Introduction

Hypersaline solutions such as mannitol and hypertonic saline are essential tools for ICP management, yet much remains to be learned about how these solutions and their effects differ. Mannitol has been more well-studied than hypertonic saline and is currently the solution of choice in many hypersaline therapy recommendations and practice guidelines. In addition to lowering intracranial pressure (ICP) through osmotic effect, it is believed that mannitol may improve blood viscosity in the microcirculation, thereby indirectly offering neuroprotection. An additional, third beneficial mechanism of mannitol as a free-radical neutralizing agent has also been proposed. Because of the variability that has been noted in terms of clinical response which seems to have no relationship with dosage, and because of the known dose-dependent relationship with side-effects, it is currently recommended that the minimum effective dose of mannitol be given and that this be titrated to ICP in conjunction with ICP monitoring.

Hypertonic saline solutions have not been as well-studied as mannitol, and accordingly there are no practice guidelines specific for their use. Due to the common mechanism of action, it may be reasonably inferred that hypertonic saline has the same osmotic effect as mannitol, particularly in patients who are refractory to mannitol. When compared directly with mannitol, there has been no benefit shown in favor of hypertonic saline in human or animal models. Nevertheless, crucial key differences may exist in terms of additional mechanisms and have yet to be fully explored.

While much of what is known about mannitol and hypertonic saline came from observation of their effects on patients or under tightly-controlled basic science laboratory settings, little is known about the basic properties of mannitol and hypertonic saline in situ - that is, as they exist on ICU shelves and as they exist when infused into patients. More-detailed characterization of the physical properties of these solutions as they exist may lead to improved understanding of differential responses to the agents and how they should best be administered to attempt to decrease complications associated with their use.

We measured pH, osmolality, and salinity/specific gravity in 22 hypersaline solutions from 3 manufacturers and 8 lots. Solutions were obtained by the ICU pharmacist using normal supply chain distribution. Solutions were inspected for any signs of damage, noted to be within their expiration dates, and labeled (Table 1). pH was determined digitally and with litmus paper. Osmolarity was determined by two methods: freezing point osmometry and vapor pressure osmometry. Salinity and corresponding specific gravity were determined for all solutions using a portable refractometer. We profiled solutions using dynamic light scattering nephelometry and visual microscopy of 0.8 micron filters for crystals and particulate matter.

Statistical analyses were performed with SAS version 9.4. We used ANOVA with Tukey’s honestly significant difference post hoc test with alpha = 0.05 to compare means across multiple groups; linear regression analysis was used to assess for concentration-dependent trends within hypertonic saline.

Table 1: summary of solution characteristics

Table 2: results by solution type - mean (sd)

Results

Our overall ANOVA statistical model incorporated independent variables solution contents (i.e. 14.6% NaCl), type (i.e. saline), manufacturer, lot, and concentration (i.e. 14.6). p-value for this model was < 0.0001. In post hoc testing using Tukey’s test, digital pH measurement was significantly different between mannitol (mean 6.46, sd 0.35) and pooled containing crystalloid (mean 7.13, sd 0.21); each hypertonic saline solution was more acidic than any solution of mannitol as measured by digital pH meter. We also found significant difference in paper pH between mannitol (5.17, 0.61) and hypertonic saline (4.60, 1.01); each hypertonic saline solution except for 5% NaCl was more acidic than any solution of mannitol. Our results by solution type are displayed in Table 2.

Within hypertonic saline, no pH trend was statistically significant based on 95% prediction limits (Figure 1). All solutions showed considerable heterogeneity of particle size by dynamic light scattering nephelometry and crystals or particulate matter were found in all solutions using visual microscopy.

Conclusions

Through our investigations of pH, osmolality, and salinity/specific gravity, we were able to detect significant differences in physical properties between mannitol and hypertonic saline as these solutions exist in situ in the ICU. Both digital and analog pH measurement showed that pH of all solutions was below physiological range and that saline was consistently more acidic than mannitol.

The consistent acidity of these solutions may be clinically relevant for patients with acid-base disturbances and warrants further investigation with additional sampling. Our results support the notion that acidosis and renal injury following massive transfusion may be partially or completely iatrogenic, due to the plausible mechanism of overwhelming the naturally occurring bicarbonate buffer system. If acidity is found to be a consistent trend in hypersalmon solutions in situ, it may be necessary to augment the infusion of acidic hypersalmon solutions with some alkaline buffering solution, such as bicarbonate.