Review Article

Metabolic Acidosis in Critically Ill Patients

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Abstract

Metabolic acidosis is a common finding in ICU patients. Metabolic acidosis in ICU patients is not usually a simple acid base disorder but a mixed acid base disorder. Severe metabolic acidosis is said to be present when pH is < 7.2 and it's found to be associated with very high mortality especially when it occurs rapidly. Clinical Manifestations of severe acidosis are hyperventilation, decreased myocardial contractility, decreased cardiac output, cardiac arrhythmias, systemic vasodilatation, diaphragm dysfunction and CNS depression. For management of metabolic acidosis, understanding its pathophysiology is important. The prognosis of a patient with metabolic acidosis is usually determined by the underlying disorder causing acidosis. Treatment is directed towards the etiological factor causing acidosis and not towards treatment of acidosis. Treating acidosis with intravenous sodium bicarbonate is controversial.

Key words : Mixed Acid Base disorders, High Anion Gap Acidosis, Normal Anion Gap Acidosis, Delta Delta Gap, THAM

Introduction

In this article we will discuss about the following 1. Identification of metabolic acidosis 2. Difference between simple and mixed acid base disorders 3. Classification of metabolic acidosis into High anion gap acidosis and Normal anion gap acidosis 4. Meaning of Adjusted Anion Gap, 5. Meaning of Delta Delta Gap, 6. Causes of Metabolic acidosis in ICU setting and its pathogenesis 7. The adverse consequences of metabolic acidosis on the outcomes of the patient and 8. Possible ways to correct them.

Identification of Metabolic acidosis

Though Metabolic acidosis means increase in H+ ion, the amount of H+ ion in plasma is very low for routine measurement (around 40 mmol/L). So arterial pH which is 1/ log H+ measured by ABG is used for diagnosing Acidosis. Metabolic acidosis is present when there is low arterial pH (pH < 7.35) along with low HCO3- (<20 mEq/L). 64% of critically ill patients have acute metabolic acidosis1. Severe Metabolic acidosis is said to be present when arterial pH is <7.20.[2]

Difference between Simple & Mixed Acid Base disorders

In the body, Acid base balance is maintained within a narrow range of 7.35 - 7.45 mainly by Carbonic acid buffering system. When acids accumulate in the body, H+ ions increases, HCO3- buffers and neutralises it resulting in production of H2CO3 (Carbonic acid). This H2CO3 dissociates into H2O and CO2 and CO2 is exhaled thro' lungs. This is how metabolic acidosis gets compensated in the body. This compensatory response occurs within a few hours.

For full compensation of Metabolic acidosis, CO2 should be exhaled more to make pCO2 fall by 1.25 mmHg for every 1 mmol/L decrease in HCO3- . If not, compensation is not full and the reason might be a coexistent other organ involvement - for example, a lung condition which will prevent exhalation of CO2 resulting in persistence of low HCO3- and inappropriately high pCO2 . This is what is called a Mixed Acid Base disorder. In this example, the type of Mixed Acid Base Disorder is

- Metabolic acidosis with Respiratory acidosis.

There can be other combinations of Mixed acid base disturbance like

- Metabolic acidosis with Respiratory alkalosis
- Metabolic acidosis with Metabolic alkalosis and rarely
- Triple acid base disorder

In ICU patients who generally have Multi organ dysfunction Mixed Acid Base Disorders is more common than Simple Acid Base Disorders.

Classification of Metabolic acidosis based on Anion Gap (AG)

The next step after confirming the presence of Metabolic acidosis is to use Serum Anion Gap (AG) to differentiate Metabolic acidosis into high AG and normal AG Metabolic acidosis. Serum Anion Gap is a measure of the difference between Unmeasured Anions and Unmeasured Cations in the serum.

AG = Unmeasured Anions - Unmeasured Cations.[3] If all Anions (Negatively charged ions) and Cations (Positively charged ions) can be measured, serum Anions and Cations will be equal. But the problem is not all Anions and Cations can be measured. Examples of Unmeasured Anions and Unmeasured Cations are given below.

Unmeasured Anions

- Albumin
- Inorganic acids like sulphate (SO42-), phosphate (PO4 3-)
- Organic acids like lactic acid, ketoacids

Unmeasured Cations

- Potassium (K+)
- Calcium (Ca2+)
- Magnesium(Mg2+)
- Paraproteins

Generally, Unmeasured Anions are higher than Unmeasured Cations. This means that Measured Cations will be higher than Measured Anions. The formula for calculating Anion Gap is

AG = Na+ - (Cl- + HCO3-).

