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Review Article

Clopidogrel Interactions: Consider while prescribing

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Abstract

Clopidogrel reduces the cardiovascular risks because of inhibitory action on platelets aggregation but some co-administered drugs compromise its main therapeutic effects. Clopidogrel is a prodrug and converted into active metabolite by the hepatic cytochrome P450. The active thiol metabolite inhibits the P2Y12 adenosine di-phosphate receptors and decrease the platelet aggregation processes. The activity of clopidogrel is dependent on the metabolic conversion by cytochrome P450 due to this fact proton pump inhibitors, atorvastatin and several other drugs that competitively inhibit the clopidogrel metabolism might alter its therapeutic response.

Conversely other agents potentiate the clopidogrel responsiveness by inducing the cytochrome activity. Combinational drug therapy increases the risks of drug-drug interactions. The previous pharmacodynamic studies have reported clinically significant risks that are associated with combined therapy of clopidogrel with other drugs which are commonly used in coronary artery disorders. These reported studies did not demonstrate the consistent evidence for sever drug-drug interaction hazards in cardiovascular events.

This review highlights the various controversies among the studies about common clopidogrel interactions when prescribed in various cardiovascular disorders to achieve targeted therapeutic outcomes. The clopidogrel is commonly prescribed in many serious disorders such as cardiovascular, hypercholesteraemia and lack of information or uncertainty may cost serious outcomes.

Keywords: Clopidogrel, Interactions, Cardiovascular, Proton pump inhibitors

1. Introduction

Clopidogrel is a thienopyridine derivative and its chemical structure is related to ticlopidine (Terry et al., 2010; Robinson et al., 2007; Mitakos et al., 2002). Clopidogrel is a pro-drug and converted to its active metabolite through hepatic biotransformation (Hulot et al., 2006; Richter et al., 2006). Clopidogrel metabolized mainly through cytochrome P450 and oxidized into 2-oxoclopidogrel which further hydrolyses and a thiol compound is formed (Raghunada et al., 2010). CYP3A4/5 and CYP2C19 are mainly responsible for the biotransformation of clopidogrel to its active metabolite that is thiol derivative (Eric et al., 2011).

It has ability to inhibit the platelets aggregation. The parent drug and its active metabolite are not detectable in plasma. The main circulating metabolite is carboxylic acid derivative that is present in the plasma up to 85% (Sonu et al., 2005; Hanna et al., 2006). Esterases play an important role in the conversion of clopidogrel to its inactive metabolite, carboxylic acid derivative (Guillermo et al., 2010).

Clopidogrel is used prophylacticaly and has benefit in Prevention and therapy of various conditions like Ischemic stroke, and Myocardial infarction (Sonu et al., 2011). It is used as an efficient substitute to aspirin in patients who experience cardiovascular diseases like stroke, myocardial infarction, or peripheral arterial disease. Clopidogrel has supplementary effects against platelet activation when it is used with Aspirin in combination especially in patients with acute coronary syndrome and percutaneous coronary intervention (Terry et al., 2010).

2. Mechanism of action of clopidogrel

Clopidogrel, chemically being a thienopyridine, its active metabolite shows its effect against platelets activation and aggregation by irreversibly binding to adenylatecyclase-coupled ADP P2Y12 receptors that are present on the platelets surface. As a result the activation of glycoprotein IIb/IIIa pathway is blocked. This pathway is an ultimate pathway for platelet aggregation (Terry et al., 2010). The platelet aggregation process is the definite target of Clopidogrel (pereillo et al., 2002). The antiaggregating properties of clopidogrel are much more than ticlopidine (Savi et al., 1998). Clopidogrel is more effective than that of Aspirin in various conditions like myocardial infarction, and vascular diseases (Mitakos et al., 2002; Eduardo et al., 2010). Mechanism of clopidogrel has been shown in figure 1.

