



# PULMONARY AND CRITICAL CARE BULLETIN

Vol. X, No. 3, July 15, 2004  
 Website : www.indiachest.org  
 (p. 17-28)

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## EDITORIAL COMMENT

*Arterial blood gas values are the mirror reflection of various metabolic events that take place inside the body. Further, this helps to assess the adequacy of ventilation. This is quite helpful particularly in the management of acutely ill patients of almost all kinds and the intensivist cannot do without this. However, it is imperative to carry out the test correctly and the result need to be interpreted wisely to arrive at a meaningful conclusion. This article gives a bird's eye view of the arterial blood gas analysis in various clinical situations including its pitfalls.*

## Published under the auspices of

Pulmonary C.M.E. Programme of  
 The CHEST  
 (Chest Health Care, Education & Research Trust)

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Annual : Rs. 100

Life Subscription : Rs. 700

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## INTERPRETATION AND CLINICAL IMPLICATIONS OF ARTERIAL BLOOD GAS ANALYSIS

Blood gas analyses are commonly performed to assess the adequacy of ventilation (including oxygenation capacity of the cardiopulmonary system) as well as the acid-base status. Arterial blood is used most frequently though other sources for blood gas analysis like peripheral venous blood, mixed venous blood (from pulmonary artery) and capillary blood are also utilised in specific situations.

Before one proceeds to interpretation of arterial blood gas (ABG) analysis, one should be familiar with conditions that can invalidate or modify the results of such an analysis. These include:

### 1. Delay In Analysis

PaCO<sub>2</sub> increases and PaO<sub>2</sub> decreases, by approximately 1mmHg and 0.1 volume percent every 10 minutes respectively, after blood has been drawn into the syringe. This rate of change (at 37°C) is reduced by 90% at 4°C. Hence sample should be iced if it cannot be processed immediately.

### 2. Excessive Heparin

Excess of heparin causes a fall in bicarbonate and PaCO<sub>2</sub> values. Hence the syringe should be completely emptied of heparin after flushing. Risk of alteration of results increases with bigger size of syringe/needle and smaller volume of sample.

### 3. Hyperventilation Or Breath Holding

#### 4. Air Bubbles

Air bubbles have the composition of room air ( $PO_2$  and  $PCO_2$  of around 150 mmHg and 0 mm Hg respectively). Hence mixing of air bubbles with the sample would lead to a rise in  $P_aO_2$  and a fall in  $P_aCO_2$ . Mixing and agitation of the sample in an attempt to expel air bubbles often increases the available surface area for diffusion and more erroneous results. Hence one should discard the sample if excessive air bubbles are present and a seal with a cork/cap should be made immediately after taking the sample.

#### 5. Fever or Hypothermia

Most ABG analyzers report data at normal body temp ( $37^\circ C$ ). In the presence of severe hyper/hypothermia, values of pH and  $PCO_2$  that are reported at  $37^\circ C$  can be significantly different from patient's actual values. The changes in  $PO_2$  values with temperature are predictable while there are no significant changes in bicarbonate levels, oxygen saturation and oxygen capacity/content as well as carbon dioxide content values with changes in temperature. There is no consensus regarding reporting of ABG values especially those of pH and  $PCO_2$  after doing 'temperature correction'. Some advocate interpretation of values measured at  $37^\circ C$  while others favour the use of nomograms to convert values at  $37^\circ C$  to patient's temperature.

#### 6. WBC Count

There can be marked increases in oxygen consumption in patients with very high TLC/platelet counts since 0.1 ml of oxygen is consumed per dL of blood in 10 min in patients with normal leukocyte count. Hence immediate chilling or preferably analysis is essential to avoid erroneous results.

#### 7. Type Of Syringe

pH &  $PCO_2$  values are unaffected while  $PO_2$  values drop more rapidly in plastic syringes. Chances of air bubbles entering plastic syringes are also more. However, the differences are

usually not of clinical significance and plastic syringes can be and continue to be used in clinical practice for determination of blood gas analysis.

#### 8. Quality Control & Calibration

An ABG machine has different electrodes for measuring pH,  $PCO_2$  and  $PO_2$  while bicarbonate levels are calculated. It is recommended that each electrode be regularly calibrated.

