Letter to the Editor: More balanced fluids?

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“Editorial

Should we really be more 'balanced' in our fluid prescribing?

The use of intravenous fluid to maintain the extracellular fluid compartment composition and circulating volume is a fundamental component of modern medicine either as synthetic fluids containing either a dissolved solute osmotic load (crystalloid) or suspensions of largely insoluble macromolecules (colloids). It is also big business with intravenous fluid use worldwide running into hundreds of millions of pounds. … While it is beyond the scope of this editorial to consider the 'crystalloid vs colloid' debate further, it is of note that many fundamental 'truths' regarding intravenous fluid therapy have not been validated by research [1] and it is in this environment of physiological dogma and research drought that clinicians find themselves evaluating intravenous fluids.

The anion composition of crystalloid (or base solution in the case of colloid suspensions) is increasingly being considered. While close to plasma, 'normal' (0.9%) saline is relatively hyperchloraemic 154mEq.l^{-1} (plasma 95-105mEq.l^{-1}),hypertonic and acidic in plasma. The replacement of chloride with alternative anions is not new and Ringer's lactate solution attempted to recreate physiological conditions by substituting excess chloride with another anion (racemic lactate), arguably the first 'balanced' solution. … While 'balanced' may be an appealing term it is also potentially misleading; that they are close to plasma in terms of pH, (effective) osmolality, or chloride concentration can be challenged. 'Balanced' intravenous solutions are receiving a lot of clinician attention and the manufacturers are marketing these agents hard. It is also likely that more balanced solutions will become available with time. While increasingly promoted as 'state of the art', we would argue that such claims are premature and furthermore, while the superiority of these new agents is largely unproven, so is their safety.

It has been well demonstrated that routine quantities of 0.9% saline produce acidosis; less apparent perhaps is that many colloid preparations are suspended in 0.9% saline [2-4]. … Chloride related acidosis is distinct from tissue acidosis in the setting of shock; the outcome from acidosis represents the pathophysiology rather than proton concentraion per se [10]. …

Most 'balanced' solutions have chosen to replace inorganic chloride with an

organic class 2 anion, e.g. lactate (racemic) or acetate [6]. ... One less clear implication of such preparations is that after metabolism of the organic anion, they are potentially hypotonic and, rather like 5% dextrose in vivo. ...

Racemic sodium lactate has a long and distinguished history, is cheap to produce and stable in solution. ... While exogenous lactate is a less potent source of (lactic) acidosis as it is usually sodium buffered, accumulating iatrogenic lactate curiously appears to attract less concern than hyperchloraemia. ...

Historically sodium acetate has been used as an anion in (intermittent) renal replacement solutions. The fact that it is rarely used now is testament to its haemodynamic instability, exerting vasodilatory and negative inotropic effects. ... Whether haemodynamic instability proves to be a significant clinical issue, and whether administration of large quantities of acetate is safe remains to be seen, but this is an example where the assumption 'less chloride is better' requires validation. ...

One option which has not been explored in the realm of intravenous fluids but is well established in renal replacement circles is to use sodium bicarbonate itself to achieve 'balance'. ... Currently available 'balanced' solutions are poor physiological mimics and no commercially available 'bicarbonate' fluids exist, although some clinicians do use renal replacement fluids during fluid resuscitation. ...

The recent Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study was a comparison of a high molecular weight, hypertonic 10% pentastarch colloid (200 kDa, 50% substitution) versus a 'control' group of critically ill patients [15]. Despite a number of study design issues, the control group actually received large volumes of lactate containing fluid, i.e. a 'balanced' solution. ...

The market is being flooded with 'balanced' solutions and buffer anions which are cheap and easy to prepare; it is likely that more elaborate preparations will become available judging by clinician uptake, and costs will escalate. ...

So, for over 50 years 0.9% saline has been both hero and villain, is still available and used by some, vigorously avoided by others. ... Racemic lactate is well evaluated, but we don't know the fate of D-lactate, perhaps an acidic anion as relevant as chloride. Inclusion of acetate would seem a step backwards given its haemodynamic instability during large volume administration. ...

Fundamentally, the *presumed* deleterious effects of excessive chloride, the underlying rationale for this sea change, remain unproven. It is quite conceivable that the balanced alternatives may be more expensive and confer adverse clinical effects relative to saline- we just don't know. ... If we afford fluids the same prescribing responsibilities as drugs then surely we owe it to our patients to evaluate these solutions more completely and to hard clinical outcomes before we abandon saline for a more 'balanced' viewpoint?

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Letter to the Editor

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What do we need in 2009?

In general, what would be optimal: Various solutions producing physiological conditions in patients, or alternatively only a few physiologically compound solutions called balanced ones? The latter was suggested in 1970 [5]: "A balanced multiple electrolyte solution isotonic with plasma and, containing sodium, potassium, calcium, magnesium, chloride and dextrose in concentrations physiologically proportionate to the corresponding plasma constituents would be far superior as a routine replacement and maintenance therapeutic solution".

What does balanced mean?

