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Research Article

AN UPDATE ON THE CLINICAL USEFULNESS OF ANION GAP IN A SELECTED CATEGORY OF PATIENTS

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Abstract

Anion gap is an important parameter used in the interpretation of acid base disorders. This study is undertaken to update the recent understanding of the clinical usefulness of Anion gap in a selected category of patients in our Hospital. Anion Gap and 95 % confidence limits were calculated using the results for Na, Cl and HCO_3 of 200 non hospitalized out patients, 300 MICU hospitalized patients, 110 neonatal hospitalized patients and 51 normal male blood donors. Standard procedure was used to collect random blood samples. Beckman coulter AU400 analyzer which employs ISE direct principle was used to measure Na / K / Cl and enzymatic method for HCO_3. Appropriate assayed accuracy controls from Bio-Rad were used to validate the accuracy of the results obtained. As this study was to update the usefulness of anion gap, selection of patients with respect to inclusion or exclusion criteria were not followed. The mean $\pm$ 2 SD limits obtained for blood donors were Na: 131-143, K: 3.4-4.6 Cl: 97-107, HCO_3: 21-29 and AG 6–14, (all in mmol / L) all of which agree well with the normal values used in this laboratory. While AG range for blood donors was 6 to 14, for out patients it was 4 to 16, for MICU group it was 3 to 19 and for neonates 1- 23 suggesting that MICU and Neonates group patients may have different types of Acid base disorders. MICU patients AG were more or less close to normal blood donors. The AG range for neonates was the widest ranging from 1 to 23. This study gives some awareness on the usefulness of AG in interpreting acid base disorders.

Keywords: Blood donors, OP, MICU, Neonates, electrolytes, Bio rad, Na, K, Cl, HCO_3

INTRODUCTION

Anion gap (AG) is the difference in concentration between unmeasured anions (UA) and unmeasured cations (UC) and it is calculated using the measured cations and anions according to following equation

