Aspirin abstracts number 5 : risk of Aspirin-induced major bleeding exaggerated.

Aspirin Abstracts

Number 5

RISK OF ASPIRIN-INDUCED MAJOR BLEEDING EXAGGERATED

Aspirin can cause acute mucosal damage in the stomach. The slightly increased faecal blood loss often found in association with aspirin intake is generally attributed to this local effect. Clinically, patients occasionally complain that aspirin causes dyspepsia, heartburn, nausea and even vomiting.

These, too, are attributed to local irritation. In certain circumstances, so logic suggests, the adverse effect on the gastric mucosa must be so severe as to bring about a major bleeding. Empirical support for this hypothesis appeared to come from the observation that, in about a quarter of cases of major bleeding from the upper gastrointestinal tract, no obvious cause could be found and that many of these patients, on questioning, admitted to recent consumption of aspirin.

Potential Fallacy

The potential fallacy in this argument lies in the widespread use of aspirin as a household remedy. Purely by chance alone, a patient may have taken the analgesic for a few days before the acute episode. To try to overcome this objection, various investigators over the past 25 years have carried out retrospective studies of the case-controlled type, which provide — at least superficially — convincing evidence of a cause-and-effect relationship.

For example, an early study revealed that 43 per cent of the patients with a major bleeding had taken aspirin, compared with only 22 per cent of the control group — a statistically significant difference (i).

The apparent association has nevertheless led to increasing criticism in the last few years. These criticisms are summarised by W.D.W. Rees and L.A. Turnberg of the University of Manchester School of Medicine in a review article, which questions whether the evidence is really as convincing as it first appears (ii).

The selection of the control groups in the various studies may not reflect accurately the analgesic habits of the general population, if only because of the considerable variations in aspirin consumption among the different control groups: the figures ranged from 4 to 44 per cent. In most of the studies, admittedly, aspirin consumption was higher in the patients, but then people who experience a major bleeding are possibly more likely to recall having taken a supposedly-known gastric "irritant" than a control subject without gastric symptoms.

Yet another inconsistency arises from the considerable variation in aspirin consumption among the patient groups, from a figure as low as 25 per cent (lower than that of some of the control groups) to as high as 72 per cent. The dosage of aspirin likely to be associated with a major bleeding has also received less attention in most of the studies than it probably deserves. What is generally regarded as the best of these investigations, that reported by Levy for the Boston Collaborative Drug Surveillance Program, indicates that "heavy" aspirin usage is a probable factor in causing major bleeding but that occasional or less frequent usage is not (iii).

Out of 88 patients who bled in the absence of a known predisposing cause, 16 per cent gave a history of taking aspirin on four or more days a week, most of them for longer than a year, compared with only 6.9 per cent of nearly 15,000 controls. Since the risk of a major bleeding worked out at only 15 per 100,000 heavy aspirin takers per annum, Rees and Turnberg speculated that aspirin ingestion had to coincide with another factor — perhaps concurrent intake of alcohol — for a major bleeding to occur.

Post hoc or *Propter hoc?*

They further emphasised that demonstrating an association between two variables, such as heavy aspirin intake and acute gastric bleeding, did not necessarily prove cause-and-effect. Patients might take aspirin in the days preceding an acute bleeding for the prodromal symptoms of the underlying gastric condition. At the Aspirin Symposium held in London in 1980, D. Coggan and M.J.S. Langman of the department of therapeutics at Nottingham presented evidence which suggested that this possibility explained at least some of the cases of aspirin-associated major bleeding.

The Nottingham investigators compared the drug exposure of patients admitted to hospital because of haematemesis or melaena with that of control subjects from the community. In particular, they looked for any differences between aspirin and paracetamol consumption, reasoning that if patients took an analgesic to relieve the early symptoms of bleeding they were just as likely to choose paracetamol as aspirin. Both aspirin and paracetamol consumption was higher in the patients who bled than in the controls, but the association of bleeding with aspirin intake was stronger than that with paracetamol.