### Assessment of Oxygenation Status

#### Arterial Oxygen Tension ( $PaO_2$ )

Normal value in healthy adult breathing room air at sea level is around 97 mm Hg. This falls progressively with increasing age. At the age of 60 yrs, it is around 80 mm Hg and falls by approximately 1mm Hg/year thereafter till the age of 90 years. It is also dependant upon both the concentration of inspired oxygen ( $FiO_2$ ) and the partial pressure of gas in the atmosphere ( $Pa_{atm}$ ). Hypoxemia is defined as  $PaO_2 < 80$  mm Hg while breathing room air. Since most patients who need arterial blood gas monitoring usually require supplemental oxygen therapy, it should not be withheld or interrupted 'to determine  $PaO_2$  on room air'. As a rough guide, if  $PaO_2$  is less than 5 times the  $FiO_2$ , patient is probably hypoxemic on room air.

#### Classification of Hypoxemia :

##### A) Classification according to severity:

- Mild:  $PaO_2 < 80$  mm Hg
- Moderate:  $PaO_2 < 60$  mm Hg
- Severe:  $PaO_2 < 40$  mm Hg

##### B) Classification on oxygen therapy :

- Uncorrected Hypoxaemia:  $PaO_2 < 60$  mm Hg ( $PaO_2$  less than value expected on room air and for corresponding  $FiO_2$ )
- Corrected Hypoxaemia:  $PaO_2 = 60-100$  mm Hg ( $PaO_2$  less than value expected for corresponding  $FiO_2$ )
- Excessively Corrected Hypoxaemia :  $PaO_2 > 100$  mm Hg ( $PaO_2$  more than value expected on room air but less than that expected for corresponding  $FiO_2$ )

- If PaO<sub>2</sub> more than value expected for corresponding FiO<sub>2</sub> :
  1. Error in sample or analyzer
  2. Patient's oxygen consumption is reduced
  3. Patient does not require oxygen therapy (if 1 and 2 are not applicable)

**Assessment of Acid-Base Status**

**Definitions And Terminology**

BICARBONATE (HCO<sub>3</sub><sup>-</sup>): It is a reflection of non respiratory (metabolic) acid-base status but it does not quantify degree of abnormality of buffer base or actual buffering capacity of blood. There are 2 commonly used terms with respect to bicarbonate measurement.

- Standard HCO<sub>3</sub><sup>-</sup>: HCO<sub>3</sub><sup>-</sup> levels measured in laboratory after equilibration of blood PCO<sub>2</sub> to 40 mm Hg (similar to routine measurement of other serum electrolytes)
- Actual HCO<sub>3</sub><sup>-</sup>: HCO<sub>3</sub><sup>-</sup> levels calculated from pH & PCO<sub>2</sub> directly

**BASE EXCESS/BASE DEFICIT :**

This is calculated from pH, PaCO<sub>2</sub> and hematocrit and is expressed as meq/L of base above the normal buffer base range. A negative Base Excess is also referred to as Base Deficit. It is a true reflection of non respiratory (metabolic) acid base status.

Normally a three component terminology is used to describe interpretation of acid-base status namely:

1. Compensated/Uncompensated
2. Respiratory/Metabolic
3. Acidosis/Alkalosis

ACIDEMIA - reduction in arterial pH (pH<7.35)

ALKALEMIA - increase in arterial pH (pH>7.45)

ACIDOSIS - presence of a process which tends to reduce pH by virtue of gain of hydrogen ions (H<sup>+</sup>) or loss of HCO<sub>3</sub><sup>-</sup>

ALKALOSIS - presence of a process which tends to increase pH by virtue of loss of H<sup>+</sup> or gain of HCO<sub>3</sub><sup>-</sup>

**RESPIRATORY VS METABOLIC**

Respiratory processes are those which lead to acidosis or alkalosis through a primary alteration in ventilation and resultant excessive elimination or retention of CO<sub>2</sub> while metabolic processes lead to acidosis or alkalosis through their effects on kidneys and the consequent disruption of H<sup>+</sup> and HCO<sub>3</sub><sup>-</sup> control.

**COMPENSATION**

This is the normal response of the respiratory system or kidneys to a change in pH induced by a primary acid-base disorder. In the presence of acidosis or alkalosis, regulatory mechanisms occur which attempt to maintain the arterial pH in the physiologic range. These processes result in the return of pH towards, but generally just outside the normal range.