Balanced infusion therapy requires almost physiological compound solutions [6]: physiological values (mmol/l) of the most important plasma electrolytes sodium (140 ± 5), potassium (4.5 ± 0.5), calcium (2.5 ± 0.5) as well as chloride (103 ± 3) with their contributions to osmolality (isotonic), as well as a physiologically balanced acid-base with bicarbonate or metabolizing anion as a substitute. The administration of bicarbonate would be desirable, unfortunately, an expensive bi-chamber system is required for galenic reasons. Volume substitute requires that a colloid (iso-oncotic) is added in the form of low molecular gelatine (4%, 30 kDa) or hydroxyethyl starch (6%, 130 kDa). Ideally the calculated in vivo osmolality of a balanced solution is 290 ± 10 mosmol/kg H_2O(like plasma) and the potential Base Excess (BEpot) 0 ± 10 mmol/l (iso-hydric). The term potential BE describes the possible effect of the infused solution as well as the metabolisation of anions. Such preparations are distributed by 3 manufacturers of infusion solutions in Germany. Most importantly, the infusion of such a solution (iso-ionic, -tonic, -hydric and -oncotic) does not generate iatrogenic disturbances of the electrolyte status, osmolality, and acid-base balance [7].

Examples of non-balanced solutions

For the following reasons physiological saline (0.9 g /dl NaCl) and Ringer's Lactate (Hartmann's) solutions should not be administered:

0.9% NaCl as a hyperchloraemic solution (154 mmol/l) causes renal vasoconstriction, a decrease in urine production as well as the suppression of the renin-aldosterone system. This leads to expansion of the extra-cellular

liquid volume and possible long-term hyper-hydration with an increase in body weight for days in a dose-dependent fashion.

Administration of Ringer's Lactate prevents lactate being a diagnostics marker for hypoxia; needless to say that oxygen consumption will rise and calcium will be bound, thereby increasing the risk of coagulation disturbances (as little as 10 mmol/l lactate leads to a 50% reduction in ionized calcium). Diabetics suffer from the potential risk of hyperglycemia, and, furthermore during shock lactate loses its effect due to metabolisation by the liver (i.e. shock related liver dysfunction). In addition, Ringer's Lactate is a hypotonic solution which may lead to brain edema which should be avoided in particular in babies and toddlers [3].

Due to the fact that D-Lactate can cause considerable problems in patients [4], it is not licensed in Europe. In the VISEP Study no balanced solutions were administered as a control. Instead, in this trial a 45 mmol/l lactate solution was used with a strong alkaline effect (BEpot +21 mmol/l).

Optimal declaration for the physician

Unfortunately, legal declarations of infusion solutions do not reflect medical requirements: the composition of the ready-to-use solution in the container (in vitro; g/l or mmol/l) has no meaning when its effect differs in the patient. Most importantly for the physician is therefore the effect of the solution in the patient (in vivo), as depicted by the following two examples:

A solution is regarded as "isotonic" (similar to plasma) when it's calculated in vivo osmolarity is 290 mosmol/kg H_2O.*In vivo* is defined as following infusion and metabolisation of possible molecules. An osmolarity of ~ 290 mosmol/kg $H_2O$is clearly present in a 5 % glucose solution; however, after quick glucose metabolisation this solution is comparable to that of pure water with an in vivo osmolality of 0 mosmol/kg H_2O.In contrast, acetate or lactate containing solutions remain isotonic after conversion of acetate/lactate into HCO_3.

A solution without bicarbonate is called then "iso-hydric", i.e. without impact on the acid-base balance, when additional acetate (or lactate; 24 mmol/l) releases 24 mmol/l HCO_3.The BE of this solution *in vitro* is -24 mmol/l; the solution acidifies (dilution acidosis). However, the potential Base Excess (BEpot) of this solution in vivo averages out to 0 mmol/l; the solution has no impact on the acid-base equilibrium due to the quick metabolism of acetate (delayed with lactate), which releases an equimolar amount of HCO_3.In contrast to lactate (liver 80%), acetate is metabolized very fast in nearly all tissues. Therefore, during shock its use is superior to lactate.

Why do balanced solutions guarantee medical safety?

Infusion of a balanced (iso-ionic, -tonic, -hydric and -onkotic) solution does not cause electrolyte, osmolality and/or acid-base disturbances. This is an important safety issue for patients and physicians. Furthermore, all potential lapses will be automatically corrected in a physiological direction. This can be

observed, e.g. for hypo- and hyperkalemia as well as for acidosis and alkalosis or osmolar derailments. In particular iatrogenic alkalosis will be avoided. The clinician can't do wrong – except with volume – if "an almost 'fool-proof' solution" will be used [3].

Summary

Infusion of safe balanced (iso-ionic, -tonic, -hydric and -onkotic) solutions is warranted. 0.9 % NaCl solution heralded as the "Hero of the last 50 years" and the well evaluated racemic lactate [1] are have shortcomings that clinicians should be aware of (e.g. Hartmann's solution) [2].

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