence in the literature, for obvious reasons it seems reasonable to use CVVH therapy in such a severe derangement. Moreover, CCVH therapy has proven effective in correcting metabolic acidosis by removal of other unmeasured anions.

In conclusion, the presented case nicely illustrates the usefulness of this approach in a complex clinical situation. In practice, after quantifying the metabolic component of an acidosis by calculating the standard base excess (SBE), the next appropriate step is to determine its aetiology. Thus, further studies are needed to clarify the nature and contribution of the “unmeasured” anions involved in metabolic acidosis.

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anions [5], which, although their identity remains unknown, are abundant and largely responsible for the metabolic acidosis in this case.

In conclusion, the presented patient had a dual acid-base disorder consisting of both lactic acidosis and strong ion gap acidosis (the latter only partially explained by increased concentrations of pyroglutamic acid) and illustrates the usefulness of the quantitative approach of metabolic acidosis in clinical practice.

References