No evidence exists linking para-▶

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cetamol with gastric irritation or major bleeding, so it seems that at least part of analgesic intake, in the days before a major bleeding, arises from the prodromal symptoms. Even so, the higher aspirin intake cannot easily be disregarded. Coggan and Langman suspect that aspirin does cause major bleeding, but that the risk is smaller than has previously been estimated.

Probably about a third of the aspirin intake in patients with bleeding can be accounted for by the intake expected in the general population; another third can be accounted for by the prodromal symptoms of the bleeding lesion; the last third remains unexplained, but could represent aspirin intake which was responsible for the bleeding. If this is so, then Coggan and Langman endorse Levy's estimate that the order of risk is probably about 15 per 100,000 regular users a year.

Rees and Turnberg reach a similar conclusion. Infrequent or low-dose aspirin intake may predispose to peptic ulceration or acute bleeding, but the evidence is inconclusive. Even in those who consume more than 15 tablets per week or take aspirin for more than four days per week, the risk of a major complication seems low. Gastric damage from aspirin is thus a hazard that has probably been over-estimated.

And, in contrast to reports of a few years ago that a quarter of the cases of major bleeding had no obvious cause (and should probably be attributed to aspirin), recent endoscopic studies tend to reveal a different pattern. An American study on 289 patients showed no difference in the frequency of ulcer and acute mucosal lesions as the sites of bleeding between patients who consumed aspirin and those who did not (iv).

Similarly, Devine and his colleagues in Glasgow reviewed the findings on 157 patients with major bleeding seen during the course of a year and concluded that only 11 per cent appeared to have bled as a direct result of aspirin ingestion (v).

Prospective Studies

It might be thought that much of the uncertainty could be resolved by the long-term, prospective, controlled trials of aspirin in the secondary prevention of myocardial infarction. In fact, the information does not turn out to be all that helpful. The largest of these studies, AMIS, included more than 4,500 patients, half of whom took aspirin in a dose of 1 g a day for thirteen months (vi).

Gastrointestinal side-effects were certainly more common in the aspirin group, with an incidence of 23.7 per cent — a much higher figure than is generally reported in the literature. What was surprising, though, was the high incidence of these complaints in the placebo group as well (14.9 per cent). Bloody stools occurred more commonly in the aspirin group (4.9 per cent); once again, the incidence in the placebo group was surprisingly high (2.9 per cent). As regards haematemesis, there was no statistically significant difference between the two groups, the respective figures being 0.6 and 0.3 per cent.

All in all, the association between aspirin and major gastrointestinal bleeding begins to look much more questionable than it did only a few years ago. Nor does there seem to be any obvious way of resolving the dilemma. Earlier investigators suggested that major bleeding might be an idiosyncrasy, but there is no convincing evidence of this. One might expect that a patient who had suffered a major bleeding would unwittingly sooner or later take another aspirin preparation and experience another episode of bleeding. But, once again, there is a remarkable lack of convincing evidence that this happens.

References

(i) *Gastroenterology* (1956) **31,** 198.
(ii) *Lancet* (1980) **ii,** 410.
(iii) *New England Journal of Medicine* (1974) **290,** 1158.
(iv) *Digestive Diseases* (1978) **23,** 76.
(v) *Gut* (1979) **20,** A433.
(vi) *JAMA* (1980) **243,** 661.■

ASPIRIN AFTER A HEART ATTACK– THE TANTALISING DILEMMA

Does aspirin after a heart attack reduce the risk of another coronary catastrophe? Six randomised controlled trials, involving more than 10,000 patients, have left clinical medicine with a tantalising dilemma because the evidence of benefit, though suggestive, is not clear-cut.

Differing Trial Results

At the Aspirin Symposium held in London in June, 1980, P.C. Elwood of the MRC Epidemiology Unit at Cardiff emphasised that, overall, there was a reduction in "all cause" mortality of about 7 per cent, despite considerable variations in the mortality reduction among the different trials. Five of the six showed a benefit for the aspirin group ranging from 15 to 30 per cent. The one exception to the trend was the Aspirin Myocardial Infarction Study (AMIS) in America (i).

