The Antiplatelet Activity of Aspirin

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The synthesis of aspirin in the late nineteenth century marked the development of what was to become the most widely used household analgesic in the twentieth century. However, with the increased understanding of the major role of platelets in vascular occlusion over the last ten years, the importance of aspirin as an antiplatelet drug and, consequently, its applications in reducing the risks of thrombotic vascular events, have received major attention.

Pharmacology and Mechanism of Action

Aspirin, otherwise known as acetylsalicylic acid, acts by acetylation of the two isoenzyme forms of prostaglandin G/H synthase. This results in the irreversible inactivation of the cyclooxygenase activity of this enzyme, preventing the conversion of arachidonic acid to prostaglandin G_2, and consequently decreasing biosynthesis of prostaglandin H_2 and thromboxane A_2. The type one isoenzyme of prostaglandin G/H synthase is constitutively expressed in platelets, where synthesis and release of thromboxane A_2 occurs in response to a variety of stimuli, resulting in irreversible platelet aggregation. Platelets, platelet products and thombosis play important roles in the occurrence of acute occlusive vascular events, including myocardial infarction (MI) and ischemic stroke, since the disruption of platelet- and fibrin-rich atheroschlerotic plaque may be followed by aggressive platelet deposition and, ultimately the development of a thrombus that can precipitate an acute occlusive event. The decreased platelet aggregation caused by aspirin is the most plausible mechanism for the cardioprotective effects of this drug.

Dose-dependant inhibition of platelet cyclooxygenase activity occurs with single aspirin oral doses of 5 to 100 mg, with the latter dose resulting in practically total suppression of thromboxane A_2 biosynthesis. The onset of activity of the drug is extremely rapid and unrelated to systemic bioavailability, probably due to platelet prostaglandin synthase suppression in the portal circulation. Furthermore, since platelets lack the intracellular machinery necessary to regenerate prostaglandin synthase, recovery from the effects of aspirin is related to platelet turnover (7 to 10 days), with repeated doses exerting a cumulative effect. This accounts for the fact that a drug with a half-life of 20 minutes is effective even when administered once daily.

Primary Prevention of Occlusive Cardiovascular Disease

The efficacy of aspirin at preventing important cardiovascular events, chiefly myocardial infaction, stroke and cardiovascular mortality has been assessed in healthy subjects and subjects with stable chronic angina. Also, since patients with insulin-dependent and non-insulin-dependent diabetes mellitus, and hypertensive individuals have an increased risk of cardiovascular complications, including myocardial infarction and stroke, these categories of patients have also received attention in studies assessing the antiplatelet activity of aspirin. The results of these studies are summarised in Table 1.

Despite the significant reduction in MI incidence noted in the Physicians' Health Study, the benefit of aspirin in healthy individuals appears to be minor, given the very low absolute risk of cardiovascular events in healthy individuals (only 5% had an event during approximately 5 years of follow-up). However, in patients with an existing medical condition predisposing to a cardiovascular event, the use of aspirin appeared to have significant benefits. In particular, in the medium-risk population investigated in the Swedish Angina Pectoris Aspirin Trial, the results suggested the potential to prevent 51 important cardiovascular events in 1000 patients over four years, an absolute benefit at least tenfold greater than that obtained in the British Doctors' Trial and the Physicians' Health Study. Similar benefits were also observed in hypertensive patients.

Secondary Prevention of Occlusive Vascular Disease

The benefits afforded by aspirin in the prevention of secondary cardiovascular events supercede those

Table 1: Trials of Aspirin in the Primary Prevention of Occlusive Cardiovascular Disease.

Study	Type of Subjects	Number of Patients	Aspirin Dose	Outcome
British Doctors' Trial	Healthy males, 50-78 yrs old	5,139	500 mg daily vs placebo	No significant difference
Physicians' Health Study (USA)	Healthy males, 40-84 yrs old	22,071	325 mg every other day vs placebo	39% decrease in MI; 18% decrease in important cardiovascular events
Swedish Angina Pectoris Aspirin Trial	Patients with chronic stable angina without previous MI	2,035	75 mg daily vs placebo	34% decrease in MI and sudden death occurrence; 22 - 32% decrease in secondary outcomes
Early Treatment Diabetic Retinopathy Study	Patients with diabetes, 49% of whom with cardiovascular disease history	3,711	650 mg daily vs placebo	28% decrease in MI, 16% increase in stroke, 18% decrease in important cardiovascular events
Hypertension Optimal Treatment Trial	Hypertensive patients (diastolic BP100-115 mmHg), 50-80 yrs old	18,790	75 mg daily vs placebo	36% decrease in MI, 15% decrease in major cardiovascular events

