Antiplatelet Agents

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Definition

Effective platelet inhibition is the main goal of the antiplatelet therapy recommended as a standard treatment in the secondary prevention of non-embolic ischemic stroke. Acetylsalicylic acid (aspirin) and clopidogrel are commonly used for this purpose worldwide. A low biological response to antiplatelet agents is a phenomenon that significantly reduces the therapeutic and protective properties of the therapy. The mechanisms leading to high on-treatment platelet reactivity are still unclear and remain multifactorial.

1. Introduction

The appropriate inhibition of platelets is the main goal of secondary prevention of non-cardioembolic ischemic stroke. According to the updated guidelines of stroke management, the use of antiplatelet agents is recommended for every ischemic stroke without cardioembolic background. The selection of an agent should be personalized; however, acetylsalicylic acid (aspirin) and clopidogrel are commonly used for this purpose. In some cases, such as a minor stroke or high risk transient ischemic attack, it is possible to use dual antiplatelet therapy for a period of 21 days, to minimize the risk of early recurrent stroke. The efficacy of antiplatelet therapy is essential to reduce cardiovascular events.

However, there are some issues that could reduce a patient’s responsiveness to antiplatelet therapy. The most common is a phenomenon referred to as a resistance to antiplatelet agents, which results in a low biological platelet response, leading to an inappropriate platelet inhibition. Low biological responders may present clinical manifestation in the form of recurrent vascular events despite regular drug intake. This is due to the failure of an antiplatelet agent to prevent cardiovascular incidents. There is still a lack of a standardized definition of a low biological response to antiplatelet agents. The prevalence is estimated at 5–65%, which confirms the scale of this phenomenon and its potential significance. However, the mechanisms leading to high on-treatment platelet reactivity are still unclear and remain multifactorial.

2. Antiplatelet Agents

Aspirin is the most commonly used antiplatelet agent worldwide. The antiplatelet properties are a result of the acetylation of cyclooxygenase-1 at serine 529 leading to the irreversible inhibition of the transformation of arachidonic acid to prostaglandin G2 and, finally, to thromboxane A2. Thromboxane A2 is one of the most important factors responsible for platelet activation. In contrast to aspirin, clopidogrel is a pro-drug and needs to be biotransformed by the cytochrome-P450-complex-dependent pathway to be active and to achieve antiaggregative properties. Clopidogrel inhibits platelet activation as an adenosine diphosphate (ADP) inhibitor by binding P2Y12 receptors on platelets, which results in reduced ADP-mediated platelet aggregation with the glycoprotein IIb/IIIa (GPIIb/IIIa) complex pathway.

Other drugs, such as cilostazol, dipiridamol, ticlopidine or triflusal were also accepted for use in the secondary stroke prevention. However, due to the lack of some evidence of their efficacy confirmed in clinical trials, the lack of numerous studies on low biological response and their marginal application in everyday practice, they were excluded from further considerations.

3. High On-Treatment Platelet Reactivity

The biological response may be estimated by platelet function testing. The measurement of platelet reactivity, especially aggregation and activation, is the most commonly used for this purpose. Normally, platelet reactivity values remain low, reflecting the effective platelet inhibition by antiplatelet agents. In case of decreased platelet sensitivity, platelet reactivity reaches higher levels, despite the antiplatelet
drug intake, indicating the reduced therapeutic effect. The high on-treatment platelet reactivity corresponds to a low platelet response to an agent or a drug failure. As a result, stroke subjects are not protected properly. The phenomenon of high on-treatment platelet reactivity contributes to the greatest extent to the reduced efficacy of the applied antiplatelet treatment. However, the definition of high on-treatment platelet reactivity is not widely accepted and clinical importance remains uncertain. Several assays were developed to evaluate the platelet function. The vast majority is based on the measurements of platelet aggregation. They all have similar platelet sensitivity and specificity and can be used interchangeably. They are treated as equivalent, as none of the devices achieved a significant advantage over others. Their strength lies in the simplicity of performance, automatic measurement, quick results and high repeatability. Their limitation is still the high cost and, above all, the lack of standardization of measurements. The cut-off values of the most common platelet function assays are shown in Table 1.

<table>
<thead>
<tr>
<th>Platelet function assay</th>
<th>Cut-off values—Aspirin</th>
<th>Cut off values—Clopidogrel</th>
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</thead>
<tbody>
<tr>
<td>Light transmission aggregometry (LTA)</td>
<td>MAP &gt; 20%</td>
<td>MAP &gt; 46%</td>
</tr>
<tr>
<td>Impedance aggregometry (Multiplate)</td>
<td>AUC &gt; 40</td>
<td>AUC &gt; 46</td>
</tr>
<tr>
<td>Turbidimetric aggregometry (VerifyNow)</td>
<td>ARU &gt; 550</td>
<td>PRU &gt; 230</td>
</tr>
<tr>
<td>Platelet Function Analyzer-100 (PFA-100)</td>
<td>CT &lt; 193 sec.</td>
<td>CT &lt; 106 sec</td>
</tr>
<tr>
<td>Vasodilator-stimulated phosphoprotein (VASP)</td>
<td>—</td>
<td>PRI &gt; 50%</td>
</tr>
</tbody>
</table>

AUC—area under the curve units; ARU—Aspirin reaction units; PRU—P2Y12 reaction units; CT—closure time; MAP—maximal platelet aggregation; PRI—platelet reaction index.