Normal AG is 7 ± 4 mmol/ L i.e 3 - 11 mmol/L.[3] When Anion gap is higher, Unmeasured Anions are higher and when Anion gap is normal, Unmeasured anions are lesser. High Anion gap acidosis (AG > 11 mmol/L) occurs when there is excess acid accumulation (Unmeasured Anions are mostly Organic acids) which uses up HCO3- for neutralisation of acidosis. Normal Anion Gap acidosis (AG 3-11 mmol/L) also called Hyperchloremic metabolic acidosis occurs when HCO3- is lost either from Urine or GIT and there is a counter increase in serum chloride (Cl-) which gets reabsorbed from the urinary system.

Following are the causes of High anion gap acidosis-

1. Lactic acidosis (accumulation of Lactic acid),
2. Ketoacidosis (accumulation of Ketoacids namely beta-hydroxybutyric acid and acetoacetic acid),
3. Renal Failure (under excretion of normally produced acids) and
4. Poisoning due to Methanol, Ethylene glycol, Propylene glycol or Salicylic acid

Following are the causes of Normal anion gap acidosis -

1. Renal tubular acidosis (RTA)
2. Diarrhoea
3. Infusion of large volume of isotonic saline (accumulation of chloride)
4. Taking carbonic anhydrase inhibitor like acetazolamide (Causes HCO3 - loss in urine) and
5. Patients who have Ureteral diversion like fistula connecting ureter and GIT (Urine Cl- is reabsorbed and urine HCO3 is not reabsorbed in the gut).

Among the 2 types of Metabolic acidosis, High AG acidosis is more common in ICU.[4]

Adjusted AG

Once AG is calculated, AG has to be corrected based on serum albumin levels. The formula for Adjusted AG is

- Adjusted AG = Observed AG + 2.5 * (Normal Albumin - measured albumin in g/dl).[3]

This is especially true in ICU patients who mostly have low albumin.

Delta Delta Gap (DD Gap)

This is a formula used in patients with High AG metabolic acidosis to find out whether the high AG metabolic acidosis is a pure high AG metabolic acidosis or whether there is a superimposed Normal AG acidosis or a Metabolic alkalosis on the High AG acidosis. The formula is

- Delta Delta Gap = Delta Anion Gap (D AG)/ Delta HCO3- (DHCO3-)
- Also written as Delta Delta Gap = Change in AG/ Change in HCO3-

It's the change in the Anion Gap over the change in HCO3 - . Normally, when acid is produced in the body, there should be a proportionate decrease in the HCO3- . This is because proportionate amount of HCO3- gets used up for neutralisation of acid. So change in AG/ change in HCO3- should normally be around 1. This means there is a Simple Acid Base Disorder which is a High AG Metabolic Acidosis

If Delta Delta Gap is significantly <1, it means Combined High AG Metabolic acidosis plus Normal AG acidosis.

- The fall in HCO3- is disproportionately larger than the rise in AG
- This is possible only when there is an associated normal Anion Gap acidosis

If Delta Delta Gap is significantly >1, it means Combined High AG Metabolic acidosis plus Metabolic Alkalosis.

- The fall in HCO3- is disproportionately lesser than the rise in AG
- This is possible only when there is an associated Metabolic Alkalosis

High Anion Gap Acidosis in ICU Settings

Lactic acidosis

Lactic acid is the Organic acid which accumulates in this type of High AG acidosis. This is the commonest cause of High AG acidosis in ICU settings. The normal serum lactate level is 0.5 - 2 mmol/L and it can be measured from arterial or venous sample. Blood lactate levels >4 mmol/L is considered abnormally high. Lactic acidosis can occur due to 2 reasons - 1. Increased Lactate production 2. Decreased clearance of the produced lactate .Increased lactate production occurs when there is decrease supply of O2 to tissues (hypoxia) or when there is interference with oxidative phosphorylation. This result in anaerobic glycolysis causing increased production of lactate compared to pyruvate. This is seen frequently in ICU patients where patients with shock & sepsis are common.

There are 2 types of Lactic acidosis based on whether Hypoxia also called "Oxygen debt" is the reason. They are

- Type A Lactic Acidosis
- Type B Lactic Acidosis

Type A Lactic acidosis

Conditions causing it are all forms of Shock, Sepsis, Severe Anemia (Hb<5), Seizures, Vigorous exercise and Rhabdomyolysis (O2 requirement is more) , CO poisoning (due to decreased O2 delivery to tissues) and Malignancy (tumour tissue hypoxia).

