Oxygen Therapeutics: Perfluorocarbons and Blood Substitute Safety

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KEYWORDS

- Blood substitute • Perfluorocarbons (PFC)
- Hemoglobin-based-oxygen-carrier (HBOC)

The United States health care system depends on access to a blood supply that satisfies two important, but potentially conflicting, goals: safety and availability. Our donor-based system has demonstrated resilience in handling challenges as varied as seasonal shortages in supply to safety risks presented by emerging infectious diseases. Although we can be confident in future innovations in blood supply management, the aging United States population will present twin challenges to our system. First, as procedure volumes increase to care for senior citizens, demand for blood components will increase. Second, the availability of blood components could be challenged as the donor pool shrinks; younger generations have yet to demonstrate the altruism of blood donation shown by their forebears.

Although the need for a blood substitute has become more urgent, the clinical usefulness of blood substitutes has encouraged centuries of exploration. Early recorded efforts included the use of milk and wine as blood substitutes. The use of animal blood in transfusions was explored more recently with no success.[1–3] Subsequent initiatives led by the military (seeking a battlefield solution to blood loss) and the private sector (recognizing the risk of HIV to the blood supply) have focused on two general categories of oxygen carriers: perfluorocarbons (PFCs) and hemoglobin-based oxygen carriers (HBOCs). PFCs are completely synthetic, whereas HBOCs are made from human or animal-derived hemoglobin (Hb). Other products, such as recombinant Hb, are in preclinical development. Several of these oxygen carriers are undergoing clinical trials; however, many prior attempts have resulted in adverse events and have been discontinued.

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Crit Care Clin 25 (2009) 399–414
doi:10.1016/j.ccc.2008.12.007 **criticalcare.theclinics.com**
0749-0704/08/$ – see front matter

It is important to differentiate between ''blood substitutes'' and ''red cell substitutes.'' Red cell substitutes are oxygen carriers and do not replace all components and functions of blood (coagulation factors and white blood cells).

At the time of this writing, the many functions of human red blood cells have no true substitute and the authors do not believe that blood substitutes will replace the need for blood donation in the foreseeable future. Over time and with improvements, they believe that these technologies have the potential to dramatically reshape the practice of transfusion medicine. In this article, the authors define the attributes of an ideal blood substitute (**Box 1**), discuss the history, mechanism, and current status of PFCs, and review the shortcomings of all oxygen therapeutic products in development today.

MEETING THE NEED: THE IDEAL BLOOD SUBSTITUTE

The ideal blood substitute would answer the challenges of safety and availability (see **Box 1**). To ensure safety, the ideal blood substitute would reduce disease transmission and immunosuppressive effects while enhancing oxygen delivery. To improve availability, the ideal blood substitute would be eligible for cost-effective mass production, universal compatibility, prolonged shelf life, and ease of administration. As an added clinical benefit, blood substitutes could address some medical needs in a better fashion than intact red cells.

Many attempts have been made to develop blood substitutes under the current regulatory structure, but no product has been able to fulfill all of the above criteria or meet the Food and Drug Administration's (FDA's) requirements of purity, potency, and safety. The unmet clinical need has inspired several companies to continue to research red cell substitutes and fund preclinical development and clinical trials.

Box 1
Characteristics of an ideal blood substitute

- No risk of disease transmission
- No immunosuppressive effects
- No interaction with the immune system
- Maintenance of arterial blood pressure and pH
- Availability of abundant supply
- Universal compatibility (no need to type and crossmatch)
- Rapid metabolization and elimination in vivo
- Prolonged shelf life and stability at a range of temperatures
- In vivo half-life similar to the red blood cell
- Similar viscosity to blood
- Availability at a reasonable cost
- Ease of administering
- Ability to access all areas of the human body (including ischemic tissue)
- No interference with capillary circulation
- Effectiveness at room air or ambient conditions