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Clopidogrel: An Antiplatelet Agent

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ABSTRACT:

Clopidogrel is an important antiplatelet medication widely used in the prevention of cardiovascular events in patients with acute coronary syndromes and those undergoing percutaneous coronary interventions. This abstract provides a concise overview of the key aspects covered in an article on clopidogrel, including its pharmacology, efficacy, safety, and potential adverse effects.

The article highlights the mechanism of action of clopidogrel, which involves irreversibly inhibiting the ADP P2Y12 receptor on platelets. This inhibitory effect reduces platelet aggregation, thereby mitigating the risk of thrombotic events. The pharmacokinetics of clopidogrel are discussed, with an emphasis on its rapid and extensive metabolism by cytochrome P450 enzymes, particularly CYP2C19. The article also explores the impact of genetic variations in CYP2C19 on clopidogrel's efficacy, reinforcing the need for personalized medicine in optimizing treatment outcomes.

Efficacy data presented in the article demonstrate that clopidogrel, when used in combination with aspirin, significantly reduces the incidence of major adverse cardiac events, including myocardial infarction, stroke, and cardiovascular death. The article outlines the recommended dosing regimens and duration of therapy based on various clinical scenarios and patient populations.

Safety considerations are thoroughly addressed in the article, with a focus on potential adverse effects of clopidogrel. Commonly reported side effects, such as bleeding, including major bleeding, are discussed, along with precautions for high-risk groups, such as the elderly and patients with impaired liver function.

In conclusion, the articles provides healthcare professionals with a comprehensive understanding of clopidogrel, its pharmacology, therapeutic applications, and potential risks. By emphasizing personalized medicine and evidence-based prescribing practices, the article underscores the importance of optimizing treatment outcomes and patient safety.

Keywords: Antiplatelet, Bleeding, Cardiac events

1. HISTORY & DISCOVERY

The first antiplatelet drug in this family, ticlopidine (Fig. 1), is structurally linked to the thienopyridine molecule that is clopidogrel (Fig. 1). The narrative began in 1972 when, Dr. Fernand Eloy, decided to look for novel anti-inflammatory medications associated with Tinoridine (Fig. 1), a thienopyridine molecule whose anti-inflammatory and analgesic effects had been disclosed by the Yoshitomi Company two years earlier. [1]

Utilising what we knew about the chemistry of thienopyridines, we created a variety of derivatives in grammes and tested them on a variety of animal models that explored various physiological systems or mimicked human illnesses. Nearly majority of these studies were carried either on or outside of mice and rats. Fortunately, several of the synthesised thienopyridine compounds showed surprising antiplatelet and antithrombotic activity following oral treatment to rats. It seems that none of the compounds had anti-inflammatory or analgesic effects.It is important to note that looking for novel antiplatelet medications was not prevalent at the time. Some cardiologists continue to dismiss or question the connection between platelet aggregation, thrombosis, and cardiovascular events; in reality, vascularspasm is thought to be the primary contributor to the clinical problems of atherosclerosis. Ticlopidine, one of the most active substances discovered, was quickly chosen for development and was tested in clinical settings where platelet association with artificial surfaces can result in thrombotic complications, such as in cardiac operations with extracorporeal circulation or in patients receiving hemodialysis.

Under the brand name Ticlid, the medication was first sold in France in 1978 for these specific therapeutic indications. Other individuals with a high probability of thrombosis events, such as those with a history of stroke, peripheral artery disease, or ischemic heart disease, were found to benefit from ticlopidine in later, big clinical trials. The product was then utilised on a global scale and entered the US marketplace in 1991.

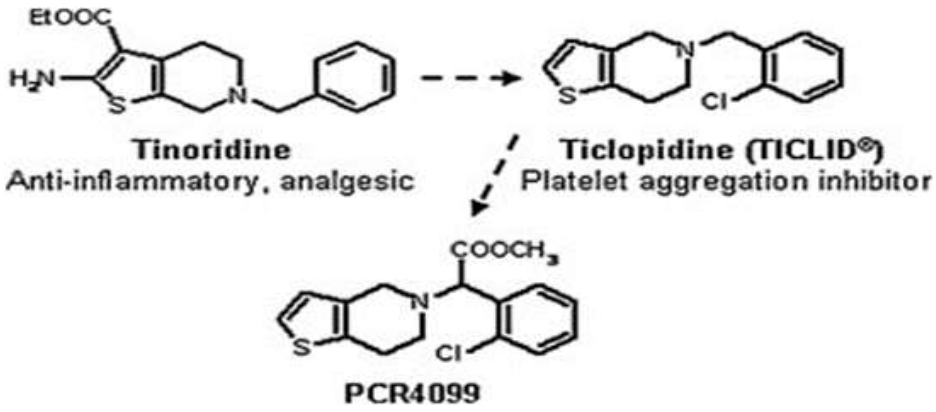

Fig. 1. From tinoridine to ticlopidine and PCR4099.

