REVIEW ARTICLE

Aspirin—the novel antiplatelet drug

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Aspirin is a non-steroidal anti-inflammatory drug that has potent antiplatelet actions. Aspirin was initially used as an analgesic and antipyretic drug before its anti-inflammatory properties were discovered. Aspirin also has antithrombotic effects due to the inhibition of cyclo-oxygenase activity in platelets, which reduces the extent of thromboxane A_2 formation and consequently the aggregability of platelets. Prophylactic low-dose aspirin therapy reduces the risk of future cardiovascular events in a variety of clinical settings. The maximum effect of aspirin in reducing risk of myocardial infarction is achieved soon after the initiation of therapy. The selective inhibition of platelet thromboxane A_2 may be the pharmacological basis for the effectiveness of aspirin in treating pregnancy-induced hypertension. Aspirin can virtually abolish thromboxane A_2 production in patients receiving fish oil. Thus, aspirin has been and will be the standard reference compound for long-term oral treatment of platelet hyperactivity, most notably in the secondary prevention of myocardial infarction.

HKMJ 1998;4:415-8

Key words: Aspirin; Cyclooxygenase inhibitors; Platelet aggregation; Thromboxane A2

Introduction

Aspirin is a non-steroidal anti-inflammatory drug that has potent antiplatelet actions. It was first produced commercially in 1899 and next year marks its 100th anniversary. Aspirin is regarded as one of the most important drugs of the century, yet its use dates back to the ancient Egyptians, who knew about the pain-relieving properties of plants.[1] Hippocrates (460-377 BC) knew of the pain-relieving effect of the juice obtained from the bark of the willow tree and in the Middle Ages, the bitter extract from boiled willow bark was a popular remedy for pain.[1] In 1838, salicylic acid was isolated from the glycoside salicin and was identified as the active ingredient of willow bark.

Acetylsalicylic acid was first synthesised in 1853 by Von Gerhardt, by mixing salicylic acid with acetic acid.[2] In 1894, Felix Hoffmann, a pharmacist at the Bayer company in Elberfield, Germany, gave acetylsalicylic acid to his father to treat rheumatoid arthritis; formal clinical trials soon followed.[3] In 1899, acetylsalicylic acid was patented by Bayer Co. under the trade name of Aspirin: 'a' stood for acetyl and 'spir' stood for Spirsaure (a German word for salicylic acid). So overwhelming was the popularity of acetylsalicylic acid, that its original trade name eventually became the generic name.

Initially, aspirin was used as an analgesic and an antipyretic. It was thought that aspirin affected the thalamus, thereby increasing the pain threshold. The anti-inflammatory properties of aspirin were subsequently recognised in 1971. The mechanism of action of aspirin—the inhibition of prostaglandin synthesis—was elucidated by Sir John Vane,[4] who was awarded the Nobel Prize in 1982 for this important contribution to medicine.

Mechanism of action of aspirin

The antithrombotic action of aspirin depends on the irreversible inhibition of arachidonate cyclo-oxygenase activity in platelets, thereby reducing the extent of thromboxane A_2 (TXA_2) formation and consequently the aggregability of platelets (Fig). The formation of intra-arterial thrombi is thus reduced. Aspirin effects a balance between TXA_2, which is released from platelets, and prostacyclin, which is made by the blood vessel walls.

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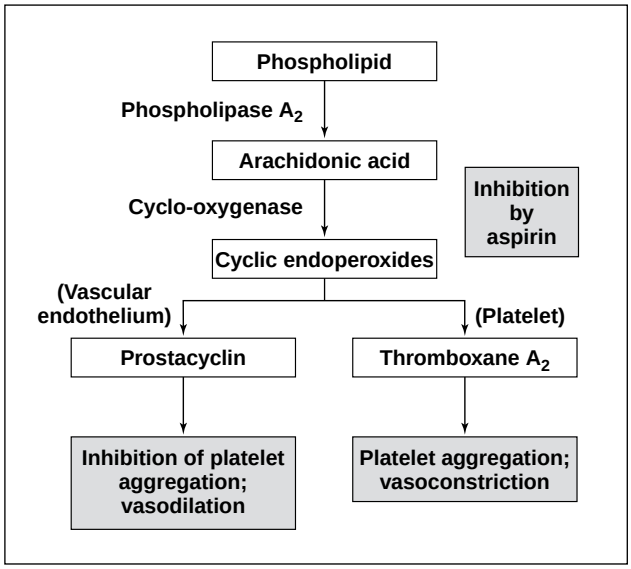

Fig. Mechanism of action of aspirin in platelets and vascular endothelium

Prostacyclin and thromboxane balance

Prostacyclin and TXA_2 are formed from the endoperoxide prostaglandin H_2, which is derived from arachidonic acid from the phospholipids of cell membranes (Fig). Thromboxane A_2 is an unstable but powerful vasoconstricting agent and an inducer of platelet aggregation. Prostacyclin is also unstable but induces vasodilation and inhibits platelet aggregation. Thromboxane A_2 and prostacyclin represent opposite poles of a homeostatic mechanism that regulates platelet aggregability in vivo.[5]

A number of cardiovascular thrombotic diseases have been associated with an imbalance in the prostacyclin-TXA_2 system. Platelets from patients with arterial thrombosis, deep venous thrombosis, or recurrent venous thrombosis produce higher than normal levels of TXA_2 and have a shortened survival time.[6] Platelets from patients who have survived myocardial infarction or ischaemic stroke are abnormally sensitive to aggregating agents and also produce more TXA_2 than do controls.[6]