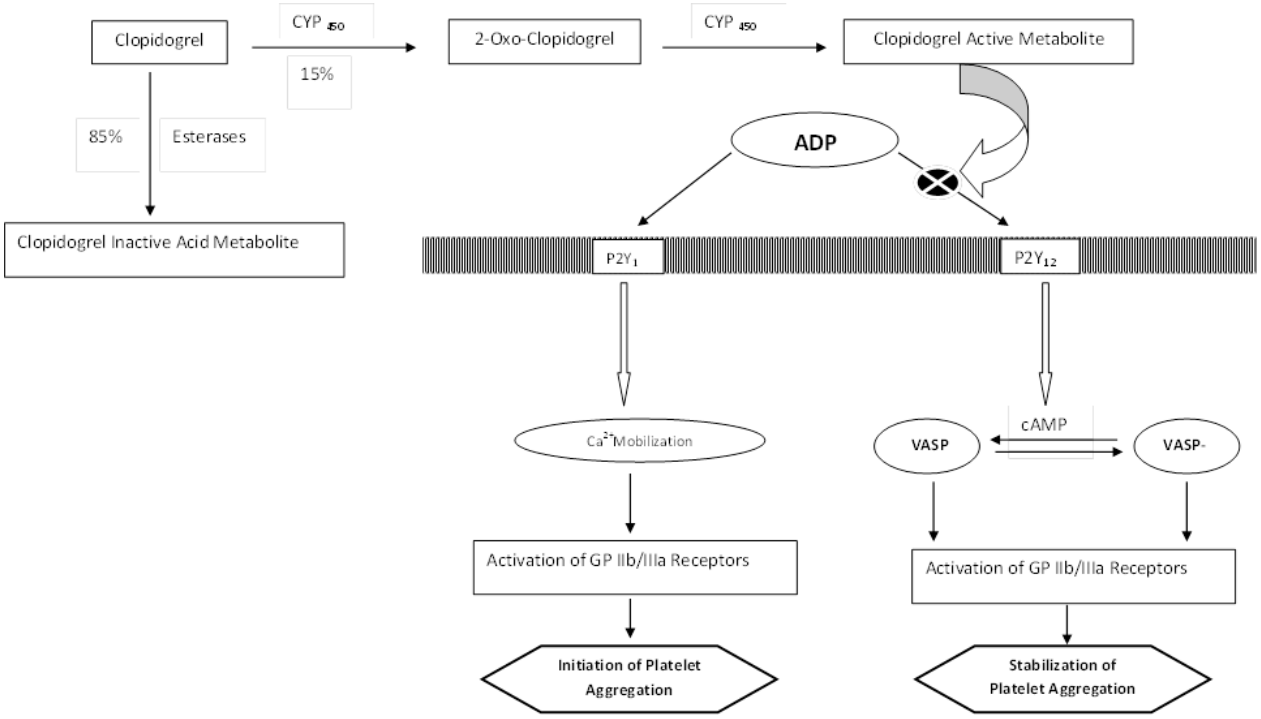

Figure: 1 Mechanism of Clopidogrel

3. Drug interactions

The drug interactions are effects of a drug that are altered by the existence of another drug moiety or herbal product, chemical agents, or by food items. When there is an effect of drugs on the processes of the body like absorption, distribution, metabolism, and excretion, then this type of interaction is called pharmacokinetic interaction of drugs. Pharmacokinetic drug interaction also involves the interactions, in which there is induction or inhibitions of metabolizing enzymes e.g. CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, in the body especially in liver, dislocation of drugs from plasma proteins binding sites (Baxter et al., 2010).

3.1 Clopidogrel drug-drug interaction possibilities

Currently and in the last few years numerous studies have been conducted to evaluate the ability of the drug interaction of clopidogrel and its metabolite with other drugs, chemicals, and food items (Ramesh et al., 2009). As clopidogrel exhibits drug interaction with the drugs that are metabolized by the cytochrome P450 enzymes (Paul et al., 2009). Combinational therapy of clopidogrel can aggravate the pharmacodynamic responses of other agents as in case of aspirin this can increase the gastrointestinal bleeding complications in ulcer patients. The common food (caffeine containing products) or habits (smoking) can also alter the clopidogrel responses.

3.2 Clopidogrel and Aspirin

Thromboxane and Adenosine diphosphate are important agonists; these two play an important role while causing platelet activation and aggregation. The pathways of their production are blocked; Thromboxane production by Aspirin and ADP receptor activation pathway is blocked by Clopidogrel (Desmond et al., 2007). Aspirin and clopidogrel both have anti aggregating and antiplatelet activity and are used in patients to cope with and to prevent cardiovascular events. When Aspirin is given to the patients in combination with ticlopidine, it has far better effects that of single therapy of Aspirin. Similarly the combination of Aspirin with clopidogrel is as effective like Aspirin/ticlopidine combination. There is an increased risk of hemorrhagic problems as a result of Aspirin clopidogrel combined therapy (Paul et al., 2010). When aspirin is prescribed in combination with warfarin or clopidogrel the major complication is GI bleeding that is not seen when clopidogrel or warfarin is prescribed alone (Ramesh et al., 2009). The use of low dose of aspirin and clopidogrel are useful (Bexter et al., 2010).

3.3 Clopidogrel and proton pump inhibitors (PPIs)

A protective barrier of gastric mucosa includes prostaglandins and thromboxane A2.Usually clopidogrel and Aspirin are prescribed in combination, Aspirin inhibits these protective agents and increase the risks of gastric ulcers and bleedings in response to various agents. So the need raised for the co-prescription of clopidogrel and PPIs (Desmond et al., 2007).

