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(REVIEW ARTICLE)

Antiplatelet drugs overview

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Abstract

Platelets are essential factor in the pathophysiology of atherothrombosis, abnormal platelet function guiding to many cardiovascular complications such as myocardial infarction and ischemic stroke. There are numerous antiplatelet drugs approved for use in the clinical management and several under examination. Antiplatelet drugs with the high potency are mostly associated with the intensifying incidence of bleeding. Aspirin and clopidogrel (alone or dual) are the mostly used drugs with the best favorable risk-benefit profiles of drugs available. While cangrelor and ticagrelor may produce further benefits but need more studies .Other drugs such as prasugrel, dipyridamole and cilostazol are not widely used.

Keywords: Aspirin; Thienopyridines; Coronary heart disease

1. Introduction

Platelets are vital parts of normal hemostasis and key components in atherothrombosis .Therefore, the diseases that associated with thrombus formation such as arteriosclerosis are treated mainly by antiplatelets drugs [1].

Platelets are non-nucleated cells that formed from megakaryocyte and have a maximum circulating life span of 7-10 days. Adjustment of platelet production is mediated by thrombopoietin, which is produced by liver, bone marrow and kidney, binding to high-affinity receptors on platelets and megakaryocytes [2].

Platelets provide a circulating source of chemokines, cytokines, and growth factors, which are preformed and packaged in storage granules. Although platelet adhesion, activation, and aggregation regarded as a normal repairing response to the sudden fissuring or rupture of an atherosclerotic plaque, but uncontrolled progression of such process can cause intraluminal thrombus formation, vascular occlusion, and subsequent ischemia or infarction [3].

As noted in figure 1, Thrombin binds to protease activated receptor1(PAR-1), which leads to shape change, phospholipase C (PLC) activation, thromboxane A2 (TXA2) generation, and activation of the glycoprotein (GP) IIb/IIIa receptor, resulting in sustained platelet aggregation. Cyclooxygenase (COX)-1 catalyzes the production of TXA2, a potent platelet aggregator, generated by platelets activated by thrombin and other agonists [4].

Adenosine 5′-diphosphate (ADP) binds to its 7-transmembrane domain receptors, P2Y1 and P2Y12, to activate platelets. P2Y1 is coupled to Gαq and G12. Gαq is linked to a signaling pathway involving PLC activation, resulting in a rise in the intracellular calcium concentration ion [Ca^{+2}] and protein kinase C (PKC) activation, leading to GP IIb/IIIa activation and transient platelet aggregation [4].

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G12 mediates platelet shape change. P2Y12 is linked to Gαi-coupled signaling cascades associated with adenylcyclase (Ac) down-regulation and decreased cyclic-3′, 5′-monophosphate (cAMP) production, which mediates GP IIb/IIIa receptor activation, leading to sustained platelet aggregation [4].

Although activated platelets are incapable of de novo protein synthesis, they can translate constitutive mRNA into protein over the course of several hours. Thus, platelets may play a role in inflammation, angiogenesis, and wound healing, and antiplatelet therapies may have an impact on these processes by blocking platelet-derived protein signals for inflammatory or proliferative responses [5].

In addition to cardiac troponin I, Myeloperoxidase is another test used for the inspection of the existence of inflammatory reaction and oxidation that escorted thrombus formation and aggravated acute atherosclerosis symptoms [6].

Antiplatelet drugs are indicated for the management of thrombotic diseases that included stroke, acute myocardial infarction (AMI), acute coronary syndrome (ACS), angina, percutaneous coronary intervention (PCI), cardiac surgery, primary and secondary cardiovascular disease prevention, peripheral vascular disease, and thrombotic disorders such as atrial fibrillation.
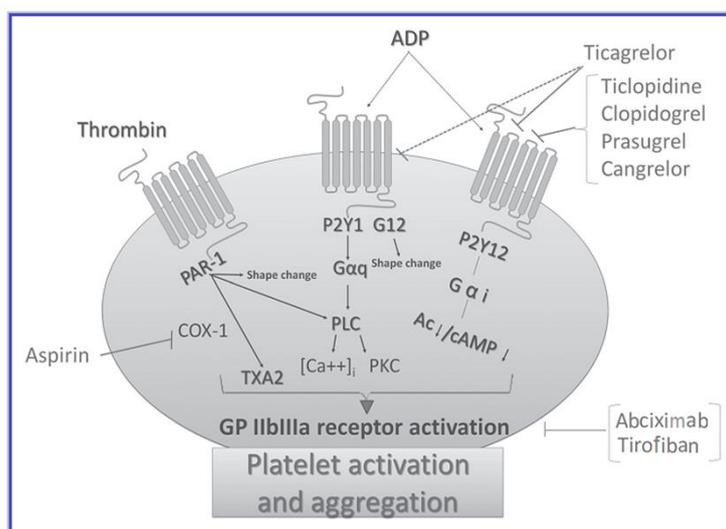

