Factors modifying clopidogrel (antiplatelet drug) responsiveness

Essay
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Summary

Atherothrombosis, the unhealthy coupling of atherosclerosis and thrombosis, is the most common cause of acute ischemic events. The atherosclerotic process is diffuse, generalized, and progressive, affecting multiple vascular beds. This leads to a number of clinical manifestations, the natures of which are influenced by the target organ and specific vascular bed involved. Ischaemic events related to atherothrombosis include coronary, cerebral, and peripheral arterial disease.

Disease in one vascular bed increases the risk of disease in other, a concept known as "cross-risk" .Stroke and myocardial infarction (MI) share common risk factors and pathological mechanisms.

Antiplatelet agents have a great importance in the management of atherothrombotic syndromes, whether in acute treatment or for secondary prevention. They are classified according to the mechanism of action into: Cyclooxygenase inhibitors (Aspirin), Phosphodiesterase enzyme Inhibitors (Dipyridamole and cilostazol), ADP receptor blockers (Clopidogrel and ticlopidine), Glycoprotein IIb/IIIa antagonist (Abciximab, Eptifibatide, Tirofiban). Prostaglandin analogues (Epoprostenol).

Clopidogrel is a prodrug that needs to be metabolized by hepatic cytochrome P450 (CYP) to an active compound that specifically and irreversibly targets the platelet P2Y12 receptor for the platelet lifespan. CYP 3A4 metabolizes clopidogrel faster than other human CYP isozymes and is the most abundant CYPs in the human liver, suggesting that they are primarily responsible for in vivo clopidogrel metabolism.

Several clinical trials have evaluated the efficiency of clopidogrel as a mono or dual therapy in combination with other antiplatelet agents as treatment for percutaneous coronary intervention and acute coronary syndromes . Whereas multidrug therapy with antiplatelet drugs, lipid-lowering and glucose-lowering agents, antihypertensive drugs, and even antidepressants has been suggested as a therapeutic strategy to reduce cardiovascular risk, multiple drug prescriptions increase the risk for drug– drug interactions. This is particularly true if more than 1 agent requires significant hepatic metabolism . Clopidogrel, atorvastatin, omeprazole, and many other drugs require hepatic cytochrome P450 (CYP) metabolism. Importantly, clopidogrel–atorvastatin and clopidogrel–omeprazole drug interactions have been described that limit the ability of clopidogrel to inhibit platelet activation and aggregation processes. The inter-individual variability in amount and activity of specific type of CYP 450 may lead to the so-called resistance to clopidogrel. It has been proposed that the term 'resistance' should be used when a drug is unable to reach its pharmacological target, due to inability to reach it or alterations of the target. Clopidogrel resistance is multifactorial and the mechanisms responsible for the inter-individual variability are not yet clearly defined.

Several clinical trials showed that clopidogrel reduces the overall rate of thromboembolic events in patients with recent myocardial infarction, stroke, or peripheral arterial disease as compared with aspirin. However, these clinical trials focused mainly on bleeding as a major side effect of clopidogrel therapy. Some studies reported an increase in the incidence of bleeding following dual

clopidogrel and aspirin treatment. Other clinical trials demonstrated that patients with clopidogrel treatment had a significantly increased requirement for platelet and red blood cell transfusions compared with the non clopidogrel recipients. Lastly, landmark studies have established the importance of clopidogrel in the treatment of non-ST and ST elevation myocardial infarction, in percutaneous coronary intervention, stroke, and peripheral arterial disease by reducing death, reinfarction, and adverse cardiac events. These trials proved these findings after accurate measurment of the benefits and risks of this valuable drug.

