# Infusion fluids: why should they be balanced solutions?

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**What is normal about a 'normal' solution? In this article, the author makes the case for a better description of infusion fluids and their composition.**

In 1970, a multiple electrolyte solution with physiological concentrations of ions isotonic with plasma was defined as balanced and, therefore, 'normal' 0.9% salt solution described as neither 'normal' nor physiological [1]. In 2000, there was a call for a new crystalloid infusion fluid, containing additional sodium bicarbonate [2]. In 2003, Reid et al. warned clinicians to be aware of the shortcomings of (ab)normal saline and Hartmann's solution [3].

The 2006 definition of a 'normal' infusion fluid could be [4]: a balanced solution having the physiological electrolyte pattern of plasma in terms of Na, K, Ca, Mg and Cl, and their relative contribution towards osmolality, and achieving a normal acid-base balance with bicarbonate ($HCO_3$) or metabolisable anions.

A major benefit for the physician is that infusion of such a balanced solution is devoid of the risk of iatrogenic disruptions in the electrolyte and acid-base status including osmolality.

## Volume versus fluid replacement: the two aspects of fluid therapy

For decades, inadequate knowledge of the composition of intravenous (IV) fluids has caused substantial problems in fluid therapy resulting from clinicians' failure to differentiate between volume and fluid replacement. Volume replacement aims to replace the intravascular fluid volume loss with an essentially physiological solution, i.e. both iso-oncotic and isotonic. Fluid replacement, on the other hand, aims to compensate for an extracellular fluid volume deficit by infusing with an isotonic solution. Electrolyte replacement or osmotherapy has to restore a normal total body fluid volume (intra- plus extracellular). The composition and use of IV fluids should only be dictated by the targeted fluid space, without differentiating between replacement and maintenance fluids [5].

## What should go into a balanced solution?

The electrolyte pattern of plasma should mimic as closely as possible all cations and anions including $HCO_3$ (or metabolisable anions in lieu of $HCO_3$).

Therefore, the electrolytes (mmol/L) should amount to Na 142 ± 4, K 4.5 ± 0.5, Ca 2.5 and Mg 1.25. Ideally, a balanced solution has a Cl of 103 ± 3 mmol/L, but this is difficult to achieve in practice.

This is strictly in contrast with the Na and Cl in 154 mmol/L of 'normal' saline (0.9 g/dL), where both are much too high. Ringer's lactate solution contains too little Na (130 mmol/L) and too much Cl (112 mmol/L).

There are several arguments against infusing a solution containing too much chloride. An increase by 12 in the plasma Cl concentration (not the Na), bringing it to 115 mmol/L leads to an increase in renal vascular resistance by as much as 35%, a decrease in glomerular filtration rate by 20%, and a drop in blood pressure as a result of a decrease in plasma renin activity [4]. As shown in volunteers after infusion of 2 L of normal saline, the suppression of the renin-aldosterone system to 60% for two days is caused by a 'harmful' hyperchloraemia of 108 mmol/L [6]. Under clinical conditions this hyperchloraemia is meaningful or significant: infusion of 4-6 L normal saline within two to three hours increases the chloride concentration to 115 or 116 mmol/L [7, 8].

## Dilution acidosis

In contrast to fluids for dialysis and haemofiltration, IV fluids worldwide do not contain the physiological buffer base $HCO_3$. They produce dilution acidosis because the $HCO_3$ content of the entire extracellular space is diluted (reduced), while the partial pressure of $CO_2$ (buffer acid) remains constant.

Dilution acidosis was first described in dogs in 1948 after infusion of 0.9% NaCl [9], and again in 1966 after infusion of 5% dextrose or 5% mannitol solution [10]. Obviously, this acidosis was solely because of $HCO_3$ dilution, rather than chloride delivery. This can also be predicted, i.e. an acidosis without hyperchloraemia [11]. The classical description 'hyperchloraemic acidosis' [referred to in 5, 12] is correct only for dilution commonly caused by normal saline. Logically, a strong relationship between hyperchloraemia and base deficit can be shown [13]. Under clinical conditions, dilution acidosis can also be demonstrated: infusion of 4-6 L of normal saline within two to three hours decreases the $HCO_3$ concentration caused by dilution (29-35%) of the extracellular fluid volume from 24 down to 17-21 mmol/L [7, 8], corresponding to base excess values of minus 7-9 mmol/L.

