



Original article

Biochemical Approach of Acid-Base Disturbances: Diagnosis Algorithm

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Abstract

Context: The biochemical approach to acid-base balance classifies disturbances in two categories based on cellular mechanisms. The first one being cellular respiration (ATP), which presents high anion gap and changes in carbon dioxide levels, and the second one, cellular metabolism (ion transport through membrane channels), which evidences normal anion gap and changes in other cations and anions.

Objective: To present a new diagnostic algorithm for acid-base disturbances, based on the biochemical approach.

Method: Original research with systematic analysis and data organization, following biochemical processes that affect acid-base balance.

Results: A simple, three-step algorithm which classifies information in a diagnostic table that connects blood gas analysis results (pH, anion gap or base excess, bicarbonate, carbon dioxide and unmeasured anions) with the biochemical cause and most probable clinical findings.

Conclusions: The biochemical approach is considered the new model to understand, explain and diagnose acid-base balance and disturbances. All high anion gap disturbances occur in cellular respiration, while all normal anion gap disturbances occur in membrane channel function. The diagnosis algorithm simplifies and organizes the information to describe medical conditions with data from a blood gas analysis. This approach is the first model to establish a linear correlation between lab results, biochemical cause, and clinical findings of acid-base disturbances.

Keywords: Acid-base balance, Acid-base disturbance, Metabolic acidosis, Metabolic alkalosis, Respiratory acidosis, Respiratory alkalosis, Urea cycle disorders, Salicylate poisoning, Respiratory chain, ATP, Renal tubular acidosis, Hyperkalemia, Hypercapnia, Hypocapnia, Critical care, Emergency, Point of care, Biochemical approach.

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Algoritmo diagnóstico para el abordaje bioquímico de trastornos ácido-base

Resumen

Contexto: el abordaje bioquímico de trastornos ácido-base clasifica las alteraciones en dos categorías basándose en mecanismos celulares. La primera categoría es la respiración celular (ATP), que presenta una brecha aniónica elevada y cambios en niveles de dióxido de carbono. La segunda, es el metabolismo celular (transporte de iones a través de canales de membrana), el cual presenta una brecha aniónica normal con cambios en otros cationes y aniones.

Objetivo: presentar un nuevo algoritmo diagnóstico para trastornos ácido-base con base en el abordaje bioquímico.

Método: investigación original con análisis sistemático y organización de datos siguiendo procesos bioquímicos que afectan el balance ácido-base.

Resultados: un algoritmo simple de tres pasos que clasifica la información en una tabla diagnóstica que conecta los resultados de gasometrías sanguíneas (pH, brecha aniónica o exceso de base, bicarbonato, dióxido de carbono y aniones no medidos) con la causa bioquímica y hallazgos clínicos más probables.

Conclusiones: el abordaje bioquímico es el nuevo modelo para entender, explicar y diagnosticar el equilibrio ácido base y sus trastornos. Todas las alteraciones que presentan brecha aniónica elevada se originan en la respiración celular, mientras que todas las que presentan brecha aniónica normal se originan en canales de membrana. El algoritmo diagnóstico simplifica y organiza la información para describir condiciones médicas desde la información de una gasometría sanguínea. El abordaje bioquímico es el primer modelo que conecta los resultados gasométricos con la causa bioquímica y los hallazgos clínicos más probables de los trastornos ácido-base.

Palabras clave: equilibrio ácido-base, Trastorno ácido-base, acidosis metabólica, alcalosis metabólica, acidosis respiratoria, alcalosis respiratoria, trastorno del ciclo de la urea, intoxicación por salicilato, cadena respiratoria, ATP, acidosis tubular renal, hiperkalemia, hipercapnia, hipocapnia, cuidados críticos, punto de cuidado, abordaje bioquímico.

