

6. ASPIRIN AND CLOPIDOGREL RESISTANCE

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Atherosclerotic vascular disease is a major cause of premature morbidity and mortality throughout the world. Atherosclerosis begins to affect the arteries of many people in the second and third decades of life. Typically, however, the symptoms of atherosclerosis do not occur until several decades later. Despite this long time course and the prolonged period of clinical inactivity, the complications of atheroma such as myocardial infarction, unstable angina or stroke typically appear suddenly. Atherosclerotic lesions not only lead to flow-limiting critical stenoses of the affected vessels, but may be complicated by thrombosis, resulting in ischaemic episodes. The platelets play a major role in this arterial thrombotic process. Drugs that inhibit the platelet function have proved to be effective in preventing the clinical complications of atherothrombosis. The benefits and limitations of two important antiplatelet agents, aspirin and clopidogrel, are discussed.

6.1 Characteristics of aspirin

Aspirin permanently inactivates the cyclooxygenase (COX) activity of prostaglandin (PG) H synthase-1 and PGH synthase-2, also referred to as COX-1 and COX-2. These isoenzymes catalyse the conversion of arachidonic acid to PGH₂. PGH₂ is the immediate precursor of PGD₂, PGE₂, PGF_{2a}, PGI₂ (prostacyclin) and TXA₂ (thromboxane).

Aspirin exerts an inhibitory effect on platelet COX-1 that is approximately 50-100-fold more potent than that on monocyte COX-2. Aspirin induces a permanent defect in the TXA₂-dependent platelet function. It is assumed to inactivate megakaryocytes too. Since approximately 10% of the platelet pool is exchanged each day, once-a-day dosing of aspirin is able to maintain an almost complete inhibition of platelet TXA₂ production. The inhibition of COX-2-dependent pathophysiologic processes requires larger doses of aspirin because of the decreased sensitivity of COX-2 to aspirin. A much shorter dosing interval is also necessary because nucleated cells rapidly resynthesize the enzyme. Thus, there is an

approximately 100-fold difference in the daily dose of aspirin when it is used as an anti-inflammatory rather than as an antiplatelet agent.

Human platelets process PGH₂ to produce TXA₂, while vascular endothelial cells produce PGI₂. TXA₂ induces platelet aggregation and vasoconstriction, while PGI₂ inhibits platelet aggregation and induces vasodilatation. TXA₂ is largely a COX-1-derived product and is highly sensitive to aspirin inhibition. Vascular PGI₂ can derive from both aspirin-sensitive COX-1 and largely aspirin-insensitive COX-2, which results in substantial residual COX-2-dependent PGI₂ biosynthesis in vivo at doses of aspirin in the range 30-100 mg.

Aspirin is rapidly absorbed in the stomach and upper intestine. Peak plasma levels occur 30 to 40 min after ingestion and inhibition of the platelet function is evident by 1 h. The oral bioavailability of regular aspirin is approximately 40-50%. A considerably lower bioavailability has been reported for enteric coated tablets and microencapsulated preparations. Aspirin has a short half-life (15-20 min) in the human circulation. Despite this rapid clearance, the platelet-inhibitory effect lasts for the life-span of the platelet because aspirin inactivates platelet COX-1 irreversibly. The mean life-span of human platelets is approximately 10 days.

The main side-effects of aspirin include gastric ulcers, renal failure and haemorrhagic complications.

6.2 Characteristics of clopidogrel

Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor, and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. The hepatic biotransformation of clopidogrel to an active metabolite is necessary to induce the inhibition of platelet aggregation. Clopidogrel also inhibits platelet aggregation induced by agonists other than ADP by blocking the amplification of platelet activation by released ADP. Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their life-span. This justifies a once-daily regimen of clopidogrel.

Clopidogrel is rapidly absorbed after oral administration, with peak plasma levels of the main circulating metabolite occurring approximately 1 h after dosing. Clopidogrel is extensively metabolized by the liver. The dose-dependent inhibition of platelet aggregation can be detected 2 h after a single oral dose of clopidogrel. Repeated doses of 75 mg clopidogrel per day inhibit ADP-induced platelet aggregation on the first day, and the inhibition reaches a steady state between day 3 and day 7. The platelet aggregation and the bleeding time gradually return to the baseline values after treatment is discontinued, generally in about 5 days. The elimination half-life of the main circulating metabolite after either single or repeated administration is 8 h.

Clopidogrel treatment leads to fewer gastrointestinal bleeding complications than those observed with aspirin.

6.3 Clinical trials

A meta-analysis of 287 randomized antiplatelet trials by the Antithrombotic Trialists' Collaboration documented that antiplatelet therapy reduced the overall risk of serious vascular events in high-risk patients by 22% as compared with the controls. Antiplatelet therapy is effective for patients with acute myocardial infarction, stable or unstable angina, stroke, transient ischaemic attack, and intermittent claudication. The meta-analysis concluded that daily aspirin doses of 75-150 mg seem to be as effective as higher doses for long-term treatment.

