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Aspirin resistance in stroke: 2004

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Abstract

Aspirin is a well-established medication in the treatment of atherothrombotic vascular disease. However, despite aspirin treatment a substantial number of patients experience recurring ischaemic episodes. Aspirin resistance denotes those situations when it is unable to protect individuals from thrombotic complications, or when it fails to produce an anticipated effect in laboratory tests of platelet function. There are various laboratory techniques with which to evaluate the effectiveness of aspirin and other antiplatelet drugs. It has been estimated that in 5–60% of patients, aspirin does not achieve adequate efficacy in various measures of platelet activity. Some studies have revealed that vascular patients shown by laboratory tests to be aspirin-resistant are at an increased risk of major vascular events. The suggested mechanisms of aspirin resistance, among others, include genetic polymorphisms, alternate pathways of platelet activation, aspirin-insensitive thromboxane biosynthesis, drug interactions, or low aspirin dose. An increase in the dosage of aspirin or conversion to clopidogrel or clopidogrel plus aspirin might be beneficial in the management of those patients who are aspirin resistant. Additional work is required to improve and validate laboratory tests of platelet function, so that they may become useful tools for selecting the most appropriate antiplatelet therapy for an individual patient. Improvements in antiplatelet treatment strategies in the future should lead to a reduction in premature vascular events.

Keywords: Antiplatelets; Aspirin resistance; Ischaemic stroke; Prevention; Pharmacotherapy

1. Introduction

Atherosclerotic vascular disease is a major cause of premature morbidity and mortality throughout the world, beginning 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 stroke, transient ischaemic attack (TIA), myocardial infarction or unstable angina, invariably appear suddenly. This course can be explained by the fact that, besides leading to flow-limiting critical stenoses of the affected vessels, atherosclerotic lesions may also be complicated by thrombosis, resulting in ischaemic episodes. The platelets play a major role in this arterial thrombotic process [1]. Drugs that inhibit the platelet function have also proven to be effective in preventing the clinical complications of atherothrombosis. The most commonly administered antithrombotic medication is aspirin (acetylsalicylic acid). A considerable number of patients, however, develop repeated ischaemic episodes despite aspirin treatment. Data obtained by various laboratory tests of platelet function indicate that aspirin does not attain adequate antiplatelet efficacy in a significant proportion of these cases. Therefore, increasing attention has recently been paid to the relationship between clinical symptoms and laboratory measures of aspirin resistance.

2. Characteristics of aspirin

Aspirin permanently inactivates the cyclooxygenase (COX) activity of prostaglandin (PG) H synthase-1 and

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PGH synthase-2, also referred to as COX-1 and COX-2. These isoenzymes catalyse the conversion of arachidonic acid to PGH_2. PGH_2 is the immediate precursor of PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2 (prostacyclin), and TXA_2 (thromboxane) [2].

Aspirin exerts an inhibitory effect on platelet COX-1 that is approximately 50- to 100-fold more potent than that on monocyte COX-2. Aspirin also induces a permanent defect in the TXA_2-dependent platelet function. It is assumed to inactivate megakaryocytes too. The mean life span of human platelets is approximately 10 days [2]. Platelet aggregation may be sustained through the thromboxane pathway even if only 10–15% of the platelets remain functional [3]. Since approximately 10% of the platelet pool is exchanged daily, once-a-day dosing of aspirin is recommended to maintain an almost complete inhibition of platelet TXA_2 production. Inhibition of the COX-2-dependent pathophysiologic processes requires larger doses of aspirin because of its lower sensitivity to aspirin. A much shorter dosing interval is also necessary because nucleated cells rapidly resynthesize the enzyme. Thus, a much higher daily dose of aspirin is required when it is used as an anti-inflammatory rather than as an antiplatelet agent [2].

Human platelets process PGH_2 to produce TXA_2, while vascular endothelial cells produce PGI_2. TXA_2 induces platelet aggregation and vasoconstriction, while PGI_2 inhibits platelet aggregation and induces vasodilatation. TXA_2 is largely a COX-1-derived product and is highly sensitive to aspirin inhibition. Vascular PGI_2 can be derived from both aspirin-sensitive COX-1 and largely aspirin-insensitive COX-2, which results in substantial residual COX-2-dependent PGI_2 biosynthesis in vivo at doses of aspirin in the range of 30–100 mg [2].

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 after 1 h. The oral bioavailability of regular aspirin is approximately 40–50%. A considerably lower bioavailability has been reported for enteric coated tablets and micro-encapsulated 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 a platelet because aspirin irreversibly inactivates the platelet COX-1 [2]. The main side effect resulting from the use of aspirin is the occurrence of hemorrhagic complications, most frequently gastrointestinal bleeding.

3. Clinical benefits of aspirin

Antiplatelet therapy is effective for patients with stroke, transient ischaemic attack (TIA), acute myocardial infarction, stable or unstable angina, and intermittent claudication. 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% (odds reduction) as compared with the controls [4]. Allocation of patients with suspected acute ischaemic stroke to a mean duration of three weeks of antiplatelet therapy produced an 11% proportional reduction in vascular events. Among patients with a history of previous stroke or TIA, the odds reduction was 22% at a mean duration of 29 months of antiplatelet therapy [4]. The most widely studied antiplatelet drug in the analysed studies was aspirin. A metaregression analysis of 11 randomized, placebo-controlled trials by Johnson et al. found that aspirin decreased the risk of stroke in patients with previous TIA or stroke by about 15% (relative risk reduction) [5].

There does not appear to be a dose dependence for the clinical antithrombotic efficacy of aspirin spanning a wide range of daily doses (30–1300 mg) [2,4]. In fact, the ASA and Carotid Endarterectomy trial reported that the risk of stroke, myocardial infarction or death within 3 months of carotid endarterectomy is significantly lower for patients taking low doses (81 or 325 mg) of aspirin than for those taking high doses (650 or 1300 mg) [6]. A low dose might be more antithrombotic because it inhibits endothelial PGI_2 production less than a high dose. The side effects of aspirin appear to be dose-related and smaller doses are associated with fewer bleeding complications [2]. The meta-analysis [4] concluded that daily aspirin doses of 75–150 mg appear to be effective in the long-term prevention of serious vascular events among high-risk patients. In clinical situations where an immediate antithrombotic effect is required (e.g., acute ischaemic stroke), a loading dose of about 150–300 mg should probably be given [4].

Among 1000 patients with acute myocardial infarction who are given 1 month of aspirin and then continue to take low dose aspirin over some years, about 40 would avoid a serious vascular event during the first month and about a further 40 would avoid a vascular event in the next couple of years. Similar-sized long-term benefits are likely to be seen if antiplatelet therapy is started soon after stroke or transient ischaemic attack and continued on a long-term basis [4].

Recent data indicate that patients with coronary artery disease who stop taking aspirin abruptly may be placing themselves at risk of developing withdrawal-related coronary events [7].

4. Aspirin resistance

The term "aspirin resistance" is generally used to describe the inability of aspirin to protect individuals from thrombotic complications, or to produce an anticipated effect on one or more in vitro tests of platelet function [2].

Approximately one in eight high-risk patients (12.9%) will experience a recurrent atherothrombotic vascular event in the subsequent two years despite taking aspirin, while it also fails to prevent 81% of recurrent serious vascular episodes among high-risk patients [8]. Resistance to the