Which Clot-Dissolving Drug Is Best?

Clot-dissolving drugs can save the lives of heart attack victims, but there is controversy about which of the various competing agents works best

DESPITE GREAT EXPECTATIONS for its success, the clot-dissolving enzyme known as tissue plasminogen activator (TPA) has had rough sailing since it was launched. Produced by Genentech, Inc., of South San Francisco, TPA is used to dissolve the clots that form in the coronary arteries and cause heart attacks. It is made by recombinant DNA technology and is the first such agent for which a large potential market exists. Nearly three-quarters of a million heart attack victims enter U.S. hospitals every year.

When recombinant TPA became available in the mid-1980s, however, another clot-dissolving enzyme, called streptokinase, was already on the market. Streptokinase, a product of Hoechst-Roussel Pharmaceuticals, Inc., of Somerville, New Jersey, is made without recombinant DNA technology and costs less than one-tenth of the $2200 price tag of TPA. The expectation was that TPA would be enough better than streptokinase to justify its use in this day of soaring medical expenditures.

Nevertheless, in the clinical trials completed so far, in which the two agents have been tested separately, they have apparently performed about equally well with regard to reducing the mortality of heart attack victims. "The bottom line is, nobody knows which is best," says Eugene Passamani of the National Heart, Lung, and Blood Institute (NHLBI) in Bethesda, Maryland, which is sponsoring the TPA trials in this country.

As a further complication, allegations of a possible conflict of interest during the clinical testing of TPA surfaced at the end of September in a hearing conducted by the Human Resources and Intergovernmental Relations subcommittee of the Government Operations Committee of the U.S. House of Representatives. According to information gathered by the subcommittee, which is chaired by Representative Ted Weiss (D–NY), at least 13 members of the NHLBI-sponsored TIMI (for Thrombolysis in Myocardial Infarction) study group, which is conducting clinical trials of TPA, held Genentech stock or stock options, either directly or through family members.

At present, no restrictions prevent the recipients of government grants from holding stock in the companies producing the drugs they are testing, although such a restriction might be one result of the continuing investigations of the Weiss subcommittee. Moreover, Passamani says that it is very unlikely that the TIMI group participants could have influenced the outcome of the TPA trials. The first study, designated TIMI-I, included about 130 investigators at medical centers around the country.

Passamani points out that TIMI-I was done on a randomized, double-blinded basis in which neither the patients nor the investigators knew who was getting TPA and who was getting placebo. "It's hard for me to see how anyone could have beaten that design," Passamani maintains. He also points out that an independent trial, conducted by the European Cooperative Study Group, produced the same results.

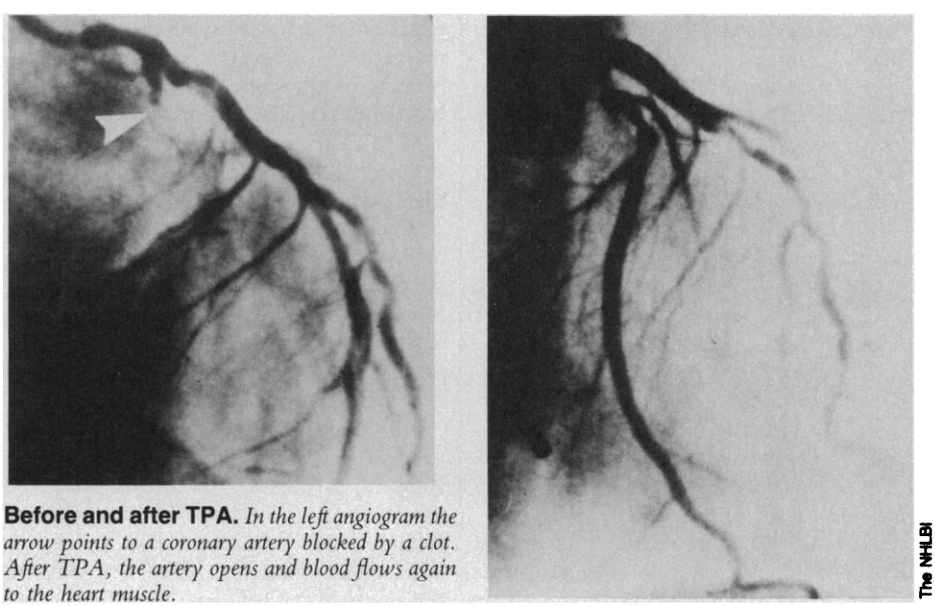
All of this follows on 18 months of turmoil for TPA and Genentech (*Science*, 3 July 1987, p. 16, and 10 July 1987, p. 120). In spring of last year, the U.S. Food and Drug Administration (FDA) withheld its approval of the use of TPA to treat heart attack victims, partly because the agency said that the data then available did not prove the enzyme's efficacy at saving lives. At the same time, Genentech was embroiled in a fight with the Wellcome Company over patent rights to TPA in Great Britain.

