ASPIRIN AND VASCULAR DISEASE

SUMMARY

- Aspirin is an effective antiplatelet agent for patients with cardiovascular and cerebrovascular disease.
- Incidence of adverse effects and drug interactions increases with higher doses.
- Aspirin should be prescribed for acute and prior myocardial infarction, stable and unstable angina, stroke or transient ischaemic attack.
- Soluble aspirin 75mg appears to be as effective as higher doses for most indications.

INTRODUCTION

Aspirin is some 100 years old and is probably the best known and most widely used medicine in the world. From its analgesic, antipyretic and anti-inflammatory properties, all recognised in its first few years, aspirin has been transformed into a cardiovascular agent. Cardiovascular disease is the single most important cause of mortality in the Western World. During the past two decades the efficacy of oral aspirin treatment in the secondary prevention of vascular disease has been established. What was once looked upon as a side effect has been transformed into a major indication. A drug that was given in gram doses is now prescribed in milligrams. It is widely used throughout the world, is very potent and very cheap.

PHARMACOLOGY/MECHANISM OF ACTION

It is believed that most of the benefits of aspirin in cardiovascular disease are derived from its antiplatelet effect. This is mediated by the irreversible inhibition of platelet cyclooxygenase and subsequent production of thromboxane A_2.[1] This compound is a vasoconstrictor, causes platelet aggregation and is thus potentially thrombotic. These benefits are fully present even at small doses e.g. 75mg.[2,3]

INDICATIONS

The Antiplatelet Trialists Collaboration examined the worldwide randomised evidence on the prevention of serious vascular events by antiplatelet therapy.[4] The most widely tested regimen was medium-dose aspirin (75-325mg/day). They found that prolonged antiplatelet therapy confers sustained protection against serious vascular events among a wide range of patients at high risk of vascular disease. Therefore in the absence of a contra-indication, aspirin should be considered in the following groups:

- Coronary Heart Disease (infarction or angina) or following revascularisation procedures.[4,5,6]

- Asymptomatic carotid stenosis, transient ischaemic attack (TIA) or ischaemic stroke.[4,7, 8]

- Atrial fibrillation where a decision not to anticoagulate has been made.[4]

- Patients with peripheral vascular disease who are at significant risk of developing atherosclerotic vascular complications. [4]

There is insufficient evidence to support the use of prophylactic aspirin in patients with diabetes mellitus who have no additional risk factors. Diabetic patients with increased risk of vascular events should be treated in line with the recommendations for those indications.[4] Diabetic retinopathy is not necessarily a contra-indication to antiplatelet therapy.[9]
There is no clear evidence for the routine use of antiplatelet therapy in patients at low risk of occlusive vascular events. [4]

DOSAGE AND DURATION

There is a growing body of evidence that aspirin 75mg daily is as efficacious as higher doses in the prevention of secondary vascular events. [10,11]

The only indications for using higher doses are for acute myocardial infarction or acute ischaemic stroke, where at least 150mg should be given and continued for one month. Patients may then be continued on 75mg aspirin daily. [6,12]

In terms of gastric bleeding associated with aspirin there is no 'safe' dose, but there is evidence to suggest that the risk is dose-dependent. [7,11,13] While some experts maintain that low dose aspirin may not be as effective as higher doses in the prevention of secondary stroke, this is unproven and any extra benefit is likely to be offset by the increased risk of gastric haemorrhage.[7]

While in theory the prolonged antiplatelet effect of aspirin may allow the use of alternate day regimens there is no significant body of evidence to support this and accordingly it cannot be recommended.

It is difficult to determine directly from the trials how long antiplatelet therapy should be used. It is generally accepted that it should be continued indefinitely in patients who remain at high risk of occlusive vascular events, unless some clear contra-indication develops. [4,12]

WHICH FORMULATION ?

Soluble aspirin is rapidly absorbed and is the preferred preparation when a rapid antiaggregatory effect is needed such as during acute myocardial infarction.

Enteric coated formulations have an outer layer designed to prevent the tablet from dissolving in the acidity of the stomach and to release their contents only on reaching the duodenum.

While the local effects may contribute to gastric haemorrhage most gastric toxicity is attributable to the systemic effects of aspirin (as with other NSAIDs).[13]

At a daily dose of 75mg the advantages of enteric coating appears to be short-lived with no significant evidence of increased safety beyond the first few weeks of therapy.[13,14]

There are anecdotal reports to suggest that some patients intolerant of soluble preparations may tolerate enteric coated preparations.[7]

The cost of the various preparations seems to defy all logic with the lower dose preparations costing more than the higher dose preparations and one soluble preparation costing over 10 times more than another equivalent preparation. Cost conscious prescribers should specify the exact preparation required.

