Scientifically Speaking

Studies of myocardial infarction

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Washington, DC—This winter has been an unsettling season for patients suffering from myocardial infarction and for their physicians who advised daily doses of aspirin to prevent another attack. That prophylactic possibility has been studied for almost a decade, and the results of most of the investigations have leaned toward the beneficial effect of aspirin, if not awarding it the laurels of statistical significance.

But now the biggest controlled trial ever conducted on the matter—the Aspirin Myocardial Infarction Study (AMIS)—has reported an inability to find any such advantage for aspirin. That result has raised all sorts of questions, their intensity perhaps heightened in a season that has seen a welter of more encouraging reports about staving off repeated heart attacks. Just before Christmas, British and German trials indicated some edge for aspirin.^{1,2} Little more than a month later, a largish study in the United States found solid and significant benefits of sulphinydrylpyrazole in preventing sudden death after myocardial infarction.³ And shortly after the AMIS report was published,⁴ oral reports of another study of similar design—the Persantine and Aspirin Reinfarction Study, acronymed PARIS—indicated some real advantage for the drug combination and the customary statistically unsatisfying benefits of aspirin alone.

AMIS and PARIS

The AMIS and PARIS investigations invite the closest comparisons, both having been co-ordinated by the same office at the University of Maryland; having begun at the same time, with the enrolment of another study of patients treated in a randomised, controlled, double-blind study; and having completed their follow-up at the same time. Each study also enrolled patients who were “qualified” by having had their infarctions eight weeks to five years before. There, however, are about where the similarities end.

AMIS, sponsored by the US National Heart, Lung, and Blood Institute, signed up 4524 people at 30 co-operating clinical centres located throughout the US. The 2267 assigned to the aspirin group were to take 1 g daily in two 0.5 g doses. They and the placebo-receiving patients in the control group were instructed not to take aspirin or aspirin-containing products other than that supplied by the study; both groups were given paracetamol to use as an analgesic should one be needed. Randomisation notwithstanding, the placebo group in AMIS turned out to be sturdier folk in matters that counted

in this study. Their medical histories showed fewer instances of heart failure, less angina pectoris, and less heart enlargement. Their use of medications was appropriately lower—fewer of them took digitalis, nitroglycerin or other long-acting nitrates, propranolol or other beta-blockers, or gout medication other than probenecid. Rather oddly, the mean values for pulse, blood pressure, weight, serum cholesterol, age, infarction history, and even smoking history were well balanced.

In adjusting the figures of the AMIS study once all the mortality and other endpoint data were in, the investigators took into account all of the baseline variables that made the placebo group healthier in heart than the aspirin group. As one of the study's co-ordinators pointed out, however, the seven variables for which there were significant differences between the groups are not all independent variables, which could mean that the process of adjustment did not put sufficient emphasis on their importance.

The PARIS investigation, funded by Boehringer Ingelheim, manufacturers of the Persantine brand of the vasodilator dipyridamole, enrolled fewer patients than AMIS—2026—and randomly assigned them to three groups. One group of 810 people had a thrice-daily dosage schedule that added up to 972 mg of aspirin and 225 mg of dipyridamole. Another group of exactly the same size got 972 mg of aspirin plus a placebo. The control group—only 406, because investigators had hoped the AMIS controls could be worked into some of the PARIS calculations—got a double placebo.

In most respects, results of AMIS came about as close to fulfilling the null hypothesis as one could ask. The study report cautions that “exact statements of statistical significance are impossible to make in this situation,” partly because of multiple data analyses conducted during the trial. Not much exactitude is needed, however, to appreciate the similarity in total mortality between 10.8% in the aspirin group and 9.7% in the placebo group after an average follow-up of 38.2 months. At three years the respective mortalities were 9.6% and 8.8%. Mortality as a function of which clinical centre was dealing out the pills was also meaningless.

An oddity of the AMIS results emerges from the figures on various non-fatal cardiovascular events in patients after they entered the study. Recurrent myocardial infarction was a “definite” event in only 6.3% of the aspirin group as against 8.1% of the placebo group—a 22% difference. Although not a significant difference by the criteria of the study, the discrepancy raises a question of how aspirin could protect against non-fatal heart attacks but not against fatal ones.

Aspirin took its customary gastrointestinal toll in the treated group of the AMIS cohort, 23.7% of whom had symptoms suggestive of peptic ulcer, gastritis, or erosion of the gastric mucosa. Only 14.9% of the placebo participants had such symptoms, and the 37% difference between the groups is significant.

The PARIS investigation (whose full report is not expected to be published until late summer at the earliest) also had its share of statistically non-significant results, such as the 18% greater incidence of coronary fatalities among the placebo

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group compared with either of the treated groups. But the study also produced some figures that seem to mean something after all the adjusted Cox z -values and χ^2 tests and p -value equivalents are taken into account. In the group receiving aspirin and dipyridamole the number of coronary events, fatal and non-fatal, was 67% less than among controls in the first four months of the study; at 12 months the difference was 56%; at 24 months it was a little more than 30%, which is still significant. The combination therapy was better than aspirin alone at each interval of the study; the latter fell to a non-significant 16% fewer coronary events than controls at the end of two years.

