COLLOID THERAPY FOR CRITICALLY ILL PATIENTS

David Liss, BA, RVT, VTS (Emergency & Critical Care, Small Animal Internal Medicine)

Options for fluid therapy in critically ill patients have become more varied as market growth has added several products in the veterinary field.

Not only do several crystalloid products, such as Plasma-Lyte A pH 7.4 (abbottanimalhealth.com) and lactated Ringer’s, exist but there are various options for colloid therapy as well. Current synthetic colloid options in veterinary patients include:

- Dextran products
- Various hydroxyethyl starch formulations.

The hetastarch formulations are more commonly used and provide fewer side effects than the dextran family.

With the release of a new, veterinary-labeled synthetic hydroxyethyl starch product, VetStarch (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection; abbotanimalhealth.com), this brief review of synthetic colloids and colloid therapy will help you and your practice team make the best decisions for patients.

COLOID PHYSIOLOGY

In a patient’s natural physiology, albumin functions as the primary colloid that makes up colloid osmotic pressure. Albumin is a protein with diverse functions that helps maintain colloid oncotic pressure (COP) and bind endogenous and exogenous substances, such as bilirubin, calcium, and some drugs. The molecular weight of albumin is 69 kDa, which is comparatively smaller than the synthetic colloids often used in veterinary medicine, which range from 130 kDa (tetra starches) to 670 kDa (hetastarches).

In contrast to the natural colloid albumin, synthetic colloid solutions are made of sugar polymers of varying sizes suspended in a crystalloid fluid carrier. The products have a wide molecular weight range, but are most typically reported as molecular weight averages. This article will focus on the hydroxyethyl starch (HES) sugar molecules.

THREE MARKERS FOR COLLOID PHARMACOLOGY

1. **Mean molecular weight**: The average molecular weight of a solution
2. **Degree of substitution**: Degree of substitution of hydroxyl groups on glucose polymers with hydroxyethyl groups, which slows amylase metabolism
3. **C2:C6 ratio**: Organization of substitution on various carbon positions; affects pharmacology of solutions
Molecular Weight

HES molecules, which are derived from the sugar polymer amylopectin, have varied molecular weights. 1

- Molecular weight of the respective colloid formulation can greatly influence the half-life of the solution’s effects, as larger molecules are not freely filtered by the glomerulus in the renal tubule.
- Thus, larger molecules remain in circulation longer. 1

Metabolism

Various biochemical properties of the starches render them more resistant to the action of alpha-amylase, a circulating enzyme that metabolizes sugar molecules.

- Since amylase metabolism reduces the half-life of the product, slowing the rate of hydrolysis is beneficial.
- Substituting hydroxyl groups on the various glucose polymers with hydroxyethyl groups slows amylase metabolism, extending the life of the product. 1

Categories

The HES family has various subcategories, depending on the degree of substitution (of hydroxyl with hydroxyethyl groups) (Table 1). In addition to substitution degree, the organization of that substitution on various carbon positions, termed the C2:C6 ratio, affects the pharmacology of various solutions (Table 2).

<table>
<thead>
<tr>
<th>Hydroxyethyl Starch Nomenclature</th>
<th>Degree of Substitution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hetastarch</td>
<td>0.7</td>
</tr>
<tr>
<td>Hexasaccharide</td>
<td>0.6</td>
</tr>
<tr>
<td>Pentastarch</td>
<td>0.5</td>
</tr>
<tr>
<td>Tetrastarch</td>
<td>0.4</td>
</tr>
</tbody>
</table>

INDICATIONS FOR COLLOID THERAPY

There are 2 typical uses for colloids in veterinary medicine:

1. Fluid resuscitation during shock states
2. Continuous infusion during hypo-oncotic states.

Use During Shock States

Colloids are often utilized in hypoperfusion states after insults, such as sepsis, trauma, or hemorrhage. Colloids can provide a dramatic improvement in perfusion parameters (heart rate, respiratory rate, mucous membrane/capillary refill time, blood pressure, central venous pressure, lactate) after infusion of aliquots that are titrated to effect. 1