Type B Lactic acidosis

Here hypoxia is not the reason. This occurs in conditions like Liver failure (impaired clearance of lactate in liver), patients with Thiamine deficiency (this affects Pyruvate Dehydrogenase complex enzyme activity), patients on certain drugs like Metformin, Nucleoside reverse transcriptase inhibitors, Propofol and Linezolid (all these drugs interferes with oxidative phosphorylation), and in poisoning due to Salicylates, Methanol, Ethylene glycol (all these poisons also interferes with oxidative phosphorylation) and due to propylene glycol poisoning.

In ICU settings both Type A and Type B Lactic acidosis are common as there is multiorgan damage and shock.

Ketoacidosis

Ketoacid is the organic acid which accumulates in this type of High AG acidosis. Examples of Ketoacids are Acetoacetic acid, Beta - hydroxybutyric acid. Ketoacids generally are produced when there is limited glucose availability for tissues. In this setting of low glucose availability, lipolysis occurs in adipose tissue and releases fatty acids. These fatty acids undergo beta -oxidation in liver to form Acetyl - CoA which enters into Kreb's cycle. When Acetyl - CoA production is more, oxidative capacity of Kreb's cycle becomes saturated and the excess Acetyl - CoA is converted to Ketone bodies. This occurs in starvation, chronic alcoholics and diabetics with severe insulin deficiency (where glucose can't be taken into cells). Doing a blood sugar can differentiate it as Diabetic ketoacidosis and nondiabetic ketoacidosis.

Diabetic Ketoacidosis (DKA)

In a diabetic, conditions like infection, sepsis, myocardial infarction, pancreatitis, usage of glucocorticoids can precipitate DKA. It is a potentially life threatening condition.

Starvation Ketoacidosis

This occurs when body stores of glycogen gets depleted which usually occurs after 2-3 days of fasting.[5] This is followed by lipolysis of adipose tissues and fatty acids are released and they get converted to Ketone bodies.

Alcoholic Ketoacidosis (AKA)

This occurs suddenly in Chronic alcoholics who have coexistent liver disease when there is acute ingestion of alcohol or when there is abrupt alcohol withdrawal5. NAD depletion is the most important reason for this. Normally, Ethanol is metabolised by Alcohol dehydrogenase to acetaldehyde and then is converted to acetic acid. This process requires NAD (Nicotinamide Adenine Dinucleotide) and during this process NAD gets reduced to NADH (Nicotinamide Adenine Dinucleotide Hydrogenase). This depletion of NAD favours conversion of acetic acid to ketone bodies.

Poisoning with Ethylene Glycol

Oxalic acid is the organic acid produced when Ethylene glycol poisoning occurs causing High AG acidosis. Ethylene glycol is metabolised in the liver by Alcohol dehydrogenase enzyme. Ethylene glycol poisoning can cause Acute Kidney Injury when oxalic acid combines with calcium to form calcium oxalate which damages renal tubules. This poisoning also causes lactic acidosis because of interference with Oxidative phosphorylation.

Poisoning with Propylene Glycol

D- lactic acid is the organic acid produced when Propylene glycol is metabolised by Alcohol Dehydrogenase in the liver and this causes high AG acidosis. The Serum Lactate tests generally measure L - Lactate. So serum lactate levels grossly underestimate the level of D- lactate accumulation. Propylene glycol is considered less toxic than Ethylene glycol. It's commonly used as a diluent or drug vehicle for many common intravenous drugs namely lorazepam, diazepam, nitroglycerine, and phenytoin. When these drugs are given in larger doses for more than 2 days, this can accumulate.

Poisoning with Methanol

Formic acid is the organic acid produced when methanol is metabolised by alcohol dehydrogenase enzyme in the liver. This unmeasured acid is neutralised by HCO3- and as a result serum HCO3 - decreases creating a High AG acidosis. It's a common

ingredient in varnish and so it's called wood alcohol. Retina, optic nerve and basal ganglia are highly susceptible to methanol.

Poisoning with salicylates

Salicylic acid (Acetyl Salicylic Acid - Aspirin) is an organic acid and is unmeasured. It's another example of High Anion Gap acidosis. Acute poisoning occurs when there is ingestion of > 150mg/kg or > 6.5 gm of aspirin. Salicylic acid interferes with oxidative phosphorylation causing anaerobic glycolysis resulting in raised lactic acid and ketoacids.