Introduction

All acid-base disorders with high anion gap relate to disturbances in cellular respiratory processes such as glycolysis, citric acid (Krebs) cycle, and respiratory chain in the inner mitochondrial membrane. Conversely, acid-base disorders with normal to low anion gap are related to disturbances in ion concentration (cations and anions) and are generally caused by changes in membrane channel function, ion gradients, and passive or active transport mechanisms. Some of these disorders are congenital and some are iatrogenic in nature [1].

Methodology

Original research article with systematic analysis and classification of data following a pattern based on biochemical processes that affect acid-base balance.

How to use the diagnostic algorithm (Table 1)

Step 1: Determine pH.

- <7.38 = acidosis
- >7.42 = alkalosis

Step 2: Determine anion gap (AG)/base excess (BE)

- High AG (Low BE) means disturbance in cellular respiration.
 - Conditions that affect oxygen supply or activate anaerobic respiration lead to elevated lactate with low CO_2
 - Conditions that affect substrates for citric acid cycle lower the production of CO_2 , leading to low CO_2 and low HCO_3^-
 - Conditions that affect the mitochondrial respiratory chain lower the production of H_2O , leading to high CO_2 (hypercapnia) and low HCO_3^-
 - In severe MRC blockage, cells resort to anaerobic respiration, leading to elevated CO_2 , low HCO_3^- and elevated lactate. Therefore, hyperlactatemia with hypercapnia indicates mitochondrial respiratory chain dysfunction.
- Normal AG (neutral BE) means disturbance in ion transport across membranes
 - Most cases affect sodium, potassium and chloride levels.
 - If lactate is elevated, consider hypovolemia, and refer to step 2.1 high AG [2].

Step 3: Determine the byproduct or metabolite.

Past and recent medical history, clinical examination, and biochemical analysis play an important role. Metabolites analyzed with CO_2 and HCO_3^- levels will explain the underlying process.

- Lactate
 - Low CO_2 : tissular hypoxia – ventilation: alveolo-capillary membrane, cardiac output, hemoglobin alterations, hypovolemia, ischemia

- High CO₂: mitochondrial respiratory chain blockage – uncouplers: alcohols, poisons, anesthetics
- Ketones – citric acid cycle with fatty acids instead of pyruvate – diabetic ketoacidosis, starvation, infections, alcohol abuse.
- Organic anions – citric acid cycle with amino acids instead of pyruvate – inborn errors of metabolism, severe catabolic state.
- Nitrogen derivatives: Urea, ammonium – urea cycle disorders and generally related to citric acid cycle blockage in the alpha-ketoglutarate dehydrogenase enzyme.
- Salicylates – citric acid cycle blockage in succinic acid dehydrogenase and alpha-ketoglutarate dehydrogenase enzymes, coupled with ketoacid production [3].
- Hypercapnia (high CO₂) – buildup from lack of H₂O production in respiratory chain due to blockers or uncouplers (anesthetics, metformin, remdesivir, organophosphates, coenzyme deficiency, etc.) [4].

Once the disturbance is identified, proper treatment can be initiated [5].

Some anions, such as organic anions and respiratory chain blockers, are not routinely measured but can be inferred and then ordered to confirm and establish the correct diagnosis.

Discussion

Alterations in cellular respiratory (i.e. ATP) processes yield certain byproducts in weak acid form, which later dissociate, releasing hydronium ions and an anion [6]. Hydronium ions are responsible for changes in pH and cellular function (depolarization or hyperpolarization), leading to clinical manifestations. The dissociated anions elevate the anion gap, and their identification can help clinicians determine which step of the process is altered.

Most disturbances that present with high anion gap manifest as acidosis (pH <7.38). However, there are two exceptions: Urea cycle disorders and salicylate toxicity, which manifest as alkalosis with high anion gap. The most plausible explanation is that the byproducts of urea cycle and salicylates have a very high pH (9.8 and 13, respectively). Their buildup in plasma exerts an alkalinizing effect on serum pH (alkalemia) and masks the real acidosis occurring due to the disturbance of cellular respiration [7].