In summary, dilution acidosis is an iatrogenic disruption brought on by $HCO_3$ dilution in the extracellular space, which may be associated with hyper- or hypochloraemia [11].

## Metabolisable anions

Dilution acidosis can be prevented by the use of adequate amounts of metabolisable anions to replace $HCO_3$. The following anions of organic acids are used: acetate, lactate, gluconate, malate and citrate. Consuming H ions and oxygen in the process, these anions are metabolised in the intact liver (mainly lactate) or in muscle (mainly acetate and malate) to produce $HCO_3$. For every mole of acetate, gluconate or lactate oxidised, one mole of $HCO_3$ is produced, while for every mole of malate or citrate oxidised, 2 or 3 moles of $HCO_3$ are produced, respectively.

The alkalising effect of acetate was first described in 1910 in the treatment of cholera, and first used in haemodialysis in 1964. Lactate has been the most popular metabolisable anion in a wide variety of infusion fluids, in particular Ringer's lactate (Hartmann's) solution.

A number of considerations argue against the use of lactate, especially in patients with pre-existing elevated plasma lactate levels (lactic acidosis). Lactic acidosis is a manifestation of disproportionate tissue lactate formation in relation to impaired hepatic lactate metabolism. In such patients, Ringer's lactate solution will invariably exacerbate pre--existing acidosis by producing dilution acidosis, and preclude the diagnostic use of lactate as an important marker of hypoxia.

Plasma lactate has a similar high predictive power to base excess for mortality in patients with various forms of shock: subsequent mortality is approximately 50% if plasma lactate exceeds 5 to 8 mmol/L in the first 24 to 48 hours of shock [4].

Apparently, many physicians are not aware that the use of lactate-containing infusion fluids such as Ringer's lactate, and the diagnostic use of lactate as a marker of hypoxia are mutually exclusive. It is medical nonsense to infuse up to 50 L of Ringer's lactate within 24 hours [4] and at the same time attempt to establish a correlation between lactate and oxygen deficiency.

In Europe, the special problem of D-lactic acidosis is not observed because only physiological L-lactate is used, whereas racemic lactate (D and L) is used in the US [4].

The effects of malate are less well documented than those of acetate. Compared with $HCO_3$, lactate or acetate, the alkalising effect of gluconate is almost zero. Citrate is another metabolisable anion because it has a substantial alkalising effect (trivalent) and is metabolised in practically all organs, especially in the liver.

## The osmolality (milliosmol/kg $H_2O$) and osmolarity (milliosmol/L)

The osmotic activity of an infusion fluid is described in terms of its osmolality or osmolarity. A balanced infusion fluid is isotonic if it has the same actual osmolality as plasma (288 ± 5 mosmol/kg $H_2O$) or the same theoretical osmolarity of a physiological (isotonic) NaCl solution of 308 mosmol/L. What counts is the osmolality that is effective in vivo rather than that measured in vitro. Dextrose 5% in water is clearly isotonic in vitro, but its in vivo effect is that of pure water because glucose rapidly enters the intracellular space to be metabolised.

**Infusion of larger volumes of hypotonic solutions should be avoided.**

The theoretical osmolarity of a solution is obtained by the addition of all osmotically active molecules relative to 1 L of solution. These data can be used to calculate the actual (real) osmolality of the solution based on the osmotic coefficients (NaCl 0.926, i.e. only 93% of NaCl is osmotically active) and the water content (plasma 94%), but now relative to 1 kg of the solvent water. Actual osmolality can also be determined from freezing-point depression.

By pure chance, the actual osmolality of plasma (288 mosmol/kg $H_2O$) is practically identical to the theoretical osmolarity (291 mosmol/L) calculated from its analytical composition.

Normal saline, however, has a theoretical osmolarity of 308 mosmol/L (154 Na +154 Cl) and its osmolality is 286 mosmol/kg $H_2O$ (osmotic coefficient 93%, water content ≈ 100%).