The results of the CAPRIE study indicated that the long-term administration of clopidogrel to patients with atherosclerotic vascular disease leads to a significant, 8.7% relative reduction in the risk of vascular events as compared with aspirin treatment. The overall safety profile of clopidogrel was at least as good as that of medium-dose aspirin. The recommended daily dose of clopidogrel is usually 75 mg.

The synergistic antiplatelet effect produced by using clopidogrel on top of aspirin may be beneficial in high-risk patients. The CURE study demonstrated that long-term treatment with clopidogrel in addition to standard therapy including aspirin was superior to the standard therapy alone in the prevention of major vascular ischaemic events in patients with unstable angina or non-Q-wave myocardial infarction. However, the risk of major bleeding among patients receiving this combined antiplatelet treatment was found to be increased.

6.4 Aspirin resistance

Aspirin fails to prevent approximately 80% of recurrent vascular events among high-risk patients. There are several reasons why aspirin may not be totally effective in preventing recurrent serious vascular events. One possible explanation is that some patients are resistant to the antiplatelet effects of aspirin. Other possible reasons include an incorrect diagnosis, non-compliance with the medication, drug interactions or an insufficient dose.

The term "aspirin resistance" has evolved to describe the failure of aspirin to produce the expected response as concerns one or more laboratory measures of platelet activation and aggregation. It has been estimated that therapy with aspirin does not result in adequate antiplatelet efficacy in 5-40% of patients with vascular disease.

There are various techniques with which to measure platelet aggregation, including optical platelet aggregometry, whole-blood aggregometry, and determination of the platelet aggregate ratio and platelet reactivity index. The PFA-100 is a semiautomated platelet function analyser which allows a rapid assessment of platelet adhesion/aggregation. The urinary 11-dehydro-thromboxane B2 level may also be used as a measure of the antiplatelet effects of aspirin.

Previous studies have revealed that cerebrovascular and cardiovascular patients found by laboratory tests to be aspirin-resistant are at an increased risk of major vascular events. In one of their recent publications, Eikelboom et al. defined aspirin resistance as a failure to suppress thromboxane generation. They measured the levels of urinary 11-dehydro-thromboxane B2, a marker of in vivo thromboxane generation, in cases treated with aspirin who had vascular events during a 5-year follow-up period, and in age- and

sex-matched controls who also received aspirin, but who did not undergo such an event. It was concluded that, in aspirin-treated patients, the urinary concentrations of 11-dehydro-thromboxane B2, a possible marker of aspirin resistance, predict the future risk of myocardial infarction or cardiovascular death. Gum et al. defined aspirin resistance on the basis of optical platelet aggregation testing. Aspirin resistance was associated with increased risks of death, myocardial infarction and cerebrovascular events as compared with patients who were aspirin-sensitive.

The results of several relatively small studies of stroke patients have suggested that larger doses may be more effective than lower doses in limiting laboratory aspirin resistance. However, a much larger database failed to substantiate a dose-dependent effect of aspirin in stroke prevention. Platelet aggregation, as measured by conventional methods *ex vivo*, may display limited sensitivity to the *in vivo* effect of aspirin.

6.5 Clopidogrel resistance

Although clopidogrel has been associated with a lower rate of ischaemic episodes than that observed with aspirin, it still fails to prevent a significant proportion of vascular events. Furthermore, platelet aggregation studies have revealed an increasing body of evidence of the existence of non-responsiveness to clopidogrel. However, little is known as yet about the prevalence and clinical relevance of clopidogrel resistance.

6.6 Clinical decision-making

With regard to the management of patients with aspirin resistance, an increase in the dose of aspirin, followed by repeat testing or conversion to clopidogrel or clopidogrel plus aspirin, might be beneficial. When the aspirin dose is increased, it should be taken into consideration that low-dose aspirin (81 or 325 mg/day) was associated with lower risks of stroke, MI or death as compared with high-dose regimens (650 or 1300 mg/day) in a large group of patients undergoing carotid endarterectomy. Little is known about the clinical relevance of clopidogrel resistance determined by laboratory tests.

A uniformly applied antiplatelet regime based on the overall results of clinical trials might not be the best treatment option for every patient. Platelet function tests may help individualize treatment. Platelet function tests preceding any kind of antiplatelet treatment may provide useful baseline information for further monitoring.

In summary, both the mechanisms and the clinical relevance of aspirin and clopidogrel resistance need to be investigated further. Appropriate platelet function tests may become useful tools in the future for selection of the best antiplatelet therapy for an individual patient. However, none of the currently available laboratory tests for measurement of the antiplatelet effect of aspirin or clopidogrel have been demonstrated to be specific, accurate or reproducible enough. Additional work is required to standardize and validate laboratory tests of the antiplatelet effects of aspirin and clopidogrel. In the meantime, clinicians should ensure the continued use of established antiplatelet agents in all eligible patients.

References

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