

## Hospital Practice

### THE INCREMENT IN THE ANION GAP: OVEREXTENSION OF A CONCEPT?

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**Summary** The calculation of the anion gap is widely used in the diagnosis of metabolic acidosis. It is often taught that the increment in the anion gap will exactly match the fall in serum bicarbonate during a simple metabolic acidosis of the high anion gap type; if the changes in the anion gap and bicarbonate level are not equivalent, a second acid-base disorder should be suspected. The assumptions upon which this formulation is based are largely unsubstantiated. This review critically examines these assumptions and their clinical implications. Discrepancies between the increment in the anion gap and the reduction in serum bicarbonate must be interpreted cautiously.

THE anion gap has proved a valuable tool in the diagnosis of acid-base disorders,<sup>1-3</sup> although the importance of slight rises in the anion gap remains unclear.<sup>4</sup> It is often taught that the increment in the anion gap ( $\Delta AG$ ) should equal the decrement in the serum bicarbonate ( $\Delta HCO_3$ ) in a simple metabolic acidosis with a high anion gap<sup>5-7</sup> (table I). A discrepancy between the  $\Delta AG$  and the  $\Delta HCO_3$  would therefore imply a mixed (complex) acid-base disturbance. Here, I shall review the implications of this theory, the assumptions upon which it is based, and the clinical data that test its predictions.

The  $\Delta AG$  is calculated by subtracting the normal value for the anion gap (usually 12 meq/l\*) from the patient's actual anion gap. The  $\Delta HCO_3$  is the difference between a normal bicarbonate level and the patient's level. According to proponents of the  $\Delta AG/\Delta HCO_3$  ratio, a value greater than one suggests a relative elevation of the bicarbonate level due either to a coexistent metabolic alkalosis or to a compensated respiratory acidosis. Likewise, a ratio of less than one implies the coexistence of a metabolic acidosis of

\*Although the SI unit for substance concentration is mol/l (or a submultiple such as mmol/l), meq/l has been used in this article since the valencies of all the ions contributing to the anion gap are not known.

TABLE I—CAUSES OF METABOLIC ACIDOSIS WITH A HIGH ANION GAP

|  |  |
|--|--|
| <i>Overproduction</i>  |  |
| 1. Ketoacidosis (diabetic, alcoholic, starvation)  |  |
| 2. Lactic acidosis (L-lactate: types A and B; D-lactate)   |  |
| 3. Intoxications (salicylate, ethylene glycol, methanol, toluene, ? paraldehyde, ? intravenous infusion of protein hydrolysates) |  |
| <i>Underexcretion</i>  |  |
| 4. Renal failure   |  |
| <i>Shift</i>   |  |
| 5. Cell lysis (rhabdomyolysis)   |  |

TABLE II—SERUM ELECTROLYTES IN A TYPICAL PATIENT WITH CHOLERA, SEVERE DIARRHOEA, AND HYPOVOLAEMIC SHOCK<sup>8</sup>

| Electrolyte | Level (meq/l) | Acid-base status (meq/l)              |
|-------------|---------------|---------------------------------------|
| Sodium      | 135           | $AG = 135 - (103 + 11) = 21$          |
| Potassium   | 4.7           | $\Delta AG = 21 - 12 = 9$             |
| Chloride    | 103           | $\Delta HCO_3 = 26 - 11 = 15$         |
| Bicarbonate | 11            | $\Delta AG/\Delta HCO_3 = 9/15 = 0.6$ |

*Interpretation:* complex acid-base disturbance with a high anion gap metabolic acidosis superimposed on a hyperchloraemic metabolic acidosis and/or a compensated respiratory alkalosis.

Normal values used for calculations above: anion gap = 12 meq/l, bicarbonate = 26 meq/l. Note that if different values within the normal ranges are used for anion gap and bicarbonate level,  $\Delta AG/\Delta HCO_3$  could vary from 0.5 (for  $AG = 12$  meq/l,  $HCO_3 = 30$  meq/l) to 1.0 (for  $AG = 8$  meq/l,  $HCO_3 = 24$  meq/l).

the hyperchloraemic type or a compensated respiratory alkalosis. Table II applies these concepts to the acidosis of severe cholera.<sup>8</sup>

These conclusions can be derived from several mostly unsubstantiated assumptions: each anionic equivalent is associated with one proton, which is subsequently buffered by a bicarbonate ion; the volumes of distribution of the anion and bicarbonate are equivalent; the elimination of the anion and the regeneration of bicarbonate are quantitatively similar; and there are no concurrent processes other than the high anion gap acidosis affecting the anion gap.