4. Factors Contributing to a Low Biological Response to Antiplatelet Agents

4.1. Genetic Factors

Genetic disturbances, related to the metabolic pathways of aspirin action, are one of the most common...
causes (account for about 30%) associated with a low response to aspirin [9]. Variations in the cyclooxygenase-1 genotype (single nucleotide polymorphisms) may result in changes of the active center that could effectively block the acetylation from aspirin, leading to a drug failure. Polymorphisms of cyclooxygenase-2, associated with the hyperexpression of isoforms that are non-sensitive to aspirin, are also reasons of a low response to antiplatelet agent. Other single nucleotide polymorphisms that may reduce the therapeutic effect of aspirin are associated with: the thromboxane the A2 receptor; von Willebrand factor gene, glycoprotein; Ia/IIa, IIa/IIIb, or VI genes; and P2RY1 or P2RY12 genes [10].

Other genetic disturbances that may affect aspirin resistance involve microRNAs. These gene regulators, involved in the mRNA post-transcriptional translation and degradation processes, may regulate platelet activation and aggregation and the biological efficacy of aspirin. miRNAs, such as miR-230, miR-19b, miR-150, and miR-126, were demonstrated to be responsible for a low response to aspirin [11].

Due to the complex process of the bioactivation of clopidogrel, there are many more genetic variations and polymorphisms of genes involved in biotransformation- influenced drug resistance, compared to aspirin [12]. The most common gene polymorphism associated with a low response to clopidogrel is related to cytochrome P450 (CYP) 2C19 variants. This gene is involved in the hepatic metabolism of clopidogrel [13]. Authors demonstrated that carriers with one or more CYP2C19 loss-of-function alleles (2* or 3*) were characterized by lower levels of the clopidogrel active metabolite in serum leading to reduced antiplatelet responsiveness [14]. Researchers suggested that this genetic variety may be present in up to 32% of subjects and the incidence of high on-clopidogrel platelet reactivity among them may be as high as over 70% [15].

Polymorphisms of CYP3A4, another gene involved in the oxidative biotransformation of clopidogrel in the liver, particularly loss of the 1G* allele, are considered for risk factors of clopidogrel resistance due to a low concentration of active metabolites [16]. Genetic variants of the ABCB1 gene, associated with clopidogrel absorption from intestinal cells, especially the TT variant and wild-type CC, have been demonstrated to be correlated with nonresponsiveness [6].

Polymorphisms of P2RY12 and GPIIa genes, encoding receptors related to the biological activity of clopidogrel, have been also described as having an impact on drug failure [17][18]. In addition, there are reports highlighting that gene combinations or multiple interactions play a greater role in the incidence of the phenomenon of a low response to clopidogrel compared with single nucleotide mutation or variants at specific loci [13]. Research also reported that paraoxonase 1 (PON-1) polymorphisms may be associated with a higher risk of a low response to clopidogrel. PON-1 is involved in the last stages of the transformation of 2-oxo clopidogrel into its active metabolite. The mutant allele (PON-1 Q192R) may decrease its active form and reduce the inhibition of platelets [19].

4.2. Alternative Pathways of Platelet Activation

It is estimated that chronic inflammation and oxidative stress may significantly affect the aspirin response, in particular by alternative pathways of platelet activation. The cytokines produced in the inflammatory processes may induce the activation of cyclooxygenase-2 leading to the synthesis of thromboxane-A2. Oxidative stress may result in the hyperproduction of thromboxane-A2 regardless of the arachidonic acid pathways. Catecholamine burst during inflammation and oxidative stress may directly activate platelets that are non-sensitive to aspirin [20].

The significant role of catecholamines and alpha2- adrenergic receptors in the variability of biological responses to clopidogrel has been also shown. Human platelets exhibit alpha2- adrenergic receptors that are involved in high residual platelet reactivity and thrombus stabilization. Catecholamines, especially epinephrine, may potentiate the effect of other agonists (in particular, ADP) and initiate different platelets responses from secretion to activation. As a result, increased ADP-induced platelet aggregation contributes to high-on clopidogrel platelet reactivity [21]. On the other hand, a selective blocker of the alpha-2 adrenergic receptor (atipamezol) is considered as a potential option for reducing the frequency of
clopidogrel low responses and increasing the inhibitory effect on platelets [22].

References


Keywords
platelets; ischemic stroke; antiplatelet agents

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