Figure 1 Platelet activation pathways and antiplatelet drugs targeting [4]

2. Classes of antiplatelet drugs

2.1. Platelet cyclooxygenase (COX-1) inhibitor

2.1.1. Aspirin

Aspirin is the backbone treatment for all state of atherothrombosis. The effectiveness of aspirin on platelet came from its ability to irreversibly inhibit platelet cyclooxygenase (COX-1), by acetylating a serine located near the active site of the enzyme, that is responsible for the conversion of arachidonic acid to prostaglandin (PGH2) and thereafter production of thromboxane A2 (TxA2) and prostocycline (PGI 2) [3].

Human platelets and vascular endothelial cells form PGH 2 to produce primarily TXA 2 and PGI 2, respectively. TXA 2 induces platelet aggregation and vasoconstriction, whereas PGI 2 inhibits platelet aggregation and induces vasodilation .Fulfilled inhibition of platelet COX-1 and then TXA 2 can occur with low daily doses of aspirin (75-150 mg). Conversely, the endothelium COX-2 generates PGI2 and is less sensitive to aspirin inhibition. As a result, low-dose aspirin has limited effects on PGI2-dependent vascular functions including arterial blood pressure regulation [7].

Aspirin is rapidly absorbed after oral administration in the stomach and upper intestine.it is achieved plasma peak levels on 30 - 40 min. and it is inhibit platelet function within 1 hr. while enteric-coated aspirin form take more time to reach plasma peak levels. The lower bioavailability of some enteric-coated preparations and their poor absorption from small intestine may result in inadequate platelet inhibition when these preparations are used at low doses [8].

Aspirin irreversibly inactivates platelet COX-1, therefore in spite of the rapid clearance of aspirin from the circulation, the platelet-inhibitory effects last for the life span of the platelet (10 days).Additionally, aspirin acetylates megakaryocyte COX-1, thereby inhibiting thromboxane production in newly released platelets [9].

The major adverse effect of aspirin intake is enhanced risk of bleeding tendency especially by gastrointestinal tract although this risk may be amended by the use of gastro protective drugs such as proton pump inhibitors (PPIs) [10]. The concomitant intake of nonselective reversible COX-1 inhibitors such as ibuprofen or naproxen with aspirin can interfere with the antiplatelet effect of low-dose aspirin and performing aspirin less effective when used for cardioprotection or stroke prevention. Interestingly, a competition exist between the nonselective COX inhibitors and aspirin for the common binding site within the COX-1 channel ,which may prevent aspirin from acetylating the serine residue and lead to aspirin resistance [11].

The incapability of aspirin to inhibit COX-1–dependent TXA_2 production is called aspirin resistance, and it is about 1–2%. High On-Treatment Platelet Reactivity (HPP) or resistance to antithrombotic drug is consider as an adverse thrombotic events or treatment failure which is associated with increase the risk of MI, stroke, or death [12].

Many factors effect on the platelet reactivity such as age, female sex, diabetes, concomitant therapies (particularly NSAIDs, e.g, ibuprofen). Conditions that associated with an inflammatory response such as unstable angina, acute myocardial infarction (AMI), diabetes, and cardiac surgery are associated with HPR in aspirin-treated patients [13].

2.2. Platelet P2Y12 -ADP receptor irreversible inhibitor (Thienopyridines)

Thienopyridines class involved three generations, ticlopidine, clopidogrel, and prasugrel. All of them are prodrugs that must converted by metabolic activation through the hepatic CYP450 system to their active metabolites that selectively inhibit the platelet P2Y12 -ADP receptor [14].

2.2.1. Ticlopidine

The first generation thienopyridines,Ticlopidine, has limited use due to its bone marrow toxicity, neutropenia, aplastic anemia, and thrombotic thrombocytopenic purpura [15].

