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CLOPIDOGREL RESISTANCE AND ITS SUBLINGUAL FILM FORMULATION: A COMPREHENSIVE REVIEW

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Abstract

Clopidogrel, a second-generation thienopyridine drug, is extensively utilized for inhibiting platelet aggregation in the management of coronary artery disease (CAD) and percutaneous coronary intervention (PCI). Inspite extensive use of clopidogrel its resistance poses a significant challenge, impacting its therapeutic efficacy. The mechanisms of underlying clopidogrel resistance, encompassing both pharmacokinetic and pharmacodynamic factors, and it explores various platelet function tests utilized for evaluating clopidogrel responsiveness, which includes Verify Now, VASP, and TEG assays. TEG is common application used in clinical applications. Additionally introduction of innovative drug delivery system—sublingual film formulation. The sublingual film's rapid dissolution and oromucosal absorption offer a promising alternative route for administering antiplatelet therapy giving patients choice with of more compliance. Paper discusses about future directions, pre-emptive genetic testing and artificial intelligence various approaches, aimed at optimizing antiplatelet therapy selection and improving clinical outcomes with CAD and PCI patients. This extensive review provides insight into addressing clopidogrel resistance its definition and improving the effect of antiplatelet therapy through innovative drug delivery strategies and personalized medicine approaches. Sublingual film that are available in the market with respective manufacturer, brand name and its indications. Factors such as pH, flow of saliva, residence time and drug absorption that are require for formulations stability and potency.

Keywords: clopidogrel, clopidogrel resistance, platelet function test, sublingual film, pharmacogenetic testing, artificial intelligence.

Introduction

second-generation thienopyridine drug clopidogrel is used for inhibiting platelet aggregation, for effective medication of CAD and percutaneous coronary intervention[1]. It is widely used for lower cost and rate of bleeding than third generation p2y12 inhibitors[2]. It was introduced in 1998 in the United States. Clopidogrel is a prodrug taken orally, which requires hepatic bioactivation to generate the active metabolite responsible for platelet inhibition[3,4]. Injury in CVD is triggered with platelet activation or abnormal vascular endothelium, cause platelet aggregation, subsequent pathologic thrombus formulation and ischemic events so antiplatelet therapy is the mainline and preventive treatment of CVD[5]. Clopidogrel has superseded the first generation thienopyridine ticlopidine in both better tolerability and safety. In addition, none of them requires for routine monitoring, and they have an equivalent efficacy[6]. The common side effects including bleeding, gastrointestinal

disorder and rash, hepatotoxicity and thrombotic thrombocytopenic purpura are also possible, but rare. As a result, patients tolerate them extremely well[7].

Mechanism of action

Hepatic cytochrome (CYP) P450 enzymes including CYP3A4, CYP3A5, and CYP2C19 convert, intestinally absorbed inactive clopidogrel bisulphate prodrug to active Clopidogrel thiol metabolite (CTM)[8]. CTM consists of four isomers; H1-H4, where H3 (inactive form) and H4 (active circulating form) are mainly considered in monitoring the action of clopidogrel[9]. These isoenzymes are commonly found in hepatocytes, but also in other tissues like the gut and skin[10]. CTM irreversibly bind to form a disulfide bridge with two cysteine residues (cys17 and cys270) present in the extracellular domain of the (ADP) p2Y12 receptor[11]. Thus, it inhibits platelet dense granule secretion, leading to a reduction in arachidonic acid (AA), collagen, and thrombin-induced platelet activation observed in clopidogrel. This effect causes the activation of intracellular pathways and inhibits the conformational change of platelet Glycoprotein (GP) IIb/IIIa receptors necessary for fibrinogen crosslinking and platelet activation. Additionally, clopidogrel exhibits anti-inflammatory effects by reducing CRP, platelet leukocyte aggregation, p-selectin, and CD40L levels. It may also impact the enzymatic components of coagulation, lowering speed of thrombin formation. The cumulative outcome of these processes is the activation of intracellular pathways and inhibit the conformational change of platelet Glycoprotein (GP) IIb/IIIa receptors crucial for fibrinogen cross-linking and platelet activation[11].

Clopidogrel resistance

While there is currently no universally agreed-upon definition for this occurrence, there exists a commonly accepted description that the prolonged activity for clopidogrel target, namely the P2Y12 receptors on platelets, persists despite an appropriate antiplatelet regimen[12].Clopidogrel resistance platelet function testing can be defined in two main ways. Firstly, it involves a inadequate reaction to clopidogrel therapy, evaluated by the change in ADP-induced platelet reactivity compared to the baseline. Secondly, it can be identified as high "ontreatment" platelet reactivity, aligning with the assessment of other drug responses, by applying international normalized ratio for warfarin[13].The primary association with clopidogrel resistance is linked to the loss-of-function allele CYP2C19*2 genotype. Additionally, genetic variations impact active metabolite conversion with CYP P450, which contribute significantly to resistance. Studies indicate that prevalent clopidogrel resistance in the population ranges from 4% to 30%, with variations allotted by utilization of diverse platelet function studies[14].

