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REVIEW ARTICLE

THIENOPYRIDINES: PLATELET ADP RECEPTOR ANTAGONIST

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ABSTRACT

Atherothrombosis results from atherosclerosis progression, and its clinical manifestations [acute coronary syndromes (ACS), stroke, etc]. These events are secondary to atherosclerotic plaque disruption and subsequent thrombus formation. Atherosclerosis prevention focuses mainly on the management of 'cardiovascular risk factors' whereas thrombosis-related complications use antithrombotic therapies. The central role played by platelets in pathophysiology of arterial vascular disease has focused attention on the development of effective platelet inhibitor modalities to mitigate the clinical consequences of atherothrombotic disease. Aspirin has been the mainstay; the thienopyridines provide new opportunities for those patients who are intolerant, resistant or have failed to respond to aspirin, and for those who can derive greater benefit from combined therapy. Thienopyridines **(**ticlopidine, clopidogrel etc.) are a class of ADP receptor/P2Y_{12} inhibitors used for their anti-platelet activity. The co-administration of aspirin-clopidogrel results in enhancement of platelet inhibition as they act via different platelet receptors. This article reviews the current antiplatelet agents in ACSs and role of thienopyridines as antiplatelet agents in management.

Key words: Acute coronary syndrome, Antiplatelet therapy, Thrombosis, Thienopyridines, Clopidogril

INTRODUCTION:

The central role of platelets in the pathophysiology of arterial vascular disease has focused attention on the development of effective platelet inhibitor modalities to mitigate the clinical consequences of atherothrombotic disease.[1] Aspirin has been the gold standard of therapy and is effective in cerebral, coronary and peripheral arterial disease with a 25% reduction in myocardial infarction, stroke and vascular death. The platelet ADP receptor antagonists were developed to further improve the clinical results of therapy.[2] Thienopyridines are a class of ADP receptor/P2Y_{12} inhibitors used for their anti-platelet activity. These are a fascinating family of aromatic compounds with two different heterocyclic rings which still continue to attract the chemical interest. These drugs include: Clopidogrel, Prasugrel, and Ticlopidine.[3]

Atherosclerosis is a diffuse process that starts early in life, asymptomatically progressing through adulthood, until clinically manifested.[4] Atherothrombotic disease is the result of atherosclerosis progression, and its clinical manifestations [acute coronary syndromes (ACS), stroke, etc]. These events are mostly secondary to atherosclerotic plaque disruption and subsequent thrombus formation.[5,6] Atherosclerosis prevention is mainly focused on the management of the so-called 'cardiovascular risk factors' whereas thrombosis-related complications are mainly prevented and/or treated by antithrombotic therapies.

At the site of vascular lesions, platelets adhere to the exposed matrix proteins, prompting platelet activation, resulting in the secretion of multiple platelet agonists mostly modulated by intracellular calcium release. Among them, ADP, thromboxane A_2, thrombin, and others play a critical role in maintaining a 'pro-platelet-activating' environment. In fact, the understanding of the processes of platelet activation/aggregation and the role of acute thrombus formation on the onset of ACS has led to a widespread use of antiplatelet therapy in cardiovascular disease.[2] Long-term antiplatelet therapy is effective in the secondary prevention of vascular events in patients with acute coronary or cerebrovascular events who are at a high risk of subsequent thrombotic events.[7]

ADP is released from activated platelets, erythrocytes and endothelial cells, and induces platelet adhesion and aggregation. ADP activates platelets by binding to membrane-bound nucleotide receptors (purinoceptors) on the platelet surface called P2 receptors.[8] Human platelets possess two major G protein-coupled ADP receptors, the P2Y_1 and P2Y_{12} receptors, and a third ionotropic receptor, P2X_1. The human P2Y_1 receptor is a Gq protein-coupled receptor that activates phospholipase C to form inositol triphosphate (IP_3) and causes calcium to be released from intracellular stores. The P2Y_1 receptor is necessary to trigger a response and initiates the formation of platelet pseudopodia in response to low concentrations of thromboxane A_2 or thrombin, and transient platelet aggregation occurs. However, activation of the P2Y_1 receptor is insufficient for a full platelet response. The P2Y_{12}, formerly known as P (2T), P2T (AC), P2Y (ADP) or P2Y (yc), receptor is a Gi protein coupled receptor that inhibits adenylyl cyclase. This results in a decreased platelet cyclic adenosine monophosphate (AMP) level in response to ADP, activating platelet glycoprotein IIb ⁄ IIIa (aIIbb3 integrin) receptors that bind fibrinogen, leading to stabilization of platelet aggregation and enhanced platelet secretion. Platelets also possess a third ADP receptor, $P2X_1$, which is a ligand gated ion channel that mediates rapid transient calcium ion influx. However, the $P2X_1$ receptor does not contribute to platelet aggregation.[9] Aspirin was the first effective platelet inhibitor drug to be identified.