$$\text{Anion gap} = UA - UC = [Na^{+} - (Cl^{-} + HCO_3^{-})].$$

The AG provides an estimate of unmeasured anions in plasma and its usefulness in interpreting acid-base disorders. It is mainly useful in the differential diagnosis of metabolic acidosis, as well as following the response to therapy. In an inorganic metabolic acidosis (e.g. due to HCl infusion), the infused chloride replaces HCO_3 and the AG remains normal. In an organic acidosis, the lost bicarbonate is replaced by the acid anion which is not normally measured and therefore AG is increased and in this instant AG is useful in assessing the biochemical severity of the acidosis and follow up the response to treatment. The anion gap in normal conditions will be a positive number since the sum of the serum anions used in the calculation represent a smaller value compared to the serum sodium concentration. Several Studies have established the normal value for the anion gap as 12 $\pm$ 4 mmol / L. The normal value may vary widely, due to differences in the methods used and inter individual variability.[2] An increase in AG indicates the presence of metabolic acidosis, unless large doses of certain antibiotics or sodium salts of organic acids are infused and a decrease in the AG occurs in dilutional states, hypoalbuminemia, hypercalcemia, hypermagnesemia, hypernatremia, diseases associated with hyperviscosity, bromide intoxication and in certain paraproteinemias. A low or negative AG is useful in the diagnosis of certain life-threatening disorders.[1] AG is mostly used in the detection and analysis of acid-base disorders, assessment of quality control in the chemical laboratory, and detection of such disorders as multiple myeloma, bromide intoxication and lithium intoxication.[2] It is also useful for inter checking electrolyte values as an additional and inexpensive means of laboratory quality control.[3] Averaging at least eight patient AG provides a sensitive technic for the detection of systematic error in electrolyte analysis and it could also be used as an early indicator of drift and it must be used in conjunction with standard quality control procedures such as the multi-rule approach.[4] Both clinicians and lab personnel should check the incidences of increased (> 24 mmol / L) or decreased (< 2 mmol / L) AG. AG > 24 mmol / L will suggest the presence of metabolic acidosis and it is very rare to find AG with the negative sign.[5] Nephrotic syndrome, liver cirrhosis, intestinal obstruction and severe hemorrhage were the common disorders associated with decreased AG and most patients with decreased AG had hypoalbuminemia and all hypoalbuminemic patients did not necessarily have decreased AG.[6] A positive correlation between sodium concentration and AG was observed and the average AG was found to be 16.25 mmol / L. The most common cause of a low AG was presumptive laboratory error.[7] A low or negative AG in the diagnosis of certain of these life-threatening disorders has been emphasized in an earlier study.[8] The magnitude of the primary change in HCO_3 concentration (in metabolic disorders) defines the limits of compensation and the importance of the equality of the increment in the AG (delta AG) and the decrement in the serum bicarbonate concentration (delta HCO_3) in diagnosing a simple high AG metabolic acidosis.[9] Low values most commonly indicate laboratory error or hypoalbuminemia but can denote the presence of a paraproteinemia or intoxication with lithium, bromide, or iodide. Calculation of AG remains an inexpensive and effective tool that aids detection of various acid-base disorders, hematologic malignancies and intoxications.[2] Theoretical and practical limitations beset the use of AG and awareness of these limitations reduces but does not eliminate wrong diagnosis based on AG. A study states that AG has a limited value in the differential diagnosis of acid-base disorders and can be misleading.[10] Data from healthy subjects showed that overall mean AG values of the 9 analyzers ranged from 5.9 to 12.4 mmol / L.[11] If the AG is to remain an effective tool in diagnosing acid-base disorders, clinicians need to be aware that the traditional reference range may not be appropriate with new instrumentation.[12] It is worthy for clinicians to understand the range of normal AG and the measuring methods for electrolytes in the laboratories that support their practice. While an increase in the AG is almost always caused by retained unmeasured anions, a decrease in the AG can be generated by multiple mechanisms.[13] The serum AG is a derived laboratory value that can be readily calculated at the bedside from routine serum electrolyte measurements. Its chief use is in the recognition and differential diagnosis of metabolic acidosis. It is particularly useful in identifying certain mixed acid-base disturbances and as a means of quantifying the degree of underlying acidosis after exogenous alkali has been administered to patients with certain forms of metabolic acidosis. Not uncommonly, the AG provides the initial clue that prompts specific diagnostic studies that lead to a definitive diagnosis.[14] Based on current clinical data, AG value of < 3 mmol / L should be considered as low and is a useful diagnostic tool, but its clinical significance is often unrecognized. However, it may give some clinical clue for the diagnosis of life-threatening intoxications or occult neoplasms, such as multiple myeloma. The baseline low AG may mask the identification of a high gap metabolic acidosis in certain patients. Interpretation of a low AG may provide valuable clinical information.[15] AG greater than 30 mmol / L may be usually due to identifiable organic acidosis (lactic acidosis or ketoacidosis). Lactate and ketoanions accounted for 62 % of the increments in AG and changes in the equivalents of total proteins, phosphorus, potassium and calcium accounted for 15 %.[16] Metabolic acid–base disorders are common in critically ill patients. Clinicians may have difficulty recognizing their presence when multiple metabolic acid–base derangements are present in a single patient.[17] The variables of the traditional approach should be replaced by $[Na^+\text{-}Cl^-]$ difference to detect the disturbance of acid-base status not caused by the retention of undetermined anions.[18] For the past 5 decades, a bicarbonate-based approach has been the dominant method used for the diagnosis and treatment of acid-base disorders.[19] The decreased bicarbonate in pre dialysis patients results from a combination of decreased sodium-chloride difference and mildly increased unmeasured anions.[20] The traditional evaluation of acid-base status relies on the Henderson-Hasselbach equation.[21] If the anion gap is to remain an effective tool in diagnosing acid-base disorders, clinicians need to be aware that the traditional reference range may not be appropriate with new instrumentation.[22] The anion gap is independently associated with higher blood pressure. Further research is needed to elucidate the relation between organic acid and hypertension.[23] It is typically negative in patients with normal AG metabolic acidosis secondary to diarrhoea. Utilization of AG calculations helps clinicians in identifying and treating acid–base disorders.[24] A higher serum anion gap and lower bicarbonate level were associated with higher levels of inflammatory biomarkers in a healthy sample of the general population. Further studies are needed to elucidate the relation between acid–base status and inflammation.[25]

MATERIALS AND METHODS

Selection of Patients

The following categories of patients were selected for the evaluation of AG in this study.

