Short Research Communication

Why Is Saline So Acidic (and Does It Really Matter?)

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Abstract

Commercial 0.9% saline solution for infusion has a pH around 5.5. There are many reasons for this acidity, some of them still obscure. It is also true that infusion of normal saline can lead to metabolic acidaemia, yet the link between the acidity of saline solution and the acidaemia it can engender is not straightforward. This commentary draws together the known and putative sources of acidity in saline solutions: it turns out that the acidity of saline solution is essentially unrelated to the acidaemia complicating saline infusion.

Key words: saline, acidaemia, titratable acidity, crystalloid, balanced solution, Grotthuss.

Introduction

One might well think that ordinary commercial 0.9% saline solution for infusion would be neutral, with a pH of 7. In fact it is quite acidic: pH being reported as low as 4.6.[1] Why does this simple solution have a pH so far removed from the physiology it is designed to support? And should junior doctors be concerned about what impact this *in vitro* acidity has on their patients? It is widely recognized that resuscitation with 0.9% saline can cause acidaemia, but oddly enough the natural assumption that this is because of the intrinsic acidity of the infusion fluid turns out to be wrong. As we shall see, and counter-intuitively, the metabolic acidosis caused when we infuse 0.9% saline has little to do with its intrinsic acidity. This paper tries to shed light on this confusing state of affairs.

Why is 0.9% saline solution for infusion acidic?

There are basically three kinds of factors that affect the pH of a commercial saline solution: the *atmosphere*, the *ions* in solution, and the *container*.

Dissolved carbon dioxide

Pure distilled water has a pH of 7 at 25^0C. However, in contact with the atmosphere, carbon dioxide is absorbed and the pH falls. CO_2 makes up approximately 0.036% of the atmosphere, and its solubility coefficient s in water is approximately $0.034 mol.L^{-1}.atm^{-1}$ at 25^0C. Henry's Law then tells us that the concentration of CO_2 is the product of s and pCO_2, or about $0.012 mmol.L^{-1}$. Of this dissolved CO_2 about 0.1% converts to carbonic acid, which dissociates to hydrogen and bicarbonate ions. Bicarbonate further dissociates to carbonate, liberating a second hydrogen ion (though the dissociation constant for this reaction in water, saline or dextrose solution is negligible - seven orders of magnitude lower than that of carbonic acid). Unlike in plasma, the hydrogen and bicarbonate ions arising from dissolved carbon dioxide in water or saline exist at equal concentrations, so:

$$Ka = \frac{[H^+_{(aq)}][HCO^{3-}_{(aq)}]}{[CO_{2(aq)}]} = \frac{[H^+_{(aq)}]^2}{[CO_{2(aq)}]} = 4.45 \times 10^{-7}$$

From this, we can work out that the pH of water exposed to atmospheric pCO_2 should be approxi-

mately 5.65; this is indeed close to what we find for both water and 0.9% saline solutions.

The influence of the ions in solution

All that is fine for pure water, but in saline solution some other factors need to be considered. Firstly the 'salting out effect'. CO_2 solubility depends on the lone electron pair on its oxygen atom attracting the positively charged face of a hydrogen atom of water; but other electrolytes in the solution compete for the hydrogen, reducing the stability of the CO_2 in solution. As a result, CO_2 concentration is slightly lower in saline than in water. Secondly, the presence of electrolytes in the solution favours dissociation of H_2CO_3 by stabilising the daughter ions, increasing the dissociation constant for carbonic acid,[2] and therefore the acidity. Thirdly, positive and negative ions – Na^+, Cl^-, H^+ and HCO_3^- alike – cluster around one another in a thermodynamically favourable arrangement, imposing a structured charge distribution that affects the properties of the ions.[3] The activities of the ions are then no longer proportional to their pure concentration: the activity of H^+ in particular is significantly reduced in the presence of saline.[4]

To summarise, sodium chloride decreases the solubility of CO_2, and reduces the activity of the hydrogen ions; but it also increases the dissociation of carbonic acid. The net effect is a small reduction in pH (by about 0.01).[1]