Aspirin in coronary artery disease

Despite the anti–cyclo-oxygenase activity of aspirin, prostacyclin is produced continuously in endothelial cells because they recover the ability to synthesise cyclo-oxygenase within a few hours. However, platelets (being non-nucleated) cannot make fresh cyclo-oxygenase; consequently, TXA_2 synthesis only resumes when new platelets are made. (The life of a platelet in the circulation lasts for 8 to 11 days.) Thus, while a treatment regimen of low-dose aspirin (75-100 mg/d) will lead to a cumulative inhibition of TXA_2 formation in platelets, the production of prostacyclin in endothelial cells will continue.[7] A recent study shows that a controlled-release dose of aspirin 75 mg inhibits platelet TXA_2 generation without affecting the systemic production of prostacyclin by the vascular wall.[8] The selective action of aspirin in platelets has been ascribed partly to the regeneration of endothelial cell cyclo-oxygenase and partly to platelets encountering orally administered aspirin in the presystemic circulation before the aspirin is deacetylated in the liver and diluted by venous blood from other organs.[9]

Prophylactic low-dose aspirin therapy reduces the risk of future cardiovascular events in a variety of clinical settings.[10,11] The maximum effect of aspirin in reducing the risk of myocardial infarction is achieved soon after the initiation of therapy and does not change with time. Thus, the primary effect of aspirin is to inhibit platelet aggregation and acute thrombus formation during critical periods of increased TXA_2 production.[12,13] As a majority of acute myocardial infarctions results from the thrombotic occlusion of a coronary artery,[14] the net effect of long-term aspirin therapy appears to result from the inhibition of the platelet response at the time of platelet rupture.[15] This finding is consistent with laboratory studies that report an increased level of thromboxane metabolites in patients with acute ischaemia syndromes,[15] as well as clinical findings from the Second International Study of Infarct Survival—namely, that when aspirin therapy is started within hours of acute myocardial infarction, the overall mortality is reduced by 23%.[16]

Low-dose aspirin therapy reduces the risk of acute myocardial infarction among patients with a history of stroke or unstable angina and among apparently healthy individuals.[17] In addition, it is possible that patients who have infarctions while receiving chronic aspirin therapy have fewer complete coronary occlusions, achieve earlier repercussion, and have an increased likelihood that the infarction will be of the small, non–Q-wave type.[18]

Aspirin and vein/artery graft surgery

Vein graft patency is significantly improved when aspirin 324 mg is given within 1 hour of coronary artery bypass graft surgery and continued once daily for at least 12 months.[17] Protection against occlusion is observed at 1 week, and further significant improvement in late graft patency is observed at 1 year for grafts involving a small diseased vessel. The benefits are achieved without significantly increasing postoperative blood loss or the re-operative rate.[19] Aspirin

is also protective against occlusion of vein grafts involving arteries that require endarterectomy.

Aspirin and pregnancy-induced hypertension

Pregnancy-induced hypertension (PIH) encompasses a range of disorders that includes isolated hypertension, pre-eclampsia, and eclampsia; PIH occurs in 5% to 15% of all pregnancies. Although the exact cause of PIH is unknown, several mechanisms have been suggested; they include the development of enhanced sensitivity to vasopressors, the immunogenic reaction, and an imbalance in the production of vasoactive prostaglandins (ie TXA_2 and prostacyclin), thus resulting in the vasoconstriction of small arteries, platelet activation, and uteroplacental insufficiency.

The selective inhibition of platelet TXA_2 production by aspirin may be the pharmacological basis for the effectiveness of aspirin in treating PIH. Various clinical trials have suggested that aspirin, when taken in doses of 60 to 150 mg during the second and third trimester, reduces PIH and improves maternal and neonatal outcomes. A meta-analysis performed by Imperiale and Petrulis[20] suggests that low-dose aspirin reduces the risk of PIH and severe low birthweight, without adversely affecting the mother or foetus.

Aspirin and fish oil

In 1978, two important concepts about eicosanoid formation were published.[21,22] The first was that blood vessels can utilise endoperoxides that have been released by adhering platelets to form prostacyclin.[17] The second was that eicosapentaenoic acid from fish oil can produce an antithrombotic state that protects against cardiovascular disease by giving rise to an active analogue of prostacyclin—prostaglandin I_3.[22]

There is convincing epidemiological evidence that the risk factors for heart disease are decreased by eating fish or fish oil.[23] By monitoring urinary metabolites following the administration of fish oil and aspirin, Force et al[24] have shown that fish oil alone halves TXA_2 production in platelets, whereas aspirin in any dose (50-1300 mg/d) virtually abolishes it. In addition, low-dose aspirin substantially reduces prostacyclin production in patients who are receiving fish oil, but higher doses of aspirin have no further effect.[24]

Conclusion

Aspirin has been and will be the drug of choice for the long-term oral treatment of platelet hyperactivity, most notably in the secondary prevention of myocardial infarction. Aspirin is also the basic antiplatelet agent for all kinds of acute disease that may cause platelet-dependent thrombotic vessel occlusion.[25]

During the second conference on antithrombotic therapy in 1989, the American College of Chest Physicians recommended that aspirin be considered a part of treatment for all individuals who show evidence of coronary artery disease and for those with risk factors for coronary artery disease. Perhaps, if the suggestion of Dr Lawrence L Craven in 1953[26] of "an aspirin a day" had been adopted to treat cardiovascular diseases, hundreds of thousands of myocardial infarctions and strokes might have been prevented.

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