Disorder	Primary Responses			Compensatory Response
Metabolic acidosis	↑ [H <sup>+</sup> ]	↓ pH	↓ HCO <sub>3</sub> <sup>-</sup>	↓ pCO <sub>2</sub>
Metabolic alkalosis	↓ [H <sup>+</sup> ]	↑ pH	↑ HCO <sub>3</sub> <sup>-</sup>	↑ pCO <sub>2</sub>
Respiratory acidosis	↑ [H <sup>+</sup> ]	↓ pH	↑ pCO <sub>2</sub>	↑ HCO <sub>3</sub> <sup>-</sup>
Respiratory alkalosis	↓ [H <sup>+</sup> ]	↑ pH	↓ pCO <sub>2</sub>	↓ HCO <sub>3</sub> <sup>-</sup>

Table 1 - Characteristics of Primary Acid-Base Disorders

Disorder	Compensatory response
Metabolic Acidosis	PCO <sub>2</sub> ↓ by 1.2 mmHg per 1.0 meq/L ↓ in HCO <sub>3</sub> <sup>-</sup>
Metabolic Alkalosis	PCO <sub>2</sub> ↑ by 0.7 mmHg per 1.0 meq/L ↑ in HCO <sub>3</sub> <sup>-</sup>
Respiratory acidosis (Acute)	HCO <sub>3</sub> <sup>-</sup> ↑ by 1.0 meq/L per 10 mmHg ↑ in PCO <sub>2</sub>
Respiratory acidosis (Chronic)	HCO <sub>3</sub> <sup>-</sup> ↑ by 3.5 meq/L per 10 mmHg ↑ in PCO <sub>2</sub>
Respiratory alkalosis (Acute)	HCO <sub>3</sub> <sup>-</sup> ↓ by 2.0 meq/L per 10 mmHg ↓ in PCO <sub>2</sub>
Respiratory alkalosis (Chronic)	HCO <sub>3</sub> <sup>-</sup> ↓ by 4.0 meq/L per 10 mmHg ↓ in PCO <sub>2</sub>

Table 2 - Renal & Respiratory Compensations To °1 Acid-Base Disturbances

**SIMPLE AND MIXED ACID-BASE DISORDER**

Simple acid-base disorder is a single primary process of acidosis or alkalosis whereas a mixed acid-base disorder is when more than one acid base disorders are present simultaneously.

**STEPWISE APPROACH TO ABG ANALYSIS**

- Determine whether patient is alkalemic or acidemic using the arterial pH measurement
- Determine whether the acid-base disorder is a primary respiratory or metabolic disturbance based on the pCO<sub>2</sub> and serum HCO<sub>3</sub><sup>-</sup> level
- Respiratory Conditions are suggested if pH changes in the opposite direction as pCO<sub>2</sub>/HCO<sub>3</sub><sup>-</sup> or when pH is abnormal but HCO<sub>3</sub><sup>-</sup> remains unchanged
- Metabolic Conditions are suggested if pH changes in the same direction as pCO<sub>2</sub>/HCO<sub>3</sub><sup>-</sup> or when pH is abnormal but pCO<sub>2</sub> remains unchanged
- If a primary respiratory disorder is present, determine whether it is chronic or acute
- In metabolic disorders, determine if there is adequate compensation of the respiratory system
- In respiratory disorders, determine if there is adequate compensation of the metabolic system
- Determine patient's oxygenation status (PaO<sub>2</sub> & SaO<sub>2</sub>) and whether he/she is hypoxemic or not
- If a metabolic acidosis is present, determine the anion gap and osmolar gap
- In high anion gap acidosis, determine the change in anion gap (ΔAG) & ΔHCO<sub>3</sub><sup>-</sup> in order to assess for the presence of coexisting metabolic disturbances
- In normal (non) anion gap acidosis, determine the urinary anion gap which is helpful to distinguish renal from non renal causes

**RESPIRATORY ACID BASE DISORDERS**

Respiratory alkalosis is one of the most common acid base disorders. Attention to the presence and severity of hypoxemia should always assume priority while analyzing a patient who is suspected to have a respiratory acid-base disorder.

**Respiratory Alkalosis**

Respiratory Alkalosis can result from direct stimulation of the respiratory center by structural and non structural causes as well as from stimulation of

the peripheral chemoreceptors (and reflex stimulation of the respiratory center) by hypoxaemia resulting from lung diseases, high altitude and hypotension. Manifestations are mainly neuromuscular and cardiovascular and result from alkalosis induced arterial vasoconstriction and resultant reduction in regional blood flow. Neuromuscular manifestations include changes in higher mental status and features of neuromuscular irritability. The homeostatic response to respiratory alkalosis is characterized by an immediate fall in  $\text{CO}_2$  (&  $\text{H}_2\text{CO}_3$ ) leading to release of  $\text{H}^+$  by blood and tissue buffers.  $\text{HCO}_3^-$  is also taken up by cells in exchange for Chloride ( $\text{Cl}^-$ ). The steady state is reached in 15 minutes and persists for 6 hours after which the kidneys increase excretion of  $\text{HCO}_3^-$ . The new steady state after initiation of renal compensation is reached in 1½ to 3 days.

