



'Aspirin: the developing story'

Aspirin Foundation Conference

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Professor Peter Elwood, University of Wales College of Medicine, opened the conference by outlining the history of aspirin. He said aspirin was synthesised in 1897 and, by the end of the century, it was a popular medicine with no real competition. Adverts in the *British Medical Journal* of the time described it as '*the most used and beloved medicine*' for treating fever, pain, migraine, rheumatic fever, arthritis, tonsillitis, cancer, corns and warts.

The first randomised trial of aspirin in the prevention of cardiovascular events was published in 1974 and showed that it reduced total mortality by 24 percent. Since then, more than 140 randomised trials have found that aspirin reduces the risk not only of myocardial infarction but also of stroke. There is also suggestive evidence that aspirin use may be associated with a reduced risk of Alzheimer's disease, though this has not been confirmed in a randomised trial.

Evidence is now accumulating that aspirin may also be of benefit in preventing certain cancers - in particular, it has been shown to prevent the recurrence of colorectal adenomas (a precursor of cancer). Several randomised trials are now underway in the UK to determine the efficacy of aspirin in cancer prevention.

Professor Ronald Eccles, Director of the Common Cold Centre, University of Cardiff, reviewed the use of aspirin in the treatment of colds and flu. He noted that its effectiveness for relieving cold symptoms is widely accepted but there has been little formal evaluation of its efficacy and tolerability.

The Common Cold Centre in conjunction with Bayer therefore conducted a randomised placebo-controlled double-blind trial. They found that aspirin significantly relieved sore throat compared with placebo, with a 20 - 30 percent difference in pain intensity scores between the two groups. Aspirin also significantly relieved pain due to headache and muscle ache. Overall, its duration of action was 6 hours.

The study revealed no safety concerns with aspirin. Reported adverse events included minor symptoms such as gastrointestinal upset and headache; some of these are part of the cold syndrome and there was no significant difference in their frequency between the two groups.

People with migraine often don't expect to be taken seriously by health professionals said **Dr Anne MacGregor, Director of Clinical Research and Trustee of the City of London Migraine Clinic**, and many do not consult their GP because they believe there is no effective treatment. Even those who have access to prescribed treatment also use OTC medicines: approximately 70 percent use paracetamol or ibuprofen and around 50 percent use an analgesic and antiemetic combination or aspirin⁶.

OTC analgesics are the treatment of first choice for migraine and both the dose and the formulation are important. The usual dose of aspirin in the UK (600 mg) is too low - 1,000 mg is more effective and should be taken as a dispersible tablet for a quicker

onset of action. Aspirin can be effective even in patients accustomed to using a triptan to treat migraine and its duration of action is at least 6 hours. Patients should be encouraged to carry aspirin so that they can take it early in the course of an attack.

Aspirin is widely perceived to be associated with poor gastrointestinal tolerability - indeed, abdominal pain is its commonest side effect. However, over-sensitivity to this issue erects a greater barrier than is appropriate to its short-term use for self-limiting pain conditions, said **Dr Timothy Steiner, Division of Neuroscience and Mental Health, Imperial College London.**

A meta-analysis of randomised placebo-controlled trials of single doses of aspirin 1000 mg found that adverse events most often involved the gastrointestinal tract but most were mild to moderate in severity. Of these, investigators concluded that events possibly, probably or definitely related to treatment had occurred in 3.1 percent of patients taking aspirin and 2.0 percent taking placebo. Many were more likely due to the underlying condition (e.g. nausea or vomiting in patients with migraine) and unmasked by treatment that relieved pain rather than caused by it. These findings are supported by interventional and observational studies.

Overall, the risk of gastrointestinal events with aspirin used OTC for short-duration pain is not high. Between 1 in 40 and 1 in 90 people taking a single dose of aspirin will have an adverse gastrointestinal event and most such events will be minor and unimportant.

Reviewing the role of aspirin in the management of dementia, **Dr Tony Bayer, Director of the Memory Team, and Senior Lecturer in Geriatric Medicine, Cardiff**

University, said there are currently around 750,000 people with dementia in the UK and 125,000 new cases occur each year. It was formerly believed that Alzheimer's disease accounted for at least half of all cases but it's now clear that vascular dementia is more common than previously thought and mixed dementia (Alzheimer's disease plus vascular dementia) accounts for about one-quarter of cases.