In this very large-scale study, the mortality was 11 per cent higher in the aspirin group, compared with the placebo group. But Elwood, who with his colleagues had carried out the earlier British studies on the use of aspirin after a heart attack, felt it only reasonable to draw attention to serious inconsistencies in the AMIS results.

In particular, the 11 per cent excess mortality in the aspirin group contrasted very strangely with a reduction of 22 per cent in non-fatal infarctions by aspirin in the same group. Other experts have also reviewed the six trials and agreed that the evidence of benefit cannot easily be dismissed. Among them were the participants at a meeting of the Society of Clinical Trials in America, as reported in an editorial comment (ii).

Aspirin appeared to have prevented 70-odd cardiovascular deaths in these trials, a benefit that must be considered as real because it was supported by a highly-statistically significant reduction ($P < 0.0001$) in cardiovascular morbidity. In each trial fewer reinfarctions than expected were recorded in the aspirin group; indeed, the overall reduction in the odds of reinfarction was 21 per cent, with a standard error of about 5 per cent.

Interpreting the results in this way nevertheless strikes some observers as questionable, for in none of the individual trials did the differences in mortality between aspirin and placebo reach the conventional level

of statistical significance. The results, while clearly favouring aspirin in five of the six trials, could thus have occurred by chance. This problem troubled J.R.A. Mitchell, professor of medicine at Nottingham, in his general review of secondary prevention of myocardial infarction (post-infarction) studies (iii).

The logic of using aspirin was not in doubt, because the drug profoundly altered platelet behaviour. It irreversibly acetylated the platelet enzyme cyclo-oxygenase, thus preventing the formation of thromboxane A_2, a powerful proaggregatory material. But aspirin also inhibits the same enzyme in the vessel wall, stopping the production of prostacyclin. So failure to show an aspirin benefit might arise from using a dose that blocks both the "bad" thromboxane A_2 and the "good" anti-aggregatory prostacyclin.

At present, Mitchell concluded, we had no convincing evidence that aspirin, whether in conventional or lower dosage, reduced mortality after a heart attack. Various explanations could be offered. If the theory of the action of aspirin in preventing platelet aggregation is correct, then a much lower dose than those selected for the six trials could be adequate to block the "bad" substance and spare the "good" one. Perhaps 300 mg or less every third day would suffice — instead of the daily aspirin dosage, sometimes reaching 1 g or more, used in the trials done so far.

Another explanation might be that our concepts about the mode of action of aspirin are irrelevant from a clinical viewpoint. The effects on platelet behaviour could have little true physiological or pathological importance. A third explanation arises from the inevitable complexity of clinical trial design, especially with large numbers of patients.

Clinical Trial Problems

How early in convalescence after a heart attack should inhibition of platelet aggregation begin? Are patients who suffered their attack six months before or earlier to be included in a trial? Should we exclude patients with poor prognostic features, such as previous congestive heart failure or cardiac arrhythmias, because these are likely to outweigh any likely benefits from anti-platelet activity? Is there possibly an age or sex difference in the protection afforded by aspirin?

Questions such as these were posed at a high-level conference held in Bethesda, Maryland to consider the problems of the various aspirin trials and reported by Dr Richard J. Jones, a member of the scientific staff of the American Medical Association (iv).

As was almost inevitable, the experts at the conference were troubled by the flaws and inconsistencies in some of the individual trials and by the tantalising, if not entirely persuasive, evidence of benefit. The general conclusion (wrote Dr Jones) could be reached that non-fatal myocardial infarction was inhibited in those receiving aspirin for secondary prevention, but the reduction in total mortality did not seem to reach statistical significance.

And he had another explanation to offer: "This may be because those patients who die late after myocardial infarction may include too many with myocardial insufficiency, irritable arrhythmogenic foci, and critical areas of myocardial ischaemia whose course will not be significantly affected by a salutary influence on the platelet aggregative mechanism — even though that may inhibit progression of the disease."

In other words, anti-platelet therapy can reasonably be expected to prevent those deaths due to coronary thrombosis, but not necessarily all the deaths that may take place after an initial heart attack. Most of the trials have taken "all cause" or total mortality as their major endpoint, thus making it more difficult to determine the exact effectiveness of aspirin in preventing recurrent infarction as a result of coronary thrombosis.