for primary events. The drug remains the standard antiplatelet reference compound for secondary prevention of myocardial infarction, cardiovascular-associated death, and stroke. To this date, no other antiplatelet agent can compete with aspirin in these indications. Three main areas, in increasing order of severity, have been identified where the antiplatelet activity of aspirin plays a significant role in preventing secondary cardiovascular events. These are:

a) unstable angina and nonacute myocardial infarction

b) suspected acute evolving myocardial infarction and acute nonfatal myocardial infarction, and

c) transient cerebral ischaemia and stroke.

Three major studies all established that the administration of aspirin, both short- and long-term, was particularly effective at reducing the risk of acute myocardial infarction and/or death (Table 2). Subgroup analysis in the RISC study also showed that the risk of myocardial infarction was reduced both in patients with silent ischaemia as well as in those with asymptomatic ischaemia detected during a presdischarge exercise test. However, doubt remains as to whether aspirin can affect the incidence or severity of myocardial ischaemia after an episode of unstable angina. However, the drug did reduce incidence of death and myocardial infarction in patients with this syndrome, regardless of any influence on episodes of transient ischaemia.

Although the results of most early studies in the benefits of aspirin against secondary cardiovascular events in patients with suspected acute evolving myocardial infarction and acute nonfatal myocardial infarction were consistent with the benefits of antiplatelet therapy, most trials were too small individually in sample size. In 1988, an overview was published by the Antiplatelets Trialists' Collaboration of the 25 completed trials in secondary prevention, followed by an updated overview in 1994. The results are summarised in Table 3 and, together with those of the Second International Study of Infarct Survival, demonstrate the effectiveness of antiplatelet treatment in promoting survival following myocardial infarction. Moreover, in the latter study, the combination of aspirin with intravenous streptokinase proved to be more effective than either agent alone. In absolute terms, the percentage reductions observed imply that the treatment of 1000 patients with acute myocardial infarction with aspirin for one month would prevent 38 fatal and nonfatal cardiovascular events.

The efficacy of aspirin in reducing the risk of recurrent vascular complications in patients with a history of transient ischaemic attacks or stroke was evaluated in various trials. An overview of these trials carried out by the Antiplatelets Trialists' Collaboration concluded that the administration of antiplatelet therapy for three years was effective at reducing the risk of nonfatal stroke, nonfatal myocardial infarction and cardiovascular death by about 25%, respresting, in absolute terms, the prevention of 37 cardiovascular events per 1000 patients over three years. Some doubt remains over the magnitude of the aspirin dose which is effective; while some investigators claim that larger doses are more effective, patients receiving larger doses in those studies reporting a beneficial effect were also receiving other antiplatelet drugs, in particular dipyridamole and sulfinpyrazone.

Maintenance of Vascular Grafts or Arterial Patency

A further outcome of the overview conducted by the Antiplatelets Trialists' Collaboration was the evidence of the benefits provided by antiplatelet therapy in reducing the incidence of arterial or graft occlusion after coronary-artery surgery (30% decrease) or angioplasty (50% decrease), and after the formation of a haemodialysis shunt or fistula (56% decrease). The data provided represented absolute benefits of 90 patients protected per 1000 over 7 months following coronary artery surgery, 40 patients per 1000 over 6 months following angioplasty, and 200 patients per 1000 over two months following formation of a haemodialysis shunt. The same group also concluded that antiplatelet therapy was effective at reducing the incidence of deep vein thrombosis and pulmonary embolism by 26% and 64% respectively, respresenting absolute prevention in 90 and 17 patients, respectively, per 1000 treated. While effective prevention was observed in a wide range of medical and surgical patients, the highest benefits were seen in general and orthopaedic surgery.

Side Effects and Safety of Antiplatelet Therapy with Aspirin

The regulation of several homeostatic mechanisms, including haemostasis, renal function, gastric acid secretion and blood pressure control, is modulated locally through eicosanoid synthesis. Inhibition of the constitutive prostaglandin G/H synthase pathway responsible for the production of these mediators is essentially responsible for the side effects associated with the long term administration of aspirin.