❖*List of content:*

❖*List of abbreviations:*

- µMol → Micro-mole.
- ACS → Acute coronary syndrome.
- ADP → Adenosine Di Phosphate.
- AMI → Acute Myocardial Infarction.
- ASA → Acetyl salicelic acid.
- CABG → Coronary Artery Bypasses Graft surgery.
- CAD → Coronary artery disease.
- cAMP → cyclic Adenosine Mono Phosphate.
- CD40L → Cluster of Differentiation Ligand 40.
- CHD → Coronary Heart Disease.
- Clop → Clopidogrel.
- Comb → Combination.
- COX → Cyclo-Oxigenase enzyme.
- CV → cardiovascular
- CYP → Cytochrome P enzyme.
- d → Day.
- DM → Diabetes Mellitus.
- ECG → Electro CardioGraphy.
- ECVD → Extra cardiovascular disease.
- FMD → Flow-Mediated Dilation.
- GI → Gastro-Intestinal.
- GPIIb/IIIa → Glycoprotein IIb/IIIa receptor.
- h → hour.

- H2 → Histaminergic 2 receptor.
- HbA1c → Haemoglobin A1c.
- HF → Heart Failure.
- HMG Co-A → Hydroxy MethylGluteryl Co-A.
- hsCRP → high-sensitivity C-reactive protein
- ICM → Inactive Carboxyl Metabolite.
- ICU → Intensive Care Unit.
- IPA → Inhibition of Platelet Aggregation.
- IRA → Infarct Related Artery.
- IST →In-Stent Thrombosis.
- IU/kg → International Unit per Kilogram.
- LTA → Light Transmittance Aggregometry.
- MACEs → Major adverse cardiovascular events.
- maxSTR → Maximum ST-segment resolution
- mg → Milligram.
- MI → Myocardial infarction.
- Min → Minute
- mMol → milli-Mole.
- mV → milli-Volt.
- n → number.
- NACE → Net Adverse Clinical Events.
- NMD →Nitroglycerin-Mediated Dilation.
- NO → Nitric Oxide.
- NSAIDs → Non-Steroidal Anti-Inflammatory Drugs.
- NSTEMI→ Non S-T segment elevation myocardial infarction.
- OPCABG → Off-Pump Coronary Artery bypass graft surgery
- PAD → Peripheral Arterial Disease.
- PAOD → Peripheral Arterial Occlusive Disease.

- PDEs → Phosph-Di-Esterase enzymes.
- PGI2 → Prostaglandin I2.
- PCI → Percutaneouse Coronary Intervention.
- PPI → Proton Pump Inhibitor.
- PRI → Platelet Reactivity Index.
- PRI VASP → Platelet Reactivity Index Vasodilator Stimulated Phosphoprotein.
- PTCA → Percutaneous Transluminal Coronary Angioplasty.
- PVD → Peripheral Vascular Disease.
- RCT→ Randomized control trial.
- RPA → Residual Platelet Aggregation.
- rt-PA → recombinant tissue Plasminogen activator.
- sCD40L → serum soluble Claster of Differentiation 40 ligand.
- sICH →Symptomatic Intracerebral Hemorrhage.
- SK→ Steptokinase.
- STEMI→ S-T segment elevation myocardial infarction.
- STRes → resolution of ST-segment deviation from baseline.
- sumSTR → sum of ST-segment deviation.
- TAT →Thrombin-Antithrombin III.
- TIA → Transient Ischemic Attack.
- TTP → Thrombotic Thrombocytopenic Purpra.
- Tx → Thromboxane.
- U → Unit.
- UGIB → Upper GastroIntestinal Bleeding.
- UTVR → Urgent Target Vessel Revascularization.
- VASP → Vasodilator Stimulated Phosphoprotein.
- VS → Versus.