Once ticlopidine was chosen for preclinical testing, we nonetheless continued to make thienopyridine analogues in an effort to get back-up drugs with a higher activity/toxicity ratio in animals, which would translate into a better benefit/risk ratio in people. This goal became even more important when it emerged that some of the treated patients had serious haematological abnormalities such leucopenia, thrombocytopenia, agranulocytosis, and pancytopenia a few months after ticlopidine was introduced in France. In following extensive clinical studies and post-marketing pharmacovigilance, these potentially fatal side effects have been verified and quantified.

However, they cannot be anticipated by any identifiable demographic or clinical variables. The majority of them happened during the first three-month period of medication and were reversible upon stopping therapy. As a result, the Health Authorities mandated that throughout that three-month period, patients receiving ticlopidine treatment were hematologically and clinically examined.

Over one thousand ticlopidine analogues have been created and tested on animals to see how they affect blood clotting and platelets. Just the last one, PCR4099 (Fig. 1), shown to be significantly more active and well-tolerated than ticlopidine during phase 1 investigations in healthy volunteers out of the eight that had been produced. Additional early phase II clinical investigations on patients who had already experienced thrombotic events supported its potent antiplatelet effects. PCR4099 is actually a racemic.

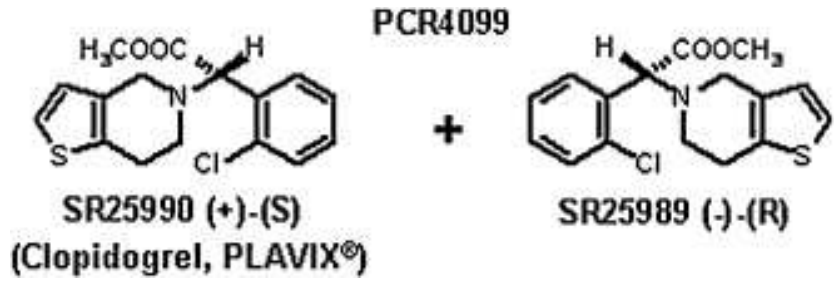

Fig. 2. PCR4099 is a racemic mixture: only the dextrogyre (S)-isomer (clopidogrel) has antiplatelet and antithrombotic effects while the inactive levogyre isomer is less well tolerated

To separate both of the enantiomers in order to determine if, by chance, any of them could have a better activity/toxicity ratio because we were extremely concerned about the first reported adverse reactions of ticlopidine in humans and because we wanted to create the best backup we could. However, we kept in mind that it was impossible to reliably replicate in animals or with in vitro studies of human hematopoietic cells the rare ticlopidine haematological effects observed in humans. We established a separation process that could be industrially generalised [after a lot of fruitless tries. While the inactive (-) - (R)-isomer was obviously less well tolerated in animals, it seemed that only the dextrogyre (S)-isomer (clopidogrel) showed antiplatelet and antithrombotic actions. As a result, we halted the clinical research. [2]

2. PHYSIO-CHEMICAL PROPERTIES:

2.1 Structure

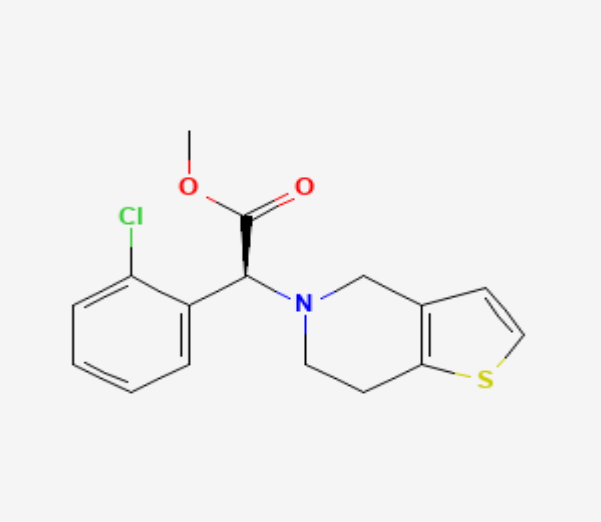

Fig. 3: Clopidogrel Structure

Molecular Formula	$C_{16}H_{16}ClNO_2S$
Molecular Weight	321.8 g/mol
IUPAC Name	methyl (2*S*)-2-(2-chlorophenyl)-2-(6,7-dihydro-4*H*-thieno[3,2-c]pyridin-5-yl)acetate
Physical Description	Solid
Color / Form	Colorless oil
Melting Point	158°C
Solubility	15.1 [ug/mL] (The mean of the results at pH 7.4) In water, 51 mg/L at 25 °C (est)
Vapor Pressure	2.9X10-7 mm Hg at 25 °C (est)
Dissociation Constants	pKa = 5.3 (tertiary amine
UV Visible	**Clopidogrel shows λmax at 230.**

Table 1: Physiochemical Properties

UV Visible spectrum - Scan standard solution in UV spectrophotometer between 200 nm to 400 nm on spectrum mode, using diluents as a blank.

Clopidogrel shows λmax at 230.