1. 200 non hospitalized out patients who registered for general health check up.
2. 300 Medical Intensive Care Unit (MICU) patients.
3. 110 hospitalized neonates
4. 51 healthy male blood donors for establishing normal values.

Blood collections were done as per standard protocol followed in the hospital clinical lab services, such as the use of vactuainers, disposable needles and other auxillary items. 5 ml blood was collected from each patient in a plain vacutainer so as to use serum uniformly for all patients and controls. Analysis was carried out immediately after separating serum. Na / K / Cl measurements were done using Beckman-coulter AU 400 analyzer, which uses direct Ion Selective Electrode (ISE) principle. Enzymatic method was used to measure bicarbonate. Bio-Rad assayed controls at two levels were used with each batch of analysis to validate the accuracy of results obtained.

Table 1: Mean and SD for All Analytes (All Groups)

S. No	All groups			Na	K	Cl	HC03	AG
1	OP patients (n = 200)	All (n = 200)	Mean	136	4.3	104	22	10
			SD	4.1	0.8	5.3	4.7	3.2
		Male (n = 126	Mean	135	4.3	103	22	11
			SD	4.3	0.8	5.9	5.0	3.3
		Female (n = 74)	Mean	137	4.2	104	23	10
			SD	3.6	0.7	4.1	4.1	3.0
2	MICU Patients	All (n = 300)	Mean	135	3.81	102	22	11
			SD	5.2	0.7	6.0	4.6	3.9
		Male (n = 181)	Mean	135	3.8	102	22	11
			SD	5.2	0.6	5.6	4.6	4.0
		Female (n = 119)	Mean	135	3.8	103	22	11
			SD	5.1	0.8	6.6	4.7	3.8
3	Neonates	All (n = 55)	Mean	134	4.2	104	17	14
			SD	5.0	0.7	6.7	4.4	5.2
		Male (n = 21)	Mean	138	4.0	104	17	15
			SD	4.3	0.5	4.4	3.1	3.9
		Female (n = 34)	Mean	134	4.2	104	17	13
			SD	5.4	0.8	7.8	5.1	5.9
4	Blood Donors	(n = 51)	Mean	137	4.0	102	25	10
			SD	2.9	0.3	2.4	1.8	1.9

Table 2: Anion Gap (Mean $\pm$ 2 SD) for All Groups

S. No	Patient Group	Patient Classification	AG Mean $\pm$ 2 SD
1	Out patients	All (n = 200)	3.6 – 16.4
		Male (n = 126)	4.7 - 17.3
		Female (n = 74)	4.0 - 16.0
2	MICU patients	All (n = 300)	3.2 - 18.8
		Male (n = 181)	3.0 - 19.0
		Female (n = 119)	3.4 - 18.6
3	Neonates	All (n = 55)	1.4 - 22.6
		Male (n = 21)	7.2 - 22.8
		Female (n = 34)	2 - 24.8
4	Blood donors	Male (n = 51)	6.2 – 13.8

Table 3: Cumulative Statistical Data for All Patient Groups

S. No	Patient Group	Statistical Analysis compared	Type of correlation	Probability range
1.	Out patients (All) (n = 200)	K Vs AG Na Vs Cl,HCO_3	Positive	< 0.001
		Na, Cl, HCO_3 Vs AG	Negative	< 0.001 to < 0.000001
2.	Out patients (Males) (n = 126)	K Vs AG Na Vs Cl, HCO_3	Positive	< 0.05 to < 0.000001
		K Vs AG Na Vs Cl, HCO_3	Negative	< 0.01 to < 0.000001
3	Outpatients (Females) (n = 74)	Na Vs Cl, HCO_3	Positive	< 0.01 to < 0.000001
		Cl, HCO_3 Vs AG	Negative	< 0.05 to < 0.000001
4	MICU (All) (n = 300)	Na Vs Cl, HCO_3	Positive	< 0.05 to < 0.000001
		Cl, HCO_3 Vs AG	Negative	< 0.001 to < 0.000001
5	MICU (Males) (n = 181)	Na Vs Cl, HCO_3	Positive	< 0.05 to < 0.000001
		Cl, HCO_3 Vs AG	Negative	< 0.05 to < 0.000001
6	MICU (Females) (n = 119)	K Vs AG	Positive	< 0.05
		Cl to AG	Negative	< 0.01
7	Neonates (All) (n = 55)	Na Vs Cl, HCO_3	Positive	< 0.01 to < 0.000001
		Na, HCO_3 Vs AG	Negative	< 0.05 to < 0.000001
8	Neonates (Males) (n = 34)	K, Cl, HCO_3 Vs AG	Negative	< 0.05 to < 0.000001
9	Neonates (Females) (n = 21)	Na Vs Cl,HCO_3	Positive	< 0.05 to < 0.001
		Cl Vs AG	Negative	< 0.001
10	Blood donors (n = 51)	Na Vs Cl, HCO3	Positive	< 0.05 to < 0.000001
		Na , HCO_3 to AG	Negative	< 0.01

