Blood Substitute Passes Its First Test

Perfluorochemical emulsions are being put into use in Japan, but American investigators are searching for a better chemical

The 65-year-old patient at the Fukushima Medical Center in Japan was bleeding heavily last April after his prostate had been removed in a cancer operation, and the medical staff did not have enough of his rare O-negative blood for a necessary transfusion. Faced with a crisis, surgeon Kenji Honda gave the man an infusion of 1 liter of a new, oxygenated perfluorocarbon emulsion; the emulsion carried oxygen through the patient's body until more of the rare blood could be obtained. Subsequently, doctors at Fukushima and other hospitals used the blood substitute on eight other patients threatened with death from excessive bleeding. Most of these patients had rare blood types that were not immediately available, but one refused a conventional transfusion for religious reasons. All nine patients are well today and form a select group of the first humans to have their lives saved with an artificial blood.

Oxygen is highly soluble in most liquid perfluorochemicals—hydrocarbons or other organic chemicals in which all hydrogen atoms have been replaced by fluorine atoms. Most perfluorochemicals can dissolve as much as 60 percent oxygen by volume; whole blood, in contrast, can dissolve only about 20 percent, and salt water or blood plasma only 3 percent. In 1966, Leland C. Clark, Jr., of the University of Cincinnati College of Medicine demonstrated that perfluorochemicals could sustain life when he immersed rodents in the liquids for long periods (*Science*, 16 February 1973, p. 669) and perfused hearts with the chemicals.

Pure perfluorochemicals, however, are immiscible with blood. Major milestones were thus reached in 1967 and 1968 when Henry A. Sloviter of the University of Pennsylvania and Robert P. Geyer of the Harvard School of Public Health demonstrated that the perfluorochemicals could be emulsified—broken up into microdroplets that remain suspended in solution—with bovine albumin and with a family of surfactants known as Pluronics. Since the late 1960's, most research has been devoted to finding the most appropriate perfluorochemicals and improving the emulsions. Most of the original work was done with perfluorobutyltetrahydrofuran and perfluorotripropylamine. These carry oxygen splendidly, but they tend to concentrate in certain organs of the body, particularly the liver and spleen. Investigators have thus sought compounds that can be cleared from the body more quickly.

Clark made a major step in that direction in 1973 when he found that perfluorodecalin is completely eliminated from the body—either by expiration or transpiration through the skin—in 1 to 3 weeks without being metabolized. This compound has one drawback, though. The microdroplets of perfluorodecalin in the emulsion tend to agglomerate into larger droplets with time; if the droplets get large enough, they could block capillaries and create many problems. In response to this problem, research in Japan and the United States has gone in different directions.

In Japan, Ryoichi Naito of the Green Cross Company, a pharmaceutical firm in Osaka, chose to overcome the problem by adding a small amount—perhaps as much as 25 percent—of perfluoropropylamine to the perfluorodecalin, producing a commercial emulsion known as Fluosol-DA. Addition of the second chemical increases the stability of the emulsion, but it also increases the half-life of the chemicals in the body to about 65 days, which the company thinks is a fair compromise. The availability of a commercial perfluorochemical emulsion has been a boon to investigators in both Japan and the United States, where Fluosol-DA is distributed by Green Cross subsidiary Alpha Therapeutics, Inc. of Pasadena.

The first clinical test of Fluosol-DA occurred last year when Naito infused himself with 50 ml of the agent. Subsequently, several other investigators at the firm infused themselves with as much as 500 ml, and early this year a full-scale safety test was conducted with healthy volunteers from two Japanese medical schools. At about the same time, a team of investigators at the University of Mainz in West Germany and the Linz Hospital in Linz, Austria, used the blood substitute to maintain biological functions for as long as 24 hours in several brain-dead victims of accidents. These studies all showed no apparent harm to body tissues.

In addition to the use on nine patients, Fluosol-DA has been used to perfuse the kidneys of a brain-dead donor prior to transplantation. Both recipients of the kidneys are reported to be doing well. These projects will continue, Naito says, since Japanese law requires that a new substance be tried successfully in 150 patients before approval is given for routine use. Meanwhile, Japan's Self-Defense Forces have contracted with Green Cross to conduct their own trials with the blood substitute, which has many obvious advantages in a military situation.

American investigators, though, have preferred to look for a single substance that would form an adequate emulsion and still be cleared from the body quickly. To this end, the National Institutes of Health recently sponsored a program in which some 80 different perfluorochemicals were synthesized and screened for emulsion stability and rapid clearance. Four of the most promising chemicals from this group will now undergo additional testing for 2 years in order to study their effects in animals.

Investigators are also giving greater attention to the aqueous phase and investigating other surfactants. One gauge of the success of their refinements is the length of time isolated organs can be maintained by perfusion with the emulsion-containing preparations: the maximum now is about 16 hours before degradation begins, but Geyer thinks 48 hours can be obtained in the foreseeable future. He likens current experiments on the emulsions to early work on tissue culturing, in which the length of time tissues could be maintained was slowly increased by artful changes in the medium.

It seems clear that the perfluorochemical emulsions are beginning to fulfill some of the promise they first showed. It now appears to be only a matter of time and hard work before they can be used on a regular basis to sustain life in situations where whole blood is not available.

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