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Review Article

USE AND RISK FACTORS FOR ADRs ASSOCIATED WITH CLOPIDOGREL IN THE MANAGEMENT OF ATHEROSCLEROSIS

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Abstract:

Atherosclerosis is one of the main causes of vascular disease all over the world. Ischemic heart disease, ischemic stroke, and peripheral artery disease are some of the most prevalent clinical manifestations of this condition. Acute coronary syndrome (ACS), transient ischemic attack (TIA) or small stroke, and peripheral artery disease are all treated and prevented with antiplatelet medication in the majority of cases. Clopidogrel was the first of the P2Y12 inhibitors to be developed, and these drugs are now widely used in the primary and secondary prevention of cardiovascular disease. This article summaries the current research on the effectiveness of antiplatelet therapy for atherosclerosis patients, with particular emphasis on clopidogrel. Clopidogrel's potential side effects and risks, as well as the drug's contraindications and toxicity characteristics, are discussed.

Keywords: Atherosclerosis, clopidogrel, P2Y12 inhibitors, ADRs, ACS.

Introduction:

Hyperlipidemia and lipid oxidation lead to atherosclerosis, a leading cause of death in developed countries. It is characterized by intimal plaques and disease of the vascular intima, which has the potential to impact the coronary arteries as well as the aorta, any portion of the vascular system (1,2). Both athetosis and sclerosis are manifestations of atherosclerosis, which is characterised by the accumulation of fat cells and a significant number of macrophages (fibrosis consisting of smooth muscle cells [SMC], leukocytes, and connective tissue) (3,4).

About 50% of all deaths in contemporary Western societies can be attributed to atherosclerosis, i.e., a persistent inflammatory condition that affects the arteries. Atherosclerotic cardiovascular disease (ASCVD) is predominantly low-density lipoprotein and residual lipoprotein particles accumulate along with an active inflammatory process in focal parts of arteries, especially in locations where non-laminar flow is disrupted at

artery branch sites, to start a lipid-driven process (5-7).

Since atherosclerosis is often symptom-free, its true prevalence is hard to assess. It is universally believed that atherosclerosis is a significant contributor to stroke and cardiovascular disease. The two main cardiovascular diseases linked to atherosclerosis are coronary heart disease (CHD) and haemorrhage. CHD and haemorrhage are the first and fifth most common causes of death worldwide, according to various sources (8–11).

ATHEROSCLEROSIS

Over the past two decades, increasing amounts of data have substantiated the inflammatory concept (3,12,13) that characterises the inflammatory process that underlies atherosclerosis in the vascular endothelium. Endothelial dysfunction is due to prolonged exposure to dietary risk elements such as elevated cholesterol and blood pressure, inflammatory cytokines, glucose intolerance, elevated blood sugar and other abnormalities in cardiovascular function (14–16). This pathogenic condition initiates the deposition of material beneath the endothelium and alteration of particles comprising low density lipid (LDL) and chemokine-mediated cell activation (12). There is an enhancement of immune cell and platelet adherence and penetration through the membrane. In order to initiate a sterile inflammatory response, ApoB-lipoproteins (LDL, chylomicron remnants, Lipoprotein) are retained sub endothelial, primarily in sites where laminar blood flow is interrupted (17, 18). This results in endothelial activation and the production of chemokines, including monocyte chemoattractant protein 1(MCP-1, CCL2). When the endothelium is active, monocytes in the blood engage with it in a series of steps involving monocyte integrins (VLA-4, LFA-1) and endothelial ligands (ICAM-1, VCAM-1) that mediate leukocyte rolling, firm adhesion, and tethering (19). Early lesions, known as fatty streaks, are characterised by an accumulation of immune cells in the sub endothelial space (20). NK cells, mast cells, neutrophils, T and B-lymphocytes, macrophages, dendritic cells, and a variety of other cells make up this group. When macrophages take in modified, mostly oxidised LDL particles through scavenger receptors (type A scavenger receptor, SR-A; CD36), they release growth factors (PDGF-1, IGF-1) and proinflammatory cytokines (IL-1, TNF-), proteolytic enzymes (mostly matrix metalloproteinase; MMPs), and foam cells (12).

CLOPIDOGREL

In 1987, Clopidogrel’s property to inhibit platelet activation in response to adenosine diphosphate (ADP) was identified. However, pharmacological action alone could not determine clopidogrel's molecular target until much later (21). Second-generation thienopyridine clopidogrel has mainly replaced ticlopidine because of its superior safety profile. Due to its efficacy and low toxicity, it has replaced other antiplatelet therapies as the first line of defence against stent thrombosis (22).