Respiratory alkalosis by itself is not a cause of respiratory failure unless the work of increased breathing cannot sustained by respiratory muscles. Hence treatment involves treatment of the underlying cause and administration of oxygen if hypoxaemia is co-existent. Usually extent of alkalemia produced is not dangerous. However if pH increases more than 7.55, the patient may require to be sedated or paralyzed and may even require mechanical ventilation especially in the presence of refractory hypoxaemia.

## RESPIRATORY ACIDOSIS

Respiratory Acidosis results from either disturbances in the 'Control Component' that is the CNS and peripheral nerves/spinal cord or the 'Excretory Apparatus' namely the lungs and surrounding structures of the thorax especially chest wall. Clinical features of respiratory acidosis include neuromuscular manifestations (that result from increased cerebral blood flow arising from hypercapnia induced cerebral arterial vasodilatation)

and vary from mere anxiety to headache, tremors, myoclonus and changes in sensorium. Clinical signs that may be appreciated include asterixis and papilledema. Cardiovascular manifestations arise from coronary vasodilatation and include tachycardia and predisposition to ventricular arrhythmias. The homeostatic response to respiratory acidosis is uptake of  $\text{H}^+$  ions by blood and tissue buffers leading to dissociation of carbonic acid and release of bicarbonate. The steady state is reached in 10 minutes and lasts for around 48 hours after which the kidneys generate bicarbonate and a new steady state is reached in approximately 3-5 days.

The alveolar gas equation represented as

$$\text{PAO}_2 = \text{FIO}_2 \times (\text{P}_B - \text{P}_{\text{H}_2\text{O}}) - \text{PaCO}_2 / \text{R}$$

(Where  $\text{PAO}_2$  is alveolar  $\text{PO}_2$ ,  $\text{FIO}_2$  is the fractional concentration of inspired air,  $\text{P}_B$  is the barometric pressure,  $\text{P}_{\text{H}_2\text{O}}$  is the water vapor pressure and R is the respiratory quotient). It follows that with all other variables remaining constant,  $\text{PAO}_2$  (and hence the  $\text{PaO}_2$ ) is inversely proportional to the  $\text{PaCO}_2$ . Thus a rise in  $\text{PaCO}_2$  leads to an obligatory hypoxemia in patients who are breathing room air. However this rise in  $\text{PaCO}_2$  is generally limited to an approximate level of 80 to 90 mm Hg because higher  $\text{PaCO}_2$  levels are associated with  $\text{PaO}_2$  levels that are incompatible with life. Thus, as mentioned earlier, correction of hypoxemia and not hypercapnia or acidemia is the primary aim of treatment of respiratory acidosis since the former is the main determinant of survival.

While treating respiratory acidosis, the main aim is to ensure adequate oxygenation while taking care to avoid inadequate oxygenation in an attempt to prevent worsening of hypercapnia by suppression of hypoxemic respiratory drive. Again one should make attempts to correct the underlying disorder. Rapid decrease in chronically elevated  $\text{PCO}_2$  should be avoided to prevent development of post hypercapnic

metabolic alkalosis that can lead to arrhythmias and seizures. An adequate intake of chloride is usually helpful in this setting. Alkali (Bicarbonate) therapy is used rarely in acute and never in chronic respiratory acidosis and that too if acidemia is directly inhibiting cardiac functions.

Problems with alkali therapy include:

1. Decreased alveolar ventilation by a decrease in pH mediated ventilatory drive
2. Enhanced carbon dioxide production from bicarbonate decomposition
3. Volume expansion.

## METABOLIC ACID BASE DISORDERS

### Overview Of Acid-Base Physiology

Acid Production in the body is in the form of either volatile or non-volatile acids.  $\text{CO}_2$  is the principal volatile acid. According to the Henderson Hasselbach Equation, free  $\text{H}^+$  are produced if  $\text{CO}_2$  is not eliminated and in such cases the latter behaves like a non-volatile acid. The range of variation of ECF as well as intracellular pH is very small (intracellular pH is normally maintained at around 7.2 while blood pH around 7.4). They are maintained in a narrow range to preserve normal cell, tissue and organ function. The regulation of arterial pH is achieved through various means:

1. **BUFFERS** - Presence of buffer systems minimize the change in pH resulting from production of acid and provide immediate protection from acid load. The main buffer system in humans is bicarbonate/carbonic acid.

