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SUBJECT: Hextend® use with Dehydration

CONCLUSION

Combat life saver treatment of combat casualties with significant hemorrhagic or head injury requires focused and immediate management. As a plasma volume expander, Hextend® more effectively maintains intravascular and large organ perfusion than crystalloid resuscitative fluids (normal saline and Ringer's lactate). Furthermore, Hextend® is not considered to be contraindicated if dehydration coexists with decreased mental status and/or absence of radial pulse in a combat casualty with a significant extremity, trunk or head traumatic injury.

BACKGROUND

1. Hextend® (6% Hetastarch in Lactated Electrolyte Injection) is FDA approved for the treatment of hypovolemia when plasma volume expansion is desired.[i] The 6% hetastarch acts as an oncotic agent to permit retention of intravascular fluid until the hetastarch is replaced by blood proteins. The lactated electrolyte solution is an isotonic electrolyte solution with physiological sodium, chloride and calcium levels; and slightly lower than normal physiological potassium and magnesium levels. Hextend® also contains dextrose (99 mg/100mL) and lactate (28 mEq/L).

2. Hextend® has recently been selected to replace other resuscitative fluids (e.g., normal saline and/or lactated Ringer's solution) in the Combat Life Saver (CLS) bag for the treatment of casualties with significant trunk or extremity injuries.[ii] The 25 July 2005 revision to the CLS training manual directs intravenous administration of Hextend® to trauma casualties presenting with hypovolemic shock who also have either decreased mental status and/or absence of a radial pulse.

3. A contraindication listed on the FDA approved label reads as follows: "Solutions containing lactate are NOT FOR USE IN THE TREATMENT OF LACTIC ACIDOSIS." This same provision is on each bag of LR.

4. Some medical personnel at both TRADOC and non-TRADOC sites have replaced Hextend® in CLS bags with normal saline. These replacement decisions were apparently based on the following rationale:
   a. Combat life savers providing medical support at TRADOC installations are unlikely to see combat casualties, and are much more likely to see dehydration and/or heat casualties. Lactic acidosis is listed as a contraindication for this product, and heat casualties may also have elevated lactic acid levels with rhabdomyolysis (25%) and/or renal failure (13%)[iii].
   b. Theoretical risk that a plasma expander may draw intracellular fluid (ICF) from vital organs into the intravascular space and thereby aggravate heat injuries within the tissues and organs.
   c. Theoretical inferiority to normal saline as a total body water rehydrating agent.

USARIEM OPINION ON HEXTEND® SAFETY CONCERNS IN DEHYDRATION

1. Is Hextend® contraindicated during heat injury/stroke when lactic acidosis or rhabdomyolysis are present? All FDA approved label contraindications are intended to prompt consideration of a patient's clinical condition when making risk versus benefit decisions of appropriate interventional therapy. In the 25 Jul 05 CLS training curriculum, Hextend® is only directed as a resuscitative fluid in the setting of a hemorrhagic injury with either decreased mental status and/or absent radial pulse. In this clinical setting, we consider restoration of intravascular perfusion to the brain to take a higher clinical priority over avoiding any remote possibilities of worsening any co-existing acid-base disturbances. In fact, one limited animal study at Letterman Army Medical Center demonstrated that solutions containing lactated Ringer's solution actually alleviate lactic acidosis in hemorrhagic shock.[iv] Another study by Hoyt suggested that NS is inferior to LR because of the resulting hyperchloremic metabolic acidosis. Therefore, any concurrent lactic acidosis due to pre-existing dehydration and/or heat injury in a combat casualty is not expected to be the critical determinant of survival, and therefore takes much lower priority to restoring adequate intravascular perfusion with Hextend®.

2. Could Hextend® aggravate heat injury / stroke? There are no specific clinical studies which evaluate the use of Hextend in hemorrhagic patients who also have co-existing heat injury / stroke. However, one small rodent study reports increased efficacy of Hextend over normal saline for prolonging survival in heat injured rats.[v] In the absence of stronger experimental evidence, the risk of aggravating heat injury / stroke can be considered from a fluid balance perspective. A 500 mL Hextend® infusion provides much of the water needed to support the plasma volume expansion, and it does not draw greatly from extravascular water. An average soldier's body is made up of ~ 45 L of total body water (TBW), of which ~30L are intracellular fluids (ICF). According to a recent Institute of Medicine report, if that soldier was severely dehydrated (8% of body weight), their TBW and ICF would be reduced to ~42 L and ~27 L, respectively. In a traumatically injured and hypotensive combat casualty with decreased mental status and/or absent radial pulse, the oncotic pressure gradient between the intravascular and extravascular spaces is expected to draw in less than 300 mL of extravascular fluid for every 500 mL of Hextend® that are administered intravascularly. As a worst case scenario, if all of the 300 mL fluid loss from the extravascular space came from the ~ 27L of intracellular space in a 8% dehydrated patient, this 300 mL represents a mere 1% of that ICF fluid volume, and is not expected to be clinically significant. Therefore, limited animal data and theoretical fluid balance calculations suggest that Hextend® will not aggravate any co-existing heat injury / stroke.

3. Does Hextend® rehydrate as effectively as saline? If total body water rehydration in the absence of hemorrhagic shock is desired, crystalloids such as normal saline and/or Ringer's lactate solution might be preferred. The mechanism of action of Hextend® centers on its creation of an oncotic gradient for expanding plasma volume, whereby a greater percentage of the infused fluid stays within the vascular space and does not leak out into the extravascular spaces. Therefore, less fluid

would be available to rapidly rehydrate the extravascular volumes in the extracellular fluid (ECF) and intracellular fluid (ICF) spaces. However, plasma volume expansion with Hextend® will support improved cardiovascular stability in dehydrated soldiers. Therefore, by their mechanism of action, plasma volume expanders such as Hextend® are not as effective as saline to rapidly and uniformly rehydrate all fluid spaces in dehydrated soldiers, but also are not expected to cause harm and are expected to be superior than delivery of no intravenous solution at all.

4. What is the optimal resuscitative fluid for a heat casualty? Oral fluid consumption should be the first option of rehydration therapy when soldiers are conscious and can tolerate fluid ingestion.[vi] If soldiers require rapid rehydration without trauma/ hemorrhage, then saline infusion would be optimal. If soldiers are unconscious and trauma/hemorrhage is suspected / known, then Hextend® should be the first choice for infusion therapy. If heat injury / dehydration is present in soldiers with trauma/hemorrhage, Hextend® can be administered initially, with subsequent delivery of clinically appropriate intravenous fluids at higher levels of care for reestablishment of normal total body water and acid-base balance.

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[i] FDA Package Insert, http://www.biotimeinc.com/HextendPI4pageHospiraApr04.pdf.
[ii] Combat Lifesaver Course: Student Self-Study, IS0871, "A" edition, 25 July 2005.
[iii] Carter R et al, Epidemiology of hospitalizations and deaths from heat illness in soldiers. Medicine & Science in Sports & Exercise. 37(8):1338-1334, 2005.
[iv] Yuan XQ and Wade CE, Lactated Ringer's solution alleviates brain trauma-precipitated lactic acidosis in hemorrhagic shock. Journal of Neurotrauma. 10(3):307-13, 1993.
[v] Liu et al, Hydroxyethyl starch produces attenuation of circulatory shock and cerebral ischemia during heat stroke. Shock. 22(3):288-294, 2004.
[vi] TBMED 507, Heat Stress Control and Heat Casualty Management, http://www.usariem.army.mil/download/tbmed507.pdf.