MECHANISM OF ACTION

The antiplatelet drug clopidogrel belongs to a

class known as thienopyridines. This substance is a prodrug that must undergo hepatic cytochrome P450 metabolism in order to become active. By preventing ADP from activating the downstream glycoprotein IIb/IIIa complex, the active metabolite reduces platelet aggregation by acting as an irreversible inhibitor of the P2Y12 class of surface adenosine diphosphate receptors (23). Clopidogrel must undergo a two-step bioactivation process involving several CYP enzymes, including CYP2C19 and CYP3A4. Variations in these enzymes' genes can affect how well a patient responds to treatment. One or both alleles of the CYP2C19 enzyme are the most widely discussed genetic polymorphisms in relation to clopidogrel. Patients with a loss-of-function allele cannot suppress platelet activity by metabolising clopidogrel properly (24).

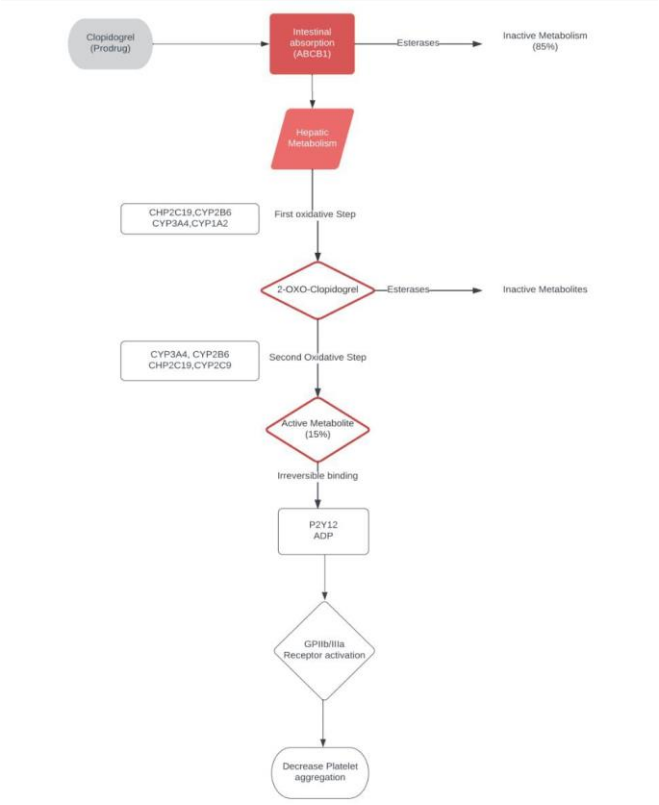

Figure 01. Mechanism of action of clopidogrel

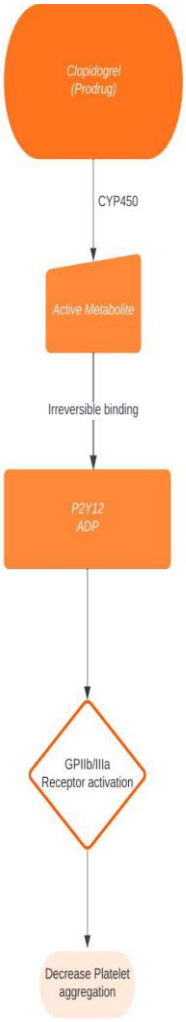

Figure 02. Mechanism of action of clopidogrel

The FDA has approved clopidogrel as an alternative to aspirin for the short-term treatment of temporary ischemic stroke and the long-term preventive care of ischemic stroke in patients who are allergic to aspirin. Depending on the severity of the condition, a loading dosage of 300 or 600 mg of clopidogrel is recommended (25), with 75 mg taken daily afterwards (26).

First, in 19185 patients with known atherosclerotic vascular disease, the CAPRIE study investigated the efficacy of clopidogrel versus aspirin for the prevention of vascular events in humans. There were 6431 people who

had recently suffered an ischemic stroke. Patients on clopidogrel had an overall relative risk reduction (RRR) of 8.7% (27).

CONTRAINDICATIONS

Patients with a history of anaphylaxis to clopidogrel or any of its components, such as those who are already bleeding, should avoid using clopidogrel (28).

TOXICITY

Adverse bleeding effects have been reported after a clopidogrel overdose. Results from animal investigations show that a single dose of 1500–2000 mg/kg is fatal for mice and rats, and that a dose of 3000 mg/kg is fatal for baboons (28).

Potential Triggers For Clopidogrel-Related Adverse Events

Most cardiac patients still use clopidogrel as an antiplatelet medication. Antiplatelet drug safety needs to be re-evaluated because of the potential impact on clinical practice. The relative safety data for antiplatelet therapies is extremely complex and perplexing (29).

In a study released in 2017 by the Italian Pharmacovigilance Network, it was shown that between 2009 and 2016, Clopidogrel appeared to be the antiplatelet medication that caused the greatest adverse effects (ADRs) among Italian patients. Ticlopidine (1,169), Ticagrelor (471), and Prasugrel (126) cannot be compared to Clopidogrel (3,298), clopidogrel presented number alleged ADRs. The order of safety hazards, however, varied when examining the incidence of ADRs with relation to the entire population of patients treated: clopidogrel > ticlopidine > ticagrelor > prasugrel (30).