As clopidogrel is metabolized to its active thiol metabolite that shows its antiplatelet activity, cytochrome P450 isoenzymes are involved in this metabolism, these isoenzymes greatly affect the clopidogrel anti platelet activity. Proton pump inhibitors and other drugs that inhibit P450 isoenzymes cause the decrease amount of active metabolite to circulate in plasma. As a result the pharmacokinetics of clopidogrel is totally changed and patient is now at high risk of cardiovascular risks (Ishkizaki et al., 2007).

Juurlink et al. (2009) conducted a population based study and concluded that PPI's could reduce the effects of Clopidogrel therapy (Jurlink et al., 2009). As a result European Medicines Agency (EMEA) and FDA warned for this problem in 2009 (FDA, 2010).

According to Eric et al. (2011) like clopidogrel, Proton pump inhibitors are also prodrugs, and parietal cells of stomach are the site for PPIs activation to its active metabolites. Hydroxyomeprazole and omeprazole sulphate are the main metabolites of omeprazole. Omeprazole is converted to its active metabolites mainly by CYP2C19 and CYP3A4. As both Clopidogrel and Omeprazole utilize CYP2C19, therefore omeprazole decreases the conversion of clopidogrel to active form but other PPIs have no such affects.

Another study reported by Dirk et al. (2009), the patients on clopidogrel-omeprazole therapy, most of them were not responding due to less inhibition of platelet activation. On the other hand when esomeprazole or pantoprazole is given along with clopidogrel the results were comparatively good. Similarly patients using Clopidogrel but no other PPI, shows good response.

The Martine et al. (2008) clearly described that efficacy of clopidogrel is reduced when prescribed with omeprazole and studied by the use of vasodilator-stimulated phosphor protein (VASP) technique. It is suggested that omeprazole should not be prescribed along with clopidogrel. David et al. (2009) conducted a survey based study to explore the inhibition of bioactivation of clopidogrel by PPIs in acute myocardial infarction cases. The PPIs (omeprazole, lansoprazol and rabeprazole) inhibits the cytochrome P450 2C19 that indirectly inhibit the bioactivation of clopidogrel into its active metabolite, but this inhibition does not occur by pantoprazole. This interaction increases the risks of recurrent myocardial infarction.

But according to Small et al., there is no interaction among Lansoprazole and Clopidogrel. The drug-drug interaction of Clopidogrel and PPIs boosts the risk of Myocardial infarction up to 40% (Small et al., 2008).

Rassen et al. (2011) studied the potential effects of clopidogrel therapy with and without PPIs and clearly concluded that this interaction has been overestimated. Loren et al., 2010 summarized the previous data on clopidogrel and PPIs interactions and finally concluded that studies on this interaction are based on observations without clinical significant evidences and their results are conflicting. Patients treating with clopidogrel and omeprazole simultaneously, no considerable increase in cardiovascular risks has been seen and there are no harmful effects of clopidogrel and PPIs combine therapy. The claim that efficacy of

clopidogrel is decreased when used along with PPIs, cannot be proven to be true and further investigation and studies are required. Deepak et al. (2010) also studied that no apparent cardiovascular interaction occurs between omeprazole and patients taking clopidogrel with aspirin. Omeprazole effectively reduced the upper gastrointestinal bleeding along with clopidogrel.

Siller-Matula et al. (2009) studied the PPIs (omeprazole, pantoprazole and esomeprazole) interaction with clopidogrel effectiveness by VASP assay and ADP aggregometry. Omeprazole negatively affect the clopidogrel results but pantoprazole and esomeprazole have no effect on the clinical efficacy of clopidogrel when given in combination. Pantoprazole and esomeprazole may share other types of metabolizing enzymes that do not decrease the efficacy of clopidogrel as by omeprazole.

Gastric acid suppression can be achieved by administering H2 receptor antagonists by replacing PPI's. The effect of H2 receptor antagonists on CYP2C19 is not same e.g. Ranitidine do not inhibit CYP2C19 activity but cimetidine do (Johan et al., 2011).

Clopidogrel and PPI's interaction is controversial in various studies but unfortunately the interaction between PPI's and Aspirin is also gaining importance as it is not clear. A study conducted for interaction of PPI and Aspirin on 14 patients using omeprazole resulted that these agents don't interfere with each other (Inarrea et al., 2000). Another study on 24 patients had also the same results when Lansoprazole was used (Adamopoulos et al., 2009). But in another study in which Pantoprazole was administered with Aspirin, that enhanced the antiplatelet activity of aspirin (Kasprzak et al., 2009). Conversely, one of the largest study on 418 subjects showed that the antiplatelet activity of aspirin is reduced when co-administered with PPI's (Wurtz et al., 2010).