Alternatively, it could be the quantitative interplay of many factors that "fortuitously" results in the equivalence of the  $\Delta AG$  and  $\Delta HCO_3$  in an uncomplicated metabolic acidosis of the high anion gap type.<sup>5</sup> Let us examine the major clinical processes associated with high anion gap acidosis and the empirically derived relation between the  $\Delta AG$  and  $\Delta HCO_3$  in these conditions.

Ketoacidosis is classically regarded as the prototype of a high anion gap acidosis. Although in series of patients with diabetic ketoacidosis the mean  $\Delta AG$  approximates the mean  $\Delta HCO_3$ ,<sup>9</sup> this stoichiometric relation shows wide variability in individual cases.<sup>10,11</sup> In patients who are not severely volume depleted, renal losses of ketoanions exceed the capacity of urinary acidification to regenerate alkali, resulting in a net loss of bicarbonate precursors.<sup>10</sup> This is

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TABLE III—PROCESSES THAT AFFECT THE ANION GAP

| High anion gap  |
|---|
| Metabolic acidosis (see table I)*   |
| Dehydration or loss of fluid with relatively little unmeasured anions                             |
| Infusions of salts of organic acids (lactate, acetate, citrate, penicillin, carbenicillin)        |
| Reduced unmeasured cations (potassium, calcium, magnesium)  |
| Alkalaemia*   |
| Systematic underestimation of serum chloride (in azotaemic patients receiving allopurinol)†       |
| Random laboratory error*  |
| Low anion gap   |
| Volume expansion with free water or fluid containing relatively little unmeasured anion           |
| Systematic underestimation of serum sodium (hypernatraemia, hyperviscosity, hyperlipidaemia)*†    |
| Systematic overestimation of serum chloride (bromism, iodide intoxication, hyperlipidaemia)*      |
| Raised unmeasured cations (potassium, calcium, magnesium, immunoglobulin G, lithium, polymyxins)* |
| Reduced unmeasured anions (hypoalbuminaemia)*   |
| Acidaemia from a respiratory or hyperchloraemic metabolic acidosis‡                               |
| Random laboratory error*  |

\*Realistic clinical situations in which the  $\Delta AG$  may exceed 6 meq/l.

†Systematic errors critically depend on laboratory methods used to measure particular ions under described conditions.

‡The acidaemia usually associated with a high anion gap acidosis tends to reduce the increment in anion gap caused by the higher concentration of unmeasured anions.

probably the primary mechanism for the hyperchloraemic acidosis that develops in many patients during treatment for diabetic ketoacidosis;<sup>9</sup> in fact, patients with uncomplicated diabetic ketoacidosis, depending on their volume status, may present with a pure hyperchloraemic acidosis (ie,  $\Delta AG = 0$ ).<sup>10</sup>

Oh and colleagues<sup>12</sup> speculated that the volume of distribution for ketoanions may be less than the bicarbonate space. This difference would tend to increase the relative concentration of ketoanions, compensating for their renal excretion, and would explain why the  $\Delta AG$  matches the  $\Delta HCO_3$  in some patients with diabetic ketoacidosis despite the loss of ketoanions in the urine.

Patients with lactic acidosis often have a  $\Delta AG/\Delta HCO_3$  greater than one.<sup>9</sup> This observation has a multifactorial basis. Lactate is cleared by the kidney more slowly than ketoanions, allowing the renal defence of acid-base homeostasis to generate additional bicarbonate without the loss of unmeasured anion (lactate).<sup>13,14</sup> Furthermore, the lactate space is probably smaller than the bicarbonate space.<sup>14</sup> The hyperuricaemia and hyperphosphataemia<sup>15</sup> that often develop during lactic acidosis may also contribute to the disproportionate increase in the anion gap. When the production of lactic acid ceases, the metabolism of the "excess" lactate to form bicarbonate can result in an "overshoot" alkalosis.<sup>1</sup>

During lactic acid infusion in dogs<sup>16</sup> and after seizures in patients,<sup>17</sup> the  $\Delta AG$  nearly matches the  $\Delta HCO_3$  for the first hour. These observations may reflect a lag in the distribution of acid out of the extracellular compartment, the recruitment of non-bicarbonate buffers, and the generation of new bicarbonate by the kidneys.

