THE NORTHERN HOSPITAL

SODIUM BICARBONATE

Leaf sequence in Sidalcea malviflora (photo, by Gordon L. Miller, in 2009 MIT press edition of "The Metamorphosis of Plants", by Johann Wolfgang von Goethe, 1790)

Researchers have been generally aware for some time that there is a hidden relationship amoung various external parts of the plant that develop one after the other and, as it were, one out of the other (for example leaves, calyx, corolla, and stamens); they have even investigated the details. The process by which one and the same organ appears in a variety of forms has been called the metamorphosis of plants.

"The Metamorphosis of Plants", Johann Wolfgang von Goethe, 1790

One of the greatest pre-Darwinian debates in the biological sciences was the so-called "structuralist" versus "functionalist" debate. The former viewpoint, championed by the great anatomist Geoffroy Saint-Hilaire, and later by the even greater anatomist Sir Richard Owen, held that all animals, vertebrate at least, owed their form to a primal "archetype" from which all the diversity of the animal world sprung. Teleological reasoning then suggested that the vertebrate archetype originated with the "primary cause", in other words the divine plan of God. As variations in an animal's structure arose, they would then seek out a suitable environmental niche in which to thrive.

The latter viewpoint, championed by the great French zoologist Georges Cuvier, held that it was the environment itself which shaped the variety of external forms that were evident in the great diversity of vertebrate animals. Elements of both arguments we know today are correct. Charles Darwin explained the "archetype" as common ancestry of all life, not just an archetype for each type of animal, and of course the "functional" aspect of animal diversity was indeed shaped by the environment, and it was Darwin's brilliance to explain just how this was done – by natural selection.

As Saint-Hilaire put the structuralist case for the vertebrate animals, the same case for the plant world came from an altogether unexpected source, not from a great zoologist or anatomist, but rather from one of the Eighteenth century's greatest writers and poets, the German, Johann Wolfgang von Goethe. Unknown to many today, Goethe was an accomplished amateur botanist. He took the structuralist theory and applied it to the plant world, publishing his thoughts in 1790 in a small landmark pamphlet of Eighteenth century plant biology, which he entitled "The Metamorphosis of Plants". Although suffused with archaic ideas of the ever more perfect "refinement of sap" as this substance moved up the stem of a plant, and the "expansion and contraction" of parts as the plant developed, he did make a major contribution to the intellectual scaffolding of biological thinking of the time that would eventually help point the way to Charles Darwin's, theory of evolution. What the structuralist's sought out was an underlying pattern to all living things, no matter how diverse their outward appearance seemed. In the Metamorphosis of Plants, Goethe put forward the idea of the "archetype" of all plant life, just as Saint-Hilaire had advocated an ancient archetype of all the "vertebrated animals". His plant archetype was in fact the leaf, a structure which he believed was the basis upon which all other components (apart from the roots, which he apparently did not consider even worthy of consideration), of plants, such the calyx, corolla, and stamen were based. These other components were merely leaves that had in some way "metamorphosed".

Although archetypes are today considered an archaic concept, the idea of an underlying pattern or unity to all living things, now forms the very basis of our understanding of life on Earth. Charles Darwin showed that the underlying unity of all life was more profound than either the structuralists or the functionalists could possibly have even imagined. Twenty first century molecular biology has now proven this underlying unity to a degree that would have astounded even Darwin himself. What would have astounded all biologists of the Eighteenth as well as the Nineteenth Centuries is that the molecular evidence, (let alone the fossil evidence) tells us that all life, from bacteria, virus and fungus, to elephants, emus, palm trees, dragonflies and humans are based on the most ancient "archetype" of all, deoxyribonucleic acid, or DNA.