2.2.2. Clopidogrel

Clopidogrel, a second generation thienopyridine, is a prodrug that irreversibly binds to the P 2 Y 12-ADP platelet receptor by forming disulfide bridges after a two-stage of activation by cytochrome P450 (CYP) liver isoenzymes. Conspicuously, clopidogrel is more safer than ticlopidine, and is more effective than aspirin for prevention of secondary vascular events .As clopidogrel and aspirin act on discrete and complementary pathways of platelet inhibition, dual therapy is evaluated in high-risk clinical conditions [16].The use of clopidogrel is certified for the reduction of atherosclerotic events in diabetic patients and in patients with recent stroke, recent MI,or established peripheral arterial disease [17,18].

After oral administration of clopidogrel, the drug is variable absorbed. 108 and the majority of absorbed clopidogrel (85%) is extensively hydrolyzed by esterases to the inactive carboxylic acid metabolite. In the liver, clopidogrel is metabolized in a 2-step process by CYP3A4/3A5 and CYP2B6 / 1A2/2C9/2C19 to a very short-lived active metabolite , which is responsible for its effect on platelet aggregation [19].

Peak concentrations of the parent drug, its active metabolite and the carboxylic acid metabolite occur within 1- 2 hr .The drug and its metabolite are extensively bound to serum proteins. Elimination is by the feces (50%) and urine (50%). Inhibition of platelet aggregation reaches a steady state 50 - 60% inhibition after 4 - 7 days of daily administration of 75 mg [20].

There are interpatient variability's in response to clopidogrel and thereafter in antiplatelet activity ,the most important one is the genotype variability of liver cytochrome enzyme e.g.*CYP2C19* genotypes are associated with diminished platelet response to clopidogrel but this may be overcome by monitoring and adjusting the dose based on the platelet reactivity [21].

Loading dose of 300 mg of clopidogrel results in more-rapid platelet inhibition than is achieved with the 75 mg maintenance dose. Moreover, inhibition of ADP-induced platelet aggregation was also significantly greater with a 600-mg loading dose of clopidogrel compared with a 300-mg loading dose [22].

The major side effect of clopidogrel administration is the increased risk of bleeding. Compared with aspirin, there were fewer GI symptoms but an increased incidence of diarrhea and rash. A rare but significant complication of clopidogrel is the development of thrombotic thrombocytopenic purpura [23].

Because of the requirement for metabolism of clopidogrel by CYP3A4/3A5 to generate the active metabolite, many drugs that metabolize by CYP3A or CYP2C19, e.g. statins drug or proton pumps inhibitors drugs respectively can interfere with the metabolism of clopidogrel and thereafter with its clinical effect. Concurrent used of atorvastatin with clopidogrel may provoke hepatic injury cholestasis type resulting from abnormal bile flow caused by either drugs or their metabolites [24]. Additionally, atorvastatin has been found to amend the functions of endothelium by its effect on peroxisome –proliferator-activated receptors (PPAR-α) pathway [25].

Erythromycin, calcium antagonists, macrolide antibiotics, or ketoconazole,CYP3A inhibitors, can produce lessening in antiplatelet activity of clopidogrel .While Rifampin, a CYP3A inducer, can reveal enhancing antiplatelet activity of clopidogrel [26].

Many studies found that there are variability in patient's response to clopidogrel and may be associated with adverse thrombotic events especially in those with high on-treatment platelet reactivity. Particularly, Several factors can associate with increased incidence of high platelet reactivity in patients with clopidogrel such as diabetes, dyslipidemia, concomitant therapies that effect on metabolism of clopidogrel and related to insufficiency of active metabolite such as (lipophilic statins, e.g, simvastatin and atorvastatin; proton pump inhibitors, eg, omeprazole; and calcium channel blockers), and genetic polymorphisms of CYP450 isoenzymes (2C19, 1A2, 2B6, 2C9, 3A4) that involved in the production of clopidogrels' active metabolite [27].

2.2.3. Prasugrel

Prasugrel, a prodrug of the thienopyridine family, after a rapid one-step conversion by CYP3A4 and to a lesser extent CYP2B6 into a highly bioavailable metabolite, causes an irreversible block of the P2Y12 ADP receptor prevent platelet activation. Because of a distinct chemical structure, the conversion to its active metabolite is less dependent on specific cytochrome P450 enzymes than that of other thienopyridines [28].