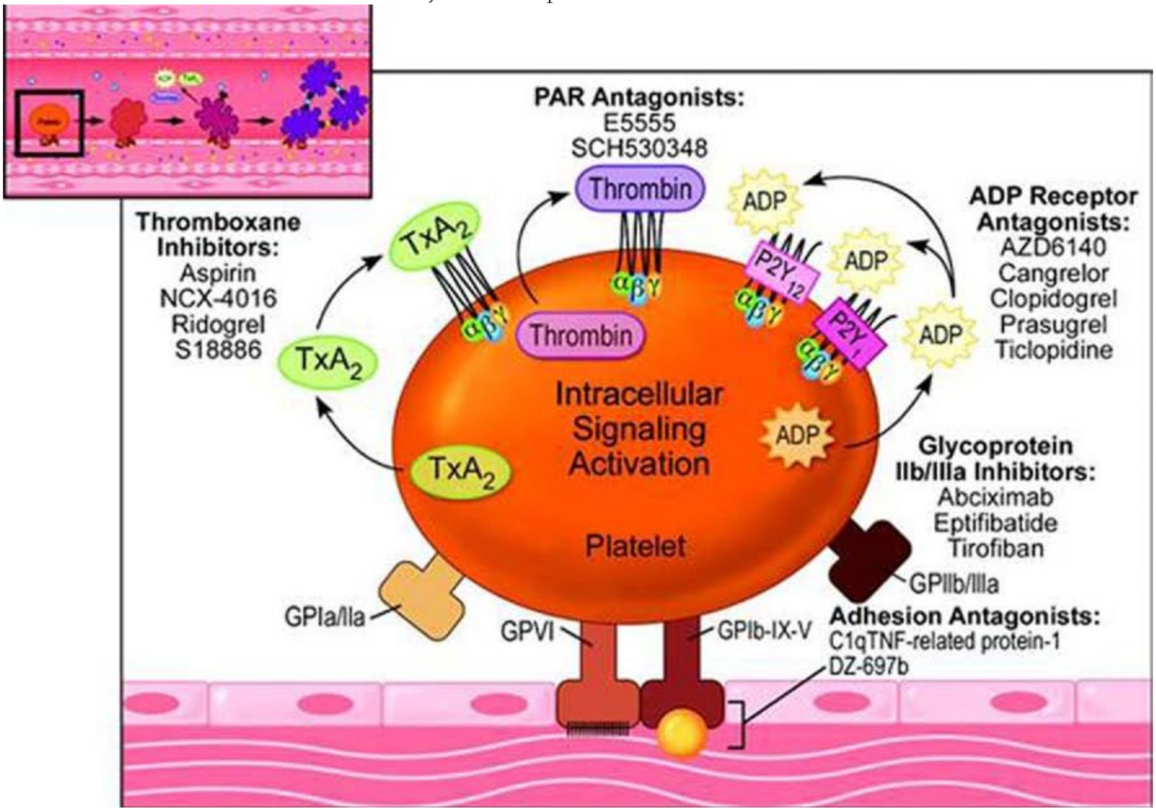


Figure 1: Target sites for thromboxane inhibitors, ADP receptor antagonists, GPIIb/IIIa inhibitors, and novel PAR antagonists and adhesion antagonists. ADP, adenosine 5=-diphosphate; TxA_2, Thromboxane A_2; vWF, von Willebrand factor; GP, glycoprotein

