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NEWS BRIEFS from the Aspirin Foundation

Aspirin: still learning....

It is well over 100 years since aspirin was discovered but there is still much to learn about its properties and therapeutic effects. It is now established as effective in the secondary prevention of cardiovascular events and as primary prevention in people at high risk and its safety profile is reassuring. This newsletter summarises some recent research on aspirin's tolerability, aspirin sensitivity and its importance in preventing stroke. Recent evidence concerning Reye's syndrome will be reviewed in a later issue.

GI myths challenged

Popular myths about the gastrointestinal tolerability of aspirin have been challenged by research reviewed at a recent expert consensus meeting (see www.aspirin-foundation.com/documents/NewsBriefsfromtheAFDec2004_Prof_.pdf). It is now accepted that the most widely-used over-the-counter analgesics are associated with a low risk of adverse effects and have broadly comparable tolerability. Many single-dose studies have shown that OTC doses of aspirin are well tolerated across a broad range of indications, and aspirin is also well tolerated in the treatment of rheumatoid arthritis and osteoarthritis. The importance of risk factors for gastrointestinal intolerance is well recognised but new data suggest that aspirin scavenges free radicals and may actually have a protective effect on endothelial cells. Overall, the experts concluded, there is little to show that OTC aspirin is associated with a greater frequency or intensity of gastric side effects than other OTC analgesics.

Meta-analysis confirms lower doses of aspirin are safer

A meta-analysis presented at the European Society of Cardiology Congress in Stockholm in September has confirmed that the best tolerated dose of aspirin for cardioprotection is 100 mg/day or less.

(www.biospace.com/news_story.cfm?StoryID=21054820&ull=1).

The analysis was carried out by US investigators and included 31 clinical trials with at least one month's follow-up, involving a total of 192,000 patients. The total incidence of any bleeding events (ranging from minor to potentially life-threatening) was 3.26 percent at the lowest dose of <100 mg/day, 11.3 percent at 100 - 200 mg/day and 9.4 percent at over 200 mg/day.

The authors concluded that it would be prudent for patients and physicians to consider a lower dose aspirin for cardioprotection. In the UK, the recommended dose is 75 mg/day.

Aspirin: dose and resistance

The US study linking aspirin dose with the risk of gastrointestinal events poses a dilemma when considered in light of a study from China, where researchers suggest that lower doses of aspirin may be associated with a greater risk of aspirin resistance in patients referred to a cardiac centre (*Am J Med 2005;118:723-7*).

Defining aspirin resistance as failure to reach a threshold platelet aggregation time, they found that the prevalence decreased from 30 percent in patients taking up to 100 mg/day to 17 percent with 150 mg/day and zero with 300 mg/day. Other factors that predicted aspirin resistance included older age, being female, anaemia and renal insufficiency. The investigators say that randomised studies should now be conducted to determine the optimal aspirin dose for cardioprotection.

From resistance to sensitivity

Two studies have recently explored how the diagnosis of aspirin sensitivity could be improved. Polish investigators report a new test for aspirin sensitivity based on a blood test (*Allergy 2005;60:1139-45*). They noted that, in aspirin-sensitive people but not in others with asthma or rhinosinusitis who were aspirin-tolerant, aspirin triggers the release of the arachidonic acid metabolite 15-

hydroxyeicosatetraenoic acid (15-HETE) by epithelial cells from nasal polyps and by leucocytes in the blood.

To determine whether this could be used as a diagnostic test, they measured in vitro 15-HETE production by leucocytes using cells taken from aspirin-sensitive or aspirin-tolerant people with asthma and healthy controls. In the absence of aspirin, 15-HETE production was similar in the three groups. However, incubation with aspirin resulted in a 4-fold increase in 15-HETE by leucocytes from aspirin-sensitive people but little change in the other groups. The authors calculated that the sensitivity of their test was 83 percent and its specificity was 82 percent, making it a potentially useful tool.

A patient's history of reactions to aspirin can be unreliable but oral challenge under controlled conditions provides definitive evidence to confirm or refute the diagnosis of aspirin sensitivity. This procedure involves gradually increasing the dose of aspirin from 30 mg until symptoms occur. Reviewing their oral aspirin challenge service for patients with suspected aspirin sensitivity, asthma specialists at London's Guy's Hospital made an interesting observation (*Clin Exp Allergy* 2005;35:7171-22).

The Guy's team report that reducing the interval between doses from 2 hours to 90 minutes achieves substantial savings in clinic time - an important difference when only 28 of 80 people they tested for this study were found to be aspirin-sensitive. Interestingly, they noted that the vast majority of patients who tested positive for aspirin sensitivity reported a history of multiple symptoms: around 90 percent of those with asthma or angio-oedema, 60 - 70 percent of those with rhinosinusitis or urticaria, and all of those with anaphylaxis had previously developed bronchospasm or nasal symptoms, plus urticaria or angio-oedema. Only a minority of patients with confirmed aspirin sensitivity reported having only single symptoms.

Reports of multiple symptoms due to aspirin sensitivity should therefore raise the index of suspicion and help to target resources to patients who are likely to be truly aspirin sensitive.

Poor compliance increases stroke risk

Stopping aspirin prophylaxis is an important cause of stroke recurrence, say Swiss investigators (*Arch Neurol* 2005;62:1217-20).

They compared aspirin use in 309 patients who were admitted after suffering an ischaemic stroke or transient ischaemic attack (TIA) with that in controls who had not had a stroke within the previous 6 months. The two groups were well matched, except that twice as many of those admitted had coronary heart disease (36 vs. 18 percent).

Aspirin had been discontinued in the 4 weeks before admission by 13 patients admitted but by only 2 controls. After adjusting for risk factors, stopping aspirin was found to have increased the odds of a stroke or TIA by a factor of 3.4. The authors say their finding emphasises the importance of compliance with low-dose aspirin for continued protection against stroke, particularly for patients who also have coronary heart disease.

Incomplete platelet inhibition after stroke

Aspirin may not fully inhibit platelet function in some patients who have suffered an ischaemic stroke, say researchers in London (*Platelets* 2005;16:269-80).

They measured platelet activity in 103 patients with recent stroke (within 4 weeks or less) or who were convalescing after a stroke (within 3 months). None met conventional criteria for aspirin resistance but it was found that aspirin 75 - 300 mg/day had not fully inhibited platelet function in 60 percent of patients after recent stroke and in 43 percent of those convalescing. In these patients, platelets appeared to be hyperreactive when stimulated by exposure to collagen or adenosine phosphate.

One explanation may be an abnormality of the clotting process due to a functional loss of von Willebrand factor (a protein that reduces platelet adhesion to collagen but not platelet aggregation): in the subgroup of patients with recent stroke, plasma levels of antigens to von Willebrand factor were raised.

The authors conclude that low to medium doses of aspirin do not completely inhibit platelet function in some patients with ischaemic cerebrovascular disease, apparently due to mechanisms independent of the cyclo-oxygenase pathway.

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