RESULTS

Table 1 presents the mean and Standard Deviation (SD) for electrolytes and AG for all the groups studied. This Table also contains data for mean and SD for Males and Females in each group. The SD is least for blood donors suggesting that all the values for electrolytes and AG are within the normal values used in the author's laboratory. The 95 % confidence limits were used to set the normal range as shown in Table 2.

Table 2 shows the 95 % confidence intervals for AG for all the groups as well as for males and females in each group. It is interesting to observe that the mean $\pm$ 2 SD limits for blood donors are 6 to 14 which is the accepted normal range for AG. While AG for out patients range was 4 to 16, it was 3 to 19 for MICU and 1 to 23 for neonates suggesting that both MICU and neonates patients may have different types of Acid base disorders. No significant difference in the range for AG is observed when males and females AG ranges are compared with all patients in each category.

Table 3 presents the cumulative statistical data for all groups of patients. Negative correlation of Na to both Cl and HCO_3 was observed for patients under serial nos 1,3,4,5 and 8; confirming that both anions contributing for AG are negatively correlated to those groups of patients. A positive correlation of Na to both Cl and HCO_3 were observed for 8 out of 10 patients groups viz 1,2,3,4,5,7,9 and 10 indicating that AG determiants are positively associated to each other. Cl and HCO_3 were inversely related to AG in 50 % of patient groups.

DISCUSSION

The experimental work done in this study by analyzing several groups of patients has demonstrated the usefulness of AG in interpretating Acid base disorders between any two acid base analytes, notably between Na, Cl, HCO_3 to AG and is in accordance with a previous report[7]. The normal values established using blood bank donors agrees well for all electrolytes and AG[12]. The normal range for AG established in this study is in agreement with those established for healthy subjects[11]. The normal AG for out patients agrees well with normal blood bank donors of 4 to 16 versus 6 to 14 mmol / L and is in consistent with a previous study[12]. MICU patients AG established in this study give a range of 3-19. For neonates, AG ranges from 1 to 23, the widest range observed compared to the other 3 groups suggesting that this group may have variety of acid base disorders. Such observation is in agreement with previous study[6,11,24]. The lowest AG levels found in this study for MICU as well as neonates patients are in agreement with previous study.[13] AG measurement will help not only to interpret the patients acid base disorders but also will help the laboratory to check the quality of results incase it is not in line with clinical diagnosis[5]. In all the group of patients studied, a positive association of Na was observed to both Cl and HCO_3 suggesting that these 3 analytes are indeed the true determinants of AG. Such observations found in this study are in agreement with a previous study[7]. AG as shown in this study will help clinicians to identify acid-base disorders. The normal values established using blood donors for AG is in agreement with previous studies. Further, the 95 % confidence limits for out patients are in close agreement with blood donor's level. MICU unit patients have the lowest to highest range in normal range suggesting that such variations are due to extreme metabolic disturbance associated with such patients. The AG range for neonates is the widest ranging from 1 to 23. In all groups of patients, the anion gap determiants, Na, Cl and HCO_3 are inversely correlated to AG. In the normal blood donor group, Na is positively associated to AG, Cl and HCO_3. Hence in MICU and Neonates patients, the criteria for interpreting acid base disturbances solely depend on the correctness of reports received for Na, Cl and HCO_3, making clinicians and lab personnel to work in close coordination. On the whole, this study gives some awareness on the usefulness of AG in interpreting the disorders associated with acid-base disturbances. More such studies are to be carried out to arrive at a consensus value for AG for other group of patients, such as NICU, SICU etc. The final cumulative Table will be very useful for clinicians to interpret acid base disorders based on the associations observed in 3 category of patients studied.

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