Where does all this uncertainty, confusion and disagreement leave the clinician? Mitchell considers the present verdict as "not proven". Elwood finds it difficult to reject the evidence of benefit, but carefully points out that the practical implications are small. His 1979 trial showed a difference between aspirin and placebo groups of 18 per cent in terms of survival, but the figure represents a proportionate reduction in death rates from 10.3 per cent in the placebo group to 8.5 per cent in the aspirin group.

What this means in practice is that of every 100 patients 2.5 more will, on average, survive for a year if given aspirin than if treated expectantly. Admittedly, this is a small benefit if viewed in epidemiological or public health terms — though, perhaps, not entirely to be dismissed as negligible, at least by the 2 or 3 patients concerned.

Elwood himself, at the 1980 Aspirin Symposium, gave a disarming reply to a question from the floor about the approach a GP should adopt to this use of aspirin. He didn't think he was the right person to answer the question, but speaking personally he said he did not take aspirin daily to prevent a heart attack. On the other hand, he confessed that he seemed to get a headache on most days!

Primary Prevention

Elwood's wry comment highlights an aspect of the problem which has received much less attention — the role of aspirin in *primary* prevention. All the trials done so far involved patients after a heart attack, when (it might reasonably be argued) most of the damage has already been done. The drug should work more effectively in preventing the first heart attack, especially in view of the evidence that it protects patients at high risk of a stroke (those with transient ischaemic attacks).

Such a trial of primary prevention is being undertaken by Sir Richard Doll and his colleagues at Oxford in association with the Aspirin Foundation. A total of 6,000 physicians have been allocated either to daily, low-dose aspirin or to the control group, who were asked to avoid all aspirin-containing preparations and to use an alternative such as paracetamol should they need a mild analgesic. The trial began in 1978 and may have to continue for a few more years before any firm conclusions are possible. A similar trial among physicians is being planned in the United States.

This trial may also provide evidence on the safety of aspirin when taken by otherwise healthy people. The *Lancet* editorial cited above noted that in 1 g daily doses employed in most trials, dyspepsia, nausea and even vomiting occurred in between 10 and 20 per cent of patients, gout and melaena each in about 0.1 per cent a year and haematemesis in about 0.1 per cent a year. Stopping treatment usually resolved the problem, but the editorial maintained that these adverse effects could not be dismissed as trivial.

To attribute these adverse reactions to aspirin so categorically does not seem altogether just. In the largest of the secondary prevention trials▶

(AMIS, with a total of more than 4,500 participants) there was no statistically significant difference between the aspirin and placebo groups as regards the incidence of haematemesis, black, tarry stools or gout — although aspirin undoubtedly tended to cause more upper gastrointestinal side-effects than the placebo. A lower dose than the 1 g daily aspirin used in the AMIS trial might well of course give rise to fewer of these complaints.

Nor is aspirin likely to cause unduly troublesome problems in everyday clinical use. Some patients will refuse to take it because previous experience suggests that it tends to upset them. Another small group of people will find that it causes heartburn, stomach pain, nausea or some similar upset and stop the drug within a few weeks. But about 90 per cent of people should be able to tolerate a daily dose of 500 mg or less without any inconvenience or distress, even if the drug is taken for a long time.

In Greek mythology, Tantalus was condemned by the gods to hang from the bough of a fruit tree over a pool of water. When he bent his head to drink, the water receded — and when he reached for a fruit, the wind blew it beyond his grasp. What better word than tantalising to describe the outcome (so far) of all our efforts to establish the value of aspirin in preventing a heart atack?

References

(i) *JAMA* (1980) **243**, 661.
(ii) *Lancet* (1980) **i**, 1172.
(iii) *British Medical Journal* (1980) **280**, 1128.
(iv) *JAMA* (1980) **244**, 667. ■

FOOD INTOLERANCE AND ITS PREVENTION BY ASPIRIN

The role of diet in causing atherosclerosis, diverticulosis and colon cancer has received intensive study during the last decade. But, as an editorial comment noted, the possible short-term adverse effects of the various components of the diet have generally been ignored (i).

