Battle of the clotbusters

Michael O'Donnell

The moment of revelation—maybe even of truth—came at 8.51 on a Tuesday morning in the vast auditorium of the Georgia World Congress Centre in Atlanta. It was the second day of the 40th annual scientific session of the American College of Cardiology and Peter Sleight, professor of cardiovascular medicine at the University of Oxford, with his colleagues Rory Collins and Richard Peto, was reporting preliminary results from the largest clinical trial in medical history.

Coordinated by Dr Rory Collins from Oxford, the data for the third international study of infarct survival (ISIS-3) came from investigators in nearly 1000 hospitals in Europe, North America, and Australasia who had treated over 46 000 patients suffering an acute myocardial infarction with one of three randomly assigned fibrinolytic agents: streptokinase, anistreplase, or tissue plasminogen activator (tPA).

When Peter Sleight summoned up the slide showing the survival rates he had to tell those at the back of the packed auditorium that they were looking not at one line but three. The survival rates achieved with the agents in this double blinded study were virtually identical (fig 1). He had no such problem with the slide showing the incidence of cerebral bleeds—significantly fewer could be seen to occur in patients given streptokinase than in those given the other two agents. The excess of haemorrhagic strokes with tissue plasminogen activator compared with streptokinase was four per 1000 patients (fig 2).

In a wholly logical world that would be the end of the argument, but this is the world of clinical medicine and the debate over the relative efficacy of these agents—which the American media have dubbed “clotbusters”—has divided cardiologists along geographic lines just as effectively as has the Atlantic. Previous data, though not on this scale, have suggested an equivalence of efficacy between the two main agents, yet American

FIG 2—Rates of cerebral bleeds with streptokinase and tissue plasminogen activator in ISIS-3

cardiologists, unlike their European counterparts, have relied almost exclusively on the high tech, genetically engineered tPA rather than the 30 year old, out of patent streptokinase, despite the fact that the new drug costs 10 times as much as the old.

Many arguments have been proposed to explain this difference: American loyalty to a homegrown product, American love of high tech, even of high cost. (American doctors, for instance, are less ready than their European colleagues to use aspirin as an anti-thrombotic agent, largely because it's too ordinary and too cheap.) Before the week was out, a prime time television documentary would suggest less savoury reasons, accusing the makers of tPA of using “questionable tactics” in their determination “to keep a competitor's drug from gaining popularity.”

Whatever the reason, the position in the United States is curious. Richard Peto, fellow of the Royal Society and the ISIS-3 statistician, described it thus: “People here behave as though tPA should be used unless you can prove good reasons why it shouldn't. This is an inversion of what would normally be considered appropriate for a new drug. If you have a new agent that's 10 times the price, you want to have good evidence that it really works before it is used widely. Yet in this case the opposite seems to have happened.”

Meanwhile, back in the auditorium, Peter Sleight was piling up the evidence, presenting the latest data from the GISSI-2 trial, another large randomised study organised from Milan, which used a protocol similar to ISIS-3 and found survival rates that were virtually identical. Combining the results of these trials, he now presented data from 60 000 patients showing that streptokinase seemed to be as effective as tPA but safer.

He feared that the dispute over the relative virtues of

FIG 1—Mortality of three agents compared in ISIS-3

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the agents had slowed the adoption of a lifesaving treatment, particularly in the United States, where only about 20% of patients who could benefit from thrombolytic therapy actually received it. "If aspirin and streptokinase were used early after an infarction—supported perhaps by a "gentle" heparin regimen—thousands of lives in the US could be saved every year, and tens of thousands worldwide. And if US physicians began to use streptokinase routinely instead of tPA, they might avoid hundreds of strokes—and save more than \$100 million every year."

Soon Richard Peto was extolling the value of large trials. When assessing the efficacy of treatments to be used in millions of patients, he said, it's sensible to randomise them in trials where the patients number tens of thousands. Thanks to the numbers involved in ISIS and GISSI, the benefits of fibrinolytic treatment could be seen to accrue to groups of patients who had previously been denied it. Some trials of thrombolysis had even excluded patients with a history of previous myocardial infarction.

More strokes with tPA

The data showed that the treatment increased survival in all age groups including the over 65s and over 75s. Hypertensive subjects did as well as normotensive subjects—and patients, Peto said, should not be denied treatment because they'd had a gastrointestinal bleed or an ulcer or a stroke. They didn't run an excess risk of bleeding, and when they were treated the balance of benefit over risk was very much in their favour. The risk of bleeding seemed to be related more to the agent than to the patient's history. "The most disturbing finding in ISIS-3," he said, "reinforced by evidence from GISSI-2, is the highly statistically significant increase in cerebral haemorrhage with the two clot specific agents. In North America, where around 200 000 patients receive fibrinolytic agents every year, the difference if everyone were given tPA rather than streptokinase would be about 800 more haemorrhagic strokes, many of them fatal and all of them serious."