Table 1. Diagnostic Algorithm for Biochemical Approach of Acid-Base Disturbances

Diagnostic Algorithm for Biochemical Approach of Acid-Base Disturbances							
Processes	Cellular respiration				Metabolism (ion exchange)		
Classification	Respiratory acidosis			Factitious alkalosis	Respiratory acidosis	Metabolic acidosis	Metabolic alkalosis
pH	↓	↓	↓	↑	↓	↓	↑
Anion gap	↑	↑	↑	↑	↑	↔	↔
CO ₂	↓	↓	↓	↓	↑	↔	↔
HCO ₃ ⁻	↓	↓	↓	↓	↓	↓	↑
Metabolite	Lactate	Ketones	Organic Anions	Salicylate Nitrogenous derivates	Lactate, unmeasured anions, toxins	Hyperchloremia hyperkalemia*	Bicarbonate
Altered cellular cycle	Glycolysis	Krebs	Krebs	Krebs	Respiratory chain	No	No
Specific observations	Hypoxemia, hypoperfusion, hypovolemia	Diabetes mellitus, infection, starvation, alcohol abuse	Inborn errors of metabolism	Urea cycle disorders, salicylate toxicity	Toxins: alcohols, benzodiazepines, anesthetics, carbarnates, organophosphates	Gastrointestinal fistulae, drainage, diarrhea	Bicarbonate ingestion, prolonged vomiting, milk-alkali syndrome
			Severe catabolia	*Alkaline pH due to alkaloid buildup in plasma	Coenzyme deficiency (Q10, B2, B3 etc)	Cationic exchange resins, Hippurate, acid loads, RTA 1, 2 & 4	Hyperaldosteronism, Cushing, Liddle, adrenal adenoma, hyperplasia, or enzyme deficiency
			Consider Hyperamm-onemia				*CO ₂ buildup
Clinical findings	Shock: Respiratory distress syndrome, changes in alertness status, tachycardia, hypothermia, hypotension, etc.					Diarrhea, vomiting, search for lactate.	Hyponatremia, hyperkalemia, hyperchloremia
						*If hyperkalemia, consider RTA-4	

Source: Author's elaboration with information provided in the text.

Under ideal conditions, the carbon:hydrogen:oxygen ratio and the amount of released CO₂ and H₂O remain constant [8]. This is known as the respiratory quotient (Q). The body maintains constant equilibrium between CO₂ and HCO₃⁻ levels, as HCO₃⁻ formation depends on that ratio. HCO₃⁻ levels are a key component of base excess determination. Since changes in substrates or enzymatic activity of cellular respiration that alter the anion gap will also alter HCO₃⁻ levels, it is logical to consider anion gap and base excess as mirror parameters of severity. The higher anion gap, the lower (more negative) the base excess. This is very useful in certain settings where the blood gas analyzer lacks the capacity to measure cations for the AG formula.

All disturbances in cellular respiration lower the respiratory quotient, resulting in increased oxygen demand, which is expressed clinically as tachypnea. It is also logical to consider tachypnea as a response mechanism to maintain adequate oxygen supply to ensure ATP production, rather than to eliminate CO₂ to “compensate” the “metabolic acidosis”, as previous models state [9–11].

Conclusion

The biochemical approach is the new model to understand, explain and diagnose acid-base balance and disturbances. All high anion gap disturbances occur in cellular respiration, while all normal anion gap disturbances occur in membrane channel function. The diagnosis algorithm simplifies and organizes information to describe medical conditions with data from a blood gas analysis. The biochemical approach is the first model to establish a linear correlation between lab results, biochemical cause, and clinical findings of acid-base disturbances.

Conflict of interest

The author declares no conflicts of interest regarding this publication.

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Author contribution

Alejandro Nitsch Prado, as the sole author of this article, conducted the conceptualization, data curation, analysis, research, original draft, review, and editing.

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