2. **THE RESPIRATORY SYSTEM** - Elimination of volatile acid ( $\text{CO}_2$ ) is achieved with the help of the respiratory system. Respiratory centers in the brain respond to changes in pH of CSF and blood to affect ventilatory rate. Ventilation directly controls the elimination of  $\text{CO}_2$ .

3. **THE KIDNEYS** - They help to retain and regenerate  $\text{HCO}_3^-$  thereby regenerating the body buffers with the net effect of eliminating the non-volatile acid load.  $\text{H}^+$  secretion takes place either in combination with ammonia or phosphate or as free urinary  $\text{H}^+$ ; the latter giving only a minimal contribution.  $\text{HCO}_3^-$  reabsorption takes place primarily in the proximal tubule. Factors affecting  $\text{H}^+$  secretion/reabsorption of  $\text{HCO}_3^-$  include  $\text{CO}_2$  concentration, pH, aldosterone, potassium concentration, ECF volume and chloride levels in the blood.

**Anion Gap (AG)** : This has traditionally been used to assess acid-base status especially in the differential diagnosis of metabolic acidosis while  $\Delta$  AG and D  $\text{HCO}_3^-$  have been used to assess mixed acid-base disorders

AG is based on the principle of electroneutrality:

Total Serum Cations = Total Serum Anions

$$\text{Na} + (\text{K} + \text{Ca} + \text{Mg}) = \text{HCO}_3 + \text{Cl} + (\text{PO}_4 + \text{SO}_4 + \text{Protein} + \text{Organic Acids})$$

$$\text{Na} + \text{UC}^* = \text{HCO}_3 + \text{Cl} + \text{UA}^a$$

$$\text{Na} - (\text{HCO}_3 + \text{Cl}) = \text{UA} - \text{UC}$$

$$\text{Na} - (\text{HCO}_3 + \text{Cl}) = \text{AG}$$

\* UC = Unmeasured Cations and <sup>a</sup>UA = Unmeasured Anions

Normal value of AG was previously taken as 12 +/- 4 meq/L. However with changes in the methods of measurement of Na, Cl and  $\text{HCO}_3$ , there has been a shift of Cl value to a higher range and the revised normal value of AG is now taken as 8 +/- 4 meq/L.

AG is affected by variations in the normal reference range of its components, hypoalbuminemia (decreased AG), alkalosis (increased AG), hypercalcemia (decreased AG), drugs, rate of

clearance of anions and other factors. Moreover  $\Delta AG - \Delta HCO_3^-$  relationship that has been used to assess mixed acid-base disorders in setting of high AG metabolic acidosis is also subject to limitations. It has generally been said that if

$\Delta AG/\Delta HCO_3^- = 1 \rightarrow$  Pure High AG Metabolic Acidosis

$\Delta AG/\Delta HCO_3^- > 1 \rightarrow$  Associated Metabolic Alkalosis

$\Delta AG/\Delta HCO_3^- < 1 \rightarrow$  Associated normal AG Metabolic Acidosis

However, this is based on the assumption that for each 1 meq/L increase in AG,  $HCO_3^-$  will fall by 1 meq/L. But non bicarbonate buffers especially intracellular buffers also contribute to buffering response on addition of  $H^+$ . This becomes more pronounced as the duration of acidosis increases. Thus  $\Delta AG/\Delta HCO_3^-$  may be more than 1 even in the absence of metabolic alkalosis

Also, all added anions may not stay in the extracellular component and those that diffuse inside cells could lead to a lesser rise in AG than expected Hence  $\Delta AG/\Delta HCO_3^-$  may be less than 1 even in states expected to have high AG Met Acidosis.

Hence strict use of AG to classify metabolic acidosis and of the  $\Delta AG/\Delta HCO_3^-$  relationship to detect mixed/occult metabolic acid-base disorders can be associated with errors because of the possibility of change of AG by factors other than metabolic acid-base disturbances. Use of sequential AG determinations and observation of temporal profile of AG is more important than any single value. Use of Corrected AG [Calculated AG + 2 (Albumin in gm/dL) + 0.5 ( $PO_4^{3-}$  in mg/dL)] has been recommended by some authors as an alternative.