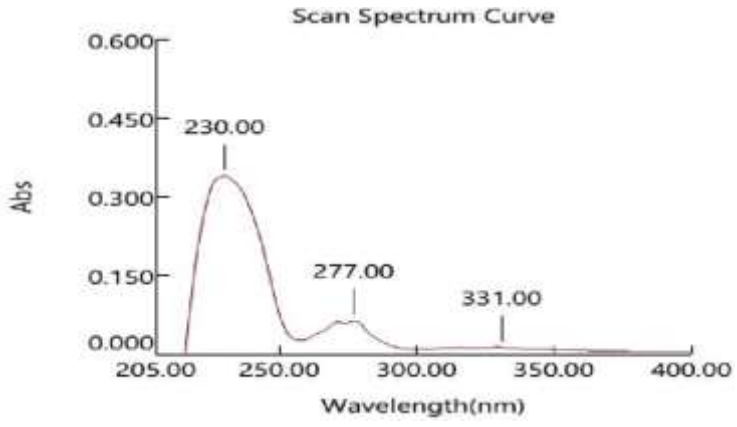

Fig. 4: Clopidogrel spectrum activity

IR- IR Spectroscopy The IR spectrum was recorded in the solid state as a KBr disk, and in Nujol as a dispersion medium, using the FT-IR (Bruker, alpha) spectrophotometer, the wave length resolution was set to 4 cm-1, the IR spectrum was collected in a range of 400–4000 cm-1, with Bruker Opus 5.5 software.[3]

2.2 PHARMACOKINETICS:

BCS Classification: Clopidogrel is categorized as a class II agent having poor water solubility and high permeability, which is responsible for its poor oral bioavailability

2.2.1 Absorption

- Tmax, oral: 30 to 60 min
- Bioavailability, oral: At least 50%
- Effects of food: No effect

2.2.2 Distribution

- Human plasma proteins bind reversibly to clopidogrel and the primary circulating inactive metabolite in vitro (98% and 94%, respectively).
- In vitro, binding is nonsaturable at 100 mcg/mL of concentration.

2.2.3 Metabolism

- Hepatic: Extensive
- Thiol derivative (major): Active
- Carboxylic acid derivative (major): Inactive
- Clopidogrel: Substrate of CYP2C19, CYP1A2, CYP2B6, and CYP3A
- Acyl-beta-glucuronide metabolite: Inhibitor of CYP2C8
- Pharmacogenomics/Pharmacogenetics, CYP2C19: Decreased active metabolite exposure and diminished inhibition of platelet aggregation were observed in CYP2C19 poor metabolizers as compared with those with normal, intermediate, or ultrarapid CYP2C19 metabolizer status .

2.2.4 Excretion

- Renal excretion: 50%
- Fecal excretion: 46%

2.2.5 Elimination Half Life

- 6 hours
- Thiol derivative (active): 0.5 to 0.7 hours [4]

Clopidogrel is quickly absorbed following single and recurrent oral dosages of 75 milligrammes per day. After just a single 75-mg oral dosage, average maximum plasma concentrations of unmodified clopidogrel peaked 45 minutes later at around 2.2–2.5 ng/mL. Based on urine excretion of clopidogrel metabolites, absorption is at least 50%.

Effect of Food: Currently, it is unknown how food affects the bioavailability of its parent substance or active metabolite.

Distribution: Human plasma proteins bind reversibly to clopidogrel and the primary circulating inactive metabolite in vitro (98% and 94%, respectively). In vitro, binding is nonsaturable at 100 mcg/mL of concentration.

Metabolism: The liver metabolises clopidogrel in great detail. Clopidogrel is metabolised via two major metabolic routes both in vitro and in vivo: one is driven by esterases and results in hydrolyzed into its inactive carboxylic acid derivative (85% of circulating metabolites), while the other is mediated by many cytochromes P450. Clopidogrel is initially converted by cytochromes into the intermediate metabolite 2-oxo-clopidogrel. The drug's active metabolite, a thiol analogue of clopidogrel, is created as a result of further metabolism of the intermediate metabolite 2 oxo-clopidogrel. In vitro, CYP3A4, CYP2C19, CYP1A2, and CYP2B6 mediate this metabolic pathway. The in vitro isolated active thiol metabolite binds quickly and permanently to platelet

receptors, preventing platelet aggregation. Elimination: About half of the total radioactivity is eliminated in humans after taking an oral dosage of clopidogrel labelled with 14C.

Elimination: Over the course of 5 days after an oral dosage of 14C-labeled clopidogrel, roughly 50% of the total radioactivity was eliminated in urine and around 46 percent in faeces. Clopidgrel has an approximately 6-hour half-life after a single 75 mg oral dosage. After single and repeated treatment, the inactive acid metabolite had an 8-hour elimination half-life. With an 11-day half-life, 2% of the radiolabel was covalently bound to platelets. The glucuronide of the carboxylic acid analogue is also seen in plasma and urine.

Cmax values (+/-SD) for SR26334 following single doses of 50, 75, 100, and 150 mg were 1.6+/-0.30 mg/L, 2.9+/-0.68 mg/L, 3.1+/-0.94 mg/L, and 4.9+/-1.22 mg/L, respectively. [5]

3. MECHANISM OF ACTION

A prodrug called clopidogrel has a metabolite that prevents platelet aggregation. In patients with known cardiovascular atherosclerotic disease as demonstrated by stroke or transient ischemic episodes, myocardial infarction, unstable angina, or the requirement for vascular bypass surgery or angioplasty, a range of medications that restrict platelet activity have been found to reduce morbid occurrences. This suggests that platelets take involvement in the beginning and/or development of these instances and that limiting platelet activity can lower the rate of occurrence.