3.4 Clopidogrel and statins

Chemically Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors. Statins are prescribed for hypercholesteremia. Like clopidogrel it is also metabolized by Cytochrome P450 in liver (Wei, 2003). As CYP3A4 and CYP3A5 converts clopidogrel in to its active metabolite, when a patient is treated with clopidogrel and Atorvastatin at same time using the same concentration of both the drugs, there were greater than 90% reduction in the conversion of clopidogrel to its active metabolite (Eric et al., 2011). Usually clopidogrel and statins both are prescribed for the same indication.Patients using both the drugs are studied and noted that statins greatly affect the anti-platelet activity of clopidogrel because of pharmacokinetic interaction (Wei, 2003). According to the Karen Baxter Atorvastatin and other statins greatly affect the activity of the clopidogrel. More lipophilic statins showed more interaction with clopidogrel because both the groups experience metabolism by same CYP450 enzyme (Jolanta et al., 2009; Bhindi et al., 2008).

According to Pertti J. Neuvonen, not all the statins have interaction with clopidogrel, however the pharmacokinetic interaction of Atorvastatin with clopidogrel is not very clear (Pertti et al., 2006). Clopidogrel antiplatelet activity is diminished by Fluvastatin because its metabolism is carried out by CYP P450 2C9 and very less by CYP3A4, also same is enzyme that metabolize clopidogrel.

In case of Rosuvastatin and pravastatin the pharmacokinetic drug-drug interaction with clopidogrel is not proved because clopidogrel do not share the same enzyme of metabolism with these agents, so plasma level of clopidogrel metabolite is not altered (Mach et al., 2005).

According to F. Mach's (2005) study there is no such interaction of Atorvastatin with clopidogrel, which change clopidogrel metabolite concentration in plasma.

Numerous studies showed that as CYP3A4 metabolize various statins like simvastatin and atorvastatin so there are negative effects of its co-administration with Clopidogrel, but in vitro assays showed that may be these interactions are present but these are not of clinical importance (Blagojevic et al., 2009; Saw et al., 2007; Saw et al., 2003; Lim et al., 2005).

3.5 Interactions with antifungals

Ketoconazole is a potent CYP3A4 inhibitor, when ketoconazole is administered along with clopidogrel; it decreases the extent of conversion of Clopidogrel into its active metabolite (Eric et al., 2011; Jolanta et al.,

2009; Farid et al., 2007; Suh et al., 2006). There is approximately 30% decline in the exposure to the active metabolite of Clopidogrel, when it is prescribed along with Ketoconazole (Ramesh et al., 2009). traconazole also inhibits CYP3A4; as a result the amount of active metabolite of Clopidogrel is decreased, and its antiplatelet activity is reduced (Eric et al., 2011; Jolanta et al., 2009).

3.6 Clopidogrel-Smoking/Caffeine Interaction

In non-emergent coronary stenting experiencing patients, smoking enhances the antiplatelet activity of Clopidogrel (Kevin et al., 2008). Smoking aggravate the antiplatelet effect of Clopidogrel as it induces hepatic cytochrome P450 enzyme CYP1A2, as a result it increases the production of active metabolite of Clopidogrel (Eric et al., 2011; Liu et al., 2010). Fewer ischemic events, bleeding risks are increased (Berger et al., 2009) in smokers after clopidogrel administration. Cigarette smoking potentiates the therapeutic effects of Clopidogrel on the basis of clinical results when compared to nonsmokers (Nihar et al., 2009). Similarly Caffeine also positively modifies the results of Clopidogrel as caffeine increases cAMP levels. Some drugs like theophylline and Cilostazol also increase the cAMP levels (Eric et al., 2011).

3.7 Interaction with CYP3A4 inducers and Inhibitors

Rifampicin is a CYP3A4 inducer and when it is administered along with Clopidogrel, it increases the antiplatelet effects of Clopidogrel. Some CYP3A4 inhibitors like erythromycin and troleandomycin reduces the production of active metabolite of Clopidogrel as a result there is negative effects on Clopidogrel efficacy (Ramesh et al., 2009). Co-administration of clopidogrel and rifampicin can increase the response to clopidogrel as rifampin is a CYP3A4 and CYP2C19 inducer, and as a result the non-responsive patients become responsive (Lau et al., 2004). It can be concluded on the basis of previous studies that combinational therapy of clopidogrel must be advised keeping the focus on risks associated with their interactions.

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