## METABOLIC ACIDOSIS

### Pathophysiology

Metabolic acidosis results from either Bicarbonate loss (renal/gastrointestinal), decreased renal acid secretion or increased production of non-volatile acids (ketoacids, lactic acid, poisons or exogenous acids)

### Classification

Metabolic acidosis has traditionally been classified as high anion gap or normal anion gap though as mentioned earlier due to the inherent limitations of the anion gap, this classification itself has been a subject of intense debate.

Causes of high anion gap metabolic acidosis include ketoacidosis (diabetic, alcoholic or starvation), lactic Acidosis (Type A due to inadequate oxygen delivery to cells, type B due to inability of cells to utilize oxygen and type D due to abnormal bowel anatomy), toxicity (salicylates, methanol, ethylene glycol, paraldehyde and toluene), renal failure and rhabdomyolysis.

Causes of normal anion gap metabolic acidosis include bicarbonate loss through GIT (diarrhoea, pancreatic or biliary drainage, etc) or kidneys (proximal RTA, during treatment of ketoacidosis and post-chronic hypocapnia). Other causes include impaired renal acid excretion as in distal (type 1) RTA, Hyperkalemic (type 4) RTA, hypoaldosteronism and renal failure. Acid administration ( $NH_4Cl$ ), hyperalimentation (HCl containing amino acid solutions), HCl therapy (during treatment of severe metabolic alkalosis) constitute some of the other causes.

### Manifestations

Attenuation of cardiovascular responsiveness to catecholamines and impaired cardiac contractility lead to a fall in cardiac output, arterial blood pressure

as well as hepatic and renal blood flow. Arteriolar dilatation, venoconstriction and centralization of blood volume also occur as does increased pulmonary vascular resistance. Sensitization to reentrant arrhythmias leads to reduction in the threshold for occurrence of ventricular tachycardia and ventricular fibrillation.

Compensatory hyperventilation occurs and can ultimately lead to occurrence of muscle fatigue and dyspnea if accompanied by concomitant reduction in the strength of respiratory muscles.

Cerebral symptoms result from inhibition of metabolism and cell volume regulation and include mental status changes (somnolence, obtundation & coma).

### Evaluation

This includes clinical profile of the patient along with arterial blood gas analysis and determinations of AG (serum and/or urinary) and osmolal gap (plasma and/or urinary)

Urinary AG, like the serum AG, is also based on the principle of electroneutrality. Determination of the urinary AG helps to distinguish GI from renal causes of loss of bicarbonate by estimating urinary  $\text{NH}_4^+$  which is elevated in GI losses but low in renal losses (as in cases of distal RTA). Hence a negative UAG is seen in the former condition while a positive value is seen in the latter. If the difference between measured and calculated osmolality is more than 15-20 mOsm/kg (normally less than 10 mOsm/kg), it suggests the presence of abnormal (osmotically active) substance(s) - usually an alcohol. Similarly if the measured urinary osmolality is more than the calculated value, it signifies that excretion of  $\text{NH}_4^+$  is occurring with a non chloride anion (e.g. hippurate). The urinary  $\text{NH}_4^+$  concentration is usually around 50% of the osmolal gap.

### Treatment

Effect of severe acidemia on cardiac function is the most important factor that determines patient survival since metabolic acidosis is rarely lethal in the absence of cardiac dysfunction. The contractile force of left ventricle increases as pH falls from 7.4 to 7.2. However, when pH falls below 7.2, profound reduction in cardiac function occurs. Hence most recommendations favour the use of base only when pH is less than 7.15-7.2 or  $\text{HCO}_3^-$  is less than 8-10 meq/L. Treatment of the underlying cause is undoubtedly very important. Bicarbonate therapy can be used with the aim of raising the pH upto 7.2 or  $\text{HCO}_3^-$  upto 10 meq/L. The quantity of  $\text{HCO}_3^-$  to be administered is calculated as follows:

$$0.5 \times \text{LBW (kg)} \times \text{HCO}_3^- \text{ Deficit (meq/L)}$$

The volume of distribution ( $V_d$ ) of bicarbonate is around 50% in normal adults. However, in severe metabolic acidosis, this can increase upto 70-80% in view of intracellular shift of  $\text{H}^+$  and buffering of  $\text{H}^+$  by bone and cellular buffers.