CONTRA-INDICATIONS

The use of aspirin is contra-indicated in those with a definite history of hypersensitivity, such as aspirin induced asthma, angioedema or urticaria. It is also contra-indicated in those at high risk of bleeding e.g. active peptic ulcer, recent major trauma, history of bleeding diathesis such as haemophilia. Aspirin may increase serum urate in patients with gout. [4,10,15]

INTERACTIONS

Cyclo-oxygenase inhibitors including aspirin and NSAIDs may attenuate the efficacy of angiotensin-converting enzyme (ACE) inhibitors by interfering with prostaglandin synthesis. Patients taking aspirin may not benefit from ACE inhibition.[16] Studies have tried to evaluate the incidence of the counteractive phenomenon and to define a minimum aspirin dosage that causes an antagonistic effect. It seems that 300mg daily may adversely affect ACE inhibition but this does not seem to occur at doses less than 100mg daily. It is generally accepted that the interaction between ACE inhibitors and aspirin becomes less significant at a dose of 75mg daily.[17]
Some NSAIDs can reduce the antihypertensive effects of beta-blockers. The situation with aspirin is a little uncertain. It seems prudent to monitor the effects when any NSAID is used with a beta-blocker.[18]

OTHER ANTIPLATELET AGENTS

There is no evidence from the Antiplatelet Trialists Collaboration that another antiplatelet agent would be more effective at preventing vascular events than aspirin.[4]

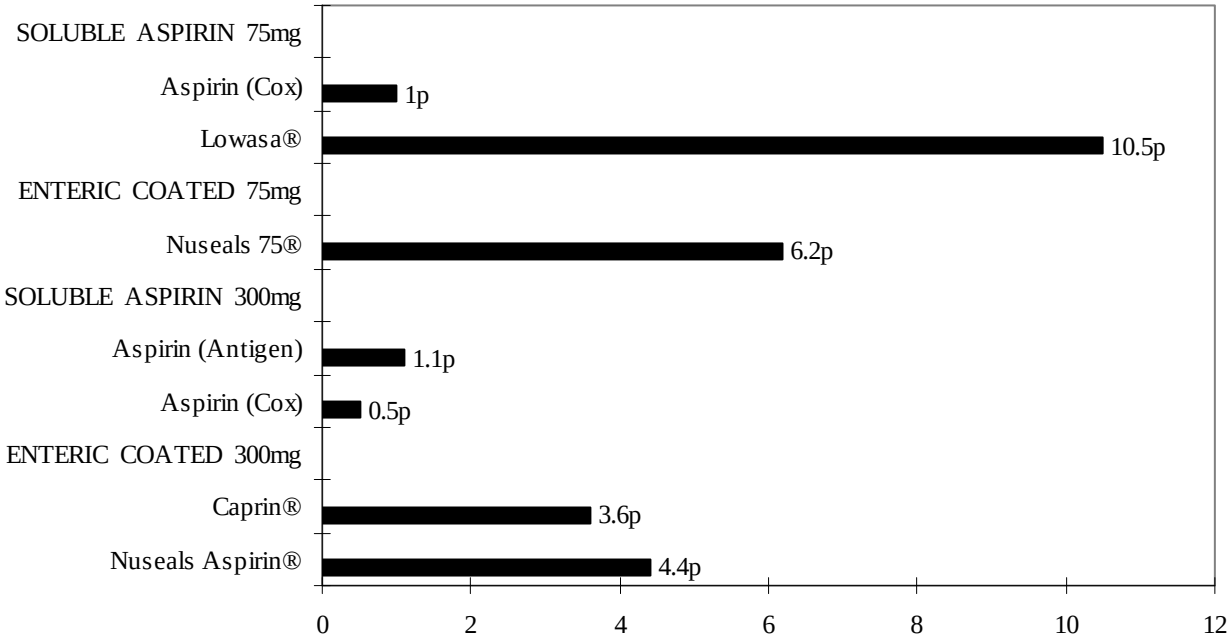
The routine use of antiplatelet agents such as dipyridamole, ticlodipine (unlicensed) and clopidogrel (license pending) are not supported by the literature. They are much more expensive but may have a role in patients intolerant to aspirin who are poor candidates for treatment with oral anticoagulants [6,7]

COST

- Almost 730,000 GMS prescriptions for aspirin were dispensed in 1997 making it the most commonly prescribed drug.
- Almost £1million was spent on aspirin in the GMS in 1997

Comparative Daily Costs Aspirin Preparations

Drug costs are based on data from GMS 1998



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