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❖*List of tables:*

Background

Atherothrombosis, the unhealthy coupling of atherosclerosis and thrombosis, is the most common cause of acute ischemic events. The atherosclerotic process is diffuse, generalized, and progressive, affecting multiple vascular beds. This leads to a number of clinical manifestations, the natures of which are influenced by the target organ and specific vascular bed involved. Ischaemic events related to atherothrombosis include coronary, cerebral, and peripheral arterial disease (PAD) ***(Adams et al., 2003).***

Disease in one vascular bed increases the risk of disease in other, a concept known as "cross-risk" .Stroke and myocardial infarction (MI) share common risk factors and pathological mechanisms. Coronary heart disease (CHD) is considered a cause of death in patients with cerebrovascular disease ***(Gibbons et al., 2003).*** Several small studies have shown that patients with (TIA) and stroke have a high prevalence of asymptomatic CHD ***(Di Pasquale et al., 1988).*** Another study included a total of 67,888 patients from 44 countries, demonstrated that 15.9% of the 55,499 with symptomatic atherothrombosis had polyvascular disease, defined as at least 2 of the following: CHD, peripheral arterial disease (PAD), and cerebrovascular disease ***(Bhatt et al., 2006).*** Patients, who tend to be older and have more comorbidities, had higher rates of cardiovascular outcomes after 1 year of follow-up compared with patients with vascular disease in a single bed and patients with one ischemic event have an increased likelihood of experiencing another event in the future ***(Steg et al., 2007).***

CHD and stroke remain major causes of mortality worldwide, responsible for 10% of the disability in developing countries and 18% in developed countries ***(Kung et al., 2008).*** The risk of stroke has increased in low and middle income countries over the last decade ***(Feigin et al., 2009).*** Socioeconomic level in low and middle income countries increases the burden of cerebrovascular disease. Patients who suffer from stroke are almost a decade younger than in western countries ***(Truelsen et al., 2007).*** Management of ischemic risk factors, through a combination of lifestyle modifications and pharmacotherapy, reduces the incidence of ischemic events. There are number of pharmacological agents useful for primary and secondary prevention of atherothrombotic events in patients at high risk as control of coexisting risk factors such as hypertension. Hypolipidemic drugs such as statins and antiplatelet drugs also have a role in this aspect ***(Smith et al., 2004).***

Antiplatelets

Antiplatelet agents have a great importance in the management of atherothrombotic syndromes, whether in acute treatment or for secondary prevention. **They are classified according to the mechanism of action into:**