Normal Anion Gap Acidosis in ICU setting

Like High AG acidosis, this normal AG acidosis is also commonly seen in ICU patients either as a lone entity or as a combination of High AG acidosis with Normal AG acidosis. Its also called Hyperchloremic Metabolic acidosis.[6] This occurs when HCO3- loss is matched by an equivalent increase in serum chloride concentration. As a result serum anion gap is maintained. There are 3 main reasons for Normal Anion Gap Metabolic acidosis in ICU settings -

1. Conditions where there is excessive base (HCO3-) loss either in Stools (Diarrhoea - cholera) or in Urine
   - The volume depletion associated with it causes increased reabsorption of chlorides in the renal tubules causing Hyperchloremia thereby maintaining a normal AG
2. Conditions where large volumes of Chloride containing solutions are given like in 0.9% NS resuscitation of hypovolemic shock.
3. Conditions with high AG acidosis like DKA where with fluid replacement Organic acids (which are potential bases) are lost in urine and this is replaced with Normal Saline (NaCl) fluid replacement which increases chloride levels in serum.[6]

This results in the conversion of a High AG acidosis to Normal AG acidosis.

Clinical Features and Complications of Metabolic acidosis

General Clinical features of metabolic acidosis include hyperventilation (due to respiratory center stimulation in the brain stem), Kussumal's respiration, confusion, headache, nausea, vomiting, chest pain, palpitations, fatiguability, bone pain, hypotension, coma . In DKA breath can have fruity odour. In Salicylic acid poisoning - tinnitus, restlessness, seizures can occur.

Acute metabolic acidosis is associated with Vasodilatation with hypotension, Depression of Cardiac contractility and so depression of cardiac output, Cardiac Arrhythmias and Increased mortality. This is more prominent with high AG acidosis - especially Lactic acidosis than with Normal AG acidosis. This difference might probably reflect the disorders associated with causing these acidosis and may not be due to the acidosis as such.

Management of Metabolic Acidosis

Rx of Etiology

- Generally management of Metabolic acidosis is directed towards the etiology of the Metabolic acidosis

Lactic Acidosis

- Correction of Hypovolemia
- Antibiotics for Sepsis

Ketoacidosis

- DKA - Intravenous insulin and Fluid resuscitation
- Starvation and alcoholic ketoacidosis are treated with IV glucose

Ethylene Glycol & Methanol Poisoning

- Fomipezole (an inhibitor of alcohol dehydrogenase is used)[7]

Salicylic Acid Poisoning

- Activated Charcoal
- Intravenous HCO3-
- Dialysis

Treatment & Prevention of Normal AG Acidosis

- This is done using Intravenous balanced salt solution instead of Intravenous chloride containing solutions

Alkali Therapy

IV Bicarbonate

Normally, body compensates for Metabolic acidosis by exhaling pCO2. Peak respiratory compensation is said to be present when pCO2 has fallen to around 15 mmHg. This is usually given when pH is around 7.2. Any further fall in pH can't be compensated by respiration and this further worsens metabolic acidosis.[7]

Generally Intravenous HCO3- is given when pH is < 7.2. to rise the pH to around 7.2. In patients with High AG acidosis like lactic acidosis and DKA, as HCO3- can be generated from these Organic anions, correction with intravenous HCO3- is not done until pH becomes less than 7.0 - 7.1. Amount of HCO3 to be administered is estimated usingHCO3- deficit. This is calculated by the formula HCO3- Deficit = (Desired serum HCO3- - Measured HCO3-)*0.5* body weight [7] To avoid hyperosmolarity and Hypernatremia, NaHCO3 is given as infusion mixed with 1 liter of 5% dextrose with water. Complications associated with inadvertent use of Intravenous HCO3- are

- Increase in pCO2
- The generation of large quantity results in entry of CO2 into the cell and this can aggravate intracellular acidosis. This complication will be less when tissue perfusion and pulmonary functions are normal
- Fall in ionised Ca 2+
- Volume overload

- Other Alkali Therapy
  - Sodium Citrate
  - Potassium Citrate
    - This is especially used when there is a combination of metabolic acidosis with hypokalemia
- THAM (Tri Hydroxymethyl Amino Methane)[7]
  - It's a new biologically inert alkali which can buffer CO_2 and acid. It's a more effective buffer than HCO_3 and is well tolerated.

Conclusion

Analysis of Acid Base disturbance should be done systematically. It's important to classify metabolic acidosis based on Anion Gap. High Anion Gap acidosis is more common in ICU setting. Severe metabolic acidosis (pH <7.2) is associated with higher mortality. Correction of the underlying cause should be the basis for the management of high AG acidosis. Randomised controlled trials in humans are required to evaluate the different approaches towards correction of metabolic acidosis.

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