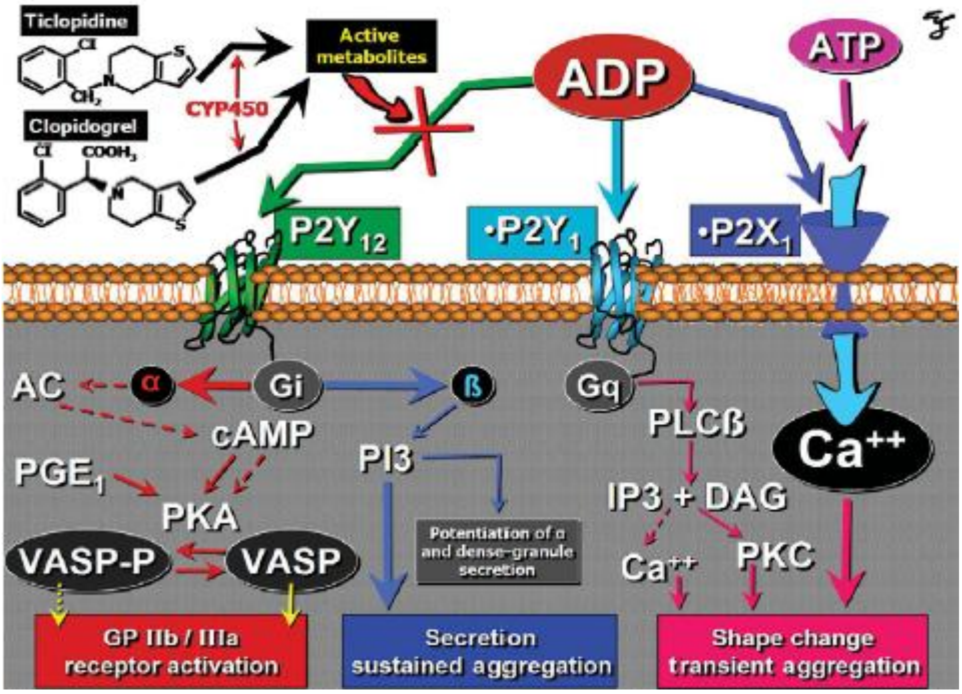


Figure 1: P2Y receptors can be clearly divided into two subgroups: the Gq-coupled subtypes P2Y1 and the coupled to Gi $P2Y_{12}$. $P2Y_1$, which are responsible for platelet shape change and calcium mobilization, are coupled to Gq and activate phospholipase Cb(PLCb) that is responsible for the formation of inositol (1,4,5)-trisphosphate (IP3) and diacylglycerol (DAG), an activator of protein kinase C (PKC). IP3 causes calcium mobilization from internal stores. The $P2Y_{12}$ receptor couples primarily to Gai2 inhibition of adenylyl cyclase (AC). The subsequent decrease in cAMP production leads, in turn, to a reduction in the activation of specific protein kinases (PKA), which can no longer phosphorylate the VASP; VASP phosphorylation is crucial for GP IIb/IIIa receptor inhibition. The subunit bg activates the phosphatidylinositol 3-kinase, which is an important signaling molecule for $P2Y_{12}$-mediated platelet-dense granule secretion and GP IIb/IIIa receptor activation. Finally, $P2X_1$ is a gated cation channel protein activated by ATP. This activation leads to increased intraplatelet calcium, platelet shape change, and transient and weak platelet aggregation responses.

Aspirin results in an irreversible modification of the enzyme cyclo-oxygenase rendering it incapable of converting arachidonic acid into thromboxane A_2. The contribution of aspirin to the reduction of vascular morbidity is significant but is accompanied by several deficiencies. Side-effects, while generally not life-threatening, are potentially serious. Therefore, the development of new agents has been an appropriate and compelling goal.

Thienopyridines is platelet adenosine diphosphate (ADP) receptor antagonists that were initially developed to provide new opportunities for those patients who are intolerant, resistant, or have failed to respond to other treatments. Clopidogrel (the most widely used thienopyridine) are considered weak and safe anti-platelet agent because it only blocks one of the multiple pathways involved in platelet activation. The thienopyridine derivatives inhibit ADP-induced platelet activation. They produce synergistic effects because they block complementary pathways of platelet aggregation without blocking thrombin-mediated platelet aggregation. In contrast, glycoprotein IIb ⁄ IIIa antagonists block aggregation induced by all agonists by preventing cross-linkage of fibrinogen mediated platelet aggregations.

The ADP receptor mediates platelet aggregation primarily through $P2Y_{12}$ receptors, and to a lesser extent through $P2Y_1$ receptors.[10] Thienopyridines inhibit ADP receptors through noncompetitive antagonism of the $P2Y_{12}$ receptor, which in turn inhibits platelet response to other stimuli for platelet aggregation (eg, thromboxane A_2, thrombin). Via transformation of the GPIIb/IIIa receptor, $P2Y_{12}$ blockade precludes the activated platelet from releasing inflammatory and prothrombotic mediators as well as preventing platelet aggregation.[11] The current agents that are Food and Drug Administration (FDA)-approved and available include ticlopidine, clopidogrel, and prasugrel.