Genentech eventually prevailed with the FDA, obtaining approval to market TPA for treatment of heart attacks in November of 1987. The company lost the patent fight, however, when the British High Court ruled that the most of the patent claims made by the company were invalid. Genentech has been granted the U.S. patent for recombinant TPA, however.

Some observers fear that controversy over which drug to use may obscure the fact that clot-dissolving therapy—thrombolysis is the term used by cardiologists—can save the lives of heart attack victims. "What's being lost in the furor is that we have a simple effective treatment for acute myocardial infarction [heart attack]," Passamani says. "The question is how to do it best."

That thrombolysis works is one of the few issues on which there is general agreement. "As far as thrombolysis for acute myocardial infarction is concerned, I think there is little doubt that it represents an important advance for immediate treatment," says Sol Sherry of Temple University School of Medicine, who a pioneer of thrombolytic therapy, but not a TPA supporter.

Another point of agreement is that the faster thrombolytic therapy with any agent



Before and after TPA. *In the left angiogram the arrow points to a coronary artery blocked by a clot. After TPA, the artery opens and blood flows again to the heart muscle.*

The NHLBI

begins the better it is likely to be for the patient. The goal of the therapy is to dissolve heart attack–causing clots before they cause permanent damage to the heart muscle, usually within 4 to 6 hours.

Streptokinase and TPA both work by splitting a protein called plasminogen and converting it to plasmin, an enzyme that helps to break up clots by degrading the fibrin that is one of their principal protein components. TPA's advantage was supposed to lie in its greater specificity. Its main action occurs after it binds to fibrin in the clots. This tends to concentrate the active plasmin just at the site where it is needed. Streptokinase, in contrast, degrades not just the fibrin of clots but also fibrinogen, the blood protein from which fibrin is formed. This latter effect causes a depletion of the blood's normal clot-forming ability.

Bleeding complications, including hemorrhagic strokes, had occurred in some patients treated with streptokinase. The hope was that TPA, with its greater specificity, would be more effective than streptokinase in opening blocked coronary arteries and saving lives, while producing fewer bleeding complications.

The results of the early clinical tests of TPA looked promising. The TIMI-I trial and another trial conducted by the European Collaborative Study Group, directly compared the ability of TPA and streptokinase to dissolve coronary blood clots. By this measure, TPA turned out to have the edge over streptokinase by a margin of as much as two to one.

The early TPA trials did not assess the agent's effects on mortality. This was one of the FDA's sticking points when it at first declined to approve the therapeutic use of the agent. But more recent trials have shown that TPA does save lives.

In October of this year, the ASSET (for Anglo-Scandinavian Study of Early Thrombolysis) group reported that TPA treatment reduces heart attack mortality by 26%. In a smaller study, the European Cooperative Study Group reported a 50% reduction in mortality by TPA.

However, clinical trials have shown that streptokinase, despite its apparent disadvantage in opening arteries, fares about as well as TPA when it comes to saving lives. For example, the GISSI (Gruppo Italiano Per Lo Studio Della Streptochinasi Nell'Infarto Miocardico) study, including a total of nearly 12,000 patients, showed that streptokinase reduces mortality by about 18% overall, but by nearly 50% if given within the first hour of the onset of pain.