Bicarbonate administration was considered the cornerstone of therapy of severe acidemia based on the assumption that it would normalize intra as well as extracellular fluid pH and reverse the deleterious effects of acidemia on organ function. However, studies have contradicted this and shown little or no benefit from rapid and complete/over correction of acidemia with bicarbonate. The adverse effects of bicarbonate therapy include  $\text{CO}_2$  production from  $\text{HCO}_3^-$  decomposition leading to hypercarbia especially when the pulmonary ventilation is impaired. Myocardial hypercarbia can lead to myocardial acidosis and then impaired myocardial contractility with consequent reduction in cardiac output, systemic vascular resistance and coronary artery perfusion pressure and even precipitation of myocardial ischemia. Intracellular (paradoxical)

acidosis can occur especially in the liver and CNS (because of increased CSF  $\text{CO}_2$  levels). Hyponatremia as well as hyperosmolarity can result leading to volume expansion and fluid overload state.

Correction of acidemia can be done with buffers other than bicarbonate. This includes THAM and carbicarb. The latter has been used in the treatment of metabolic acidosis after cardiac arrest and during surgery but data on its efficacy in humans is limited. THAM (Trometamol or Tris-(OH)- $\text{CH}_3\text{-NH}_2\text{-CH}_3$ ) is a biologically inert amino alcohol of low toxicity. It has capacity to buffer  $\text{CO}_2$  and other acids *in vivo* as well as *in vitro*. It is a more effective buffer in physiological range of blood pH since it can accept  $\text{H}^+/\text{CO}_2$  and generate  $\text{HCO}_3^-$  as well as reduce  $\text{PaCO}_2$ . It is thus effective as a buffer in closed or semiclosed system (unlike bicarbonate which requires an open system to eliminate  $\text{CO}_2$ ) and is also effective in states of hypothermia. It is indicated for use in several clinical settings when there is severe acidemia ( $\text{pH} < 7.2$ ).

Side effects include tissue irritation and venous thrombosis (especially if it is administered through a peripheral vein) as well as respiratory depression and hypoglycemia with large doses.

## **METABOLIC ALKALOSIS**

### **Introduction**

Metabolic alkalosis is a common acid base disorder and its frequency has been reported upto 50% of all disorders. Severe metabolic alkalosis is associated with a mortality rate of around 45% when the arterial blood pH is more than 7.55 and around 80% when it is more than 7.65.

### **Pathophysiology**

Metabolic alkalosis usually has an initiating event wherein either bicarbonate is gained or there is loss of hydrogen ions either through the kidney or the GIT. Some cases are caused by volume contraction

or hydrogen ion shifts. A maintenance phase is also usually present because alkaline loads are generally excreted quickly and easily by the kidney and significant metabolic alkalosis can only occur in the setting of impaired bicarbonate excretion. The latter can occur in the setting of volume depletion leading to a reduced GFR as well as cases of mineralocorticoid excess that leads to increased reabsorption of bicarbonate.

### **Classification**

Metabolic alkalosis has traditionally been classified by the response to volume/saline replacement therapy as either saline responsive or saline unresponsive. The former is usually seen in cases of volume/chloride depletion due to gastrointestinal or renal losses. The saline unresponsive cases are usually volume replete and occur as a result of mineralocorticoid excess (primary or secondary hyperaldosteronism, apparent mineralocorticoid excess due to enzymatic defects, or drug induced).

Hypercalcemic States also lead to bicarbonate reabsorption and metabolic alkalosis.

### **Manifestations**

Symptoms of metabolic alkalosis per se are difficult to separate from those of chloride, potassium or volume depletion. In fact the latter are usually more apparent than those directly attributable to alkalosis.

Cardiovascular manifestations result from arteriolar constriction and resultant reduction in coronary blood flow and include reduction in anginal threshold and predisposition to refractory supraventricular and ventricular arrhythmias. Reduction in cerebral blood flow leads to mental status changes (stupor, lethargy & delirium) and neuromuscular irritability (related to low ionized

plasma calcium) manifested as tetany, hyperreflexia or even seizures. Compensatory hypoventilation may be seen leading occasionally to hypercapnia and hypoxemia.

### Evaluation

In addition to clinical profile and ABG analysis, urinary chloride and potassium measurements before therapy are useful diagnostically. A low urinary chloride (<10 mEq/L) is seen in alkalotic states where chloride depletion predominates (except when the cause is use of chloruretic diuretic). It tends to remain low until chloride repletion is nearly complete. Urinary potassium concentration of >30 mEq/L with a low serum potassium level suggests renal potassium wasting due to either intrinsic renal defect, diuretic use or high levels of circulating aldosterone. A urinary potassium concentration of <20 mEq/L with a low serum potassium level suggests extrarenal potassium loss.

