



e-Network Forum

CALIFORNIA BLOOD BANK SOCIETY

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Updated information regarding 'Blood Substitutes'

A colleague is interested in updated information regarding 'Blood Substitutes'. Her interest in this topic arose shortly after caring for a young man diagnosed with Autoimmune Hemolytic Anemia. The patient received [Polyheme \(Northfield Labs\)](#) through a compassionate use approval by an Institutional Review Board.

Unfortunately, the patient died due to his underlying pathology. The inquiring colleague would be grateful if the e-network could assist by providing relevant information on the current status of blood substitutes, including recently published journal articles or web sites. She realizes that the upcoming conference on 'Oxygen Therapeutics' (May 30-31, 2002) would be a good source of information, but unfortunately, she cannot attend (see [ADDENDA June 10](#), below; highlights of this conference are also reproduced here on a [separate page](#)).

The following responses have been submitted:

1. **A Canadian blood banker** wrote that there is a Canadian company, Hemosol, that is doing clinical trials in the US on **Hemolink**, its blood substitute product. Information about the product, company and trials can be found on their [website](#).

ADDENDA June 3, 2002

2. **A blood bank physician in 'Chicagoland'**, in response to the individual who asked for references to update the topic of RBC substitutes and oxygen therapeutics, offered the following:

- Squires JE. Artificial Blood (viewpoint). *Science* 2002;295:1002-05.
- Hill SE. Oxygen therapeutics - Current Concepts. *Can J Anaesth.* 2001;48(4 Suppl)S32-40.
- Creteur J, Sibbald W, Vincent J-L. Hemoglobin solutions - Not just red blood cell substitutes. *Crit Care Med.* 2000;28(8)3025-34.
- Winslow RM. Red Cell Substitutes. In Anderson KC and Ness PM (eds.), *Scientific Basis of Transfusion Medicine*, 2nd Edition, Philadelphia, PA WB Saunders Co, 2000, pp 588-98.

ADDENDA June 10, 2002

3. The following are Highlights from the **AABB Oxygen Therapeutics Conference, Part I** (source *AABB Weekly Report*, Volume 8, Number 20 June 7, 2002).

In 1937, **W.R. Amberson, MD**, wrote that while "there is no complete substitute for blood " Biologists and physiologists, no less than clinicians, are so frequently confronted with situations where normal blood cannot be obtained, or where the problem at hand can only be solved by a simplification of conditions, that a substitute for blood has become one of the most pressing needs of the experimental laboratory."

More than six decades later, several blood substitute products - more accurately called oxygen therapeutics or oxygen carriers - are in the late stages of research and development. In preparation for the emergence of this totally new class of oxygen delivery agents, AABB from May 30 to 31 held an Oxygen Therapeutics and Transfusion Alternatives Conference to educate the blood banking and transfusion medicine communities about oxygen therapeutics and their potential uses in clinical practice.

"Oxygen therapeutics have great potential to treat a wide variety of illnesses, not just to replace red cells," said **Harvey Klein, MD**, chief of the Department of Transfusion Medicine at the National Institutes of Health (NIH), and conference co-moderator. "With several [products] in clinical trials, it is timely to review their use. It also is important that the users understand their indications, potential side effects, and benefits."

Oxygen Therapeutics - The Basics

Oxygen therapeutics are agents designed to sustain life by delivering oxygen to tissues and organs in need due to blood loss during surgery, life-threatening blood loss, or other situations in which the body may be experiencing diminished oxygen delivery. In a healthy individual, the hemoglobin within the red blood cells (RBCs) carries oxygen to all areas of the body. However, when the blood's ability to perform this function is compromised either through blood loss or reduced blood production due to disease, there is a need to therapeutically enhance oxygen delivery to the tissues.

"There are certain situations where there is an unmet medical need for the treatment of acute anemia, and we're on the verge of fulfilling that need," said **Aryeh Shander, MD**, director of the Institute for Bloodless Surgery at Englewood Hospital in Englewood, N.J. "Oxygen therapeutics will enhance the clinician's ability to treat acute anemia because these agents deliver oxygen to the tissues in an efficient manner. Oxygen therapeutics currently are in late-stage clinical trials and may be available in the next two years in North America, and potentially sooner in Europe."

Oxygen therapeutics molecules are a fraction of the size of a RBC and are carried in plasma, outside of red blood cells. Because of this, oxygen therapeutics are in immediate contact with tissue and can supply oxygen evenly along capillaries.

Experts currently are studying whether oxygen therapeutics can deliver oxygen more efficiently than RBCs, since the oxygen therapeutics may pass obstructions that block RBCs, such as blood clots, clogged arteries and fat emboli. Furthermore, oxygen therapeutics have a longer shelf-life than blood products and do not require typing and cross-matching because they are free of the cell-surface antigens that can cause transfusion reactions.