PHARMACOLOGY

Pharmacokinetics of thienopyridines

The chemical structures of clopidogrel and ticlopidine are very similar. Clopidogrel has an additional carboxymethyl side group. Ticlopidine and clopidogrel are inactive in vitro. They are prodrugs and are metabolized in the liver by hepatic cytochrome P450-1A to produce active metabolites that inhibit platelet aggregation by selective and irreversible binding (via covalent bonds) to the $P2Y_{12}$ receptors.[12] The active metabolite of clopidogrel is a thiol derivative of the parent molecule.[13] Inhibition of platelet aggregation by these drugs is delayed until 24–48 h after administration, with maximal inhibition achieved after 3–5 days. Recovery of platelet function after drug withdrawal is slow (7–14 days). Clopidogrel, the S-enantiomer of a racemic thienopyridine compound (PCR 4099), is six times more potent than ticlopidine and does not share any common metabolites with ticlopidine.[14] Between 60 and 70% of the ADP receptors are sensitive to the effects of the thienopyridines. Maximal inhibition of ADP-induced platelet aggregation after a single oral dose of clopidogrel 375–400 mg is 40–50% and is achieved in 2–6 h. This level of inhibition is achieved after 3–7 days of repeated dosing with clopidogrel 75 mg administered once daily.[15] In healthy human volunteer studies, maximal inhibition of platelet aggregation causes a twofold increase in the bleeding time. Platelet function recovers completely 7 days after the discontinuation of clopidogrel therapy in healthy volunteers.

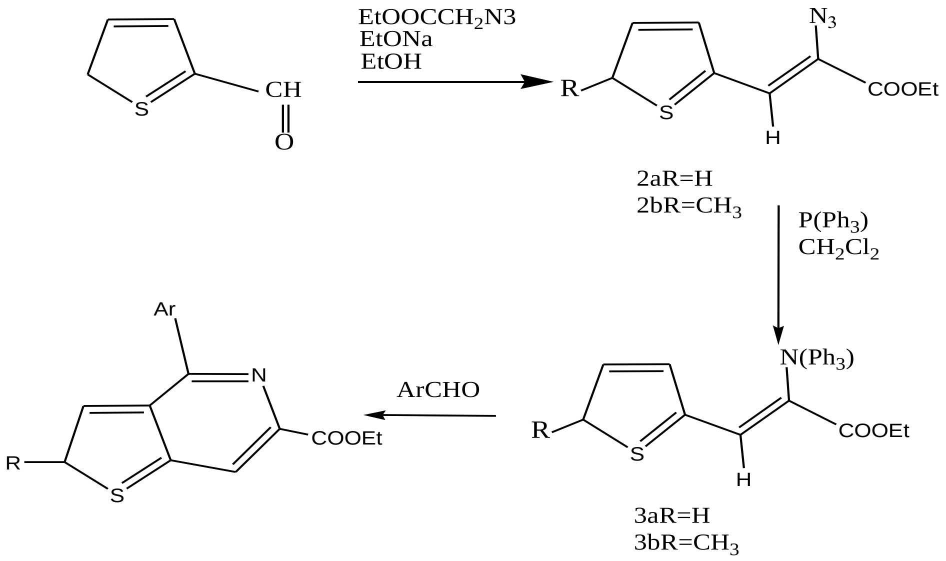
About 50% of ingested clopidogrel is absorbed rapidly from the gastrointestinal tract and is rapidly hydrolyzed in the liver to the main (85%) inactive metabolite (a carboxylic acid derivative, SR 26334), its bioavailability is unaffected by food or antacids.[16]The active metabolite has been identified only recently.[17] Unchanged clopidogrel in the plasma may be detected for only 2 h after ingestion. The renal clearance of the principal metabolite (SR 26334) is constant over a clopidogrel dose range of 50–150 mg.day, indicating that clopidogrel has linear pharmacokinetics. The elimination half-life of SR 26334 is 8 h in young healthy volunteers.[18] Steady-state pharmacokinetics can be achieved with an average of 8 days of oral administration.[19, 20] In patients with renal failure, bleeding times are not prolonged with standard doses of clopidogrel, although the renal clearance of the inactive metabolite SR 26334 is decreased significantly in patients with severe renal failure. The effect on ADP-mediated platelet aggregation by clopidogrel is not affected by liver disease.[21] Ticlopidine is rapidly and extensively absorbed from the gastrointestinal tract with an oral bioavailability of 80%. Ticlopidine is also metabolized by the hepatic cytochrome P450-1A isoenzyme.[22] The plasma level of the major metabolite peaks 2 h after oral administration.[23]