Gastrointestinal complications, such as bleeding and perforation, are observed with greater frequency in individuals on nonsteroidal antiinflammatory therapy. The incidence and severity of these complications are effected by the dosage regimen, the duration of treatment and the type of formulation used (plain vs enteric-coated). Comparison of daily doses of 900 to 1300 mg daily (300 or 325 mg three times daily) as against placebo for various studies exhibited a 40 to 60% increased incidence of stomach pain, heartburn and nausea. On the other hand, both the Veterans Administration Cooperative Study and the Research Group on Instability in Coronary Artery Disease in Southeast Sweden (Table 2) noted only minor increases in the frequency of gastrointestinal symptoms with daily doses of 324 mg and 75 mg aspirin, respectively. Similar dose-dependant results were also obtained by the United Kingdom Transient Ischaemic Attack (UK-TIA) Trial, which noted a 19% increase in upper gastrointestinal symptoms in patients given 300 mg aspirin daily over placebo, and a 58% increase in patients given 1200 mg daily.

The incidence of haemorrhagic

Table 2: Percent reductions in risk of death or acute myocardial infarction in trials among patients following episodes of unstable angina or nonacute myocardial infarction.

Study	Type of Subjects	Aspirin Regimen	Percent reduction
Research Group on Instability in Coronary Artery Disease in Southeast Sweden (RISC)	796 male patients	75 mg daily for 5 days 75 mg daily for 3 months 75 mg daily for 1 year	57-69% 64% 48%
Veterans Administration Cooperative Study	1,266 male patients	324 mg daily for 3 months	51%
Canadian Multicenter Trial	555 patients	325 mg 4 times daily for 2 years	30%

Table 3: Percent reductions in cardiovascular events among patients with suspected acute evolving myocardial infarction and acute nonfatal myocardial infarction.

Endpoint	Percent reductions in patients assigned antiplatelet therapy	
	Antiplatelet Trialists' Collaboration (long-term therpy; 1-3 years)	2nd International Study of Infarct Survival (short-term therapy; 5 weeks)
Nonfatal myocardial infarction	31	49
Nonfatal stroke	39	46
Cardiovascular mortality	15	23
Cardiovascular events	25	28

stroke amongst patients involved in antiplatelet studies was too small to permit any comparison amongst different aspirin dosage regimens. However, the UK-TIA Trial did observe a dose-response relation for extracranial haemorrhagic events, with an increased incidence of gastrointestinal haemorrhage at higher doses (5% incidence for patients taking 1200 mg aspirin daily, as against 3% for those taking 300 mg daily), possibly reflecting the presence of more severe gastric mucosal damage and thus a higher possibility of gastric bleeding.

Long-term administration of aspirin may also be associated with an increased risk of chronic renal disease and interference with blood pressure control in hypertensive individuals, since prostaglandin G/H synthase is involved in the renal synthesis of vasodilatory prostaglandins. While the use of aspirin at sub-antiinflammatory doses is unlikely to exert any effect (aspirin is only a weak inhibitor of renal prostaglandin synthase), the UK-TIA trial noted elevations in systolic blood pressures in patients on 300 mg and 1200 mg aspirin daily. Furthermore, this effect of aspirin in both renal and other peripheral tissues interferes with the action of angiotensin-converting-enzyme (ACE) inhibitors in controlling hypertension.

Conclusions

The benefits to be derived from long-term aspirin therapy are evident, particularly in secondary prevention of cardiovascular events. The progress in the understanding of the underlying mechanism of action of the drug and its dose-response relationship have led to the current recommendations of an initial loading dose of about 300 mg followed by a daily dose of 75 mg, the latter serving to decrease the possible incidence of side effects.

While the role of prescribing aspirin antiplatelet therapy and monitoring of its cardiovascular effects remain strictly that of the physician, the pharmacist, too, has a contribution to make. There exists the danger of the idea spreading among the general population that "an aspirin (or baby aspirin) tablet a day is good for one's health". Such an idea is, at the very least, questionable in the absence of predisposing health conditions and becomes certainly more so if the possibility of side effects and drug interactions discussed above is prevalent.

Nonetheless, the pharmacist remains in an ideal position to identify candidates in whom initiation of such therapy appears feasible, and should take it upon himself/herself to consult with and make recommendations to the patient's physician, particularly where administration of an aspirin antiplatelet dosage regimen might be effective in the prevention of cardiovascular events. ✶

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