In addition, chemists note that many cations in solution generate acid solutions in water. For example, Al^{3+} or Fe^{3+} are electrophilic, and attracted to the electron-rich oxygen atoms of surrounding water molecules. As the electron cloud around the oxygen is drawn towards the cation, these electrons relinquish their contribution to the O-H bond, allowing the hydrogen ion to drift off and lowering the pH. However, the low positive charge and relatively large atomic radius of the sodium ion limits its electronegativity; the hydrated sodium ion attracts electrons too weakly to behave as an acid.[5]

Finally, hydrogen ions do not exist freely in solution, but in a hydrated state as the oxonium ion H_3O^+. The oxonium ion has been found to be remarkably nimble, being far more mobile than other, similarly sized ions. The reason is thought to be the 'Grotthuss' mechanism: rather than jostling to get past water molecules, a proton hops from one water molecule to another[6], rather as a pail of water can be swiftly passed along a chain of firefighters - a 'proton wire' is an elegant analogy.[7] The presence of electrolytes such as Na^+ and Cl^- has a marked disordering effect on local water structure altering hydrogen ion conductance[8] and it has been suggested in the medical literature that this could manifest a reduction in pH by interfering with the Grotthuss mechanism.[9] However, a theoretical basis for such an effect has not been developed and evidence that electrolytes actually alter the pH of a solution through the Grotthuss mechanism is not established in the physical chemistry literature (Prof. G Metha, personal communication).

Degradation products of PVC packaging

Saline solutions for infusion are frequently supplied in polyvinyl chloride (PVC) packaging. PVC can liberate diethylhexyl phthalate (DEHP), a comprehensively studied and controversial ester that serves as a plasticizing agent.[10] In addition, formic and acetic acid - decomposition products formed by oxidation during autoclaving[11] - have been identified in PVC packaged fluids whilst sterilisation with gamma irradiation generates free radicals that may lead to the formation of hydrochloric acid.[12] Studies comparing (i) the theoretical pH of saline derived using the principles outlined above, (ii) the pH of saline prepared in the laboratory in the absence of PVC, and (iii) clinical grade saline from a widely used commercial source packaged in PVC based material revealed that whilst prepared samples had a very similar pH to that predicted (median 5.47), the median pH of the PVC packaged saline was 4.6. Interestingly, the pH of saline in polypropylene packaging was 5.71, suggesting a particular property of PVC to be culpable.[1] Of interest, concerns that constituents and degradation products of PVC/DEHP packaging might have endocrine disrupting effects have meant that polyethylene and polypropylene containers for intravenous solutions are increasingly favoured in their stead[10].

In conclusion, most of the deviation from neutral pH can be attributed to the CO_2 dissolved in the saline, and this is true for any infusion solution. There may also be a significant contribution from the degradation products of PVC-packaging. Interactions between saline and carbonic acid and the intrinsic Lewis acidity of the sodium ion, whilst interesting to the enthusiast, are probably less important.

Is it the acidity of the solution itself that causes metabolic acidosis when infused?

Infusion of 0.9% saline solution is a common cause of normal anion gap metabolic acidaemia. On the face of it, one might assume this to be the logical consequence of infusing an acid solution, but the reality is more complex.

Although pH indicates the free acid activity of a solution - the abundance of H_3O^+ ions - it does not reflect the hydrogen ion reservoir associated with, or

buffered by, weak acid anions. This can be measured by titration to pH 7.4 with sodium hydroxide, giving the *titratable acidity*. For 0.9% saline solutions this is minuscule, ranging from 0.126 – 0.152mEq/L.[13] In other words, the buffering capacity of saline is negligible. Blood, on the other hand, contains quantities of weak anions, such as bicarbonate or albumin which can associate with or liberate protons according to the prevailing [H+], effectively 'buffering' the pH around the dissociation constant of that acid anion. Since the high effective hydrogen ion activity of 0.9% saline is not backed up by a significant reservoir of dissociable hydrogen ions to replenish those consumed, when mixed with the formidable buffering capacity of plasma, the infused solution is rapidly and comprehensively titrated to physiological pH. So why *does* a 0.9% saline infusion cause metabolic acidosis?