SYNTHESIS AND DIAGNOSIS

Synthetic and theoretical interest in the behavior of systems that contain fused π rich and π deficient ring as well as the search for pharmacologically active substances led to the synthesis of various analogs of quinolines and isoquinolines in which the benzene ring is replaced by thiophene nucleus. Most of the substances described in the literature for thienopyridines systems have been synthesized by traditional methods used to build quinoline and isoquinoline systems. [24] Recently, a tandem aza–Wittig/electrocyclic ring closure strategy (TAWERS) was used to obtain this nucleus by reacting key imino-phosphorane intermediate with isocyanates or isothiocyanates. Because the interest in preparing novel thiophene analogs of biologically active benzocompounds. We used a modification of the TAWERS by reaction of the imino-phosphorane intermediate with aromatic and heteroaromatic aldehydes to afford biaryl compounds which would display interesting conformational properties. There is so much literature available that describes the synthesis of novel thienopyridines as well as their conformational analysis established by 1D and 2D NMR and X-ray crystallographic studies.[3]

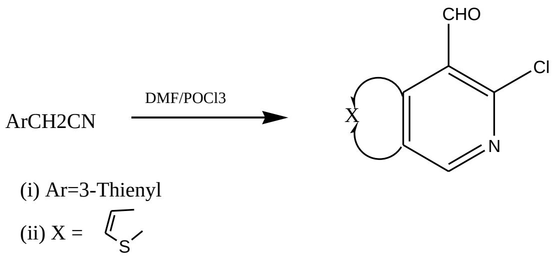
The Vilsmeier-Raack reaction is a mild but efficient method for the formylation of reactive aromatic substrates. Occasionally, unexpected cyclizations are noted accompanying or following such formylations. This method was applied to the corresponding thiophen giving the thienopyridine.

But attempts to extend the reaction to 3-acetamidothiophen led to a mixture of products. [25]

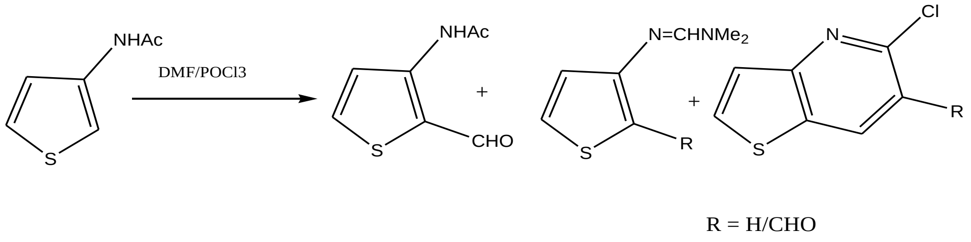


4. R=Me; Ar=2^1Fluorophenyl
5. R=H; Ar=2^1,4^1difluorophenyl
6. R=Me; Ar=4^1Quinoline
7. R=Me; Ar=2^1Quinoline
8. R=H; Ar=-(Carbomethoxy-5thieno[2,3-b]pyrrlo)
9. R=H; Ar=(2^1-Cl,6^1methoxy-3^1 quinoline
10. R=Me; Ar=(2^1-thieno[2,3-b]pyridine)
11. R=H; Ar=-4-(-N-benzyl-2^1-carbomethoxy-5^1-thieno[2,3-b]pyrrolo
12. R=Me; Ar=(2^1Cl,5^1Br-3^1pyridine)
13. R=H; Ar=(2^1Cl-3^1pyridine)

Scheme: 1



Scheme: 2



Scheme: 3

SEPARATION

Acid extraction

The measured relative basicity of compounds permits a rationalization of a number of analytical and synthetic separations which have been made for these compounds.

Chromatography on alumina

Many mixtures of isomeric thienopyridines and their derivatives have been separated by column, thin layer, or preparative thin layer chromatography on alumina. On the basis of the measured pK, values, these separations can be rationalized in terms of interaction between the thienopyridine compound as a Lewis base and the adsorbent as a Lewis acid. The stronger base is retained more tenaciously.[26, 27]

Ticlopidine

Ticlopidine is a first-generation thienopyridine. It was originally developed in the 1970s and studied as an anti-inflammatory agent. However, its potent antiplatelet effects were more notable.

