AN AUDIT OF PH, SALINITY, OSMOMETRY, NEPHELOMETRY, AND PARTICULATE MATTER IN COMMERCIALLY AVAILABLE HYPEROSMOLAR SOLUTIONS

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Introduction

Hyperosmolar solutions such as mannitol and hypertonic saline are essential tools for ICP management. Nevertheless, many varieties exist and differential responses have been reported. Short-term adverse effects of hyperosmolar therapy include hypotension - which can exacerbate underlying shock in a sick ICU patient – and acute kidney injury, especially with high concentrations. While hyperosmolar solutions are very effective in short-term management of elevated ICP, long-term consequences include further renal failure and infection.

Because of the variability in clinical response which seems to have no relationship with dosage, and because of the known dose-dependent relationship with adverse effects, it is currently recommended that the minimum effective dose of mannitol be given and that this be titrated to ICP in conjunction with monitoring. Otherwise, the most recent Brain Trauma Foundation guidelines provide no specific guidelines for hyperosmolar therapy, indicating a need for new evidence and experimentation.

Much of what is currently known about mannitol and hypertonic saline came from observation of their effects on patients or under controlled basic science laboratory settings. Little is known about the basic properties of hyperosmolar solutions in situ - that is, as they exist on ICU shelves and as they exist when infused into patients. More-detailed characterization 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 decrease complications associated with their use. We therefore measured pH, osmolality, and salinity/specific gravity in 22 hyperosmolar solutions from 3 manufacturers and 8 lots.

Methods

Solutions were obtained by the Neuro ICU pharmacist through normal supply chain, inspected, and labeled A - V. pH was determined digitally and with litmus paper. Osmolality was determined by freezing point and vapor pressure. Salinity/specific gravity was determined by portable refractometry. We profiled solutions using dynamic light scattering nephelometry and visual microscopy of 0.8 micron filters for crystals and particulate matter. ANOVA and linear regression were performed with SAS version 9.4.

Results

Our overall model incorporated solution contents, type, manufacturer, and lot (Table 1). p-value for this model was <0.0001. Using Tukey’s post hoc test with alpha = 0.05, we detected many differences in pH, osmolality, and salinity/specific gravity among multiple solution contents, types and manufacturers. While many variables differ, lots (Table 2) digital, analog pH, and analog pK of all solutions were below physiological range; saline was consistently more acidic than mannitol. Osmolality and salinity/specific gravity measurements were consistent with labels (Figure 1). 95% confidence interval for mannitol fell outside manufacturer target range for freezing point osmolality and salinity/specific gravity. All other 95% confidence intervals were in range. All solutions showed considerable heterogeneity of particle size by dynamic light scattering nephelometry, and crystals or particulate matter were found in all solutions examined (Figure 2).

Conclusions

Even with a small sample size, we were able to demonstrate heterogeneity and variance from given manufacturer target ranges for osmolality and salinity/specific gravity for 20% mannitol. Hypertonic saline solutions tended to conform more closely to manufacturer specifications, perhaps because these solutions have less tendency to crystalize. These results supports the paradigm of cautious administration and real-time monitoring for side effects.

We were able to corroborate our results with complementary techniques: digital and analog paper measurement of pH, freezing point depression and boiling point elevation methods for determining osmolality along with an analog technique for determining salinity/specific gravity. Our pilot study can provide a blueprint for similar investigations in the future in terms of ease and validity of each assay. Finally, autoclaving does not eliminate crystals and particulate matter, and these can occlude capillaries. These findings are concerning.

Table 1: summary of solution characteristics

<table>
<thead>
<tr>
<th>solution id</th>
<th>contents</th>
<th>type</th>
<th>manufacturer</th>
<th>lot</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>sterile water</td>
<td>control</td>
<td>A 1</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>5% NaCl</td>
<td>hypertonic saline</td>
<td>A 2</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>5% NaCl</td>
<td>hypertonic saline</td>
<td>A 2</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>5% NaCl</td>
<td>hypertonic saline</td>
<td>A 2</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>20% mannitol</td>
<td>mannitol</td>
<td>B 3</td>
<td></td>
</tr>
<tr>
<td>F</td>
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<td>mannitol</td>
<td>B 3</td>
<td></td>
</tr>
<tr>
<td>G</td>
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<td>mannitol</td>
<td>B 3</td>
<td></td>
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<tr>
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<td>hypertonic saline</td>
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<td></td>
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<tr>
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<td>A 4</td>
<td></td>
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<td>B 5</td>
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<tr>
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<td>23.4% NaCl</td>
<td>hypertonic saline</td>
<td>C 6</td>
<td></td>
</tr>
<tr>
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<td>B 7</td>
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<tr>
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<td>A 8</td>
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<tr>
<td>V</td>
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Table 2: results by solution contents - mean (sd)

<table>
<thead>
<tr>
<th>contents</th>
<th>digital pH</th>
<th>analog pH</th>
<th>fp osmometry</th>
<th>vp osmometry</th>
<th>salinity/g</th>
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</thead>
<tbody>
<tr>
<td>3% NaCl</td>
<td>5.42 (0.14)</td>
<td>6.43 (0.44)</td>
<td>958.33 (2.42)</td>
<td>936.73 (1.62)</td>
<td>2.71 (0.020)</td>
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<tr>
<td>5% NaCl</td>
<td>5.38 (0.23)</td>
<td>6.25 (0.43)</td>
<td>1613.00 (5.57)</td>
<td>1574.53 (3.26)</td>
<td>4.63 (0.209)</td>
</tr>
<tr>
<td>14.6% NaCl</td>
<td>5.76 (0.06)</td>
<td>4.00 (0.08)</td>
<td>7028.87 (1069.2)</td>
<td>7484.27 (2.57)</td>
<td>21.53 (0.12)</td>
</tr>
<tr>
<td>20% mannitol</td>
<td>6.46 (0.35)</td>
<td>5.17 (0.61)</td>
<td>1361.50 (10.37)</td>
<td>1278.07 (10.26)</td>
<td>15.78 (0.20)</td>
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</tbody>
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