In renal failure, unmeasured anions are retained because of reduced glomerular filtration, while the acidosis results primarily from a tubular failure of ammonia synthesis and secretion.<sup>18</sup> Since these are distinct processes, one would not expect equivalent changes in the anion gap and bicarbonate level. In most uraemic patients, the anion gap is less than 25

meq/l<sup>18,19</sup> and the  $\Delta AG/\Delta HCO_3$  is significantly less than one.<sup>6,18</sup>

Fluid replacement with exogenous alkali in any of these conditions will further distort the relation between the  $\Delta AG$  and  $\Delta HCO_3$ . Any process (except a high anion gap metabolic acidosis) that raises or lowers the patient's baseline anion gap (table III) will also confound this index.<sup>1,5,19</sup> Since there are wide ranges of normal values for both the anion gap and the bicarbonate level, the  $\Delta AG/\Delta HCO_3$  ratio will critically depend on the exact normal values used in the calculation (table II).

Certain theoretical concerns and empirical observations which could potentially affect the  $\Delta AG/\Delta HCO_3$  are often ignored. If the titration of organic acids by non-bicarbonate buffers, such as bone and intracellular proteins, is important, the rise in the anion gap would be greater than the fall in bicarbonate level.<sup>11,18,19</sup> The volumes of distribution for protons, bicarbonate, and organic anions may all be very different.<sup>11,12,20</sup> Acidaemia itself reduces the negative charges on plasma proteins and thereby lowers the anion gap;<sup>19,21,22</sup> in a high anion gap acidosis, this effect would be overwhelmed by the increment in unmeasured anions. Nevertheless, a very low pH may contribute to the discrepancy between the  $\Delta AG$  and  $\Delta HCO_3$ . The balance between these and other opposing processes determines the quantitative relation between the  $\Delta AG$  and  $\Delta HCO_3$ .<sup>5</sup>

In conclusion, the diagnostic limitations of the anion gap and its derivatives must now be recognised. Specifically, clinicians should be aware that: nearly a third of patients with anion gaps between 20 and 30 meq/l will not have a demonstrable organic acidosis;<sup>4</sup> rises in the concentrations of ketoanions and lactate are insufficient to explain the entire  $\Delta AG$  in organic acidoses;<sup>4</sup> patients with otherwise classic uncomplicated diabetic ketoacidosis may present with<sup>10</sup> or subsequently show<sup>9</sup> a metabolic acidosis with a normal anion gap; after the resolution of lactic acidosis, an "overshoot" alkalosis may develop<sup>1</sup> because "excess" lactate typically exceeds the  $\Delta HCO_3$ ;<sup>9</sup> the exact relation between the  $\Delta AG$  and  $\Delta HCO_3$  in a high anion gap acidosis is not readily predictable and deviation of the  $\Delta AG/\Delta HCO_3$  ratio from one does not necessarily imply the diagnosis of a second acid-base disorder.<sup>9,10,18,23</sup>

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References continued at foot of next page

## Conference

### SCREENING FOR BREAST CANCER: EXAMINATION AND REPORTING OF HISTOPATHOLOGICAL PREPARATIONS

AT its annual meeting in Falun, Sweden, the European Group for Breast Cancer Screening,\* whose members represent the major population screening trials, issued guidelines on the examination and reporting of specimens.

1. Mammography screening for breast cancer has led to the detection of a multitude of lesions that were seldom encountered by pathologists before the era of screening. These changes demand new attitudes to the examination, preparation, and reporting of breast specimens. It is therefore recommended that pathologists working in centres embarking on screening activities should spend time in the pathology department of a recognised screening centre.