Crystalloid fluid doses of 60 to 90 mL/kg are administered in aliquots of 20 to 30 mL/kg for treatment of shock. The comparable dose for betastarch solutions is 15 to 20 mL/kg, administered in aliquots of 2.5 to 5 mL/kg. A crystalloid dose of 20 mL/kg provides approximately the same amount of volume expansion as a hetastarch dose of 5 mL/kg, but the colloid’s effects are likely to be sustained longer than those of the crystalloid.

During acute shock resuscitation, medium molecular weight colloids, such as the tetrastarches, may be more...
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 effective volume expanders than high molecular weight colloids due to their higher COP. These solutions also persist in the circulation for a prolonged period of time; however, they persist half as long as larger molecule hetastarch products.

Use During Hypo-Oncotic States

Patients with hypo-oncotic states, characterized by hyposalbuminemia or panhypoproteinemia, have an imbalance in intravascular and interstitial fluid movement and can be predisposed to interstitial and organ edema. Continuous infusions (CRIs) of HES colloids provide oncotic support until body proteins can be replaced.

CRIs of synthetic colloids are typically calculated based on the daily recommended maximum dose divided out over a specific time interval, most often 24 hours. High molecular weight colloids are typically infused at 1 mL/kg/H. The medium molecular weight colloids have a shorter half-life but there are currently no data regarding recommended doses for use in hypo-oncotic dogs and cats in the intensive care unit setting.

The maximum daily dosage recommendation for synthetic colloids is controversial at best. These doses are modeled from experimental studies in research animals and from human product labels due to the potential adverse risks seen at higher doses.

- Typically, **hetastarch products** are given at doses up to 20 mL/kg/day.
- In critical patients, however, the benefits of the product may outweigh the risks of higher doses. For instance, a dose up to 40 to 50 mL/kg/day of hetastarch may be needed to obtain the desired effects.
- **Tetraastarch products** are labeled for doses up to 50 mL/kg/day but, in my opinion, many patients do not require that high a dose.
- The initial dosing for a tetraastarch product is similar to that of a hetastarch, but the extended dose range is provided for patients that require higher doses or prolonged support on a CRI basis. There is less concern for adverse effects within that range due to the molecular characteristics of the product.

Human labeled hetastarches have a duration of action of approximately 24 to 36 hours in humans; human labeled tetrastarches have a duration of action of approximately 12 hours in humans. There are limited data available regarding half lives in other species.

Considerations

It may be necessary to reduce the rate of crystalloid infusions (for maintenance therapy) when both types of fluids are administered concurrently as risk for fluid intolerance increases when combining the two.

As with all plasma volume substitutes, overdosing can lead to overloading of the circulatory system. The use of any colloid is relatively contraindicated in the following conditions:

- Fluid overload (especially in cases of pulmonary edema and congestive heart failure)
- Renal failure with oliguria or anuria not related to hypovolemia

