Pro Index | Journal of Science in Medicine and Life

Volume: 2 Issue: 5 Year: 2024
ISSN: 2992-9202 | http://journals.proindex.uz

Instaclop (Clopidogrel) – as a Safe Anti - Platelet Therapy

Sharipova Elvina Midatovna
Pulpit of Clinical Pharmacology, Bukhara State Medical Institute, Uzbekistan

Abstarct: *The article describes the effectiveness and clinical pharmacology of the main class of modern antiplatelet agents used in the clinical practice of a cardiotherapist, intervention cardiologist in the treatment of coronary heart disease and other pathologies of the cardiovascular system. According to the latest studies conducted on the effectiveness of the drug clopidogrel (Instaclop), the main clinical and pharmacological characteristics of the drug Instaclop.*

Key words: *antiplatelet therapy, clopidogrel, Instaclop, clinical pharmacology, safety, effectiveness.*

Introduction

Coronary heart disease (CHD) (from Latin *morbus ischaemicus cordis*) is a pathological condition characterized by an absolute or relative disruption of the blood supply to the myocardium due to damage to the coronary arteries of the heart. In 1909, at the First Congress of Russian Therapists, a classic description of the clinical picture of myocardial infarction (MI) was given in the report of the outstanding Russian therapists V.P. Obraztsova and N.D. Strazhesko "On the symptomatology and diagnosis of coronary artery thrombosis." For the first time in medical practice, it presents a classical intravital description of the clinical manifestations of coronary thrombosis, which opened a new page in the study of myocardial infarction and coronary artery disease. Since the beginning of the 21st century. thrombotic complications of atherosclerosis (coronary heart disease, myocardial infarction, stroke) are leading among the diseases that characterize the phenotype of the modern patient, along with diabetes mellitus and chronic obstructive pulmonary disease. IHD often develops in able-bodied, active individuals, significantly limiting their social and work activity, exacerbating socio-economic problems in society [3, 11, 30].

Platelets play a central role in the development of atherosclerosis and its complications, and the effectiveness of the use of drugs that reduce platelet aggregation - antiplatelet agents for the secondary prevention of coronary heart disease (CHD) and strokes is well proven. One of the most commonly used antiplatelet agents around the world today is the P2Y12 receptor blocker, the drug clopidogrel [1, 16, 24].

Major studies in recent years such as CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Event), CURE (Clopidogrel in Unstable angina Recurrent Events), CREDO (Clopidogrel for the Reduction of Events During Observation) opened up the possibility of widespread use of clopidogrel in the treatment of patients with coronary heart disease, stroke and after stenting operations , as well as for the prevention of thrombosis [4, 14, 28].

These studies have proven the absolutely positive effect of clopidogrel in reducing the incidence of myocardial infarction, stroke and overall mortality in patients. At the same time, it has been shown that from 5 to 44% of patients with coronary artery disease, during an in-depth study, show an insufficient response to the use of antiplatelet agents, which, according to the literature, is called "resistance". A meta-analysis of 15 studies, including 3,960 patients, showed that on average 25% of patients, according to laboratory testing, are resistant to clopidogrel. Overcoming resistance is possible by increasing the dose of clopidogrel or replacing it with another antiplatelet agent. Thus, B. Aleil et al showed that increasing the dose of clopidogrel from 75 mg/ day to 150 mg/ day in patients with percutaneous coronary intervention (PCI) led to a decrease in the number of resistant patients from 33% to 12% without an increase in the number of bleedings. Another study by T. Cuisset et al showed that patients with low clopidogrel sensitivity who were prescribed GP IIb / IIIa inhibitors during PCI had a lower rate of vascular events during the first 30 days after the procedure than randomized patients who received therapy was prescribed with 600 mg of clopidogrel before PCI [2, 18, 21].

The causes of resistance to clopidogrel may be genetically determined characteristics of enzymes and receptors, the state of other blood cells, the presence of ongoing inflammatory processes, non-compliance with patients, smoking, diabetes, and excess weight.

