Intravenous Fluids: *What we should do!*

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Conflicts of Interest

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SIR:

Intravenous fluids are both integral to the treatment of patients with various pathologic conditions, and an ongoing matter of discussion. Recently, *ANESTHESIOLOGY contributed* two challenging statements.[1, 2] First, the editorial by D.A. Story[1] which focuses on „Intravenous fluids – Which recipe?“[1], with respect to the report by K. Maheshwari *et al.*[3] in the same issue of the journal. Second, the respective correspondence to the Editor by A. Kasatkin *et al.*[2] discussing „Balanced crystalloid versus 0.9 % sodium chloride: What we overlook in our research“. However, we strongly feel obliged to comment on both the Editorial,[1] and the correspondence[2] in order to make an input into this conflicting topic.

One of the most decisive facts regarding infusions is the stability of the internal environment (milieu interieur) of our organism. This is mainly achieved by two parameters, i.e., the *osmotic pressure* and the *concentration of buffer bases*. The *osmotic pressure* (tonicity) is characterized by a variation of only 1.7 % (288 ± 5 mosmol/kg H_2O), and the *concentration of buffer bases* (BB) varies by only 2.1 % (BB 48 ± 1 mmol/l) or, expressed as base excess (BE), by 0 ± 1 mmol/l.

Thus, the strategy for any clinical use of infusion solutions must be to maintain or restore the patient´s extracellular fluid (ECF) composition. For this purpose, physiologically composed homogeneous fluids appear to be preferable, at least iso-tonic (osmolality), iso-hydric (base excess) and iso-ionic (sodium, potassium, chloride) solutions – not only in vitro (laboratory), but also in vivo (patient) after metabolization of the ingredients.[4, 5] This, however, requires clarification of the terms o*smolality* and *potential Base Excess (*BE_{pot}*).*

Regarding osmolality (mosmol/kg H_2O), it is crucial that isotonic fluids have the same osmolality as all fluids within the human body, including human plasma. The theoretical osmolarity of fluids is calculated by summing up all osmotically active ingredients relative to 1 liter of volume (mosmol/l). The actual (real) osmolality (mosmol/kg H_2O) – rather than osmolarity –

can be measured using freezing point depression (FPD), or calculated from osmolarity.[6] By pure chance, the actual (real) osmolality of plasma (288 mosmol/kg H_2O) is almost identical to the theoretical osmolarity (291 mosmol/l) calculated from its chemical composition. This coincidence is presumably responsible for some of the confusion in the medical literature. The following examples may show the differences:[6] Normal (0.9 %) saline has an osmolarity of 308 mosmol/l, or an actual (real) osmolality of 286 mosmol/kg H_2O. Lactated Ringer's (Hartmann's) solution is hypotonic (276 instead of 308 mosmol/l or 256 instead of 288 mosmol/kg H_2O). Glucose (Dextrose) 5 % has an in vitro osmolality of 290 mosmol/kg H_2O (isotonic) and a theoretical osmolarity of 278 mosmol/l, but an in vivo osmolality of 0 mosmol/kg H_2O, corresponding to pure water. From our point of view, and in accordance with recent warnings by the European Medicines Agency (EMA),[7] a sound understanding of the potentially confusing items osmolarity (mosmol/l) and osmolality (mosmol/kg H_2O) of plasma and intravenous fluids is urgently needed when evaluating the safety of different electrolyte solutions to avoid iatrogenic hypoosmolality and possible subsequent encephalopathy. Notably, the Pharmacovigilance Risk Assessment Committee (PRAC) recommended to include special warnings and precautions for use in the Summaries of Product Characteristics for glucose-containing electrolyte solutions.[7]

The *Potential Base Excess* (BE_{pot}; mmol/l) is a useful parameter to predict the influence of an infusion solution on the acid-base equilibrium of the patient. This parameter indicates the amount of bicarbonate that can potentially be consumed or released in the body after infusion[4] and is recommended for labeling of infusion solutions by the manufacturers in Europe, especially in Germany and Austria[6]. The following examples may serve to explain the advantages of using the BE_{pot}: Saline 0.9 %, which lacks the plasma bicarbonate of 24 mmol/l, has an acidifying effect (BE_{pot} -24 mmol/l) after infusion and may thus result in a hyperchloremic acidosis. In contrast, a so-called "acetate-buffered" crystalloid solution[8] containing 45 mmol/l of

acetate results in a BE_{pot} of +21 mmol/l (acetate 45 minus bicarbonate 24 mmol/l) and is, therefore, an alkalizing solution. After infusion, the acetate is metabolized rapidly in muscles and other tissues leading to an indirect release of equimolar amounts of bicarbonate. For several reasons,[6] we should prefer acetate over lactate. Therefore, the labeling “acetate-buffered”[8] for infusion solutions should be replaced by either “acetate-containing” or “physiologically composed balanced isotonic” solution.

In summary, we would like to suggest to the medical community to take Lönnqvist´s appeal (“time for a solution”)[9] seriously, and to urge medical companies and manufacturers to please provide physiologically composed balanced infusion solutions, i.e., at least iso-tonic (osmolality), iso-hydric (base excess) and iso-ionic (sodium, potassium, chloride) solutions. This would definitely have the potential to reduce morbidity, and potentially save lives.

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Addendum

Several Letters to the Editor associated with the present topic dating from 2008 to 2019 are available.