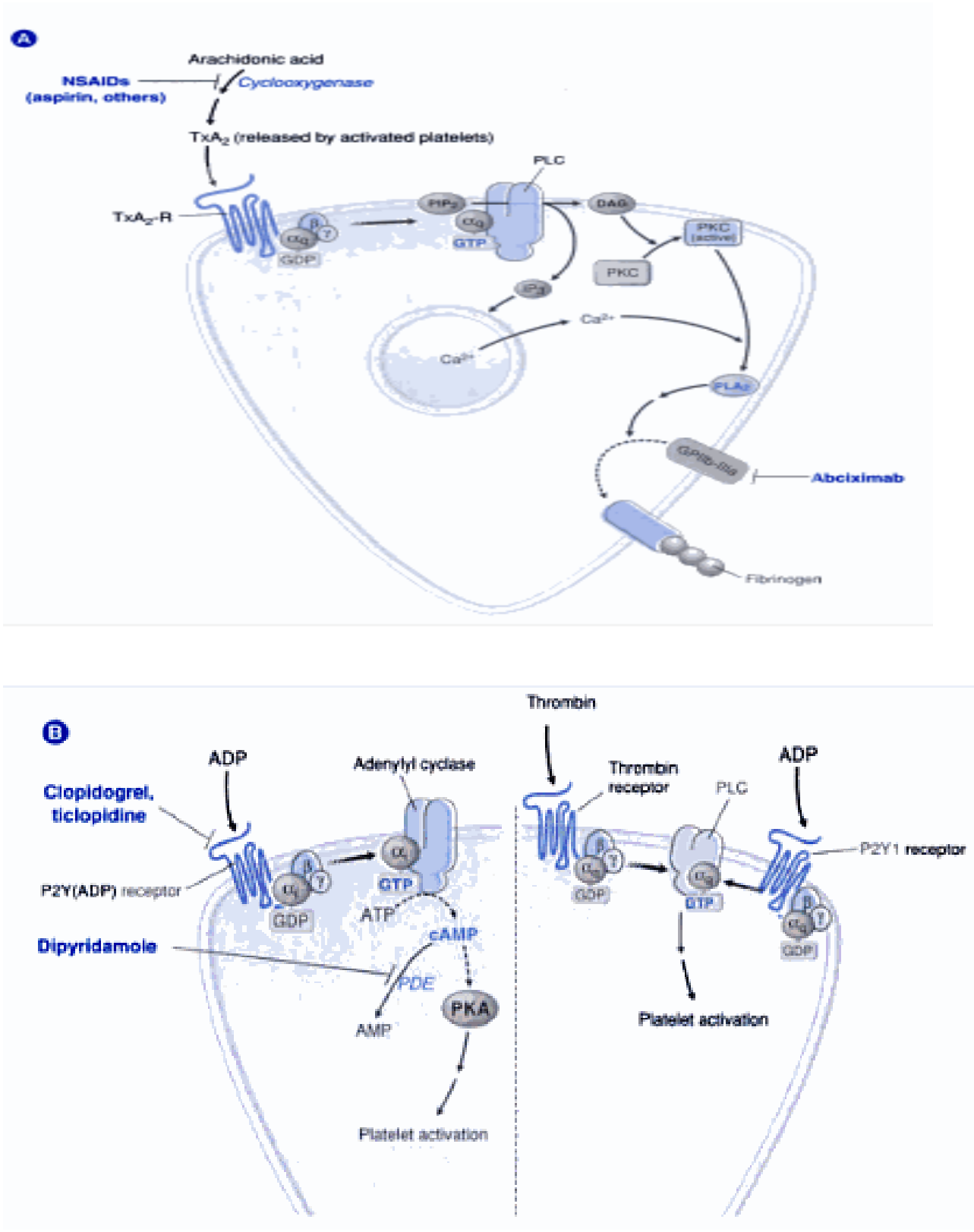

Figure (1): Mechanism of action of antiplatelet agents ***(Toscani et al, 2004).***

- **Cyclooxygenase inhibitors (Aspirin):**

Aspirin (Acetylsalicylic acid) is an inexpensive antiplatelet agent, the most extensively studied drug. Aspirin binds to and irreversibly inhibits cyclo-oxygenase (COX), the first step enzyme in the biosynthesis of prostaglandins in platelets. Pharmacologic inhibition of COX in platelets blocks the arachidonic pathway of platelet activation, effectively shutting down the formation of thromboxane TXA_2, and its end terminal product. TXA_2 is a potent platelet agonist and vasoconstricting substance. The irreversible inhibition of COX originates from the fact that platelets are non-nucleated cells, hence devoid of protein synthesis and unable to replete its pool of enzymes. The end result is a shutdown of TXA_2 production for the remaining life of the platelet, i.e., its physiologic lifespan of 10 days ***(Toscani et al, 2004).***

- **Phosphodiesterase (PDE) enzyme Inhibitors :**

PDEs are a family of nine enzymes catalyzing the hydrolysis of cyclic adenosine monophosphate (cAMP) . **Dipyridamole** and **cilostazol** act as PDE inhibitors, raising platelet levels of cyclic adenosine monophosphate and thereby inhibiting platelet function. Dipyridamole also enhances the release and prevents the degradation of endothelial prostaglandin (PGI2), a potent inhibitor of platelet aggregation. These drugs also have vasodilator activity mediated by an action on the endothelium. In addition, cilostazol inhibits the proliferation of vascular smooth muscle cells ***(Ahrens et al., 2005).*** Dipyridamole is widely used for the diagnosis of coronary artery disease (CAD) by doing perfusion imaging during coronary vasodilation. Dipyridamole, by increasing endogenous adenosine levels, induces