Clopidogrel is rapidly absorbed from the gastrointestinal tract (GIT) and, upon entering the liver, is metabolized with the participation of the cytochrome P450 system to form an active metabolite. The latter selectively and irreversibly inhibits the binding of adenosine diphosphate (ADP) to platelet purine receptors P2Y12. This leads to decreased activation of the GPIIb / IIIa complex and inhibition of platelet aggregation. Thus, it is possible to conditionally distinguish at least three groups of genes that determine the effects of clopidogrel. The first group of genes is responsible for the absorption of clopidogrel from the gastrointestinal tract. The second group is the genes of the cytochrome P-450 family (CYP2C19, CYP2C9, CYP3A4, CYP3A5), through which clopidogrel is metabolized. The third group is genes that determine the pharmacodynamics of clopidogrel - genes encoding platelet receptors P2Y12, GPIIIa [5, 20, 32].

By generic we mean a reproduced medicinal product that has proven bio- and therapeutic equivalence to the original medicinal product. One of the advantages of generics is their lower cost compared to brand-name drugs, which is especially important for long-term therapy. In this article we will study the literature data and clinical pharmacology of the generic clopidogrel registered in Uzbekistan - the drug Instaclop (Ajanta Pharm, India).

The basis of pharmacotherapy for IHD is antianginal drugs (nitrates, b-blockers, calcium antagonists), cholesterol-lowering drugs, antiplatelet agents . The progression of IHD is associated with the appearance of new atheromatous plaques, ulceration, rupture and hemorrhage into already formed plaques, and the deepening of the disorder of the blood coagulation system with the formation of blood clots. When the vascular endothelium of various etiologies is damaged, a blood clot forms and, as a result, a critical narrowing of the vascular lumen or its complete closure (partial or complete occlusion). An exacerbation of the disease, the occurrence of an ischemic attack, is usually provoked by physical activity and psycho-emotional stress, which cause activation of the sympathoadrenal system, an increase in the load on the heart and an increase in the histotoxic effect of catecholamines. It is known that platelets are the first to respond to the rupture of an atherosclerotic plaque, trigger the coagulation cascade and form the basis for the formation of an arterial thrombus [8, 13, 27].

Thus, the close relationship between the processes of atherogenesis and thrombus formation makes long-term antithrombotic therapy for ischemic heart disease pathogenetically justified.

The prescription of antiplatelet agents in the absence of contraindications is a mandatory part of the treatment of patients with various clinical manifestations of thrombosis and, above all, with ischemic heart disease and atherosclerotic stenosis of the coronary arteries. Antiplatelet agents prevent the aggregation of platelets and red blood cells, reduce their ability to glue and adhere to the vascular endothelium. Antiplatelet agents facilitate the deformation of red blood cells when passing through capillaries and improve blood fluidity [7, 15, 22].

In recent years, interesting evidence has emerged that the beneficial effects of clopidogrel may extend beyond its effect on platelet aggregation. It has been demonstrated that while taking the drug in patients with chronic forms of coronary artery disease, the bioavailability of endothelial relaxing factor (nitric oxide) increases and the content of biomarkers decreases oxidative stress. This allowed scientists to suggest that the severity of endothelial dysfunction while taking clopidogrel may decrease, and this effect of the drug is dose-dependent [5, 10, 15].

As evidence has increased that clopidogrel (Instaclop) is highly effective, there has been a need to provide evidence that it is superior to aspirin. This was dictated primarily by the fact that many authors, pointing to the relatively higher cost of the drug, questioned the justification of its use.

One of the early studies that confirmed the effectiveness of clopidogrel in preventing ischemic complications of atherothrombosis localized in various vascular territories was the CAPRIE protocol (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events). The study included 19,185 patients with myocardial infarction, stroke, or stenotic atherosclerosis of the peripheral arteries. The patients were divided into two groups, the first received ASA at a dose of 325 mg/ day, the second received clopidogrel 75 mg/ day. The study examined the ability of these drugs to prevent the development of myocardial infarction, ischemic stroke, occlusion of coronary stents and bypass grafts, as well as their viability as part of the combined treatment of ACS without ST-segment elevation. According to the results of the study, it was demonstrated that clopidogrel is no less effective than ASA, and even superior to it in preventing cardiovascular complications. The relative risk of developing MI, stroke and sudden cardiac death when using clopidogrel was significantly lower than when using aspirin ($p = 0.043$) [9, 12, 26].

Thus, it became clear that a drug had appeared that could both compete with aspirin and complement its antiplatelet effect, taking into account the difference in the mechanisms of action. In this regard, further studies of the effectiveness of clopidogrel were aimed, on the one hand, at identifying those clinical situations in which its use may be preferable compared to ASA, and on the other hand, at studying the possible advantages of their combined use [6, 19, 23].

