A NEW PACKAGING OF HYPERTONIC SOLUTION TO OVERCOME AN UNAVAILABLE FORMULATION IN FRANCE

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INTRODUCTION

Intracranial hypertension, defined as an intracranial pressure (ICP) >20 mmHg for a period of more than 5 min, worsens neurologic outcome in traumatic brain injury (TBI). Most of the time, it is an emergency that must be lowered immediately.

Hyperosmolar therapy is used to treat elevated ICP: mannitol and hypertonic saline are 2 of the commonly used agents. Mechanism of action results of an osmotic gradient that allows attraction of water from cerebrospinal interstitial into vascular compartment.

WHAT ALREADY EXISTS?

Mannitol 20% : solution which begin to crystallize when temperature inferior than 25°C.

HyperTonic Saline Solution (HTSS) : 500 mL glass vials.

Unfit to emergency practices: lost of time if crystals are observed (the container should be warmed, shaken, and then cooled to body temperature before administration) and glass vials of 500 mL are fragile and too bulky to be stored in an emergency bag.

WHAT IS ALREADY DONE?

Several studies show that effect of HTSS is comparable or potentially superior to mannitol for decreasing intracranial hypertension.

Furthermore HTSS might have less adverse effects than mannitol. Mannitol can cause acute renal failure resulting in rebound intracranial hypertension and osmotic diuresis. On the other hand, hypertonic saline have not been associated with significant neurologic, cardiac, or renal injury but could be responsible of hypernatremia and hyperchloremia.

OBJECTIVE: To provide for emergency practices a ready-to-use HTSS of 7.5% sodium chloride infusion bag.

MATERIAL AND METHODS

1) Choice of drug and concentration:

- Mannitol
  - 3%: only for pediatric use
  - 7.5%: same efficacy with other concentration and safe for pediatric use.
  - 10% and more: no more efficacy and hypernatremia risk increased.

- NaCl

2) Preparation:

Infusion bags were produced by aseptic process using the BAXA® EM2400 compounding. Ingredients used were sterile sodium chloride 20% (AGEPS®) and water for injectable preparation (Bbraun®) filled in an Ethyl Vinyl Acetate infusion bag of 100 mL. Bags were stored at room temperature without light protection.

3) Stability controls:

Microbiological and physicochemical stability were measured at day 0, 30, 90 and 180 (a last measure will be performed at day 360).

Microbiological stability included search of endotoxins and absence of microorganism (sterility test).
- Dosage of endotoxins is realized after a swab of 4 mL of solution in an endotoxin-free tube. Kinetic colorimetry was the method used for this analysis.
- Sterility test is realized from a 2 mL take off in a simple vacutainer®. Culture were realized on this sample.

Physicochemical stability was measured through concentration of sodium and osmolality evolution in time.
- Ion concentration was determined with Inductively Coupled Plasma (ICP) with AVID® 200 ICP-Optical Emission Spectrometer (PerkinElmer).
- Osmolality was determined with Advanced® Model 2020 MultiSample Osmometer using freezing point depression. It only measured osmolality between 200 - 1000 mosm/L so a 1/10 dilution was done.

RESULTS

<table>
<thead>
<tr>
<th>DATE</th>
<th>STERILITY</th>
<th>ENDOTOXINS</th>
<th>CONCENTRATION Na⁺ (mM)</th>
<th>Trueness Na⁺</th>
<th>OSMOLALITY (mosm/L)</th>
<th>Osmolality trueness</th>
<th>Visual Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>J0</td>
<td>STERILE</td>
<td>&lt;0,05 UI/mL</td>
<td>1320</td>
<td>3%</td>
<td>2560</td>
<td>0%</td>
<td>OK</td>
</tr>
<tr>
<td>J30</td>
<td>STERILE</td>
<td>&lt;0,05 UI/mL</td>
<td>1290</td>
<td>1%</td>
<td>2420</td>
<td>-6%</td>
<td>OK</td>
</tr>
<tr>
<td>J90</td>
<td>STERILE</td>
<td>&lt;0,05 UI/mL</td>
<td>1240</td>
<td>-3%</td>
<td>2350</td>
<td>-9%</td>
<td>OK</td>
</tr>
<tr>
<td>J180</td>
<td>STERILE</td>
<td>&lt;0,05 UI/mL</td>
<td>1310</td>
<td>2%</td>
<td>2380</td>
<td>-8%</td>
<td>OK</td>
</tr>
</tbody>
</table>

Neither visual nor microbiological and physicochemical alteration were observed (<10%). NaCl 7.5% was still stable at day 180.

Results expected:

<table>
<thead>
<tr>
<th>Na⁺ Concentration</th>
<th>Osmolality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1280</td>
<td>2560</td>
</tr>
</tbody>
</table>

DISCUSSIONS/CONCLUSION

The automated compounding ensures quality and safety of production for a ready-to-use HTSS of 7.5% sodium chloride with a best before use of 180 days. The stability study is still on-going but the preparation for emergency units has already begun.

This preparation met the needs of physicians demands: use in emergency situations, better preservation without crystallization and a reducing of total volume injected and compact for easier to transport.

Furthermore, this preparation has other advantages: less adverse effect and a cost reduction, with the same or even better efficiency.