The active metabolite of clopidogrel, which prevents platelet aggregation, is produced by CYP450 enzymes. Adenosine diphosphate's (ADP) binding to the platelet P2Y12 receptor and resulting ADP-mediated stimulation of the glycoprotein GPIIb/IIIa complex are both specifically blocked by the active metabolite of clopidogrel, which prevents platelet aggregation. This action cannot be undone. As a result, platelets exposed to the active metabolite of clopidogrel are harmed throughout the balance of their lives (about 7 to 10 days). By preventing the amplified platelet activation caused by released ADP, it is also possible to suppress platelet aggregation brought on by agonists other than ADP.

Not all patients will have sufficient platelet inhibition since the active metabolite is created by CYP450 enzymes, some of which are polymorphism or susceptible to pharmacological inhibition.

Two hours after receiving a single oral dosage of Clopidogrel, platelet aggregation is inhibited in a dose-dependent manner. On the first day after daily 75 mg dosages of Clopidogrel, ADP-induced platelet aggregation is inhibited, and the inhibition achieves steady state between days three and seven. With a daily dosage of 75 mg of Clopidogrel, the average inhibition level was between 40% and 60% in steady state. After therapy is stopped, platelet aggregation and bleeding time progressively recover to baseline levels, usually in approximately 5 days. [5]

4. METHOD OF SYNTHESIS

Synthetic steps

Step 1: Add the chlorobenzyl cyanide to the three apis bottles, each holding 500 ml, one at a time. The bottles are heated to 100C and kept there for four hours. Next, add the methylene chloride and water. Stirring for 10 minutes, the mixture is left to stand for 10 to 15 minutes to separate the lower organic layer. Finally, add the sodium bisulfite and mix thoroughly for 15 to 20 minutes. Anhydrous magnesium sulphate should be allowed to stand for 10 to 15 minutes to separate the organic layer, merging layer, 0.6 ml methylene chloride was used to extract it again, combining the organic layer, saturated sodium bicarbonate 0.6 L washing again, with 0.65 L saturated brine washing again, enriching to dry, oily matter, to join the 1.2 ml n-hexane, cooling, stir fully, filter, after fully dry. Light yellow crystal, can be directly into the next step response.

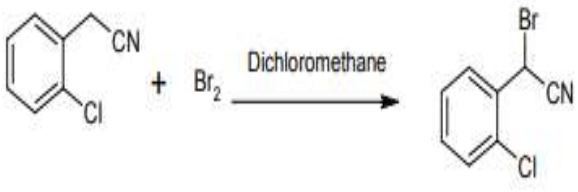

Fig. 5 : Step 1

Step 2: The results of step1 dissolved in 4.3 ml anhydrous methanol, and then add sodium bicarbonate and pyridine hydrochloride and phase transfer catalyst in turn, after feeding, heating system to reflux, reflux reaction about 5 hours, cooling the system to 0 C, keep the temperature of mixing 1.5~2 hours, filtration, cake 3 ml water washing 2-3 times, and use 1.4 ml cold methanol washing again, after dry, heating 5 hours, can get white or yellow granular crystalline powder.

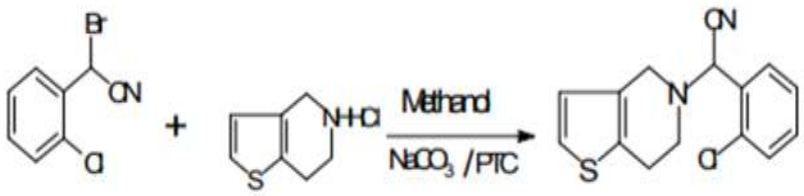

Fig. 6: Step 2

Step 3: Dissolve potassium hydroxide in 3 ml of water, cool to 10 C, add clopidogrel, isopropyl alcohol, and the phase transfer catalyst one at a time, heat to reflux while stirring, respond for more than 8 hours, cool to room temperature, add 6N hydrochloric acid, maintain a system temperature of 0 5 °C while mixing, crystallise for 2 3 hours, filter, and dry the filter cake.You may obtain white or yellow granular crystals by baking for 8 to 12 hours.