Goethe always lamented the fact that his pamphlet lacked the visual illustrations to demonstrate the wondrous underlying unity of nature. He planned that one day he would bring out a new illustrated edition of his work, to better demonstrate his ideas, but alas this was never achieved. In 2009 however the gifted photographer Gordan L. Miller rectified this deficiency providing many beautiful photographs of plants scientifically chosen to illustrate Goethe's work. In one plate the development of the leaf of the Sidalcea malviflora is demonstrated, he writes, "The leaves become larger and less rounded, the incisions grow into definite divisions, but the original plan is still evident in the pattern of the veins. Thus there is a sameness in the midst of the differences"

In the field of medical toxicology we deal with a bewildering array of disparate drugs. We strive to understand the mechanisms of toxicity, in order to better understand how to direct our treatments. As Goethe taught us to look for underlying patterns in nature to better understand it, we may use this method to better understand many aspects of toxicology. It was noticed that a seemingly diverse array of drugs produced a similar pattern of cardiac toxicity, the widened and bizarre QRS complex leading to lethal arrhythmias. This pattern is now appreciated to be caused by the blockade of fast sodium channels. In the past it was known that tricyclic overdose that produced this type of abnormality responded well to the use of intravenous sodium bicarbonate. In recognition of this distinctive pattern of cardiac toxicity it is now understood that many drugs interfere with the fast sodium channels, not just the tricyclics. By this recognition we are now better armed to treat the arrhythmias that result from this mechanism of toxicity - this treatment consists of the use of intravenous sodium bicarbonate. Thus there is a sameness in the midst of the differences!

SODIUM BICARBONATE

Introduction

Sodium bicarbonate (**NaHCO3)** is useful in the following toxicological scenarios:

1. As a **specific antidote** to any agent that produces toxicity by impairing **fast sodium channel** function.
2. As an **alkalinizing agent.**
3. As an adjunctive treatment for **hyperkalemia**
4. Some scenarios of **metabolic acidosis**
5. An adjunctive treatment in cases of severe **rhabdomyolysis.**

Preparation

100 ml bottles of 8.4% solution sodium bicarbonate.

- This provides for 1ml of solution = 1 mmol of sodium bicarbonate.
- Therefore one (100 ml) bottle equals 100 mmol of sodium bicarbonate.

Other iatrogenic sources of bicarbonate:

- Stored blood, *citrate* is metabolized to bicarbonate in the liver.
- Hartmans solution, *lactate* is metabolized to bicarbonate in the liver.

Mechanism of Action

The effects of bicarbonate include:

1. Provision of a sodium load:
    - Provides a large sodium (and osmotic load)

      This improves sodium availability for blocked sodium channels.
2. Provision of a bicarbonate load.
3. Alteration of drug distribution:
    - Elevation of the serum pH can reduce the proportion of some drugs in un-ionized form to make them ionized and so limit their ability to cross cell

membranes, and hence their distribution into certain tissues such as the CNS.

- An alkaline urinary pH can result in some drugs being predominantly in ionized form in the urine, and hence reduce their reabsorption across the renal tubules.

Pharmacokinetics

Absorption:

- Sodium bicarbonate is given IV
- It **cannot** be given via ETT

Distribution:

- Sodium bicarbonate is **$NaHCO_3$**

  It dissociates in water to sodium (Na+) ions and bicarbonate (HCO_3^-) ions

  Both are essential elements of the body's normal physiology.

  Sodium is distributed to the intracellular and extracellular fluid. It is the principle cation of the extracellular fluid.

Metabolism and excretion:

Both sodium and bicarbonate are carefully homeostatically regulated by the body.

Bicarbonate combines with H+ ions to form carbonic acid which dissociates to CO_2 and H_2O

$HCO_3^- + H+ \leftrightarrow H_2CO_3 \rightarrow CO_2 + H_2O$

Pharmacodynamics

Bicarbonate elevates the serum pH

This produces an alkalosis with the attendant features of:

- Shift of the HbO_2 dissociation curve to the left (hence O_2 is not off loaded as readily to the tissues)
- Hypocalcemia, (binds to negatively charged proteins)
- Hypokalemia, (due to movement of potassium intracellularly)

- May depress respiration.
- May alter the drug function and excretion of some drugs.

Indications

1. Severe metabolic acidosis:

   Increased anion gap metabolic acidosis:

   Sodium bicarbonate is not usually required in this situation, even in severe acidosis. The acidosis in these cases usually resolves with specific treatment.

   It may however be considered in general if:

   - The acidosis is very severe and life threatening in its own right (pH ≤ 6.7)
   - The patient is very unstable (life threatening arrhythmias).
   - Bicarbonate levels are very low (< 4)

   It may be used in severe metabolic acidosis induced by drug toxicity such as:

   - Cyanide poisoning
   - Isoniazid poisoning
   - Toxic alcohols

   Normal anion gap metabolic acidosis:

   - Here there is more rationale for giving bicarbonate, as the primary pathology is a loss of bicarbonate.

