Misunderstandings about Tonicity and Osmolality Can Lead to Patient Harm

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INTRODUCTION

Hyponatremia, the most common electrolyte disorder in hospitalized patients, is associated with both morbidity and mortality.[1-6] The use of hypotonic IV fluids has been identified as an important potential cause of hospital-acquired hyponatremia, especially among children.[1-6] During patient care rounds, one of the authors (J.R.M.) serendipitously discovered a bag of hypotonic IV fluid that was inappropriately labelled (at the manufacturing level). This observation prompted a more in-depth review of IV fluid labelling practices across randomly selected Canadian and US manufacturers to better understand the scope of this issue.

WHY ARE HOSPITALIZED PATIENTS AT RISK FOR HYPONATREMIA?

Risk factors for non-osmotic release of antidiuretic hormone (ADH) include pain, nausea, stress, and certain medications. Hospitalized patients regularly experience these symptoms and often have changes to their medication regime, which may impair their ability to excrete free water because of fluctuations in ADH release. In the setting of increased ADH, the free water available in hypotonic IV solutions can rapidly lead to clinically significant hyponatremia.[1-6]

WHAT IS TONICITY AND OSMOLALITY?

It is important for clinicians to understand the difference between tonicity and osmolality. Tonicity is a property of a solution with reference to a particular membrane, whereas osmolality is a property of a solution that is independent of any membrane.[3,5] Solutes such as dextrose (which can freely enter the cell under normal conditions) contribute to the osmolality of a solution, but they do not alter tonicity.[3,5] Although the difference between tonicity and osmolality may seem inconsequential, consider how a lack of awareness of this difference might lead to potential harm when an IV solution is prescribed.

In a patient with normal serum sodium, administration of a hyperosmolar IV solution without sodium (e.g., 10% dextrose in water, D10W) could lead to hyponatremia because the solution being administered is very hypotonic. In contrast, D10NS—an IV solution with the same concentration of dextrose but, concurrently, 0.9% sodium chloride (NaCl)—would not be expected to cause hyponatremia, because the NaCl contributes to tonicity (i.e., the solution is hyperosmotic yet isotonic).

Put another way, administration of 1000 mL of D5W is analogous to administering 1000 mL of electrolyte-free water, given that dextrose, once administered under normal physiologic conditions, will be quickly metabolized, leaving only free water. Similarly, administration of 1000 mL of 0.45% NaCl can be considered equivalent to administering 500 mL of isotonic (0.9%) NaCl plus 500 mL of free water. Finally, no free water is administered when 1000 mL of isotonic (0.9%) NaCl is given.

WHY IS THIS A PARTICULAR CONCERN IN YOUNGER PATIENTS?

Because of physiological differences, children are at higher risk than adults for hyponatremia-related complications.[3] Cases of iatrogenic hyponatremia in children (and adults) have been outlined in recent publications by the Institute for Safe Medication Practices Canada.[7,8] Partly in response to these reports, our local children's hospital established a policy listing several hypotonic solutions, which are mostly restricted to critical care areas.[9] The American Academy of Pediatrics[5] and the Canadian Paediatric Society[1] recommend the use of isotonic IV solutions as the standard for fluid maintenance in children, with the recognition that hypotonic IV solutions can be used in specific circumstances but only with careful monitoring.

CONFUSING THE ISSUE: LABELLING OF IV SOLUTIONS IN NORTH AMERICA

Given that the differences between osmolality and tonicity are well established, we reviewed the labelling and product monographs of selected dextrose-containing IV solutions

produced by a random selection of Canadian and US manufacturers. We conducted a Google search using the term "leading IV manufacturers Canada" and chose the first 3 manufacturers generated by the search. We reviewed labelling and monograph information from the Canadian and US subsidiaries of all 3 companies; in 1 case, the Canadian and US labelling was the same, so only the US labelling is reported here (Table 1). We found several examples of isotonic and hypotonic IV solutions that were designated as "hypertonic" both in the product monograph and on individual bags of IV fluid. Of the 5 manufacturers screened (Table 1), only 1 manufacturer's monograph indicated that dextrose-containing fluids could become hypotonic in vivo because of rapid metabolism.

A total of 28 IV solutions were reviewed, 27 of which had incorrect information in their respective monographs,

TABLE 1. Labelling of Individual IV Fluid Bags and Product Monographs from Randomly Selected North American Manufacturers[a]

