**Hemoglobin-based Oxygen-carrying Solutions**

**Close But Still So Far**

MULTIPLE approaches are important when attempting to limit allogeneic blood transfusions. My interest in developing strategies to decrease bleeding and transfusion requirements started in the early 1980s, when I was evaluating perioperative anaphylaxis and noted that transfused blood was an important cause of life-threatening hypersensitivity reactions.¹ There are multiple reasons to reduce transfusions in addition to the risk of reactions and transfusion-related diseases. Blood products are in limited supply; they incur significant costs, expose patients to a variety of potential cellular and humoral antigens, and may alone produce either proinflammatory or even immunosuppressive responses.¹⁻⁴ A spectrum of immune alterations that persist for months has been reported after transfusion with allogeneic blood.⁴ Even several milliliters of plasma present in packed erythrocytes contain sufficient numbers of donor leukoagglutinin antibodies to produce transfusion-related acute lung injury.²⁻³

In this issue of *Anesthesiology*, Lamy et al.⁵ report their multicenter randomized trial of diaspirin cross-linked human hemoglobin solutions as a potential alternative to blood transfusion after cardiac surgery. They note that administration of the hemoglobin-based oxygen-carrying (HBOC) solution was able to reduce the need for transfused allogenic packed erythrocytes. This finding is interesting in view of the relatively short half-life of diaspirin cross-linked hemoglobin, and its ability to reduce transfused blood cannot be explained on duration of action only.

One of the potential mechanisms by which HBOC solutions may be effective in reducing transfused blood may be a result of the fact that in hemorrhagic conditions, replenishing lost iron is difficult. Administering either oral or intravenous iron to patients is not well tolerated, free iron is toxic, and iron-containing parenteral solutions, usually bound to dextrans, have the potential to produce anaphylactic reactions.⁶⁻⁷ Although the oxygen-carrying capacity of most HBOC solutions may be quite transient, they are rapidly metabolized, and free iron is potentially scavenged by multiple mechanisms to subsequently stimulate erythropoiesis and reticulocytosis. This may explain why patients were discharged with similar hematocrits in both groups, despite the reduction in transfused allogenic packed erythrocytes in the HBOC-treated patients.

Unfortunately, diaspirin-linked HBOC solutions have been abandoned because of a higher mortality that was reported when studying these solutions in trauma patients. Regrettably, the trauma patient population is a heterogeneous group of patients, and similar to therapeutic trials in sepsis, trauma patients represent a group with an extremely high morbidity and mortality incidence that can potentially complicate interpreting data. As Lamy et al. report, an elective cardiac surgical population represents a better alternative, in which there is an established incidence of adverse events that can be easily quantified.

Based on this consideration, there are complex regulatory issues surrounding the actual approval of artificial blood products. Do the HBOC solutions need to be as good as or better than packed erythrocytes as an oxygen carrier? I believe it is important that studies of blood substitutes demonstrate that they can reduce the need...
for allogenic transfused blood as a determining factor for whether these agents will be approved. Another important point regarding regulatory approval of HBOC solutions includes safety. Safety studies are expensive to undertake. Although companies show "safety" in one setting and label the drug accordingly, the market place uses the drug in populations in which safety information is often unavailable.

Another important issue involving the future of HBOC solutions includes cost and availability. Current limitations include the accessibility of human hemoglobin derived from outdated banked blood, an unlikely source to provide an adequate amount of hemoglobin for commercial purposes. Recombinant DNA technology could ultimately produce modified human hemoglobin molecules.\textsuperscript{8,9} It seems unlikely that 30 g of recombinant proteins can be manufactured to sell at a cost that is close to the current price of a unit of packed erythrocytes. The ability to economically manufacture large quantities of proteins using transgenic technology is potentially feasible, and initial transgenic studies have been reported for antithrombin III.\textsuperscript{10} Bovine hemoglobin represents an interesting alternative that is currently in phase III studies.\textsuperscript{8,11} The major advantage of bovine hemoglobin is its availability and large quantity. A 500-kg steer has approximately 35 l of blood containing approximately 12 g/dl of hemoglobin, for approximate total-body hemoglobin content of 4.2 kg.\textsuperscript{8} Furthermore, bovine blood is a byproduct of most slaughterhouses and is available as an unlimited supply. Hemopure, a bovine product, is currently approved for veterinary use.