Stroke is a major cause of vascular dementia and for every person with post-stroke cognitive impairment of sufficient severity to lead to dementia, another develops milder cognitive impairment. The value of low-dose aspirin as secondary prevention of stroke is indisputable: over 3 years, it reduces the incidence of ischaemic stroke by 39 events per 10,000 persons at the cost of an increase in haemorrhagic stroke of 12 per 10,000. It follows that aspirin should reduce the risk of vascular dementia but unfortunately no randomised study has been carried out. It is hoped that evidence on primary prevention will be available in the next 5 - 7 years.

In the UK, over 80 percent of psychiatrists and geriatricians say they prescribe aspirin for patients with cognitive impairment and risk factors for vascular disease; and primary care guidelines for the management of dementia support the use of low-dose aspirin to reduce risk of further vascular events in people with early dementia related to cerebral ischaemia. However, many people with dementia do not receive aspirin when it is indicated.

Professor Clive Ballard, Director of Research, Alzheimer's Society and Professor of Age Related Diseases, Institute of Psychiatry/King's College London, outlined the effects of aspirin and other NSAIDs in patients with Alzheimer's disease. There is good evidence that vascular changes contribute to the impact of Alzheimer's disease, he said, and there are several potential targets for aspirin. It

may reduce the microglial inflammatory response to Alzheimer pathology. Some NSAIDs, including aspirin, inhibit the enzyme gamma secretase which is responsible for the formation of amyloid-beta. Endogenous stem cells have been identified in the brains of patients with Alzheimer's disease or stroke and aspirin has been shown to upregulate the activity of these cells.

A meta-analysis of 9 observational studies involving 13,211 patients taking NSAIDs reported that the risk of developing Alzheimer's disease was reduced by 28 percent overall and by 73 percent after 2 or more years' use. For aspirin alone, however, the risk reduction was not statistically significant. There are currently no randomised trials of aspirin in patients with Alzheimer's disease.

Stroke is the third commonest cause of death and the commonest cause of long-term disability in the UK but aspirin, which reduces death and disability associated with stroke, is under-used said **Professor Colin Prentice, Professor Emeritus, General Infirmary, Leeds.**

In 1994, the Antiplatelet Trialists' Collaborative published a meta-analysis of randomised trials in patients with stroke or transient ischaemic attack, showing that antiplatelet therapy (principally aspirin) reduced the number of vascular events and, in high-risk patients overall, was associated with a reduction of one-third in the risk of stroke. Aspirin is also effective in the treatment of acute stroke, reducing death or dependency at discharge by 11 - 13 events per 1,000 patients.

Until recently there was little evidence that aspirin is effective as primary prevention of stroke. In the Women's Health Study aspirin 100 mg on alternate days reduced

ischaemic stroke by 30 percent compared with placebo. Aspirin was associated with a higher incidence of gastrointestinal events (4.6 vs. 3.8 percent with placebo).

Atherosclerosis of the carotid artery is one cause of ischaemic stroke. Carotid endarterectomy can more than halve the relative risk of subsequent stroke in symptomatic patients but, despite prophylaxis with aspirin, up to 3 percent of patients develop thrombotic stroke postoperatively. **Dr Sally Ward-Booth, Specialist Registrar in Surgery, South West Rotation and Department of Cardiovascular Sciences, University of Leicester**, described how her research had shown that heparin transiently reverses the antiplatelet effects of aspirin in patients undergoing carotid endarterectomy, increasing the risk of postoperative thrombosis.

She and co-workers noticed that platelet aggregation, though inhibited by prophylactic aspirin, increased after heparin infusion. This was not due to a direct effect of heparin on the platelet or to the induction or activation of COX-1 or COX-2. However, unfractionated heparin was found to activate platelets via the lipoxygenase pathway when aspirin blocked the COX pathway. This phenomenon is significantly reduced in patients treated with low molecular weight heparin, suggesting that such agents should decrease the risk of postoperative stroke in patients after carotid endarterectomy. These findings illustrate there is still much to learn about aspirin and platelets despite long clinical experience.