Mechanism of Action

It irreversibly inhibits the ADP receptor, preventing platelet aggregation for the life of the platelet.[28] Despite its efficacy as an ADP receptor antagonist, the wide use of ticlopidine was significantly affected by a rare but severe incidence of neutropenia (8%). For these reasons, clopidogrel, a new agent structurally similar to ticlopidine, but with fewer side-effects (severe neutropenia in 0.5%) emerged as new antiplatelet therapy.

Conclusions

Dual-antiplatelet therapy with ticlopidine is rarely used, as clopidogrel seems to be more effective and better tolerated.

Clopidogrel

Clopidogrel is a second-generation thienopyridine.

Mechanism of Action

Like ticlopidine, it selectively and irreversibly inhibits the P2Y12 receptor. Clopidogrel undergoes a process of oxidation by the cytochrome P450 system to generate its active metabolite. There are many datasets demonstrating clopidogrel's benefits in high-risk patients. Clopidogrel plays an important role in the treatment of heart attacks and is used in the following situations:

- Clopidogrel is used instead of aspirin in patients who have an allergy to aspirin.
- Clopidogrel often is given together with aspirin in treating heart attacks. Studies have shown that the combination of aspirin and clopidogrel is more effective than aspirin alone in improving survival and limiting damage to heart muscle among patients with heart attacks.
- Clopidogrel is given together with aspirin to patients undergoing PTCA with or without coronary stunting. Studies have shown that the combination of aspirin and clopidogrel is more effective than aspirin alone in preventing formation of blood clots that can re-occlude the coronary artery unblocked by PTCA and in preventing blood clots within recently placed stunts.
- After a heart attack or after PTCA, aspirin is given indefinitely. The optimal duration of clopidogrel has not been established, and duration of use by physicians varies from weeks to months.
- clopidogrel has almost replaced ticlopidine as a therapeutic antiplatelet agent, used alone or in combination with aspirin. It has proved useful for the prevention of ischemic stroke, myocardial infarction, and vascular death in patients with symptomatic atherosclerosis. Beyond its anti-aggregation effect, it reduces the formation of platelet–leukocyte conjugates in patients with ACS41 and decreases the expression of activated platelet-dependent inflammatory markers such as CD40 ligand (a potent stimulus of vascular inflammation) and CD62 P-selectin in patients undergoing percutaneous coronary intervention (PCI). In fact, clopidogrel, co-administered with aspirin, is being considered the treatment of choice for prevention of atherothrombotic complications.[1]

Resistance and Dosing

Clopidogrel dosing has been a concern, giving significant variability in patient responsiveness. Many patients with hypo responsiveness have been called "clopidogrel resistant".[29, 30] First, clinical features, such as diabetes, have been associated with higher pretreatment platelet reactivity, which may not be sufficiently suppressed by recommended doses of clopidogrel. This observation coupled with the fact that insulin alters platelet reactivity might partially explain why diabetics fare worse after ACS.[31-33] Second; clopidogrel activation requires the cytochrome P450 enzymatic system, which is affected by many other drugs. Therefore, there is potential for drug–drug interactions with clopidogrel.[34] Finally, there are certain cellular and genetic factors that appear to underlie a subset of patients who are considered "clopidogrel low responders" or "clopidogrel resistant.[35] A higher loading dose of 600 mg achieves full antiplatelet effect in 1-2 hours v/s at least 4-6 hours with 300 mg, without a significant increase in major bleeding.[36] A higher loading dose reduced the primary endpoint of death, MI, or TVR within 30 days, driven primarily by a reduction in per procedural MI.

This suggests the possibility of counteracting the increased risk for bleeding during and after surgery in clopidogrel-treated patients by administering platelet units prior to the major surgeries.

Conclusion

Clopidogrel in combination with aspirin has become the standard of care for reducing cardiovascular events in patients with ACS. The ACC/AHA guidelines recommend clopidogrel for 12 months in the setting of DES implantation for ACS, and at least 1 month with BMS implantation.[37-39]

Prasugrel

Prasugrel (CS-747; LY-640315) is a novel, third-generation oral thienopyridine. Laboratory results with prasugrel support more potent antiplatelet effects, a lower incidence of interpatient variability in antiplatelet response.[40]

Mechanism of Action

It is a specific, irreversible antagonist of the platelet adenosine 5′-diphosphate P2Y 12 receptor. It is also a prodrug that acts as an irreversible inhibitor of the platelet ADP P2Y12 receptor. In contrast with clopidogrel, prasugrel is converted to its active metabolite much more efficiently. Therefore, prasugrel is faster acting and more potent, with less individual variability. Its rapid absorption and metabolism yields maximal concentrations in a median time of 30 minutes.[41, 42]

