Blood substitutes are gasping for air

A dreaded nightmare for any developer of a novel biological product is that as one learns more about the properties of the product, more questions are raised than are answered, especially when the product enters clinical testing. Such a nightmare is now a reality for the researchers at the Blood Research Detachment, Walter Reed Army Institute of Research in Washington, DC, who are attempting to develop a practical blood substitute as an alternative to donated blood for treating severely wounded soldiers on the battlefield.

A series of articles recently published by Colonel John R. Hess, head of Walter Reed's blood research group, conclude that the numerous toxicities associated with current blood substitute products (such as hemoglobin-based oxygen carriers, or HBOCs, and perfluorocarbon emulsions, or PFCs) caused the Army to discontinue their internal development of a blood substitute product last January. Hess notes that "the US Government invested $100 million over the past 30 years, and private industry spent $500 million in the past decade" in pursuit of both HBOCs and PFCs as blood substitutes. In addition, pharmaceutical and biotech companies have been aggressively developing HBOCs and PFCs as oxygen-carrying therapeutics.

Free hemoglobin solutions have a history of toxicities associated with their development as oxygen-carrying agents. For example, in the early development stages of HBOCs, contamination of red cell stroma in a preparation was identified as the culprit for causing toxic side effects in subjects infused with free hemoglobin solutions. However, infusion of ultrapure, stroma-free hemoglobin solutions in healthy subjects still caused renal toxicity in many cases. Glomerular nephritis observed in infused subjects was attributed to the dissociation of the hemoglobin tetramer into heterodimers that precipitated within the proximal renal tubules, causing cellular damage. Subsequent generations of HBOCs have been chemically modified and stabilized by covalently linking the two dimers, as well as by increasing molecular size to enhance its retention. In addition, Somatogen, Inc. (Boulder, [CO]) has engineered a recombinant hemoglobin molecule (rHb1.1/Optro).

Last August, at the VI International Symposium on Blood Substitutes in Montreal, Canada, Duke University's B.J. Leone reported in a ten-patient study that Somatogen's Optro was well tolerated in a dose ranging study to replace the blood volume during acute hemodilution in patients undergoing hip or knee arthroplasty surgery. Leone further noted that three out of the seven treated patients were hypertensive and two patients had elevated levels of serum lipases and amylases at the higher dose, but apparently without any symptoms suggesting acute pancreatitis.

But Hess also noted that free hemoglobin was found to be neurotoxic, and could cause seizures when the cerebral cortex was exposed. Free hemoglobin also enhanced the toxic effects of endotoxins and potentiated lethal bacterial infections.

PFCs appear to have their own unique set of clinical performance and toxicity problems. Clinical studies with first generation emulsions induced hypertension and fever that are associated with the activation of both complement and the reticuloendothelial system (RES). Some of the clinical symptoms associated with RES activation by PFCs include fever, thrombocytopenia and tachycardia.

Ironically, although newer generations of PFCs have been modified to reduce a few of their proinflammatory properties, in the process they have shorter organ dwell time and can compromise lung function (such as breathing and gas exchange) as they are being cleared by the body. Since these PFCs leave the body primarily via the lungs as a volatile gas during exhalation, some of the compound is entrapped within the interstitial space of the lung as gas bubbles to produce a rigid lung and induce hyperinflation.

With the current knowledge of toxicities associated with oxygen-carrying blood substitutes, a few biotech and pharmaceutical companies are still making a strong commitment to their development programs and are forging ahead to develop a marketable product. For example, Northfield Laboratories, Inc. (Evanston, IL) and Baxter Intl. (Deerfield, IL) are currently in Phase II clinical testing with their polymerized hemoglobin (PolyHeme) and diaspirin crosslinked hemoglobin (DCHB), respectively, as resuscitating agents.

However, Hess warns that "these materials have complex interactions with biological systems," and says that "the toxicity and pharmacological limits of the present generation of red blood cell substitutes will prevent their wide use in resuscitation." If Hess' predictions become a reality, the current generation of oxygen-carrying resuscitating agents may indeed be gasping for oxygen.

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