In Atlanta, some of the immediate reaction to the ISIS data was bizarre. True, the fighting in the Gulf war had just started and jingoism was the flavour of the month, but some American cardiologists I talked to seemed to construe any criticism of tPA as an attack on the American way of life. And at a college "mini-course" on thrombolysis, the chairman, Dr Burton E Sobel (of whom more later) spent some 40 minutes extolling tPA, having previously restricted the other panellists, including Peter Sleight, to 10 slides and 15 minutes. He also questioned the relevance of the somewhat "low tech" ISIS-3 data to the United States. (This was an even lower blow than it sounds because 5300 patients enrolled in ISIS-3 were treated in 200 hospitals in the United States.) Peter Sleight responded with the traditional eccentricity expected of an Oxford professor. He appeared at the lectern without his shoes and socks and explained that he was a visiting European "barefoot doctor."

The reaction of the media was less restrained. Cardiologists who switched on the networked television news that evening were greeted by the familiar and usually reassuring face of Peter Jennings. Only this time he was saying: "Many American doctors may not be choosing the right drug for their patients. The brand that most choose also happens to be the most expensive, and according to one of the most exhaustive medical studies ever done it is also the least safe." After reporting the ISIS results Jennings concluded: "American doctors will have to re-evaluate their choice of tPA, and the medical community will have to decide whether research will triumph over marketing."

Genentech, the manufacturers of the tPA prescribed in the United States, responded with a press conference. The company's aggressive marketing tactics had in the past run into trouble with the Food and Drug Administration and with other pharmaceutical companies, but this conference was a low key affair and many of the cardiologists who previously had been conspicuous in supporting Genentech did not attend. Genentech's main argument was that the tPA used in the ISIS trial, Burroughs Wellcome's alteplase, was not the same as its own tPA, alteplase. But, as the assembled journalists were quick to point out, Peter Sleight had anticipated this proposition by showing good evidence from over 2000 patients that both versions of tPA produced exactly the same patency rates in coronary arteries. And the tPA data from the GISSI trial, which used Genentech's alteplase, corresponded closely with those from ISIS.

Genentech was in a difficult position because it had won a legal injunction against Burroughs Wellcome for infringing its patent and the courts had found that the two agents were equivalent. Unabashed, Genetech handed out a statement saying: "The ISIS-3 study used Burroughs Wellcome's alteplase, which is not approved for sale anywhere in the world and is no longer under development."

The 1991 Battle of Atlanta rumbled on through the week, with most of the skirmishes occurring between public relations folk, "spin controllers," and company lawyers rather than between doctors, and by the end of the meeting it would have taken a person of remarkable perspicience to predict whether the evidence from ISIS and GISSI would change American clinical practice.

Then, the day after the cardiologists had packed their bags and gone home, ABC Television's current affairs programme *20/20* moved the debate into the public arena. Why, it asked, were American citizens being treated with tPA at \$2000 a dose instead of with streptokinase at \$200? Reviewing the history of the All American clotbuster, it recalled how, in early 1985, the organisers of the TIMI trial, which had been set up to compare tPA with streptokinase, brought the study to a premature halt when it was known that angiograms taken 90 minutes after administration of the agents showed that tPA had opened twice as many blocked arteries as streptokinase. The organisers decided that these initial data were sufficient proof of tPA's superiority, though their decision was much criticised at the time by scientists like Dr Victor Marder, a

The largest clinical trial in medical history: some feet

JOHN RAE PHOTOGRAPHER

haematologist at the University of Rochester who thought the effects should be measured beyond the 90 minute angiogram. "There is a difference then but it doesn't last," he said. "Two hours later you don't see a difference."

The effect of stopping the trial had been dramatic. Peter Rentrop of St Vincent's Hospital in New York and a pioneer of thrombolytic research remembers the phrase that was coined: "The winner is crowned. That was the reaction of mainstream cardiology. The feeling was that tPA was a far superior drug and that the major difference in price was justified."

Yet all TIMI had shown was that tPA reopened coronary vessels early. It had not shown whether it increased survival rates—something that had been seen in studies with streptokinase. Many researchers assumed the next step would be to compare the two drugs to measure their relative ability to reduce mortality and to preserve heart muscle. *20/20* had learned that in 1985 the National Institutes of Health in Washington had considered such a comparative study but had eventually turned it down, a decision that the institutes said, in a letter to the programme, was "based on scientific interests and merit." The National Institutes of Health went ahead instead with a study that tested tPA, and only tPA, in combination with non-drug treatment.

