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Review

A brief review on high on-aspirin residual platelet reactivity

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ABSTRACT

Although aspirin is effective in secondary prevention in coronary heart disease, new thromboembolic events in patients on aspirin are frequently seen. In trials on aspirin-treated patients, platelet function tests have revealed large variability in platelet aggregation. This phenomenon has been named aspirin resistance, aspirin non-responsiveness or high-on-aspirin residual platelet reactivity.

The mechanism of aspirin antiplatelet effect is due to the inhibition of cyclooxygenase-1 enzyme in platelets. In some trials, almost all patients on aspirin have a very low level of serum thromboxane B_2, indicating that the measured platelet reactivity in aspirin-treated patients might be due to platelet activation via other pathways, such as ADP or thrombin. The prevalence of real aspirin resistance seems to be very low, and probably the term "high-on-aspirin residual platelet reactivity" should be preferred to describe this phenomenon.

Contents

1. Introduction

The use of aspirin has become a cornerstone in secondary prevention in coronary heart disease. A large number of clinical trials have demonstrated the efficacy of aspirin in the acute treatment and in secondary prevention of coronary heart disease and ischemic stroke, and have proven to reduce the risk of new atherothrombotic events by 25–30% [1–3]. On the other hand, platelet inhibition increases the risk of bleeding, but in high-risk patients the benefit–risk ratio of low-dose aspirin in secondary prevention is favorable [4,5]. Despite the demonstrated beneficial effects of aspirin in high-risk patients, many aspirin users experience new cardiovascular events. Aspirin thus fails to prevent a substantial number of serious vascular events among high-risk patients [5–11]. This has led to the introduction of the concepts of aspirin non-responsiveness, aspirin resistance, or high-on-treatment residual platelet reactivity (RPR).

Several reports have shown, by laboratory testing, insufficient platelet inhibition in 1% to 60% of aspirin-treated patients. By laboratory testing, different methods have been used to evaluate the antiplatelet effect of aspirin, such as measurement of cyclooxygenase-1 (COX-1)-dependent platelet aggregation and determination of thromboxane levels in serum or urine (vide infra). Different mechanisms have been discussed as potential explanations of the laboratory phenomenon of high-on-aspirin RPR, but several studies have demonstrated a substantial inhibition of

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the production of thromboxane (TX) B_2 in aspirin-treated patients with high residual platelet reactivity. Thus, the term aspirin resistance seems inappropriate.

2. Aspirin

The beneficial antithrombotic effects of aspirin were recognized in the 1950s [12–14]. Over the past 60 years, the mechanisms of aspirin's antiplatelet effect have been elucidated, and multiple clinical trials have demonstrated its efficacy in the prevention and treatment of cardiovascular disease [6,15,16]. Non-enteric coated aspirin is rapidly absorbed in the stomach and upper small intestine, reaching peak plasma levels about 30 min after intake. The oral bioavailability of non-enteric coated aspirin is 45 to 50%, whereas the bioavailability of enteric-coated aspirin is significantly lower [17,18]. The antiplatelet effect of aspirin lasts for the 7 to 10 day lifespan of platelets due to the irreversible inhibition of the COX-1 enzyme, responsible for the conversion of arachidonic acid to TXA_2, even though the half-life of aspirin is only 15 to 20 min. COX-1 regeneration is not possible in the non-nucleated platelets. Therefore, the platelet inhibitory effect of aspirin is reversed only through the generation of new platelets, thus allowing the use of a once-daily regimen despite the short half-life of the drug [19].

Aspirin acetylates platelets in the portal vascular system. The systemic concentration after intake of low-dose aspirin is low, due to first pass metabolism in the liver (up to 50%). Aspirin is to some extent also metabolized in the gastrointestinal mucosa and by esterases in the blood [20,21]. The product of such de-acetylation, salicylate, is mainly excreted by the kidneys [22].

TXA_2 is formed after the phospholipase-mediated release of arachidonic acid from phospholipids in the platelet cell membrane. The enzyme TX synthase produces TXA_2 from prostaglandin H_2, which is formed from arachidonic acid by the COX-1 enzyme. TXA_2 is a powerful vasoconstrictor and platelet activator, and aspirin inhibits platelet aggregation by effectively reducing the production of TXA_2 by inhibition of COX-1 in platelets [19,23]. TXA_2 normally induces platelet activation that is amplified through the release of adenosine diphosphate (ADP) and the consequent ADP-induced platelet activation [24]. However, platelets are activated in response to many stimuli, including thrombin, collagen, and ADP, thus bypassing the COX-1 pathway (Fig. 1).

