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Intravenous fluids: issues warranting concern

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Editor,

We are making a clarion call for the development and availability of intravenous fluids that have a physiological composition and complete and transparent labeling. Intravenous administrations of fluid are used in perioperative medicine to maintain homeostasis and to restore normal physiology in a wide variety of clinical scenarios. These scenarios include their routine use during anaesthesia and surgery in adults and children, and in the treatment of the critically ill suffering from a variety of pathologies. The physiological end-points targeted by the infusions include systemic blood volume, and in turn, cardiac output, tissue perfusion, metabolic function, electrolyte concentrations and acid–base balance. Although colloids have the advantage of remaining predominantly intravascular, they may cause haemostasis and renal dysfunction. As a result, crystalloids that are free of these risks and much less expensive than colloid solutions, are currently used in nearly all situations.

Crystalloid solutions vary widely in chemical composition, affecting their efficacy and ability to cause adverse effects, including those related to volume loading and electrolyte imbalance. Their side effects may have serious consequences both in adults and children especially when the infusion volume is large and given over a long duration. The solutions used for intravenous infusions contain biologically active chemicals and so are categorised as drug products by local agencies, such as the US Food and Drug Administration (FDA), and the European Medicines Agency (EMA). However, despite this designation, fluid physiology receives little attention in medical education and in the medical and scientific literature. This problem is exacerbated by packaging of the solutions that lacks information about chemical composition, such as osmolality and potential base excess (BE_{pot}), dose, indications, contraindications and potential side-effects. This absence of transparency has prompted wide-spread frustration among clinicians, as reflected in the international nature of the contributing authors above. We recommend that labeling of the various crystalloid formulations be updated to reflect their physiological consequences, and that the protocols related to the infusion of these fluids be more widely taught, standardised and evidence-based.

The scientific evidence guiding fluid choice and dosing is limited. Indeed, the current guidelines are based on physiological experiments performed in the laboratory rather than comparative clinical trials. Although this lack of reliable clinical data was first recognised by researchers in Europe in the early 2000s,[1,2] little progress has been made since then. In 2018, Boer *et al.*[3] emphasised this shortcoming in their review article in the *British Journal of Anaesthesia*. The current interest and wide international reach of the controversy related to intravenous fluid choice is evident from discussion in three articles from Europe and the United States[4–6] published in 2020[4,5] and 2021.[6]

The rationale for new guidelines governing the use of an intravenous fluid should be based on its ability to maintain or restore the body's internal environment, the so-called

'milieu interieur'. Normally this condition is maintained by intrinsic physiological mechanisms and is exemplified by a remarkable constancy for osmotic activity and buffer base concentration in blood plasma within and between individuals. A review of values[7–10] demonstrates that osmolality varies by only 1.5%[7,8] (288 mosmol kg^{-1} H_2O^{-1}, weighted mean value $n = 263$) and buffer bases (48 mmol l^{-1}), expressed as base excess, vary by only 2.2%[9,10] (BE ± 0 mmol l^{-1}, weighted mean value $n = 90$).

The crystalloid fluids best suited to maintain an extracellular fluid (ECF) composition within stringent physiological limits are homogeneous, and iso-tonic (osmolality), iso-hydric (base excess) and iso-ionic (sodium, potassium, chloride), not only in vitro but also in the patient after metabolism of the ingredients.[1,7] Achieving wide spread implementation of this approach will require that standard definitions for osmolality and potential base Excess (BE_{pot}) be adopted.

Osmolality is a measure of solute concentration as defined as the number of osmotically active particles per kilogram water. It is critical that the infused crystalloids have the same osmolality – not osmolarity – as fluids within the body, such as blood plasma. Plasma osmolality can be measured directly using freezing point depression or, as is done routinely in clinical practice, calculated from osmolarity by summing up the active constituents per litre of water (such as sodium, chloride, glucose) and applying the appropriate correction factors.[8] By pure chance, the actual osmolality of plasma (288 mosmol kg^{-1} H_2O^{-1}) is virtually identical to the theoretical osmolarity of 291 mosmol l^{-1} 1 calculated from its chemical composition, not '308 mOsm l', according to the American Academy of Pediatrics.[12] This coincidence is a probable cause for confusion regarding the use of the terms osmolarity and osmolality.