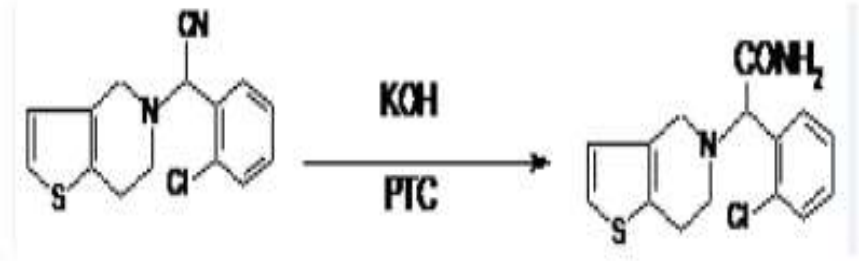

Fig. 7: Step 3

Step 4: Acetic clopidogrel After adding 1g of solubility in methanol, lowering the system to 0°C, adding 1.6g of sulfuric acid slowly, controlling the temperature in the range of 0–30°C when drops are added, heating to reflux for 24 hours (24 hours can be isolated), and cooling the system to 0–30°C after the reaction, No discernible proportion of stress concentration. Add 4 mL of cold water gently, 4 mL of methylene chloride, and cool to 0 to 5 °C. methylene chloride separation, three methylene chloride washes of the water layer Combining the methylene chloride layer with 6 ml of water, keeping the temperature between 0 and 5 degrees Celsius, and adding sodium hydroxide until the solution has a pH of 11, after 30 minutes of maintaining PH 11 at a low temperature, let stand after separation.

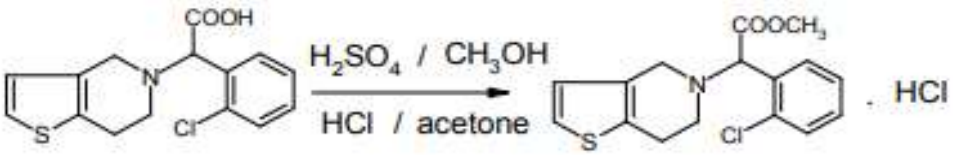

Fig. 8: Step 4

Step 5: The results of step 4 are dissolved in 50 ml of anhydrous methanol. Then, the sinistral camphor sulfonic acid is partially mixed with the clopidogrel camphor sulfonate and stirred to dissolve after it had fully dissolved. The mixture is then kept at a temperature of mixing crystallisation for 48 hours. Finally, the cake is filtered, washed with 0.5 L of toluene, dried to 0. [6]

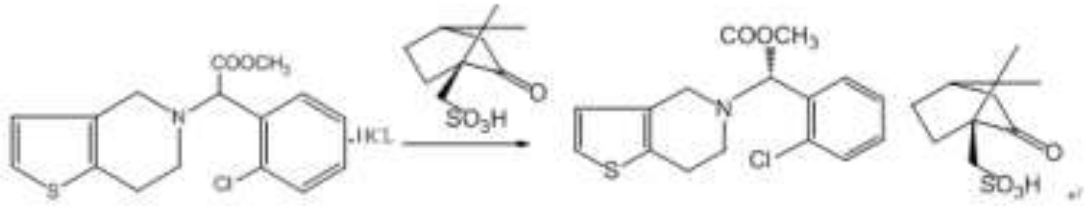

Fig. 9: Step 5

5. MEDICINAL USES:

People with recent heart attacks, strokes, or blood circulation problems (peripheral vascular disease) are prescribed clopidogrel to avoid heart attacks and strokes.Additionally, it is used with aspirin to treat newly developing or increasing chest pain (new heart attack, unstable angina), as well as to maintain blood vessel health and reduce the risk of blood clots following certain operations (such as cardiac stent). [7]

6. ADVERSE REACTIONS

The following serious adverse reactions are discussed below:

Bleeding : Clopidogrel and other thienopyridines raise the risk of bleeding.

For the duration of the platelet (7–10 days), thienopyridines prevent platelet aggregation. Exogenous platelet administration could be able to reestablish hemostasis due to the active metabolite of clopidogrel's short half-life; however, transfusions of platelets within 4 hours of the loading dosage or 2 hours after the maintenance dose might be less efficient.

Thrombotic thrombocytopenic purpura: TTP, which can be deadly, has been linked to the use of Clopidogrel, sometimes only after a brief exposure (2 weeks). Plasmapheresis (plasma exchange) is an urgently needed treatment for TTP since it is a dangerous disorder. Microangiopathy and thrombocytopenia are its defining features.

6.1 Post-marketing Experience

The following adverse reactions have been identified during post-approval use of Clopidogrel. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In individuals on Clopidogrel, haemorrhages have been documented, including some that were deadly.

- Blood and lymphatic system disorders: Agranulocytosis, aplastic anemia/pancytopenia, thrombotic thrombocytopenic purpura (TTP), acquired hemophilia A
- Gastrointestinal disorders: Colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis, gastric/duodenal ulcer, diarrhea
- General disorders and administration site condition: Fever
- Hepato-biliary disorders: Acute liver failure, hepatitis (non-infectious), abnormal liver function test
- Immune system disorders: Hypersensitivity reactions, anaphylactoid reactions, serum sickness
- Musculoskeletal, connective tissue and bone disorders: Myalgia, arthralgia, arthritis
- Nervous system disorders: Taste disorders, headache
- Psychiatric disorders: Confusion, hallucinations
- Respiratory, thoracic and mediastinal disorders: Bronchospasm, interstitial pneumonitis, eosinophilic pneumonia
- Renal and urinary disorders: Increased creatinine levels
- Skin and subcutaneous tissue disorders: Maculopapular, erythematous or exfoliative rash, urticaria, bullous dermatitis, eczema, toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis (AGEP), angioedema, druginduced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), erythema multiforme, lichen planus, generalized pruritus
- Vascular disorders: Vasculitis, hypotension

7. TREATMENT OF OVERDOSE

According to a U.S. Food and Drug Administration (FDA) analysis, people with or at risk for heart disease who take the blood thinner clopidogrel regularly do not have an overall change in risk of mortality. According to our analysis of the Dual Antiplatelet Therapy (DAPT) study and a number of other clinical trials, clopidogrel does not appear to raise the risk of developing cancer or dying from it.

