NEWS

Not Blood Simple

After decades of setbacks, compounds that act like blood to deliver oxygen are in the final stretch of clinical trials

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Until March 1998, Baxter Healthcare Corp. thought it had a sure-fire winner. The Deerfield, Illinois, company was in phase III trials of HemAssist, an oxygen-carrying solution designed to treat patients in shock from massive bleeding. Analysts were excited because blood substitutes—more accurately known as oxygen therapeutics—could be stockpiled and given to anyone regardless of blood type.

But after enrolling about 100 people who had been knifed, shot, or critically injured in car accidents, Baxter discovered that the patients given HemAssist were more likely to die than those given regular blood. "They pretty much had a disaster," says Reuven Rabinovici, chief of trauma and surgical critical care at Yale University School of Medicine. Baxter called off the trial. And although the problem may have been faulty trial design rather than HemAssist itself, the company soon ditched its decade-long development effort.

Most clinical testing involves disappointments, but blood substitutes have had a particularly tortured history. Four decades after research began, the U.S. Food and Drug Administration (FDA) has approved only one blood substitute—for treating anemia in dogs. Longtime researchers say the main reason for the delay is the complexity of hemoglobin and its sometimes surprising effects on humans when it's not ensconced in red blood cells. Also contributing to the rocky progress are the challenges of regulating a novel type of material, as well as ups and downs in Wall Street enthusiasm. A handful of companies persevere, predicting an ever greater need for blood substitutes as growing numbers of elderly patients needing blood-intensive surgery such as hip repairs or replacements strain the existing donor supply.

Scientists began working on artificial blood in the 1960s, trying to see whether iron-rich hemoglobin molecules extracted from red blood cells would be able to pick up oxygen molecules and deliver them to tissues when transfused into a patient. Those early compounds ran into problems with kidney toxicity. Work took off in the 1980s, with the realization that HIV, the virus that causes AIDS, had contaminated the blood supply. "The urgency was such that industries tried to bypass basic research and proceeded immediately into development and clinical trials," recalls blood substitute pioneer Thomas Chang of McGill University in Montreal. This generation of compounds constricted blood vessels and capillaries, which can limit circulation to oxygen-starved tissue.

Half of the companies with compounds in advanced trials still report vasoconstriction. The reason is not entirely clear, but many researchers suspect that these compounds penetrate the lining of the blood vessels and scavenge nitric oxide (NO), a molecule that would otherwise relax the muscular walls surrounding blood vessels. Others believe that excessive diffusion of hemoglobin within the vessel is the key. In any case, scientists have reduced this problem—in animal studies and early human trials—by modifying or clumping hemoglobin molecules to make them larger. Meanwhile, Baxter is working on recombinant human hemoglobin that doesn't scavenge NO.

Harvey Klein, chief of transfusion medicine at the National Institutes of Health's (NIH's) Clinical Center in Bethesda, Maryland, says he is less worried about vasoconstriction than he is about the incomplete understanding of why the side effect occurs: "It's telling us that something is happening at a basic level that might cause other problems." Other experts stress that more needs to be known about how modified hemoglobin delivers oxygen to tissue before an ideal substitute can be designed.

The novelty of blood substitutes has also raised questions about how to test them for efficacy and safety. "There is no golden standard to compare blood substitutes to," says Konrad Messmer, a professor of experimental surgery at Ludwig Maximilians University in Munich, Germany. (FDA uses surrogate endpoints, such as a decreased need for transfused blood.)

Another concern is the source of the hemoglobin. Most products in advanced trials purify hemoglobin from collected human blood that has passed its expiration date. In contrast, Hemopure, made by Biopure Corp. in Cambridge, Massachusetts, is made from cow blood. Biopure says it uses only U.S. cattle bound for slaughter and controls their feeding and care. The company says its manufacturing process removes any infectious agents that might slip through, such as the prions implicated in bovine spongiform encephalopathy, or mad cow disease. Last April, Hemopure was approved for anemia during surgery in South Africa.

For products further upstream, investment capital is harder to come by now that the blood supply is more safe from HIV. "Fifteen years ago, there was almost a bottomless well of capital," says Robert Winslow of Sangart Inc. in San Diego. "The capital markets for this have almost dried up." Sangart relies heavily on NIH funding and is planning a phase I trial in Sweden for a hemoglobin molecule modified with strands of polyethylene glycol, designed to protect the molecule and prevent vasoconstriction. The Defense Advanced Research Projects Agency is also in the game, funding research into freeze-dried blood products, for example.

Any new products that reach the market will have to compete with actual blood, Winslow notes, which is now very safe. If blood substitutes are approved in the United States for human use, they're likely to fetch a premium over blood, which can cost hospitals $200 or more per unit. Biopure hasn't set a price yet but estimates that each unit will sell for perhaps $700 to $1000. Whatever the cost, researchers and clinicians want to have supplies of blood substitutes stocked for emergencies—including the discovery of new infectious agents in donated blood. **–ERIK STOKSTAD**

BLOOD SUBSTITUTES IN ADVANCED CLINICAL TRIALS*

Product (Company)	Source	Use	Half-life†	Shelf life	Side effects‡
Hemopure (Biopure)	Modified bovine hemoglobin	Elective surgery	24–36 hours	2 years at room temperature	Vasoconstriction, transient increase in liver and pancreas enzymes
PolyHeme (Northfield Laboratories)	Modified human hemoglobin	Trauma, urgent blood loss	24 hours	1 year refrigerated	None reported
Hemolink (Hemosol)	Modified human hemoglobin	Heart surgery	18–20 hours	1 year refrigerated	Vasoconstriction, yellowing of skin
Oxygent (Alliance)	Perfluoro-chemical emulsion	General surgery	24–48 hours	2 years refrigerated	Slight rise in body temperature, drop in platelet count

* In the United States. † Dose-dependent. ‡ All transient.