2. Histopathologists may have difficulty in identifying a lesion disclosed by mammography. One of the most reliable techniques of localisation is the metal wire with hook. All surgical biopsy or segmental resection specimens should be X-rayed immediately after surgical removal.

3. Specimens should be delivered fresh, unfixed, and intact to the laboratory without delay so that preliminary dissection can be done to ensure good fixation. Good fixation and a high standard of technical preparation are particularly important with breast tissue, to avoid artifacts. Specimens should be marked by the surgeon in a way that allows orientation by pathologists. At this stage material should be taken for DNA and receptor studies.

4. Use of large histological sections is recommended to determine the exact size of the tumour and the pattern and extent of spread, particularly in relation to the margins of excision. Microwave fixation and processing has speeded the process so that rapid reporting is now possible.

5. The size of breast cancer should always be recorded. The method of tumour measurement must be consistent for all pathologists and all laboratories within the screening programme. Tumour size (maximum diameter) is best

measured on the histological section. Mammographic, clinical, and macroscopic measurements of tumour size are not satisfactory alternatives.

6. In a histopathological report, description of the characteristics of a cancer should include: (a) histological typing (eg, in-situ alone, in-situ with infiltrative cancer, infiltrative cancer alone) and category of cancer; (b) area of pure in-situ cancer ( $T_0$ ); and (c) measurement of each infiltrative cancer when multiple tumours are present (since this gives an index of total tumour mass). The distance between different infiltrative foci should be measured edge to edge in the stained slide.

7. In multiple cancers, the size of the largest tumour is the index to be used at staging.

8. A multifocal cancer is one in which two foci are more than 2 cm apart without any malignant, in-situ, or infiltrative bridging tissue.

9. The term multicentric cancer is to be reserved for cases in which foci of in-situ or infiltrative cancer are found in quadrants or segments other than that of the main cancer.

10. All lymph nodes, irrespective of size, should be identified and dissected from the axillary tissues and the number should be recorded. Lymph nodes should be embedded in toto and sections should be cut at multiple levels to detect metastases.

11. An on-line computer system is recommended for the collection, processing, and analysis of the large amount of information generated in any screening programme.

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## Round the World

### From our Correspondents

#### Nigeria

##### LEAKAGES IN THE HEALTH SERVICES

THE Federal Minister of Health, Prof Olikoye Ransome-Kuti, noted recently that one of the major troubles of Nigerian teaching hospitals is "leakages". He was referring to the continuing high rate of theft, looting, and corruption in these institutions and the resultant funding difficulties: "as you pour money into the place, so does it leak out". Leakages, however, are not confined to drugs and equipment. There is increasing concern over the steady outflow of top consultants and academics from Nigerian teaching hospitals and medical schools to Saudi Arabia and other Gulf States where their monthly salaries in hard currency are more than their annual salaries in Nigeria. The rich Gulf States are attracting the very specialists and experts who are most needed in Nigeria, as referral services evolve, and on whom most money has been spent over the years. There is also leakage from those who have remained behind in government service: many of these government employed doctors

\*I. Andersson (Sweden), H. G. Bender (Germany), S. Bianchi (Italy), N. Bjurstram (Sweden), P. Boulter (England), E. Buiatti (Italy), L. Cannell (England), L. Cataliotti (Italy), J. Chamberlain (England), S. Ciatto (Italy), J. Dacie (England), G. Eklund (Sweden) (president), R. Ellman (England), O. Eriksson (Sweden), H. Frischbier (Germany), A. Gad (Sweden), N. Gibbs (England), O. Gröntoft (Sweden), B. J. A. Habbema (Holland), J. Haselhurst (England), A. Kirkpatrick (Scotland), B. Lundström (Sweden), G. Maltoni (Italy), S. Moss (England), B. Muir (Scotland), J. Månsson (Sweden), D. Palli (Italy), J. Price (England), M. Roberts (Scotland), P. Robra (Germany) (honorary treasurer), E. Roebuck (England), T. Rombach (Holland), M. Rosselli del Turco (Italy), O. Räsänen (Finland), J. Save-Söderberg (Sweden), B. Thomas (England) (honorary secretary), A. Tucker (England), G. Zampi (Italy).

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