Dr Marder says these decisions greatly helped Genentech's marketing position. "tPA becomes synonymous with thrombolytic therapy. It has a stamp of approval. It is the only agent being tested. Streptokinase is out of the picture." Genentech itself had helped its marketing position, according to *20/20*, by offering stock options to some key researchers, a practice the company defended in a letter to the programme, saying stock options were "a substitute source of compensation" by a company that needed to "conserve cash" and "still afford the expertise of leading clinicians in developing new therapies."

One researcher to come under the scrutiny of *20/20* was Dr Burton E Sobel, director of the cardiovascular division of the Washington University School of Medicine, St Louis, and the man who provoked Peter Sleight to go "barefoot." A congressional committee had investigated evidence of Dr Sobel's financial relationship with Genentech and concluded that he held stock options to acquire 14 000 shares in the company. Dr Sobel had refused repeated requests to explain what he did with those options. *20/20* questioned his editorship of *Circulation*, the journal of the American Heart Association, at a time when he had a possible financial interest in Genentech.

While *Circulation* was not accused of publishing biased information, Dr Arnold Relman, editor of the *New England Journal of Medicine*, appeared on the programme to say that doctors who work on medical journals should have no ties with pharmaceutical companies. "Editors and their staffs should be totally free of conflicts of economic interest. They should have no economic connection at all with any health related company."

For American cardiologists—and their patients—the most significant moment of the *20/20* programme probably came when Dr Eric Topol from Ann Arbor, Michigan, another pioneer of thrombolytic therapy and one of tPA's most outspoken supporters, seemed to have had a change of heart. "Streptokinase," he said, "is the gold standard drug. tPA, while a very good thrombolytic agent, is not worth over \$2000 per dose." That could be the moment when the first harbinger of change rode into town. We shall have to wait and see.

Looking back on a week when the gentle ISIS flowed refreshingly though Atlanta, it's easy to conclude that American medicine's bizarre love affair with tPA is a purely local phenomenon and that no similar attachment could occur in our own well ordered world.

Or could it?

At least we have been warned.

A PAPER THAT CHANGED MY PRACTICE

Smallpiece and Davies on the early and adequate feeding of immature infants

During the late 1940s the hazards of aspiration and the presence of oedema were the grounds advanced for starving preterm infants for the first 48 hours of life or even longer. Starvation, it was thought, increased the chances of the infants surviving. Science and good intentions exhorted by acknowledged authorities had led to the introduction of a standard practice that now, 50 years later, simply sounds crazy. Thus it was Smallpiece and Davies, driven by common sense rather than science, who carried out a trial of immediate feeding with undiluted breast milk. As they commented, the fetus is fed continuously in utero, so it seems irrational to interrupt the process just when the infant is exposed to greater risks.

Their report is full of apologies about the inadequacies of their study. It was not a controlled trial though there was a comparison group. Once the nurses saw how much better the infants were who were fed early it was impossible for them to do otherwise. A controlled trial immediately became out of the question. They found that fewer babies died during the period of the study, that far fewer needed exchange transfusions (about 20% of the comparison group had exchange transfusions), and that hypoglycaemia did not occur in the early fed babies. The benefits to the infants were dramatic. The infants had fewer problems in the immediate period after birth and they argued that withholding feeds had probably contributed to the high numbers of handicaps seen in surviving immature infants at that time. No one would challenge that claim now. The paper was not received with acclaim, however, and many units were slow to adopt an early feeding programme despite the demonstration that it was possible, the claim of

major benefits, and the fact that it made simple common sense.

I learnt that if there is a conflict between a piece of science and your common sense to trust your common sense. Science tends to select its targets, common sense looks at the whole. I also learnt that limited studies can carry strong messages: the weakness of the design does not negate the findings, it invites thoughtful interpretation. As for my practice, I have tried to ensure if it is at all possible that all preterm infants receive some of their mothers' milk as soon as possible after birth and that they are offered as Smallpiece and Davies recommended 2½ oz per lb body weight (15 ml per kg) by the fourth day of life of a feed that is at least half breast milk. When it is not possible the infant is offered a feed that is as like breast milk as possible and given orally. If my memory is correct the first reported cases of necrotising enterocolitis in the United Kingdom were from Oxford around 1966 but it was not seen in premature infants fed immediately with undiluted breast milk but in more mature infants with umbilical catheters in place.—DAVID HULL, professor of child health, University of Nottingham

Smallpiece V, Davies PA. Immediate feeding of premature infants with undiluted breast milk. *Lancet* 1964;ii:1349-52.

Editor's note: The story of this study and the controversy it aroused is told by Dr Pamela Davies (*Arch Dis Child* 1991;66:551-3). We congratulate Dr Victoria Smallpiece on her 90th birthday this month.

We welcome further contributions of up to 400 words to the features "A paper that changed my practice" and "A patient that changed my practice."