It is in the mortality figures of PARIS that one variable jumps out and cries for attention. The treatment groups of the study included about 400 patients who had been enrolled within six months of their myocardial infarction. At the 24-month point in the study those recent-attack patients taking combination therapy had a coronary mortality 51% less than the control group, while those taking aspirin alone had 40% less mortality than did controls.

Second time round

Some earlier studies have hinted that compounds that affect platelet aggregation might also have some influence against recurrent myocardial infarction if used early after the first attack. Thus a PARIS II is in the works, scheduled to begin recruiting in July, to enrol only those patients who had their previous attack within four months of entry into the study. It will pit the combination aspirin-dipyridamole treatment against placebo, skipping the aspirin-alone comparison.

As now planned, however, PARIS II will not answer a question that has arisen about the possibility of aspirin over-dosage muddying its desired effect against platelet aggregation. That effect comes from its inhibition of thromboxane in platelets, which otherwise stimulates their clumping. But such inhibition can be handled nicely on only half a tablet of aspirin a day. And excessive aspirin has been found to interfere with a clotting mechanism concerning prostacyclin in the vessel wall. PARIS II will stick with three aspirins a day, according to the protocol announced by the heart institute.

The study to assess sulphinpyrazone's benefits after a heart attack enrolled patients only 25 to 35 days after the qualifying event. The treatment group of 775 patients were given 200 mg of sulphinpyrazone four times a day; a group of nearly equal size got placebos. At the end of 23 months, with an average follow-up of only 8.4 months, the benefit of treatment became so obvious that the investigators stopped where they were and

told all the patients what was up. But they didn't break the code, and they managed to get a new statement of informed consent from all but seven patients in the study, so they were able to finish the planned study course and get some idea of long-term effects.

Deaths due to cardiac causes totalled 62 in the placebo group but only 43 in the treated group. On analysis of the data it turned out that almost all the difference was attributable to a reduction in sudden death in the sulphinpyrazone group—74% less than in controls. Furthermore, the benefit of sulphinpyrazone showed up only from the second to the seventh month after the qualifying attack. The study was undertaken on the premise that sulphinpyrazone, an anti-gout agent that also inhibits platelet aggregation, might lessen the clotting associated with arterial disease and thus reduce reinfarction. But its main effect against sudden death in the most dangerous months after a heart attack doesn't fit in with a clotting hypothesis. The only fairly clear finding is that it works—somehow.

The season's flurries of reports about heart disease and treatment also included a note about prevention—appropriately carried in the Valentine's Day issue of an honoured journal here.⁵ High-density lipoprotein cholesterol, which is supposed to lower our risk of coronary heart disease, may be a function of running. Marathon runners have more of it, joggers somewhat less, and sedentary men least of it. The distance run had the best correlation with the ratio of high-density lipoprotein to total cholesterol and, next to weight, was the best figure for predicting triglyceride levels. The authors acknowledge that the nature of men who choose to run may have something to do with the phenomenon.

References

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What dose of oral penicillin is advised for treating beta-haemolytic streptococcal infection?

It is assumed that oral penicillin refers to penicillin V (phenoxymethylpenicillin) and not to penicillinase-resistant and broad-spectrum oral penicillins subsequently developed. The dose depends on the age and therefore the weight of the patient and the site of the infection. Penicillin V is incompletely absorbed, and the blood concentrations are neither as high nor as predictable as those obtained with parenteral penicillin. Only infections with exquisitely sensitive organisms, such as the group A streptococcus, are properly managed by oral treatment and then only when they occur at accessible sites. It would not be appropriate to treat the now infrequent case of streptococcal septicaemia by this route, and streptococcal infections of burns should also receive parenteral treatment. In fact, streptococcal tonsillitis is one of the few infections which should be treated by mouth. Even with this condition, should it occur in a hospital or other closed community, an initial intramuscular dose of benzylpenicillin for rapid clinical effect and to prevent the spread of infection is still sound practice. This is usually impracticable and largely unnecessary

in general practice but should be considered whenever an unusually severe case is encountered.

When oral treatment is used it is prudent to follow the maker's instructions as set out on the product data sheet. For phenoxymethylpenicillin these recommendations are 125-250 mg every four or six hours for adults, but this may be increased to a maximum of 500 mg every six hours—that is, 2 g a day. Above this level the gastric irritant of the compound is commonly experienced. Children over 5 years of age should receive the adult dose. Children of 5 years or less need 125 mg every six hours and infants up to 1 year 62.5 mg every six hours. Treatment should be continued for 10 days. It is important to instruct patients and especially parents of children as to the necessity to comply with the stated dose and length of treatment.¹ For phenethicillin (Broxil), for which better absorption and peak concentrations have been shown, the dosage schedule is materially the same, but in-vitro work suggests that phenoxymethylpenicillin may be the more active agent against *Strep pyogenes*.²

- 1 Colcher IS, Bass JW. Penicillin treatment of streptococcal pharyngitis. *JAMA* 1972;222:657-9.
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