Stopping the usage of clopidogrel or other antiplatelet medications might raise the risk of blood clots and heart attacks, thus patients shouldn't do so.

An antiplatelet drug called clopidogrel is used for the prevention of blood clots in people who have had a stroke, heart attack, or issues with their arms and legs' circulation. It functions by assisting in preventing the blood's platelets from congregating and creating clots, which can happen when certain medical conditions are present.

In November 2014, the New England Journal of Medicine reported findings from the DAPT experiment. In the DAPT study, patients who had undergone installation of a drug-eluting coronary stent were treated with dual antiplatelet medication (either clopidogrel [Clopidogrel] or prasugrel [Effient] plus aspirin) for 12 months vs 30 months. Patients who took clopidogrel for 30 months had decreased incidence of bleeding than those who took it for 12 months.

The results of the DAPT trial and other sizable, lengthy clinical studies of clopidogrel with information available on rates of fatalities, death from cancer, or cancer reported as a serious side effect in order to examine the increased risk of death and death related to cancer reported with clopidogrel in the DAPT trial.

To evaluate the impact of clopidogrel on the mortality rates from all causes, we conducted meta-analyses of additional lengthy clinical studies. According to the findings, whether compared to short-term (6 months or less) dual antiplatelet medication with clopidogrel and aspirin, or aspirin alone, long-term (12 months or longer) dual antiplatelet therapy with clopidogrel and aspirin does not appear to modify the overall risk of mortality. Additionally, there wasn't a noticeable rise in the chances of cancer-related fatalities orcancer-related adverse events with long-term treatment.

8. CONTRAINDICATIONS

The following conditions are contraindicated for Clopidogrel use:

Hypersensitivity to the drug's active ingredient or any other product component. active pathological bleeding, such as a cerebral hemorrhage or a stomach ulcer.

Reduced effectiveness as a result of dysfunctional CYP2C19: Clopidogrel's ability to prevent platelet aggregation is completely attributable to an active metabolite. In part through CYP2C19, clopidogrel is converted to this active metabolite. Both concurrent medicines that interact with CYP2C19 and genetic differences in CYP2C19 can disrupt this metabolism. Patients with known genetic variations that affect CYP2C19 function or patients taking medications that reduce CYP2C19 activity should not use Clopidogrel.

Genetic variations: Compared to patients with normal CYP2C19 function, people with genetically reduced CYP2C19 function have lower antiplatelet responses and generally demonstrate higher cardiac event rates following myocardial infarction.

9. DRUG INTERACTIONS

When Clopidogrel and a drug called an inhibitor of the proton pump that also inhibits CYP2C19, are taken at the same time or separated by 12 hours, the pharmacological effect of Clopidogrel is decreased. There is no proof that other stomach acid-reducing medications, such as antacids or the majority of H2 blockers (apart from cimetidine, that is a CYP2C19 inhibitor), impact the antiplatelet effectiveness of clopidogrel.

Thrombotic thrombocytopenic purpura (TTP): TTP has only seldom been linked to the use of Clopidogrel, and occasionally only after a brief exposure (2 weeks). TTP is a severe, sometimes fatal illness that needs immediate medical attention, include plasmapheresis (plasma exchange). Thrombocytopenia, microangiopathic anemia, or hemolytic anemia (schistocytes, or fragmented RBCs), neurological signs, renal impairment, and fever are its distinguishing features.

Adverse drug reactions In part through CYP2C19, clopidogrel is converted to its active metabolite. Decreased blood levels of the primary metabolite of clopidogrel and decreased platelet inhibition are the effects of concurrent use of medications that impede the action of this enzyme. CYP2C19 inhibitors such as omeprazole, esomeprazole, cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine should not be used concurrentlyThe following findings came from research into particular medication interactions: Omeprazole: In a five-day crossover clinical investigation, 72 healthy patients received either omeprazole (80 mg at the exact same time as Clopidogrel) or Clopidogrel alone (300 mg load dose then 75 mg/day). When Clopidogrel and omeprazole were given simultaneously, the amount of time exposed to the active metabolite of clopidogrel was reduced by 46% (Day 1) and 42% (Day 5) respectively. When Clopidogrel and omeprazole were taken combined, the mean inhibitory effect on platelet aggregation (IPA) was decreased by 47% (over 24 hours) and 30% (over 5 days).

The same dose of Clopidogrel and omeprazole were administered to 72 healthy volunteers in a subsequent research, but the medications were given 12 hours apart. The results were similar, demonstrating that timing the administration of Clopidogrel and omeprazole does not hinder their interaction.