### Treatment

Severe alkalosis should be viewed with concern, and correction by the appropriate intervention should be undertaken when the arterial blood pH exceeds 7.55. The immediate goal of therapy is moderation and not full correction of the alkalemia. Reducing plasma bicarbonate levels to less than 40 meq/L is the short-term goal. Most severe metabolic alkalosis is of chloride responsive type.

#### I. Treatment of Volume Depleted/Saline Responsive Metabolic Alkalosis

Treating the underlying cause responsible for volume and/or chloride depletion is important

While replacing chloride deficit, selection of accompanying cation (Na<sup>+</sup>/K<sup>+</sup>/H<sup>+</sup>) depends on:

- Assessment of ECF volume status
- Presence and degree of associated K<sup>+</sup> depletion,

- Presence, degree & reversibility of reduction of GFR.

Patients with volume depletion usually require replacement of both NaCl & KCl.

In cases of chloride depletion with increased ECF volume, administration of NaCl is inadvisable for obvious reasons. Chloride should be repleted as KCl unless hyperkalemia is present or there is a concomitant fall in GFR. Administration of acetazolamide in the presence of an adequate GFR, accelerates bicarbonaturia and causes natriuresis (helpful in cases where a high sodium excretion rate is also required simultaneously).

Cases of chloride depletion with increased ECF volume and hyperkalemia can be treated with Hydrochloric Acid (HCl) if correction is required immediately. Again half correction is given since immediate goal of therapy is correction of severe and not full correction of alkalemia. HCl has sclerosing properties and must be administered through a central venous catheter (placement confirmed radiologically to prevent leakage of HCl and sloughing of perivascular tissue). HCl can also be infused after adding it to amino acid solutions, fat emulsion or dextrose solutions containing electrolytes and vitamins without causing adverse chemical reactions. In such cases administration can be done through a peripheral vein. However frequent measurement of ABG and electrolytes is required.

In the presence of renal failure or severe fluid overload state in CHF, dialysis with or without ultrafiltration may be required to exchange bicarbonate for chloride and correct metabolic alkalosis. Usual dialysates for both HD/PD contain high concentrations of bicarbonate or its metabolic precursors and hence their concentrations must be reduced.

Adjunct therapy includes use of proton pump inhibitors to reduce gastric acid production in cases of chloride depletion metabolic alkalosis resulting from loss of gastric H<sup>+</sup>/Cl<sup>-</sup>.

## II. Treatment of Volume Replete/Saline Unresponsive Metabolic Alkalosis

In states of mineralocorticoid excess, therapy should be directed at either removal of the source or its blockade. Potassium sparing diuretics, especially spironolactone, are helpful as is restriction of sodium and addition of potassium to diet. Similarly, treatment of the underlying cause is required in cases of hypercalcemia associated metabolic alkalosis. Chloride and volume repletion is also required in some cases since these conditions may have additional mechanisms for alkalosis including vomiting and reduced GFR.

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Deptt. of Pulmonary Medicine

## "CICLESONIDE - A NOVEL DRUG FOR ASTHMA"

Inhaled corticosteroids (ICS) are the most effective agents currently used for persistent asthma of all severity grades. However their dose increase in long term therapy of asthma is limited by systemic side - effects. ICS are absorbed from the lung or nasal mucosa into systemic circulation and thus have systemic side effects. The major aim in the development of novel ICS is to design substances which have high local potency in the airways, but without systemic side effects. A novel ICS Ciclesonide (not yet available in India) has been developed keeping in view these aims.

Ciclesonide is a potent non-halogenated ICS with essentially no oral bioavailability. The drug itself is an inactive pro-drug and is converted to the active metabolite (desiso-butryl-ciclesonide) whose affinity to the glucocorticoid receptors is 100 times more than the parent pro-drug. This ciclesonide is an onsite - activated drug with high topical potency and essentially no oropharyngeal or systemic side effects. Due to high protein binding of ciclesonide in the systemic circulation, systemic exposure is reduced and potential systemic side effects diminished.

Ciclesonide, administered via MDI, is effective at dose as low as 80 microgram once daily (usual dose being 200 microgram once daily), though dosages upto 1280 microgram per day have been given 52 weeks with suppressive effects on HPA-axis. The drug is to given once daily in the morning or in the evening to meet patient's preference and

individual medical needs, though evening administration has been shown to have a more pronounced improvement in morning peak expiratory flow.

**R.S. Bedi**  
Gurdesh S. Bedi  
Patiala

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