In patients with stable coronary artery disease, prasugrel produced a faster and more effective inhibition of platelet function than clopidogrel. The incidence of poor platelet aggregation response after prasugrel 60 mg administration was lower than for clopidogrel 300 mg [29].

Prasugrel is rapidly absorbed after oral ingestion, unaffected by food, and is rapidly converted to its active metabolite, which reaches peak concentrations within 30 min of dosing. The active metabolite has a half-life of 4 h, and renal excretion is the major route for elimination of the metabolites. Prasugrel is gave as 60 mg loading and 10 mg maintenance doses [30].

The major adverse effect of prasugrel is bleeding. Prasugrel is a more potent inhibitor of platelet function than clopidogrel and therefore it associated with a significantly increased incidence of major adverse bleeding events and should be avoided in patients with known cerebrovascular disease [31]. There were a little probability of interactions with other drugs metabolized by cytochrome P450 system (CYP3A4/CYP2B6) as reported in many studies [32].

Compared with clopidogrel, use of prasugrel cause few nonresponders and better clinical response in diabetic patients. Poor response to clopidogrel was attributed to reductions in the amount of measured active metabolite available to interact with platelets as opposed to alterations in the platelet P2Y12 receptor [33].

2.3. ADP- receptor antagonists

2.3.1. Cangrelor

Cangrelor, an adenosine triphosphate (ATP) analog, is a reversible inhibitor of the platelet P2Y12- ADP receptor. It achieves greater inhibition of platelet aggregation than that obtained by clopidogrel. But other study found that the measurement of inhibition of platelet aggregation did not exhibit any variation between cangrelor and clopidogrel [34, 35].

Cangrelor present as IV-form, has a rapid onset of action (steady state at 30 min.) and elimination half-time of 9 min. Moreover, platelet activity rapidly return to its normal state within 60 minutes after interruption of drug. Cangrelor

metabolized by sequential dephosphorylation in plasma therefore it can be used in patients with renal or hepatic function abnormalities [36].

The most common adverse effects of cangrelor treatment include, bleeding, transient increases in liver enzymes, and dyspnea [37]. Cangrelor can interact with the platelet inhibitory activity of clopidogrel at active site on platelet when given concurrently. Therefore, clopidogrel can be gave consecutively after cangrelor. Hence, cangrelor might consider as P2Y12 inhibitor bridge therapy in the perioperative and operative period [38].

2.4. Platelet P2Y12 -ADP receptor reversible inhibitor

2.4.1. Ticagrelor

Ticagrelor, an orally active cyclopentyl-triazolopyrimidine, binds to the P 2 Y 12 receptor, other than those recognized by ADP, in a reversible manner and almost completely inhibits ADP-induced platelet aggregation. It has a faster onset and offset of platelet inhibition than clopidogrel [39].

After oral administration, ticagrelor is rapidly absorbed and does not require hepatic biotransformation to be pharmacologically active. It is peak effect on platelet inhibition was 2 - 4 hours. The terminal half-life was approximately 7 hours. of addition, ticagrelor is also metabolized to an equipotent, active metabolite by CYP 3 A 4 enzymes thereafter both ticagrelor and its active metabolite excreted by the intestinal route, no dose adjustment is required in kidney failure. ticagrelor is given in a loading dose of 180 – 270 mg daily and in a maintanence dose of 90-mg twice daily to optimize its efficacy, safety, and tolerability [40].

The most common adverse event with ticagrelor intake is bleeding .Major, life-threatening, or fatal bleedings did not differ between those on ticagrelor and those on clopidogrel. Another adverse events is dyspnea which is reversible and required cessation of therapy when begin [41].

A reversible increase in serum uric acid and creatinine also noted. Additionally, nausea, hypotension, and asymptomatic ventricular pauses may occur because of an adenosine-mediated response. Therefore, ticagrelor treatment was precautioned in patients with hyperuricemia, bradyarrhythmias without pacemakers, and syncope (fainting) and in those at high risk of bleeding (e.g. elderly, low bodyweight, renal dysfunction) and avoided in patients with history of stroke [42].

2.5. Phosphodiesterase inhibitor drugs

2.5.1. Dipyridamole

Dipyridamole is a pyrimidopyrimidine derivative with vasodilator and antiplatelet properties. It is act by inhibition of nucleotide phosphodiesterase, an enzyme that destroys cyclic adenosine monophosphate (cAMP), causing increase in intraplatelet cyclic AMP which resulted in inhibition of platelet aggregation and blockade of adenosine uptake thereby increasing the amount of adenosine at the platelet vascular interface. In addition, dipyridamole directly stimulate the synthesis and release of prostacyclin (PGI2) from the endothelium [43].