Company and IV Solution	Osmolality (Compared with Plasma)	Tonicity	Bag Labelled as Hypertonic	Designated as Hypertonic in Monograph
Canada				
B. Braun Medical Inc, Mississauga, Ontario				
Dextrose 10%	Hyperosmolar	Hypotonic	Yes	Yes
Dextrose 5% in 0.45% NaCl		Hypotonic	Yes	Yes
Dextrose 5% in 0.9% NaCl		Isotonic	Yes	Yes
Baxter Corporation, Mississauga, Ontario				
Dextrose 10%	Hyperosmolar	Hypotonic	Yes	No
Dextrose 10% in 0.9% NaCl		Isotonic	Yes	No
Dextrose 5% in 0.45% NaCl		Hypotonic	Yes	No
Dextrose 5% in 0.9% NaCl		Isotonic	Yes	No
Dextrose 5% in lactated Ringer's solution		Isotonic	Yes	Yes
United States				
B. Braun Medical Inc, Bethlehem, Pennsylvania				
Dextrose 10%	Hyperosmolar	Hypotonic	Yes	Yes
Dextrose 10% in 0.2% NaCl		Hypotonic	Yes	Yes
Dextrose 10% in 0.45% NaCl		Hypotonic	Yes	Yes
Dextrose 5% in 0.2% NaCl		Hypotonic	No	No
Dextrose 5% in 0.33% NaCl		Hypotonic	Yes	Yes
Dextrose 5% in 0.45% NaCl		Hypotonic	Yes	Yes
Dextrose 5% in 0.9% NaCl		Isotonic	Yes	Yes
Dextrose 5% in lactated Ringer's solution		Isotonic	Yes	Yes
Baxter Healthcare Corp, Deerfield, Illinois				
Dextrose 10%	Hyperosmolar	Hypotonic	Yes	Yes[b]
Dextrose 5% in 0.2% NaCl		Hypotonic	No	Yes[c]
Dextrose 5% in 0.33% NaCl		Hypotonic	No	Yes[c]
Dextrose 5% in 0.45% NaCl		Hypotonic	Yes	Yes[c]
Dextrose 5% in 0.9% NaCl		Isotonic	Yes	Yes[c]
Dextrose 5% in lactated Ringer's solution		Isotonic	Yes	No
ICU Medical Inc, San Clemente, California				
Dextrose 10%	Hyperosmolar	Hypotonic	No	Yes
Dextrose 5% in 0.225% NaCl		Hypotonic	No	Yes
Dextrose 5% in 0.3% NaCl		Hypotonic	No	Yes
Dextrose 5% in 0.45% NaCl		Hypotonic	No	Yes
Dextrose 5% in 0.9% NaCl		Isotonic	No	Yes
Dextrose 5% in lactated Ringer's solution		Isotonic	No	Yes

[a]This review included dextrose (> 5%) solutions and dextrose/saline-containing (≥ 5% dextrose) solutions listed in each manufacturer's online catalogue. Solutions containing ≥ 20 mmol KCl/L were excluded.
[b]Labelling and monograph contain the following statement: "10% Dextrose Injection is a hypertonic solution. In the body, however, glucose containing fluids can become extremely physiologically hypotonic due to rapid glucose metabolization."
[c]Labelling and monograph contain the following statement: "Dextrose and sodium chloride injection is a hypertonic solution. In the body, however, glucose containing fluids can become extremely physiologically hypotonic due to rapid glucose metabolization."

labelling, or both. Of the 18 hypotonic fluids that we reviewed, 11 (61%) were incorrectly labelled as "hypertonic" on the IV bag.

MISLABELLING: AN ACADEMIC CONCERN OR TRUE HARM?

In our review, most of the solutions labelled as hypertonic are in fact hyperosmolar but not hypertonic. While it may be worthwhile to know the osmolarity of IV solutions (for example, hyperosmolar solutions may be associated with an increased risk of venous irritation[10]), the tonicity needs to be correctly described on both the label and product monograph to help ensure appropriate fluid selection in the clinical environment.

Hospital policies may help to provide guidance around the principles of IV fluid therapy. As previously noted, our local children's hospital has established a policy regarding IV fluid administration. This policy lists several hypotonic solutions (for example, D5W, D10W, D5W + 0.2% NaCl, and dextrose 3.3% + 0.3% NaCl) which should not be routinely stocked outside of critical care areas,[9] in part to avoid inadvertent administration when not clinically indicated. Moreover, the policy requires some hypotonic solutions (some of which are labelled as hypertonic by the manufacturer) to be labelled with a sticker reading "high-risk hypotonic solution". Clearly, labelling a bag of IV solution with separate, yet conflicting, information is less than ideal. Correcting the labelling of these products at the time of manufacture would be a better approach to avoid potential errors.

We acknowledge that clinicians do not make decisions about IV fluid administration on the basis of product labelling, but rather according to education and teaching that would be gained through medical training. Therefore, the realized clinical impact of this labelling error has likely been negligible. However, the potential for severe harm, especially in pediatric patients, cannot be overstated. The inadvertent administration of hypotonic fluid that is labelled as hypertonic could be catastrophic and could result in morbidity and mortality.[6] Therefore, we should not wait for a negative outcome but rather should recommend that companies change their product labelling so that negative outcomes can be avoided altogether.

CONCLUSION

We intend to submit our observations regarding inappropriate IV solution labelling to Canadian and US regulatory bodies in the hope that our analysis spurs changes toward more accurate labelling in the future.

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