It is important to emphasize, however, that oxygen therapeutics are not intended to replace blood. "Oxygen therapeutics are not 'artificial blood' or 'fake blood' or even 'blood substitutes' ", said **Karen Shoos Lipton, JD**, chief executive office of AABB. "Oxygen therapeutics perform a very important function of blood by delivering oxygen in the body. However, these agents do not perform the many other functions of blood, such as fighting infection and coagulating blood during wound healing."

The 'Ideal' Oxygen Therapeutic

According to Shander, the ideal oxygen carrier not only has a high oxygen-carrying capacity, but also has the ability to deliver oxygen at the tissue level under pO₂, possesses desirable elimination characteristics, and has a long intravascular half life. "Oxygen therapeutic products should have oncotic, osmotic, and rheologic properties similar to those of blood," said Shander. "They should be both stable during sterilization and storage, and should be easy to obtain in large quantities." Furthermore, it is important that such products have a low incidence of side effects. For example, oxygen therapeutics should have no toxicity, antigenicity, or immunomodulation effects.

Potential Uses

Potentially, oxygen therapeutics could be used during trauma and elective surgeries to treat patients with allo or auto antibody problems, or who have sickle cell anemia, and to treat organ perfusion or ischemia, said **Paul Ness, MD**, director of transfusion medicine at Johns Hopkins Hospital in Baltimore, Md., and co-moderator of the conference.

Ness said the current trend toward increased demand for blood that is straining the nation's supply might be eased by the complementary use of oxygen therapeutics. According to Ness, factors that contribute to increased blood demand include an aging population that requires more cardiac surgeries and cancer therapies; less reliance on autologous transfusions due to increased confidence in the safety of the blood supply after the HIV/AIDS scares of the 1980s; an increase in invasive, 'redo' surgeries, which frequently require more blood than the first time surgery was performed; and new indications for transfusion, such as sickle cell stroke and prophylaxis.

"We are at a pivotal point in trying to determine the role oxygen therapeutics will play in the future of the blood supply," said Ness. "One of the greatest triumphs of the last few years has been being able to offer our patients transfusion alternatives. Oxygen therapeutics may prove to be an important alternative to traditional transfusion that will broaden the choices available to patients and doctors."

Hemoglobin-Based Oxygen Carriers vs. PFCs

Oxygen therapeutics can be derived from hemoglobin, called hemoglobin-based oxygen carriers (HBOCs), or can be synthetically produced, called perfluorocarbon emulsion-based carriers (PFCs).

HBOCs are purified by pasteurization and ultrafiltration, and are chemically modified to reduce the risk for bacterial or viral disease transmission. HBOCs depend on the chemical and physical properties of hemoglobin to bind and release oxygen under specific physiological conditions. Potential sources of acellular hemoglobin for the preparation of HBOCs include outdated human

Red Blood Cells, bovine hemoglobin and recombinant technologies using a non-mammalian expression system, such as e.coli.

In the 1960s and 1970s, scientists began researching hemoglobin-based products that led, in 1981, to the development of a 'resuscitation fluid' used by the United States armed services, according to **Joseph Fratantoni, MD**, vice president of medical affairs and clinical development at MaxCyte Inc. in Rockville, Md. Beginning in the late 1980s and early 1990s, several companies conducted safety trials using modified hemoglobin-based products, which continue to the present time.

Northfield Laboratories of Evanston, Ill. and Hemosol, Inc. of Toronto, Canada., both are in late-stage human clinical trials for their HBOC products. (More information on these products will be provided in **Part II** of this series, in the June 14 issue of Weekly Report.)

PFCs are synthetic fluorinated hydrocarbons that have a high intrinsic solubility for gases and can increase dissolved oxygen in the fluid phase of the blood without binding the oxygen molecule. Medical PFCs used to make emulsions for oxygen therapy do not require any further purification or processing. PFC emulsions can be administered intravenously to enhance oxygen delivery to tissues. They also may be beneficial to augment normovolemic hemodilution, a technique used to reduce surgical blood loss. PFC-based oxygen carriers do not contain blood products and can be stored for up to two years if refrigerated, and for several weeks when stored at room temperature.

In 1967, a landmark experiment showed that emulsified PFCs were smaller than RBCs and allowed oxygen delivery to areas that RBCs could not reach. Subsequently, a perfluorocarbon-based product called Fluosol was approved in 1987 by the Food and Drug Administration (FDA) for use during angioplasty. "In 1983, FDA had rejected an approval application for use of Fluosol as a blood substitute because the product did not provide enough benefit to get patients through surgery," said Fratantoni.

Fluosol, which had been produced by the Green Cross Corporation of Japan, eventually was discontinued due to lack of demand. In the 1990s, second generation PFCs were developed and studied in clinical trials by Alliance Pharmaceutical Corporation of San Diego, Calif. (More information on Alliance Corp.'s PFC product will be provided in **Part II** of this series, in the June 14 issue of Weekly Report.)

Please submit comments to the [e-Network Forum](#).



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Posted: May 31, 2002

Addenda: June 3 & 10, 2002

Link Update: Sept. 27, 2004;
Mar. 3, 2006; Jan. 2, 2007

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