Clopidogrel Resistance Mechanisms

Pharmacokinetic Factors

Firstly, intestinal absorption can be hindered, potentially because of genetic variations in ABCB1 gene, which encodes a P-glycoprotein efflux transporter. The nucleotide polymorphism of ABCB1 gene C3435T reduces clopidogrel absorption, dose ranging from 300 mg or 600 mg LD, regardless of whether it is in homozygous or heterozygous form. Significantly, in studies individuals with the homozygous form dose were more likely to experience adverse events such as death, nonfatal MI, stroke. Secondly, there exists significant interindividual change in the hepatic CYP P450 enzymes crucial for transformation of clopidogrel into active metabolite. Pharmacogenetic factors are increasingly recognized in this domain, with CYP3A4, CYP3A5, and CYP2C19 all linked to clopidogrel activation[15]. Suh et al. demonstrated that patients with the non-expressor genotype for CYP3A5 exhibited both reduced clopidogrel responsiveness and poorer outcomes following stent implantation, although conflicting studies exist. CYP2C19 may hold particular importance, responsible for clopidogrel activation. Various clopidogrel therapy revealed that individuals carrying CYP2C19 loss of function alleles experienced an increased chance of cardiovascular events, especially among PCI patients. Among these alleles, CYP2C19∗2 increases risk of cardiovascular events[16].

Pharmacodynamic

Obese associated with high weight referred from the BMI index or patients having diabetes exhibit an increased tendency for "resistance" and heightened sensitivity to ADP concerning both platelet adhesion and aggregation [17]. The genetic factors also influence clopidogrel's

efficacy involving P2RY12 and ITGB3 genes, although investigations have not consistently linked genes encoding the P2Y12 receptor with clopidogrel responsiveness. While some indicate a correlation between genetic change in the GPIIb/IIIa receptor and clopidogrel response diversity. Additionally, polymorphisms in platelet membrane receptors like GP1a, crucial for the aggregatory response, have been reported. Poor responders may exhibit upregulation in intracellular P2Y12-dependent and -independent pathways, including those reliant on the P2Y1 pathway or other platelet agonist as AA, thrombin, and collagen [18,19].

Platelet function test

The Clopidogrel PFT is used to assess an individual's reaction to antiplatelet medication. It helps identify on-treatment high platelet reactivity (HPR), correlated with a rise in events of cardiovascular, and low platelet reactivity (LPR), linked to an increased bleeding risk[13].Clopidogrel and its effect is often assessed through platelet function tests. Firstly, light transmission aggregometry with ADP stimulation is considered gold standard, but point-of-care tests like Verify Now and specific assays like VASP platelet reactivity index provide alternative for it. The VASP platelet reactivity index is a specific assay for P2Y12 receptor blockade. It measures levels of the protein VASP, which is phosphorylated in the presence of P2Y12 stimulation, using flow cytometry. VASP has shown correlation with optical aggregation and has been used to guide treatment modifications in clopidogrel poor responders, potentially leading to improved clinical outcomes secondly, Thromboelastography (TEG) assay, particularly its modified version (mTEG), offers a more comprehensive assessment of clopidogrel's impact on blood clotting by evaluating enzymatic coagulation, overall clotting tendency, and platelet activation which is induced by arachidonic acid. Clopidogrel plays a crucial role in managing cardiovascular conditions, and platelet function tests helps in evaluating its efficacy in individual patients. TEG shows a good correlation with optical aggregation in detecting the effects of clopidogrel, and results can be obtained in 15 minutes. This makes it appropriate for common clinical application, offering a more global perspective on the impact of clopidogrel on various aspects of blood clotting[20,21].

Sublingual film

Mouth dissolving films or strips represent an innovational drug delivery system designed for oral administration, leveraging the technology utilized in transdermal patches. These films consist of ultra-thin strips that are effortlessly kept on the patient's tongue or any oral mucosal tissue. Upon exposure to saliva, the film rapidly hydrates and adheres to the site of application. Subsequently, it undergoes swift disintegration and dissolution, facilitating the delivery of medication for oromucosal absorption. Moreover, through formula modifications, these strips can maintain their quick-dissolving properties, enabling gastrointestinal absorption upon swallowing. Sublingual strips share similarities with tablets, as they readily melt and dissolve rapidly in mouth, exemplified by medications like Suboxone[22]. This innovative concept introduces a novel sublingual film design utilizing a blend of components, including a water-soluble carrier encased with fine particles of active substances and a bioadhesive polymer. This formulation facilitates rapid dissolution while concurrently reducing drug dispersion within the oral cavity through bioadhesion[23,24]. The drug absorption through the sublingual region is significantly higher, ranging from 5 to 10 times greater compared to other delivery systems, making it a preferable option over hypodermic injection. Additionally, the minimal saliva present in this area reduces chance of tablet breakage. Moreover, the veins returning from this region directly enter systemic circulation, bypassing presystemic drug elimination mechanisms. Various drug properties, such as solubility, crystal morphology, particle size, hygroscopicity, compressibility, and bulk density, serve important roles in assessing the effectiveness of sublingual medications[24].