Patients who take clopidogrel frequently experience the following adverse drug reactions: bleeding at the injection site, haemorrhage, erythema, enema, and intestinal disorders, such as gastrointestinal haemorrhage, diarrhea, stomach pain, and indigestion (31). During clinical trials and post-marketing surveillance, bleeding was the most commonly reported adverse event (AE). Total bleeding incidence was 9.3% (32) in the CAPRIE research. According to a meta-analysis by Italian researchers, clopidogrel had a superior benefit-to-risk ratio than considerably more expensive medications like prasugrel and ticagrelor in patients using oral anticoagulant treatment for atrial fibrillation following recent percutaneous coronary intervention. (33). Patients in this cohort who were given ticagrelor or prasugrel instead of clopidogrel had a greater risk of clinically significant bleeding, yet there was no further advantage in lowering the frequency of serious cardiovascular events.

There are a number of contributors, both genetic (single nucleotide polymorphism of transcription factors for Cytochrome p450 and P-glycoproteins) and environmental (compliance, dosage regimen, medication interactions, and comorbidities), that may account for the wide range of responses to clopidogrel (34). Various studies, including healthy volunteers of Caucasian and Asian ancestry, have shown a relationship between the

CYP2C19 genotype, changes in the pharmacokinetics of clopidogrel and its active metabolite, and other variables (35–37). The most crucial enzyme in the metabolism of the prodrug clopidogrel is CYP2C19 because of its role in both pathways of the drug's metabolic activation to the active drug (35). There are more than 14 different allelic variants of the encoding gene (35). No therapeutic effect of clopidogrel is expected in patients with such isoforms after taking the drug at standard doses since the drug is normally metabolised by the enzyme encoded by the *1 isoform but slowly metabolised by the enzyme encoded by the *2 isoform (since the conversion of clopidogrel to the active metabolite by metabolism via cytochrome P450 is required for the achievement of the therapeutic effect of the drug). Patients younger than 45 years of age, who make up the majority of the population using clopidogrel, exhibited the strongest connection between the CYP2C19*2/*2 allelic variants with a worse response to the medication (38). Those with the CYP2C19 *17 isoforms have a higher risk of experiencing adverse effects from clopidogrel because of the drug's fast metabolism in these patients (39). By decreasing the likelihood of MACE and minimising ADRs like bleeding, individualised clopidogrel medication may maximise its benefit-risk ratio.

The goal of this study was to better understand the hereditary (CYP2C19 allelic variants *2 and *17) and predisposing (noncompliance, dose, medication interactions, and clinical factors) causes the increased prevalence of clopidogrel adverse drug reactions in cardiovascular patients.

CONCLUSION

Hyperlipidaemia and lipid peroxidation are the root causes of atherosclerosis, a leading cause of death in developed countries. In 1987, clopidogrel's property to inhibit platelet activation in response to adenosine diphosphate (ADP) was identified. However, pharmacological action alone could not determine clopidogrel's molecular target until much later (21). Second generation thienopyridine clopidogrel has mainly replaced ticlopidine because of its superior safety profile. Due to its efficacy and low toxicity, it has replaced other antiplatelet therapies as the first line of defence against stent thrombosis (22).

It is a prodrug that the hepatic cytochrome P450 system metabolises into its active form. The downstream glycoprotein IIb/IIIa complex is activated by adenosine diphosphate, which reduces platelet aggregation by activating the receptors for this molecule on the surface of platelets (23). Most cardiac patients still use clopidogrel as an antiplatelet medication. Antiplatelet drug safety needs to be revaluated because of the potential impact on clinical practice. In a study released in 2017 by the Italian Pharmacovigilance Network, it was shown that between 2009 and 2016, clopidogrel appeared to be the antiplatelet medication that caused the greatest adverse effects (ADRs) among Italian patients. The order of safety hazards, however, varied when examining the incidence of ADRs

with relation to the entire population of patients treated: clopidogrel > ticlopidine > ticagrelor > prasugrel (30). Adverse bleeding incidence was 9.3% (32) in the CAPRIE research. So, patients with a history of anaphylaxis to clopidogrel or any of its components, such as those who are already bleeding, should avoid using clopidogrel.

ABBREVIATION

SMC	Smooth Muscle Cells
ASCVD	Atherosclerotic Cardiovascular Disease
IHD	Ischemic Heart Disease
LDL	Low-Density Lipoprotein
MCP-1	Monocyte Chemoattractant Protein 1
LFA-1	Lymphocyte Function-Associated Antigen 1
ICAM-1	Intercellular Adhesion Molecule 1
VCAM-1	Vascular Cell Adhesion Protein 1
IL-1	Interleukin-1
TNF-A	Tumour Necrosis Factor Alpha
MMPS	Mainly Matrix Metalloproteinases
PDGF-1	Platelet-Derived Growth Factor 1
IGF-1	Insulin-Like Growth Factor 1
ADRS	Adverse Drug Reactions
MACE	Major Adverse Cardiovascular Events
CYPS	Cytochromes P450
CYP2C19	Cytochrome P450 2C19

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