Yet intolerance (if not allergy) to food produces a wide variety of symptoms in susceptible people. These symptoms include asthma, eczema, rhinitis, aphthous ulceration, palpitation, anxiety, behaviour disturbances and even sudden death. The variety of food substances involved is also impressive: eggs, milk, coffee, tomatoes, potatoes, chocolate, yeast and fruits. Two particular conditions associated with apparent food allergy are infantile eczema and migraine.

Excluding eggs and milk from the diet sometimes proves helpful in infantile asthma. Sophisticated tests for food allergy, especially the radio-allergosorbent (RAST) tests, have recently shown that about two-thirds of patients with severe migraine were allergic to certain foods and that eliminating them from the diet resulted in most patients becoming free from symptoms for the first time (ii).

Acute gastrointestinal complaints, among them vomiting, diarrhoea and abdominal pain (sometimes associated with migraine, headache or rhinitis), can also be provoked by apparent intolerance to food. Youlten and his colleagues at Guy's Hospital Medical School in London described six patients who, on more than one occasion, experienced acute abdominal symptoms after the ingestion of a specific food (iii).

Among the foods implicated were cream, butter, cheese, egg, citrus fruit, tomatoes, mussels and pork. The investigators suggested that the reactions might be mediated by some mechanism involving prostaglandins, an idea prompted by the experience of one patient who found that while taking a prostaglandin inhibitor, ibuprofen, for sero-negative arthritis she was able to eat mussels without her usual symptoms.

Prophylactic Treatment

At the Aspirin Symposium in London in 1980, Youlten reported that the series of cases had been extended to twelve. All the patients had been asked to take prophylactic treatment — sometimes double-blind, placebo-controlled, with either aspirin or some other non-steroidal anti-inflammatory drug, usually indomethacin — before challenging themselves with the foods to which they believed themselves sensitive. In only one patient was the prophylactic medication ineffective; the remaining 11 patients reported no symptoms from the particular food after aspirin (in a dose of 600 or 900 mg) or indomethacin (25 or 50 mg).

In some of the patients, peripheral blood levels of prostaglandins and their metabolites were measured during unprotected and protected challenge in the hospital ward. Patients who experienced symptoms generally showed a small but measurable rise in peripheral blood prostaglandin levels — usually corresponding in time to the onset of the abdominal symptoms. It thus seemed that increased production of prostaglandins in the gut might be reflected by a rise in the blood levels.

In two of the patients, the investigators measured prostaglandin levels both during prevention by using a non-steroidal anti-inflammatory agent and direct challenge with the offending food. There was no corresponding rise in prostaglandin levels when the drug prevented the reaction.

Inhibiting Prostaglandins with Aspirin

Dr Youlten concluded that some adverse reactions to food might result from excessive production of prostaglandins in the gut and that these reactions could be prevented by aspirin or another prostaglandin synthetase inhibitor. So although there has been much argument about the safety of giving aspirin to patients with gastrointestinal symptoms, because of the possible irritant effects on the gastric mucosa, this drug might well be effective in preventing the symptoms associated with food intolerance.

At the same time, Dr Youlten warned physicians against assuming that a good response to aspirin precluded the need to carry out a proper investigation in these patients. He cited the case history of a woman who presented with a history of diarrhoea, occasionally blood-stained, abdominal pain and occasional distension, all of which she attributed to a specific food intolerance. Aspirin, she added, relieved all the symptoms.

Proper investigation in fact revealed a carcinoma of the sigmoid colon.

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(i) *Lancet* (1979) **i**, 249.
(ii) *Ibid* (1980) **ii**, 1.
(iii) *Ibid* (1978) **i**, 906. ■

Material in these abstracts has been derived in part from the Proceedings of the Third Symposium held at the Royal College of Surgeons of England in 1980. Copies of the printed proceedings of this symposia (and the first two symposia) are available free on request from the Director, Aspirin Foundation, 1 Robert Mews, Lowndes Place, Belgrave Square, London SW1X 8DA.