Physiological factors influencing sublingual drug delivery

Consideration of these factors is crucial for optimizing sublingual drug delivery, ensuring effective and safe medication administration.

1. Residence Time of Formulation:

- Absorption depends on how long the drug stays in sublingual areas.
- Formulations include tablets, films, wafers, or sprays.
- Patients should avoid eating, drinking, or swallowing to prevent decreased

effectiveness.

2. Drug Absorption:

- Drug needs balance between hydrophilic and lipophilic properties.
- Should be soluble in buccal fluids and have high lipid solubility for membrane crossing.
- Suitable for low to medium molecular weight drugs.
- Open sores or inflammation can affect absorption.
- Smoking can decrease absorption due to vasoconstriction.

3. pH of Saliva:

- Affects drug absorption by influencing ionization state.
- Passive absorption pathways depend on physicochemical characteristics.
- Favorable when drug is non-ionized and lipophilic.
- High pKa drug values are preferred.
- Saliva pH can be altered by various factors, affecting absorption.

4. Flow of Saliva:

- Influences drug delivery by affecting formulation disintegration and dissolution.
- Dry mouth can hinder absorption, while excessive saliva flow can lead to swallowing before absorption.
- Saliva flow can be influenced by age, medications, and medical conditions like Sjögren's syndrome or dysphagia[25].

Table 1: Commercialized marketed products for sublingual film

drug	indications	brand name	manufacturer	references
apomorphine hydrochloride sublingual film	parkinson's disease	kynmobi®	sunovion medical.	(25)
dexmedetomidine (sublingual film)	schizophrenia	igalmi ®	bioxcel therapeutics	(25)
buprenorphine hydrochloride + naloxone	narcotic opioid analgesic	subuzone ®	reckitt-benckiser pharmaceutical	(26)
simethicone (sublingual film)	used to treat stomach bloating	gas-x thin strips®	novartis consumer healthcare	(27)

Genetic testing and artificial intelligence

The text discusses the potential benefits of pre-emptive pharmacogenetic testing in addressing the challenge of rapidly obtaining genetic test results, particularly in the context of coronary artery disease (CAD), stroke, and percutaneous coronary intervention (PCI). This approach involves incorporating CYP2C19 genotype data into electronic medical records, enabling alerts whenever clopidogrel is prescribed to individuals with a CYP2C19 LOF allele. The increasing popularity of direct-to-consumer genetic testing is noted, with results becoming available to healthcare providers. Given the low adverse event rate in PCI patients, the focus is on identifying high- or low-risk individuals through genetic testing, potentially guiding the adjustment of antiplatelet therapy. Scores combining CYP2C19 genetic testing and clinical factors have been effectively created for this objective. Additionally, approaches such as machine learning are being employed to integrate pharmacogenomic and clinical data, aiming to identify personalized risk profiles using high-resolution profiling to select antiplatelet therapy in stroke and CAD patients[28].

Conclusion

In conclusion, clopidogrel, a second-generation thienopyridine drug, plays a important part in inhibiting platelet aggregation for therapy of CAD and percutaneous coronary intervention. Overcoming the resistance of Clopidogrel, genetic variations, and other factors contribute to various challenges and reduced efficacy. Understanding both pharmacokinetic and pharmacodynamic factors also patient-specific factors, that contribute to resistance. Platelet function tests, including Clopidogrel Platelet Function Test (PFT), are employed to assess individual responses to antiplatelet therapy, aiding in identifying high platelet reactivity or resistance. To enhance the effects of clopidogrel, its sublingual film formulations offer an advance drug delivery system with possible benefits. This approach leverages rapid dissolution and oro-mucosal absorption, providing an alternative to traditional oral administration. Looking toward the future, pre-emptive genetic testing and artificial intelligence approaches hold promise in addressing clopidogrel resistance. Incorporating CYP2C19 genotype data into electronic medical records, combine with machine learning approaches, allows for personalized risk profiling and the optimization of antiplatelet therapy, particularly in the context of CAD, stroke, and PCI.

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