The answer lies again in buffering. Whilst buffering limits the effect of adding free acid of low titratable acidity, what is less easily accommodated is interference with the buffer system itself. Administration of a 0.9% saline solution, containing no buffer base, dilutes the endogenous buffer systems in the plasma. *In vivo* the important CO_2 / HCO_3^- buffer system is open: under normal physiological conditions $[CO_2]$ is independently regulated by the respiratory system (this is why the CO_2 / HCO_3^- buffer system is so effective, not being limited by accumulation or availability of H_2CO_3). Hence, whilst the bicarbonate buffer base is diluted by saline infusion, the buffer acid, CO_2, remains constant, unaffected by blood volume dilution – it is the unbalanced effect on the acid and base buffer partners that causes dilutional acidaemia. Experimentally, acidification of a plasma-like solution (containing an open CO_2 / HCO_3^- buffer system and comparable weak acid activity) by normal saline can be explained in terms of dilution of bicarbonate in a constant CO_2 environment[14]; the reduced plasma concentration of the basic bicarbonate anion tends towards acidaemia. The process can be described using a number of alternative approaches, including Stewart's strong ion difference (SID) model[15, 16], however, it must be remembered that such mathematical descriptions do not imply mechanism.

What about 'balanced' solutions?

Hartmann's solution contains no buffer base, only strong electrolytes, with *in vitro* pH reported by the manufacturer as low as 5. However, infusion is not complicated by acidaemia since the metabolism of lactate involves the regeneration of bicarbonate.[16] Infusing fluids of similar pH such as Hartmann's and normal saline has, therefore, quite different effects on plasma pH, again emphasising the insignificance of *in vitro* acidity.

It is worth noting that although the plasma concentration of buffer base is about 42mmol/L, to keep plasma pH unchanged a balanced infusion solution must have a [buffer base]/ (SID) of just 24mmol/L. This is because crystalloid infusion can bring about acid base changes in two ways: Firstly by altering [buffer base], and secondly by diluting weak acid. An infusion solution with buffer base 42mmol/L would maintain plasma [buffer base] but reduce plasma [weak acid], favouring alkalaemia. A properly balanced solution must generate a fall in [buffer base]/SID which exactly counters the alkalaemia caused by weak acid dilution.[17]

All this goes to show how important it is to ground fluid therapy in robust appreciation of the underlying science. *In vitro* the salting out effect and the influence of electrolytes on carbonic acid dissociation and proton activity appear to be quantitatively negligible, whilst the reduction in pH associated with dissolved CO_2 and PVC degradation are the predominant sources of the acidity of infusion solutions. On the other hand, *in vivo*, the buffering capacity of plasma and low *titratable* acidity of saline solutions mean that the *in vitro* acidity is largely irrelevant. Instead, the metabolic acidaemia engendered by saline infusion results from buffer base dilution and is not directly related to the pH of the infusion solution at all.

Teaching a mechanistic approach to the acidaemia brought about by intravenous infusions is important. For example, a recent prospective study has associated administration of chloride-rich fluid with poor renal outcomes[17]. The chloride restrictive vs chloride liberal treatment strategies involved the administration of fluids varying not only in chloride content but also their *in vitro* pH and *in vivo* acidifying effect (chloride restriction involved the use of more balanced solutions). In order to critically appraise the data from such studies, and propose a mechanistic basis, clinicians need to understand the chemistry of intravenous infusion fluids, specifically distinguishing the striking, but arguably unimportant *in vitro* acidity of these fluids from the numerically less arresting, but clinically more significant acidification they bring about through buffer base dilution *in vivo.*

The mechanisms summarised here may help to inform the perpetually lively debate concerning the selection of infused solutions and how they challenge our patient's homeostasis.

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Competing Interests

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