## Hypotonic infusion fluids and intracranial pressure

Infusion of a hypotonic solution may drive water into the intracellular space of all organs. Typical examples include Ringer's lactate or Ringer's acetate (276 instead of 308 mosmol/L or 256 instead of 288 mosmol/kg $H_2O$). The skull is rigid and contains three incompressible fluid compartments, two of which, intravascular fluid volume (blood) and cerebro-spinal fluid, can be partially shifted outside the skull. Any volume change in the brain, e.g. from cerebral oedema, intracerebral haemorrhage or subdural haematoma, invariably results in an identical volume change in blood or cerebro-spinal fluid. Larger volumes of Ringer's lactate solution have long been known to produce a transient rise in intracranial pressure, less pronounced than that observed after infusion of larger volumes of dextrose 5% in water. Therefore, infusion of larger volumes of hypotonic solutions should be avoided, especially in the presence of space-occupying intracranial lesions or processes (e.g. intra-cerebral haemorrhage, subdural haematoma). Ringer's lactate or Ringer's acetate are neither 'isotonic' [5] nor 'balanced' [13] because they are hypotonic.

## Effects of infusion fluids on a patient's acid-base balance

Since 1990, four clinical trials enrolling about 8,000 patients with multiple injuries have demonstrated that base excess (BE, mmol/L) on admission, is indeed the best prognostic indicator for mortality [4 (Figure 4)]. As a consequence, the product label, showing the composition of any infusion solution,

must alert the treating physician to the potential effects of the infusion fluid on a patient's acid-base balance.

The following parameters are available: titration acidity, BE and BEpot.

Titration acidity (mmol/L), while mandatory for inclusion in the product label, is practically useless in this regard.

The BE, defined in analogy to blood, indicates the amount of $HCO_3$ needed to bring the pH of the (acid) solution to the normal pH of 7.4. The BEpot (mmol/L) indicates the amount of $HCO_3$ that can potentially be released in the body after infusion and metabolism of anions. This value is obtained by adding BE (with a negative sign) in mmol/L to the sum of metabolisable anions, taking account of their valency. The BEpot, recommended for infusion solutions in 1993 [14], is actually accepted for labelling crystalloid and colloid solutions by pharmaceutical companies in Germany [4].

Another attempt to define the acid-base status of a patient, namely by the strong ion difference with its normal value of "around 40 mmol/L" [13] is limited. Under clinical conditions, the normal BE of 0 ± 1 mmol/L may be calculated from all measured values to 0 ± 2.2 mmol/L while the strong ion difference is calculated according to all measured values to 42 ± 5.0 mmol/L [15]. Predicted mortality, however, increases by about 8% when BE is decreased by only 2 mmol/L, while a decrease of strong ion difference by 5 mmol/L corresponds to an increase in mortality of about 20%. Therefore, using present standard technology, only BE is acceptable as a prognostic value for mortality as well as labelling of an infusion solution.

## What does a BEpot of 0 mmol/L mean for the patient?

Any infusion fluid that does not contain the buffer base $HCO_3$ will invariably produce dilution acidosis when administered to a patient.

Example: a solution contains 24 mmol/L of acetate which releases 24 mmol/L of $HCO_3$. The BE of this solution is thus -24 mmol/L after infusion alone. However, because acetate is rapidly metabolised in muscle and liver, the BEpot is 0 mmol/L. Now, after infusion plus metabolism of the anion, this solution has no effect on the patient's acid-base balance and, therefore, can cause neither acidosis nor alkalosis.

**Ringer's lactate or Ringer's acetate are neither 'isotonic' nor 'balanced'.**

## Conclusion

An IV fluid optimally balanced for use as either a colloid isotonic, isooncotic solution for intravascular volume replacement or a crystalloid isotonic solution for extracellular fluid replacement confers the following benefits:

- The same balanced solution could be used for both fluid and volume replacement
- Other than volume overload, infusion of such a balanced solution would be devoid of any iatrogenic electrolyte imbalances; there is no risk of hyperchloraemia of the extracellular space with its attendant renal vasoconstriction, reduced diuresis, over-hydration and weight gain
- After infusion and anion metabolism, a solution with a BEpot of 0 mmol/L has no effect on the patient's acid-base balance: neither acidosis nor alkalosis
- Acetate has many advantages, especially over lactate, which should no longer be used
- A strictly isotonic solution rules out the risk of development of cerebral oedema.

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