In 2001, the results of the CLASSICS study were presented, which randomized 1020 patients who underwent coronary artery stenting. This protocol demonstrated the superiority of clopidogrel compared to ticlopidine in terms of the incidence of adverse events. Hemorrhagic complications, thrombocytopenia, neutropenia and other side effects during observation were almost 2 times more often recorded in patients receiving ticlopidine (9.12 compared to 4.56%). This study prompted the widespread use of clopidogrel in patients undergoing PCI. The same study demonstrated good tolerability of a loading dose of clopidogrel (300 mg) [4 , 10, 25].

Currently, interventional cardiology is one of the main areas of application of clopidogrel. Most controlled clinical trials have demonstrated significant improvements in the outcomes of

revascularization procedures in patients with ACS treated with clopidogrel. Long-term (12 months) use of clopidogrel after PCI is associated with a lower incidence of the composite endpoint (CV death + MI + revascularization), as well as a 25% reduction in the relative risk of death and MI (p = 0.03 and p = 0.047, respectively) [17, 31].

In the randomized multicenter study PCI-CLARITY (PCI- CLopidogrel as Adjunctive ReperfusIon TherapY) has demonstrated the beneficial effect of clopidogrel in patients undergoing PCI and stenting for ST-segment elevation MI [3, 29].

As noted above, in recent years there has been evidence that a loading dose of clopidogrel 600 mg can achieve this effect within 2 hours. This thesis is also included in the latest edition of the European recommendations, but with a slightly lower level of evidence (IIa -B). American experts, in the latest version of the recommendations, published in 2009, recommend a loading dose of 300–600 mg [2, 14].

In addition, clopidogrel in the doses indicated above is recommended for patients with ACS as monotherapy in the presence of contraindications to aspirin (hypersensitivity, clinically significant gastrointestinal pathology).

The question of the optimal maintenance dose of clopidogrel more than 30 days after revascularization remains debatable. According to separate small studies, taking the drug at a dose of 150 mg/ day provides a better antiplatelet effect compared to the standard maintenance dosage (75 mg/ day). Of course, additional prospective studies are needed to examine the effectiveness and safety of long-term use of high doses of clopidogrel.

The optimal duration of taking the drug after coronary angioplasty and stenting has not been fully established. Most studies suggest that long-term use of clopidogrel may help reduce restenosis after implantation of both metallic and drug-eluting stents. Recently, data from a prospective, randomized, open-label study, RACS (Randomized Argentina Clopidogrel Stent), which included 1,004 patients with acute and chronic forms of coronary artery disease after successful implantation of metal stents. Patients were randomly assigned to short-term (30 days) or long-term (180 days) clopidogrel maintenance therapy. All patients in the study received ASA. The primary end point (overall mortality + MI + stroke) after 6 months of observation in patients taking long-term clopidogrel was recorded significantly less often than in the control group (in 1.74 and 4.99% of cases, respectively, p = 0.010, a decrease in relative risk was 65%) [1, 33].

Thus, the drug clopidogrel, both as monotherapy and in combination with ASA, is currently recommended for primary and secondary prevention of atherothrombotic complications. Summarizing the above, it should be noted that all the advantages that this drug demonstrated in numerous studies presented in the review were identified during the study of the original drug Plavix (Sanofi- aventis). More research is needed to confirm that generic versions of the drug have similar clinical effects. There is no data on the bioequivalence of loading doses of generic drugs [2, 8].

Conclusion

Clopidogrel is still considered the preferred agent for antiplatelet therapy both in acute conditions and in the long-term prevention of cardiovascular diseases. Its clinical effectiveness in reducing the incidence of myocardial infarction, ischemic stroke and vascular death in various groups of high-risk patients has been confirmed by the results of numerous randomized controlled trials and meta-

analyses. At the same time, the need for long-term antiplatelet therapy dictates the requirements for its safety, which especially concerns the prescription of clopidogrel.

All of the above requirements are met by the drug Instaclop, which is produced at the modern Ajanta Pharm plant (India). Instaclop is available in tablets, in a dose of 75 mg and, what is especially important at present, has a price affordable for most patients in Uzbekistan.

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