Aspirin: Aspirin had no effect on clopidogrel's ability to prevent platelet aggregation brought on by ADP. The Clopidogrel-induced lengthening of bleeding time was not significantly increased by concurrently administering 500 mg of aspirin twice day for 1 day. Aspirin's impact on platelet aggregation brought on by collagen was amplified by Clopidogrel. Aspirin and Clopidogrel can be taken jointly for up to a year.

Heparin: In a research involving healthy participants, Clopidogrel did not call for a change in the dosage of heparin or affect how the medication affected coagulation. Heparin coadministration had no impact on Clopidogrel-induced platelet aggregation's suppression.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): Clopidogrel treatment while taking naproxen was linked to an increase in occult gastrointestinal blood loss in healthy individuals. Clopidogrel and NSAIDs should not be taken together.

Warfarin: Care should be given while administering warfarin along with Clopidogrel due to the higher probability of bleeding.

Other Concomitant Therapy: When CLOPIDOGREL was taken together with atenolol, nifedipine, or both atenolol and nifedipine, no clinically important pharmacodynamic interactions were noticed. The a combination of phenobarbital or estrogen had no discernible impact on the pharmacodynamic action of Clopidogrel. The a combination of Clopidogrel (clopidogrel bisulfate) did not affect the pharmacokinetics of digoxin or theophylline. In vitro, clopidogrel inhibits P450 (2C9) at high doses. As a result, Clopidogrel may affect how phenytoin, tamoxifen, tolbutamide, warfarin, torsemide, fluvastatin, and many other non-steroidal anti-inflammatory drugs are metabolized. However, there are no data to predict how significant these interactions will be.

Any of these medications should be administered with caution if Clopidogrel is also being taken. Patients participating in Clopidogrel clinical trials also received a variety of concurrent medications, such as diuretics, beta-blockers, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol-lowering medications, coronary vasodilators, antidiabetic medications (including insulin), thrombolytics, heparins (unfractionated and LMWH), GPIIb/IIIa antagonists, antiepileptic medications, and hormone replacement therapy. No information is available on the concurrent use of oral anticoagulants, non-studied oral antiplatelet medications, and long-term NSAIDs with clopidogrel. Laboratory Test Interactions with Drugs None is known cancer development, mutagenesis, and diminished fertility When clopidogrel was given for 78 weeks to mice and 104 weeks to rats at dosages up to 77 mg/kg per day, providing plasma exposures >25 times that in people at the permitted daily dose of 75 mg, there was no evidence of tumorigenicity. In one in vivo test (micronucleus test by oral route in mice) and four in vitro studies (Ames test, DNA-repair testing in rat the hepatocyte mutation of genes assay in Chinese hamsters fibroblasts, and metaphase chromosomal analysis of human lymphocytes), clopidogrel was not genotoxic.

At oral doses up to 400 mg/kg per day (52 times the advised human dose on a mg/m2 basis), it was discovered that clopidogrel had no effect on the ovarian function of male and female rats. pregnancy Category B pregnancy. There was no evidence of fetotoxicity or decreased fertility in rats or rabbits used in reproduction experiments at dosages up to 500 & 300 mg/kg/day (respectively, 65 & 78 times the daily adult dose on a mg/m2 basis). However, there aren't any good, controlled research on pregnant women. Clopidogrel should only be used throughout pregnancy if absolutely necessary because research on animal reproduction are not necessarily indicative of a human response. Moms who are nursing Clopidogrel and/or metabolites of it are excreted in milk, according to studies done on rats. Whether this medication is secreted in human milk is unknown. A choice should be taken regarding whether to stop nursing or to stop the drug, taking into account the significance of the drug to the nursing mother, because many pharmaceuticals are excreted via human milk and because there is a chance that nursing infants could experience major adverse reactions. Children's Use Pediatric population safety and efficacy have not been determined.

Elderly Use About 50% of the patients receiving Clopidogrel treatment were 65 years of age or older, and 15% of the individuals in the CAPRIE, CURE, & Clarity controlled clinical investigations were 75 years of age or older. About 58% of the Clopidogrel-treated patients in COMMIT were 60 years of age or older, with 26% of them being 70 years of age or older. [8]

10. CONVENTIONAL MARKETED FORMULATION [9]

Table 2: Coneventional products of Clopidogrel

SR.NO.	TYPE	BRAND NAME	COMPANY NAME	DOSE	PRICE (Approx.)
1.	Tablet	Pidogrel	Alkem Labs	75 mg	120
2.	Tablet	Plagril	Sangrose Laboratories	75 mg	60
3.	Tablet	Clopitab	Cipla	75 mg	95
4.	Tablet	Clopivas	Lupin	75 mg	100
5.	Tablet	Clotrel	Abbott	75 mg	50
6.	Tablet	Clopidex	Macleods	75 mg	95
7.	Tablet	Pidogrel AP	Pidogrel AP	75 mg	270