After oral administration, dipyridamole is variably absorbed from gastrointestinal tract that lead to variable levels of its systemic bioavailability. Recently this feature has been amended with the addition of low-concentration of aspirin to dipyridamole and form a sustained release drug. Dipyridamole is greatly bound to albumin, exposed to enterohepatic recirculation, after conjugated to glucuronide it's mainly excreted by bile [44].

Use of dipyridamole is associated with an increased risk of bleeding events. The most common adverse effect of chronic administration is headache. In high doses, dipyridamole -induced vasodilation and tachycardia may produce myocardial ischemia, which may be a limiting factor for its use as an antiplatelet drug [45].

The dual therapy of dipyridamole and aspirin caused increase the risk of headache and bleeding. Moreover, As dipyridamole has vasodilator properties therefore additive vasodilation and hypotensive effects may occur when taken with other vasodilator drugs such as angiotensine converting enzyme (ACE) inhibitors inhibitors [46].

2.5.2. Cilostazol

Cilostazol, 2-oxoquinolone derivative, selectively inhibit intracellular phosphodiesterase type 3 enzyme that sequently lead to inhibit platelet aggregation and vasodilation. Cilostazol intake in a dose of 50 mg bid or 100 mg once daily was found to increase maximal and pain-free walking distance in patients with intermittent claudication [47], and averts

stent thrombosis and restenosis [48]. In diabetic patients on standard dual antiplatelet therapy (aspirin and clopidogrel), adjunctive treatment with cilostazol enhances inhibition of platelet P 2 Y 12 signaling [49].

Orally intake cilostazol has variable level of absorption. It is abundantly bound to albumin and metabolized primarily by CYP3A4/5 to inactive metabolites that eliminated by urine.The elimination half-time for cilostazol is approximately 10 hours [50].

Cilostazol treatment especially at the first –two weeks caused gastrointestinal side effects, and headache that was the basis of drug interruption by some patients. Similarly to dipyridamole, Cilostazol caused hypotension and tachycardia as a result of vasodilation. Therefore,it is contraindicated in patients with heart failure [51].

As cilostazol metabolized by CYP3A4 and CYP2C19 therefore, it may interfere with other drugs metabolized by these enzymes such as omeprazole (CYP2C19 inhibitor) or erythromycin (CYP3A4 inhibitor) that may lead to deteriorate its biological level [52].

2.6. GpIIb-IIIa receptor antagonists

This class of drugs involve Abciximab (monoclonal antibody) and Tirofiban (non-peptide tyrosine derivative) both are intake as IV bolus dose and are selectively bounds to GpIIb-IIIa receptor of platelet and inhibit its binding to fibrinogen and aggregation [53].

2.6.1. Abciximab

Abciximab is a monoclonal antibody inhibits not only GP IIb-IIIa receptor but also GP Ib receptor for von Willebrand factor (vWF) on platelets, thereby decreasing aggregation through fibrinogen and adhesion through vWF [54].

After IV bolus administration (0.25 mg/kg), abciximab rapidly bound to GpIIb-IIIa and 80% of the GpIIb-IIIa receptors blocked and platelet aggregation diminished to 20% of baseline. Half-life of equal to about 30 min. After 2hr. the clinical effect of abciximab was observed and after 24hr. the platelet activity and bleeding time regularly restore to normal [55].

It is used to decrease ischemic events of managed acute coronary syndrome and as adjunctive therapy during percutaneous coronary intervention (PCI), but trials with orally administered GP IIb-IIIa inhibitors have failed to demonstrate any benefit [56]. Thrombocytopenia is the main adverse effect that showed in 1- 2% of the treated patients and with re intake of the drug the incidence of thrombocytopenia elevated [55].

3. Conclusion

Antiplatelet drugs are used to avoid the formation of platelet-rich arterial thrombi, while anticoagulants drugs are used to avert the formation of fibrin-rich thrombi such as left atrial appendage thrombi. The appearance of many adverse effects of Antiplatelet drugs such as bleeding, and inter individual response variability enhanced the requirement for laboratory and genetic information to pursue the therapeutic monitoring for each patients.

Compliance with ethical standards

Disclosure of conflict of interest

No conflicts of interests to assert.

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How to cite this article