Conclusions

Prasugrel was recently approved by the FDA. The greater potency yielded greater efficacy but also more bleeding. First, clopidogrel exhibits substantial interpatient variability. Second, clopidogrel is rather inefficient as a prodrug. Eighty-five percent of its prodrug is hydrolyzed by esterases down a deadend pathway; therefore, only 15% is made available to the cytochrome P450 system for conversion to active metabolite. Third, recovery of platelet function is relatively prolonged after clopidogrel administration. Due to these factors, a number of patients on clopidogrel and aspirin continue to experience cardiovascular events.[1]

Side effects

Clopidogrel has a more favourable side effect profile than ticlopidine. Gastrointestinal problems are the commonest side effects. Clopidogrel is better tolerated than aspirin.[43]Clinically severe rashes are more common with clopidogrel than with aspirin. Clinically significant gastrointestinal side effects are less frequent with clopidogrel than with aspirin: indigestion ⁄ nausea ⁄ vomiting (15 v/s. 17.6%), diarrhea (4.46 vs. 3.34%) and gastrointestinal hemorrhage (0.49 vs. 0.71%). Overall, the frequency of bleeding is similar for aspirin and clopidogrel (9.27 vs. 9.28%).[43,44] Neutropenia was rare and was less frequent in the clopidogrel group than in the aspirin group.[45] The adverse effects of ticlopidine are similar to those of clopidogrel, except for neutropenia. Neutropenia generally occurs within three months of therapy and is usually reversed when the drug is discontinued. Strict haematological monitoring (every two weeks during the first three months of treatment) is therefore recommended for patients on ticlopidine .[44] The lower rate of neutropenia and the more favourable pharmacokinetic profile of clopidogrel make it the ADP receptor antagonist of choice. The most frequent side effects of ticlopidine are diarrhea and rashes. These occurred in 20% of patients in the Ticlopidine Aspirin Stroke Study and in 2% of patients were severe enough to make patients discontinue ticlopidine.[45]

GI bleeding among patients receiving antiplatelet therapy can develop from many different lesions and anatomic sites. Upper GI bleeding may be due to esophagitis[46] or peptic ulcer disease related to *H. pylori* infection, use of anticoagulants, steroids, or NSAIDs[47] has also been shown to be consistent predictors for GI bleeding. These mucosal breaks are aggravated by the antiplatelet effects of thienopyridines, promoting bleeding. Several risk factors for GI bleeding in the setting of antiplatelet therapy have been reported consistently.[48-55]Advanced age also significantly increases the absolute risk of upper GI bleeding. The risk of GI bleeding associated with thienopyridines has been assessed in several case-control studies. Dual antiplatelet therapy with clopidogrel and aspirin increased the risk of GI bleeding by 2- to 3-fold compared with aspirin alone in randomized trials, but the absolute risk increase was in the range of 0.6% to 2.0%. In studies of varying duration and design, the case fatality rates for GI bleeding associated with dual antiplatelet therapy have been low (0% to 0.3%). Nevertheless, the relative risk (RR) for death from a GI bleed has been estimated at 2.5,[56] and GI bleeding appears to be a significant predictor of death, even after adjustment for CV morbidity, age, sex, diabetes, PCI status, and concomitant therapy.[56, 57]

STRATEGIES TO PREVENT THIENOPYRIDINE-RELATED UPPER GI BLEEDING

Thienopyridines do not cause ulcers or erosions of the digestive tract[58] but their antiplatelet effects may promote bleeding at the site of preexisting lesions. Upper GI bleeding in the setting of thienopyridine use may be reduced by suppressing gastric acid production, thereby promoting healing of peptic ulcers and mucosal erosions, as well as by stabilizing thrombi.[59] Acid production can be suppressed either by H2RAs or by PPIs; the efficacy of each has been examined to prevent GI bleeding related to antiplatelet use.[60]

Histamine H_2 Receptor Antagonists

The use of H_2RAs can suppress gastric acid production by 37% to 68% over 24 hours. [61-62]

Proton Pump Inhibitors

The FDA recently released an early communication concerning a safety review of clopidogrel in the setting of proton-pump inhibitors. Patients randomized to omeprazole in addition to clopidogrel and aspirin had significantly decreased clopidogrel platelet inhibitory effects.