11. NOVEL MARKETED FORMULATION [9]

Table 3: Novel products of Clopidogrel

SR.NO.	TYPE	BRAND NAME	COMPANY NAME	DOSE	PRICE (Approx.)
1.	Tablet	Plavix	Sanofi India Limited	75 mg	93
2.	Tablet	Ceruvin	Ipca Laboratories Ltd	75 mg	111
3.	Tablet	Clopilet	Sun Pharmaceutical Industries Ltd	75 mg	164
4.	Tablet	Clavix	Intas Pharmaceuticals Ltd	75 mg	111
5.	Tablet	Deplatt	Torrent Pharmaceuticals Ltd	75 mg	192
6.	Tablet	Plagerine	Abbott Healthcare Pvt Ltd	75 mg	73
7.	Tablet	Clopiwin	Alkem Laboratories Ltd	75 mg	55
8.	Tablet	Clopicard	FDC Ltd	75 mg	99
9.	Tablet	Clopivas	Cipla Ltd	75 mg	105
10.	Tablet	Clavix-AS	Intas Pharmaceuticals Ltd	75 mg	84
11.	Capsule	Clopirest-asp 150	Matias healthcare pvt ltd.	150 AND 75	79
12.	Capsule	Rosufy-cv	Razenta pharmaceutical pvt ltd	20/75	220
13.	Capsule	Rosadix-gold	Ucardix pharmaceuticals	75/10/75	140
14.	Capsule	Rosufy-gold	Razenta pharmaceutical pvt ltd	75/20/75	225
15.	Capsule	Rojlip-gold	Doer life sciences	75/20/75	170
16.	Capsule	Rovax-gold	Thrivex lifesciences pvt ltd.	75/10/75	173
17.	Capsule	Zafrose	Metcure remedies pvt ltd.	10/75	154
18.	Capsule	Acs gold	Coliv pvt ltd.	75	145

12. PATENTS

1. Patent: US5549836A

Description: Inhibitors of platelet aggregation and method of inhibiting platelet aggregation with thienopyridines.

Inventor: Lowell D. Ferrell Jr., et al.

Year of Grant: 1996

Year of Expiry: 2013 [10]

2. Patent: EP0577176B1

Description: Clopidogrel preparation process.

Inventor: Gérard Georges Louis Cauchon, et al.

Year of Grant: 1998

Year of Expiry: 2017 [11]

3. Patent: US5969113A

Description: Thienopyridine compounds for the inhibition of platelet aggregation.

Inventor: Yung-ming Chen, et al.

Year of Grant: 1999

Year of Expiry: 2016 [12]

4. Patent: EP0944771B1

Description: A process for preparing crystalline forms of clopidogrel bisulfate.

Inventor: Yashwant G. Bajaj, et al.

Year of Grant: 2002

Year of Expiry: 2019 [13]

5. Patent: US20060025497A1

Description: Methods and compositions for the treatment of atherosclerosis using dimethyl celecoxib.

Inventor: Garth Rapundalo, et al.

Year of Grant: 2006

Year of Expiry: 2023 [14]

6. Patent: EP2493646B1

Description: Pharmaceutical composition comprising clopidogrel and atorvastatin.

Inventor: Santosh G. Kulkarni, et al.

Year of Grant: 2012

Year of Expiry: 2032 [15]

7. Patent: US8501237B2

Description: Pharmaceutical compositions of clopidogrel and aspirin.

Inventor: Amarillo O. Castro, et al.

Year of Grant: 2013

Year of Expiry: 2031 [16]

8. Patent: EP2946973B1

Description: Process for the preparation of Polymorphs of (S) Clopidogrel base.

Inventor: Sudhir Kumar Jha, et al.

Year of Grant: 2016

Year of Expiry: 2036 [17]

9. Patent: US20170289491A1

Description: Composition comprising Clopidogrel and Doxycycline for the prevention or treatment of atherosclerosis.

Inventor: Harold S. Bernstein, et al.

Year of Grant: 2017

Year of Expiry: 2035 [18]

10. Patent: EP3323990A1

Description: A process for the preparation of crystalline clopidogrel bisulfate.

Inventor: Chakradhar Kotwal, et al.

Year of Grant: 2019

Year of Expiry: 2039 [19]

13. CONCLUSION:

In conclusion, the review article on clopidogrel article presents a comprehensive overview of the medication's pharmacology, efficacy, and safety. The article highlights the importance of clopidogrel as an antiplatelet agent for the prevention of cardiovascular events, such as myocardial infarction and stroke, particularly in patients with acute coronary syndromes and those undergoing percutaneous coronary interventions.

The review provides insights into the pharmacokinetics and pharmacodynamics of clopidogrel, emphasizing its rapid and extensive metabolism. The article also discusses the influence of genetic factors on clopidogrel's effectiveness, shedding light on the importance of personalized medicine in optimizing therapeutic outcomes.

Safety considerations and potential adverse effects associated with clopidogrel are thoroughly examined in the article, emphasizing the need for patient monitoring and precautions in specific populations, such as the elderly and those with impaired liver function.

Overall, the review article on clopidogrel article provides a valuable resource for healthcare professionals, offering a comprehensive understanding of the drug's mechanisms of action, therapeutic applications, and potential risks. It underscores the significance of evidence-based prescribing practices, individualized patient care, and ongoing research to further optimize the use of clopidogrel in clinical practice.

14. REFERENCE

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