The availability of potential replacements for blood products represents a very important consideration. In some parts of the world, the donor patient pool has an inordinately high incidence of human immunodeficiency virus infections, hepatitis C, or malaria. Therefore, having a potential safe unlimited replacement for erythrocytes represents an important goal.

One additional concern regarding HBOC solutions is their potential ability to scavenge nitric oxide.\textsuperscript{12,13} Even in the study reported by Lamy \textit{et al}.,\textsuperscript{5} there were increases in systemic and pulmonary artery pressures. The ability of the ferric group of iron in free hemoglobin to scavenge nitric oxide from vascular endothelium represents a potential risk factor that additional data from large patient populations will have to answer. Although this has been suggested to be a potential problem, there were no adverse outcomes reported by Lamy \textit{et al}.

regarding excessive nitric oxide scavenging. Perhaps in certain inflammatory disease states, such as the systemic inflammatory response syndrome, this additional nitric oxide–scavenging capability may prove useful to attenuate mediator-induced vasodilation.\textsuperscript{1}

One day, perhaps the HBOC solutions will provide us with the ability to replace intravascular volume in cases of hemorrhagic shock and maintain oxygen delivery until surgical repair can occur. The HBOC solutions may have life-saving benefits in military and other applications. Clinical studies to allow regulatory approval of select HBOC solutions for clinical uses are still in progress. In the meantime, cardiac and orthopedic surgical patients are an important group to evaluate in clinical trials. The current data by Lamy \textit{et al}. is very important in supporting both the safety and efficacy of these agents. The incidences of adverse events were similar in both groups, and the ability of HBOC solutions to decrease the need for donor erythrocytes is a promising finding. Additional studies will be required to have these agents readily available. At the present time, we are so close but still so far.

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\textbf{References}


**Location, Location, Location**

THE three most important things in real estate are location, location, and location. In this issue of Anesthesiology, Ummenofer et al. show that the same is true for intrathecal drug delivery. The spinal space is not pharmacokinetically homogenous in the way that the arterial blood is homogenous. Because of the homogeneity of arterial blood, the pharmacokinetics observed in samples from the radial artery will be the same as those observed using samples from the dorsalis pedis artery. As a result, the physiologic complexity of the body almost magically resolves into the simple mammillary compartment model. The “simple” intrathecal space does not easily resolve into mammillary models. The slow flow of drug in the spinal space, combined with the rapid uptake by intrathecal tissues, produces large drug gradients within the intrathecal space. These gradients affect both the therapeutic dose and the intrinsic safety of intrathecally administered drugs. In 1977, Partain et al. represented spinal pharmacokinetics using eight sequential compartments. Recently, we turned to diffusion equations, with distributional components, to represent the spread of drug through the cerebrospinal fluid (CSF).

The model of Ummenofer et al. pushes the envelop further, using 20 compartments to describe the intrathecal pharmacokinetics of morphine, fentanyl, alfentanil, and sufentanil. Because their model incorporates nonhomogenous drug distribution within the CSF, we can use it to explore doses and relative safety.

We used NONMEM (University of California, San Francisco, CA) to find the infusion profile of morphine, fentanyl, alfentanil, and sufentanil, administered at L2–L3 that would produce a steady concentration of 1 μmol/l in CSF at L2–L3 and T7. The results for morphine and sufentanil are shown in figure 1. Not surprisingly, the infusion rate initially starts off high and decreases steadily over the first hour. Figure 1 demonstrates the expected effects of lipophilicity and how distance from injection site magnifies the lipophilic effect. The sufentanil infusion rate is approximately 10-fold higher than the morphine infusion rate when drug is being given at L2–L3, and L2–L3 is the target spinal level. Changing the target spinal level to T7 increases the morphine and sufentanil infusion rates by 200- and 3,000-fold, respectively. One can similarly calculate that changing the target from L2–L3 to T7 increases the infusion rates for alfentanil and fentanyl 300- and 2,400-fold, respectively. This simulation shows that it is theoretically possible to infuse opioids to obtain a steady drug concentration in the CSF at any level. It also shows that location matters: far more opioid is required to reach the same concentration of drug when the site of infusion is distant from the target tissue.

Similarly, the models permit us to analyze safety during continuous drug administration. Figure 2 shows the con-