In a similar vein, the Second International Study of Infarct Survival (ISIS-II), with some 17,000 patients, showed that either streptokinase or aspirin alone reduces mortality by about 25%. Together they reduce it by more than 40%.

Moreover, TPA seems to cause about as many bleeding complications as streptokinase. "The fact that it spares fibrinogen more than streptokinase does not translate into a major safety advantage," says Elliott Grossbard of Genentech.

Bleeding complications may be an inherent side effect of treatment with thrombolytic agents. Another new thrombolytic agent, called "APSAC" (for anisoylated plasminogen streptokinase activator complex), is currently coming on the market in Europe, where its cost is intermediate between that of TPA and streptokinase. APSAC, like TPA, was supposed to be clot-specific.

"The bottom line is, nobody knows which is best."

But a clinical trial conducted in England showed that while APSAC reduced heart attack mortality by about 35% at a year after treatment, it, too, is associated with a low risk of cerebral hemorrhage. "All of these drugs can cause cerebral hemorrhage, and do so," says Desmond Julian of the British Heart Foundation in London, who has been involved in APSAC testing. Indications are that the bleeding occurs because the thrombolytic agents, in addition to dissolving abnormal clots in the coronary arteries or elsewhere, attack the hemostatic plugs that normally form in the walls of damaged blood vessels and seal them off.

The incidence of strokes is sufficiently low—from about 0.5 to 1.0% of the patients who receive thrombolytic agents have the problem—compared to the life-saving benefits of the therapy to justify its use. Nevertheless, Jeffrey Anderson of the University of Utah in Salt Lake City, who is also studying APSAC, says, "Even 1% is higher than we would like it to be."

Whether thrombolytic agents can ever be made sufficiently specific to distinguish abnormal clots from normal hemostatic plugs is unclear. Meanwhile, persons whose medical histories suggest an increased risk of bleeding complications or stroke cannot receive thrombolytic therapy.

From the studies so far then, TPA appears to be comparable to streptokinase in its ability to save lives. The relative merits of the two agents will not be known with certainty, however, until their effects on heart attack mortality have been directly compared in studies large enough to produce statistically significant results.

One such study, which will include 10,000 patients and is being performed under the aegis of the GISSI study group, is already under way. Results are expected sometime before the end of 1989. In addition, the ISIS study group is beginning a large clinical trial, encompassing some 30,000 patients, that will compare TPA, streptokinase, and APSAC. "These trials are large enough to be a critical test of the question," Passamani comments.

Grossbard expects that TPA will ultimately prove itself. He points out that mortality data from a few small trials in which TPA and streptokinase have been matched in head-to-head comparisons suggest an advantage for TPA. The results of the large GISSI and ISIS studies will nonetheless be needed to confirm this.

Their outcome may be crucial for TPA and Genentech. According to Grossbard, TPA has captured 60 to 65% of the U.S. market for thrombolytic agents, but its continued success in the face of less expensive competitors may depend on a showing of decisive superiority in saving lives.

Although the question of which thrombolytic agent works best remains to be settled, researchers are moving on to address questions about how to combine thrombolytic therapy with other heart attack treatments. The second phase of the TIMI trial, for example, has focused on the use of coronary angioplasty and β-blocker drugs after thrombolysis.

According to a presentation at this year's meeting of the American Heart Association by Robert Roberts of Baylor College of Medicine, the TIMI-II trial has shown that patients who begin receiving a β-blocker drug within 2 hours of thrombolytic therapy with TPA have improved survival and fewer recurrent heart attacks.

Cardiologists may use coronary angioplasty, an invasive method of opening the arteries to the heart, after thrombolysis if the arteries still shown signs of narrowing. Another result of the TIMI-II trial, presented at the heart meeting by TIMI group chairman Eugene Braunwald of Harvard Medical School, shows that the procedure need not be routinely done after thrombolysis with TPA. It may still be necessary, however, if additional symptoms show that the patient is not doing well.

A reduction in the need for coronary angioplasty ought to represent a cost saving, although thrombolysis by streptokinase or APSAC may provide the same benefit. Cardiologists are still learning how to best use thrombolysis. Not the least of the questions remaining concerns which of the agents works best. ■ JEAN L. MARX