### Table 2. Hydroxyethyl Starch Colloid Solutions

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Solution Strength</th>
<th>Wt. Average Molecular Weight (kDa)</th>
<th>Molecular Weight Category</th>
<th>Degree of Substitution</th>
<th>C2:C6 Ratio</th>
<th>COP (mmHg)</th>
<th>Labeled for Veterinary Use?</th>
<th>Theoretical Ceiling Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hespan (bbraunusa.com)</td>
<td>6% HES</td>
<td>450</td>
<td>High</td>
<td>0.7</td>
<td>4:1</td>
<td>32.7 (+/- 0.2)</td>
<td>No</td>
<td>20 mL/kg/day</td>
</tr>
<tr>
<td>Hextend (hospira.com)</td>
<td>6% HES</td>
<td>670</td>
<td>High</td>
<td>0.75</td>
<td>4:1</td>
<td>37.9 (+/- 0.1)</td>
<td>No</td>
<td>20 mL/kg/day</td>
</tr>
<tr>
<td>VetStarch (abbottanimalhealth.com)</td>
<td>6% HES</td>
<td>130</td>
<td>Medium</td>
<td>0.4</td>
<td>9:1</td>
<td>37.1 (+/- 0.8)</td>
<td>Yes</td>
<td>50 mL/kg/day</td>
</tr>
<tr>
<td>Voluven (hospira.com)</td>
<td>6% HES</td>
<td>130</td>
<td>Medium</td>
<td>0.4</td>
<td>9:1</td>
<td>37.1 (+/- 0.8)</td>
<td>No</td>
<td>50 mL/kg/day</td>
</tr>
<tr>
<td>Albumin 5%</td>
<td>NA</td>
<td>69</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>23.2 (+/- 0.1)</td>
<td>Yes</td>
<td>NA</td>
</tr>
</tbody>
</table>

MEASURING COLLOID ONCOTIC PRESSURE

Colloid oncotic pressure (COP) can be measured by a colloid osmometry instrument to help guide use of colloids in practice. The device measures COP via injection of a blood sample into a chamber. After equilibration, the resulting pressure gradient is measured by a pressure transducer. The resultant COP can indicate whether goal directed therapy has been met for the patient. One commercial colloid osmometer is available (wescor.com/biomedical/osmometer/colloid.html), but the instrument is not often used other than in some referral practices and teaching hospitals.
Severe hypernatremia
Severe hyperchloremia
Intracranial bleeding.

SPECIFIC ADVANTAGES OF LOW MOLECULAR WEIGHT COLOIDS

Synthetic colloids, when administered in high doses, contribute to coagulopathies by diluting plasma coagulation factors. Beyond this expected mechanism, studies have documented the adverse effects synthetic colloids have on the coagulation system, most important, lowered efficacy of Factors VIII and vWF.²

These effects can cause concern for development or exacerbation of a coagulopathy, especially in a patient that may require surgery in the near future, and they represent the major driving factor for the theoretical “ceiling” dose of HES formulations with number average molecular weights > 200 kDa and molar substitution > 0.5,²

Colloids with a lower average molecular weight and substitution ratio but a high C2:C6 ratio have less, and potentially negligible, effects on the coagulation system.² This higher C2:C6 ratio allows for protection of oxygen bonds in the hydroxyethyl starch backbone, slowing the alpha-amylase metabolism of the product.

Thus, these products have an appropriate half-life for acute volume expansion in cases of shock and their smaller size does not produce detrimental coagulopathic side effects. Due to these reduced side effects, they may be administered safely in cases of coagulopathic patients in shock or patients who may require surgical procedures after resuscitation with colloids.¹,²

These products can be safely administered up to 50 mL/kg/day.²

IN SUMMARY

- Colloid solutions are effective volume resuscitators during shock states. Because they capitalize on COP, significantly less volume can be administered while achieving excellent volume expanding effects.
- While all of these products cause some degree of coagulation system disruption, those with lower average molecular weights and substitution degrees have a wider safety profile.
- However, due to the shorter half-life of low molecular weight starches, higher doses appear to be required for maintenance CRIs in the intensive care unit when compared with high molecular weight starches.

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CRI = constant rate infusion; COP = colloid oncotic pressure; HES = hydroxyethyl starch

References

David Liss, BA, RVT, VTS (Emergency & Critical Care, Small Animal Internal Medicine), serves as the Program Director for the veterinary technology program at Platt College in Los Angeles, California. He has authored over 15 articles on emergency, critical care, and internal medicine topics and has presented nationally and internationally on fluid therapy. Mr. Liss’ areas of interest include fluid therapy in critically ill patients, nursing of the critically ill patient, and critical care syndromes, such as sepsis and systemic inflammatory response syndrome.