The following examples demonstrate how the corresponding values for osmolarity and osmolality of various solutions can vary, sometimes substantially:[11]

(1) 0.9% saline has a theoretical osmolarity of 308 mosmol l^{-1} (=154 mmol l^{-1} Na^+ + 154 mmol l^{-1} 1 Cl^-) but an actual osmolality of 286 mosmol kg^{-1} H_2O^{-1}. This disparity is because some of the infused electrolytes are not osmotically effective.
(2) Lactated Ringer's (Hartmann's) solution is hypotonic relative to plasma (an osmolarity of 276 instead of 308 mosmol l^{-1} and an osmolality of 256 instead of 288 mosmol kg^{-1} H_2O^{-1}).
(3) Glucose (Dextrose) 5% has a theoretical osmolarity of 278 mosmol l^{-1}, an in vitro osmolality of 290 mosmol kg^{-1} H_2O^{-1} (isotonic), but, because of metabolic breakdown of glucose, an in vivo osmolality of 0 mosmol kg^{-1} H_2O^{-1}, which is equivalent to pure water. Simple calculations demonstrate that an infusion of 2 l of this glucose solution in an adult can have a profound impact on osmolality of the various fluid compartments in the body. The immediate increase in ECF volume from 15 to 17 l caused by such an infusion would be accompanied by a decrease in plasma osmolality from 288 to 254 mosmol kg^{-1} H_2O^{-1}. However, the excess water diffuses rapidly into the intracellular fluid (ICF) of 30 l, thus decreasing osmolality to 276 mosmol kg^{-1} H_2O^{-1} in the 45 l whole body compartment. The 2 l of water are eventually excreted by the kidney.

It is evident that a standardisation of units (osmolality vs. osmolarity) and clear labeling is necessary to avoid inappropriate use of fluids that could lead to iatrogenic hypo-osmolality and subsequent encephalopathy. We recommend that a warning label be added to glucose solutions indicating that osmolality of the combined ECF and ICF compartment could become negative after a 2 l infusion. The EMA recently issued such a warning.[13] Notably, the Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that special warnings and precautions be included in the Summaries of Product Characteristics for glucose-containing electrolyte solutions.[13]

BE_{pot} (in mmol l^{-1}) is a useful index for predicting the influence of an infused solution on the acid–base equilibrium. BE_{pot} indicates the amount of bicarbonate that can potentially be consumed or released in the body after infusion[1] of a fluid. It is currently recommended for inclusion on labeling of solutions by manufacturers in Europe, especially in Germany and Austria.[11] The following example uses BE_{pot} to explain how crystalloid solutions can differ markedly in their effect on acid–base balance. An infusion of saline 0.9%, which lacks the bicarbonate concentration present in plasma (24 mmol l^{-1}), has an acidifying effect (BE_{pot} −24 mmol l^{-1}), and thus may cause hyperchloraemic acidosis. In contrast, an 'acetate-buffered' crystalloid solution[11] containing 45 mmol l^{-1} of acetate has a BE_{pot} of +21 mmol l^{-1} (acetate 45 minus bicarbonate 24 mmol l^{-1}) and is, therefore, an alkalising solution. Acetate is rapidly metabolised in muscle and other tissues leading to an indirect release of equimolar amounts of bicarbonate. Because of its alkalising influence as well as for other reasons,[11] we prefer acetate over lactate solutions for infusions. Furthermore, we recommend that the label 'buffered'[14] or 'acetate-buffered'[14] for infusion solutions should be replaced by either 'acetate-containing' or 'physiologically composed balanced isotonic' solution, as acetate per se has no inherent buffering capability.[11]

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Table 1 Recommendations to intravenous fluid manufacturers for compositional information on labels of intravenous solutions

Iso-tonic (osmolality in mosmol kg^{-1} H_2O^{-1} instead of osmolarity in mosmol l^{-1})
Iso-hydric (potential base excess (BE_{pot}), mmol l^{-1}, instead of pH or titration acidity)
Iso-ionic (sodium, potassium, chloride in mmol l^{-1} instead of g l^{-1})
Acetate *instead* of lactate in mmol l^{-1}

In conclusion, we recommend strongly that the medical community take Lönnqvist's appeal ('time for a solution')[2] seriously, and urge medical companies and manufacturers to provide improved infusion solutions that are physiologically composed and balanced (Table 1), and which include clear and detailed guidance for their safe and effective use. We believe that these relatively simple steps, which can be achieved without increasing costs, will have a substantial clinical benefit in reducing morbidity and potentially saving lives.

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