     The conditions that lead to this type of acidosis, however, do not usually produce an acidosis that is severe.

2. Cardiotoxicity secondary to **fast sodium channel blockade**:

   - TCA:

     Sodium Bicarbonate is regarded as the specific anti-dote for the treatment of **TCA** induced cardiac toxicity, (due to its class Ia activity).

   - It can be used for cardiotoxicity for class **1a or 1c anti-arrhythmic agents**, such as flecainide, quinidine and quinine.

It can in fact also be used for any other non 1a or 1c *specific agents* that have significant fast sodium channel blockade as a part of their toxicity profile.

Specific examples of these include:

- ♥ Propranolol
- ♥ Venlafaxine/ desvenlafaxine
- ♥ Bupropion
- ♥ Dextropropoxyphene
- ♥ Carbamazepine
- ♥ Chloroquine/ Hydroxychloroquine

- pH alterations into the range of **7.5-7.55** is also beneficial for sodium channel *function*.

3. Hyperkalemia:
   - It is a useful adjunctive agent.
4. Where urinary alkalinization is useful for drug elimination:
   - Salicylate poisoning
5. Rhabdomyolysis:
   - Alkalinization will help prevent myoglobin precipitation within the renal tubules.

Contraindications/ Precautions

These include:

1. Acute pulmonary edema
2. Hypokalemia
3. Pre-existing alkalosis
4. Renal failure
5. Severe hypernatremia

Adverse Effects

1. Excessive alkalinisation:
    - A pH > **7.6** is detrimental to cardiovascular function.
2. Electrolyte disturbances:
    - **Hypokalemia,** (from alkalosis)
    - Hypocalcemia, (from alkalosis)
    - Hypernatraemia, (from excessive amounts)
3. Volume overload:
    - There is a risk of intravascular volume overload because of the high sodium content. Therefore it should be used with caution in conditions where this would be detrimental such as CCF.
4. Local tissue inflammation:
    - May cause problems if solution extravagates.
    - Bicarbonate cannot be given via an ETT.
5. Increased $PaCO_2$ levels especially if given quickly, with risk of increased ICP.
6. Bicarbonate must never be given in the same line as calcium (this will precipitate calcium carbonate)
7. *Paradoxical intracellular cerebral acidosis* is a theoretical risk:
    - HCO_3 leads to increased $PaCO_2$ levels. CO_2 then crosses the blood brain barrier readily, but HCO_3 does not. Therefore there is increased CO_2 intracellularly without the accompanying bicarbonate ions and an intracellular acidosis develops.

      One way of minimizing increased $PaCO_2$ levels is to give the bicarbonate slowly.

Dosing

IV bolus dosing:

- For serious drug induced cardiac toxicity:
    - ♥ Arrhythmias

- ♥ Widened QRS
- ♥ Refractory hypotension.

Using an 8.4% solution:

2 mmol / kg IV (= 2 ml / kg of 8.4% solution) is given over 10-15 minutes, but may be given quicker in more urgent situations.

Repeat as required every 3-5 minutes, until CVS stability is achieved.

Infusion:

- 150 mls of 8.4 % sodium bicarbonate can be added to 850 mls of 5 % dextrose and infused at 250 mls/hour. (3rd Murray p. 452)

  This will provide for 37.5 mmol of sodium bicarbonate / hour.

- 20 mmol of KCl may be added to each liter to help maintain normokalemia.

Note that bicarbonate is more helpful when used in conjunction with hyperventilation because in the absence of concomitant hyperventilation physiological reflex changes in $PaCO_2$ and renal bicarbonate excretion buffer the change in pH. [1]

Sodium bicarbonate *infusions* in particular may lead to renal compensation for metabolic alkalosis reducing their effectiveness

Boluses of sodium bicarbonate are thought likely to be more effective than infusions because they will lead to **rapid shifts** in the concentration of free drug

Therapeutic target:

- Aim for a blood pH of 7.50 - 7.55.
- Urinary pH should be > 7.5.
- In drug toxicity continue until there is clinical and laboratory improvement.

References

1. Sodium Bicarbonate in L Murray et al. Toxicology Handbook 3rd ed 2015.

2. eTG - November 2014.

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