3. Endothelial function and inhibition of prostacyclin

Aspirin inhibits the synthesis of prostacyclin from arachidonic acid in endothelial cells, and endothelial prostacyclin inhibits platelet aggregation and promotes vasodilatation. The inhibitory effect of aspirin on TXA_2 generation is considerably stronger than its inhibitory effect on prostacyclin generation. Due to the short half-life of aspirin and the endothelial cells ability to generate new COX-1, the inhibitory effect of low-dose aspirin on endothelial cells is indeed weak or absent, and in any case of short duration [25,26]. In this issue of Vascular Pharmacology, Doroszko et al. report on reduced flow-mediated vasodilation in healthy men with low response to aspirin, possibly due to degradation of nitric oxide by oxidative stress from increased lipid peroxidation [27]. The clinical importance of this observation remains to be proven.

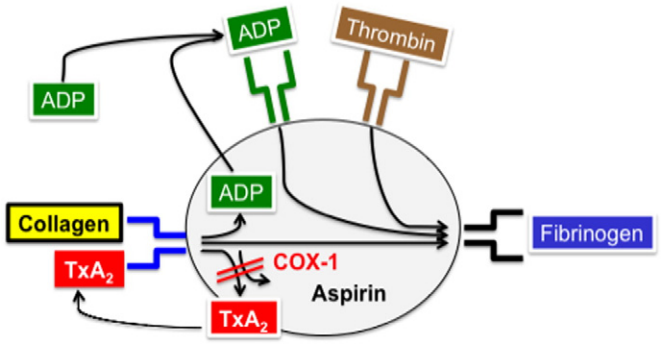

Fig. 1. Aspirin irreversibly inhibits the COX-1 enzyme in platelets, and thus the formation of thromboxane A_2. COX-1: cyclooxygenase-1. TXA_2: thromboxane A_2. ADP: adenosine diphosphate.

4. Platelet function testing

In the early 1990s, it was reported on higher cardiovascular risk in patients with high-on-aspirin RPR as shown by platelet function testing. The phenomenon was named aspirin resistance or aspirin non-responsiveness [28–31]. A substantial amount of research has since been performed to improve knowledge in this area, and the number of methods to monitor the on-treatment platelet reactivity has increased.

To assess residual platelet function in aspirin-treated patients, tests dependent on COX-1 activity have been used. Testing of platelet aggregation can be measured ex vivo by light transmission (turbidimetric) aggregometry in platelet-rich plasma, or by electrical impedance on whole blood after adding agonists such as collagen and arachidonic acid [32]. These tests are performed under non-physiological conditions, since platelets are here exposed to low shear stress, in contrast to the high shear conditions found in atherosclerotic arteries. Several reports have demonstrated a positive correlation between clinical outcome and high-on-treatment RPR, defined by aggregometry tests, which still are looked upon as the gold standard for aspirin testing. However, these tests are labor-intensive and time consuming, and because of this they are not frequently used in clinical practice. The introduction of automated and semi-automated tests has made platelet function testing more available for clinical use. Analyses on whole blood aggregation (Platelet Function Analyzer (PFA) 100® and Ultegra rapid platelet function assay® (RPFA)), and whole blood aggregation, as measured by electrical impedance (Multiplate analyzer®) have been used in numerous clinical trials. Unfortunately, the correlation between the different tests has been shown to be weak, and the reproducibility only moderate [33–36]. These tests can be categorized as COX-1-specific or COX-1-non-specific. COX-1-specific methods include measures of serum TXB_2 and arachidonic acid-induced platelet aggregation. The latter method with light transmission aggregometry has shown significantly lower prevalence of being abnormally high ("aspirin resistance") compared to less COX-1-specific "Point-of-Care" tests. In general, COX-1-non-specific methods include all platelet function tests that use collagen, epinephrine, ADP and other non-AA-agonists, which partially act through TX-independent pathways.

By inhibiting platelet COX-1, aspirin effectively inhibits the platelet production of TXA_2. TXB_2 is a stable metabolite of TXA_2, and its serum concentrations reflect the maximum platelet capacity to synthesize TXA_2. Aspirin-treated patients regularly feature very low serum TXB_2. However, TX generation should be inhibited by more than 95% to achieve sufficient platelet inhibition, and even a small residual generation of platelet TXA_2 is sufficient to induce platelet activation [37,38].

Measurement of the urinary excretion of the TX metabolite 11-dehydro-TXB_2 reflects the actual systemic production of platelet TX, and therefore allows a better estimate of the system, but a variable and non-negligible component of extra-platelet production of this metabolite implies a non-ideal low specificity of the test for the antiplatelet effects of aspirin [39,40].

5. High-on-aspirin residual platelet reactivity

COX-1 inhibition affects only one of several pathways of platelet activation, and platelets with COX-1 inhibition can still be activated by ADP or thrombin. Trials have demonstrated a large variability in platelet function during aspirin treatment, and high-on-aspirin RPR has in some earlier trials been shown to predict clinical outcome [9,28–31].

It has been reported that the frequency of high-on-aspirin RPR depends on the aspirin doses or the frequency of administration [41,42]. An increased platelet turnover has been associated with decreased