PPIs reduce gastric acid secretion for up to 36 hours. [63] Observational data suggest that PPIs reduce the risk of GI bleeding in patients on antiplatelet therapy.

Drug Interactions

The combination of aspirin and the thienopyridine derivatives causes synergistic antiplatelet effects. Similarly, the thienopyridines enhance the platelet-inhibiting effects of the glycoprotein IIb ⁄ IIIa receptor antagonists. A pharmacokinetic interaction (mediated by CYP2C9) causing an intracerebral hemorrhage in an elderly patient with atrial fibrillation was reported with the concomitant use of celecoxib and clopidogrel.[64] Phenytoin toxicity has been reported when combined with ticlopidine, probably caused by inhibition of its metabolism.[65] Increased plasma concentrations of theophylline and carbamazepine have also been reported. [66]

Combinations of Antiplatelet Agents

- Aspirin and Thienopyridines
- Aspirin and Dipyridamole
- Combinations of Antiplatelet Agents with Anticoagulants

It has been previously commented that aspirin and clopidogrel could be considered as weak antiplatelet agents with completely different mechanisms of action. This observation suggested the possibility of combining two weak and safe antiplatelet agents with the assumption of achieving stronger antiplatelet effect but still being safe. Aspirin exerts its antiplatelet effects by acetylating the serine moiety at position 529 of COX-1 and thereby irreversibly inhibiting the key enzyme required for the conversion of arachidonic acid to TXA_2. As mentioned earlier, TXA_2 is a potent platelet activating agent and results in platelet shape change, secretion of granular contents, and increased expression of GPIIb/IIIa receptors by binding to its cell surface receptor. Because platelets lack nuclei, they are unable to synthesize new COX-1 and are, therefore, permanently inhibited by aspirin. Despite being a relatively 'weak' antiplatelet agent, aspirin remains a frontline therapy with proven benefits in primary and secondary prevention of coronary artery disease (CAD).

As has been clearly depicted, there are many other platelet receptors different from the TXA_2 receptor that can activate platelets and amplify platelet response upon agonist binding. Therefore, it is intuitive to think that other compounds that block these other receptors could exert additional benefits to aspirin monotherapy. This underscores the need to continue the search for new agents that can either replace or be used in addition to aspirin for short- and long-term management. In fact, inhibition of the platelet $P2Y_{12}$ ADP-receptor by clopidogrel on a background of TXA_2 inhibition by aspirin has proved an enhancement in platelet inhibition.

Patients who are resistant to aspirin (up to 10%) have higher rates of cardiovascular events and may derive special benefit from the combination therapy. On the other hand, the co-administration of different antiplatelet therapies that act at different targets also increases the risk of bleeding. This complex equilibrium has to be taken into account when dual antiplatelet therapy is planned. Despite all this, current clinical recommendations for patients undergoing PCI suggest loading dose regimens of 300–600 mg clopidogrel plus aspirin with a maintenance daily dose of 75 mg of clopidogrel.

New Antiplatelet Strategies

• Direct Thrombin Inhibitors

• Antiplatelet Effects of Polyunsaturated Fatty Acids and Prostacyclin

• Nitric Oxide Derivatives as Antiplatelet Agents

• Soluble CD39 as an Antiplatelet Agent that Inhibits Released ADP

• Simultaneous Blockade of Platelet $P2Y_{12}$ and $P2Y_1$ ADP Receptors

SUMMARY AND CONCLUSION

Atherothrombosis is the basis for the epidemic rates of acute cerebrovascular, coronary and peripheral vascular morbidity and mortality. Antiplatelet therapy plays a central role in management. Aspirin has been the mainstay; the thienopyridines provide new opportunities for those patients who are intolerant, resistant or have failed to respond to aspirin, and for those who can derive greater benefit from combined therapy. The patient subgroups that benefit the most and cost-effectiveness concerns remain matters for further assessment. Due to its equivalence to ticlopidine, its greatly improved side-effect profile over ticlopidine, and its once-daily dosing, clopidogrel is the thienopyridine of choice.

Gastrointestinal side effects and skin rashes are common. However, neutropenia and thrombotic thrombocytopenic purpura are significant and sometimes fatal adverse effects of ticlopidine. Clopidogrel appears to offer several advantages over ticlopidine: a more rapid onset of action and a lower incidence of neutropenia and thrombotic thrombocytopenic purpura.

However, clopidogrel should be used with caution in patients with severe hepatic dysfunction because of increased bleeding risks associated with coagulation disturbances in liver failure. There is no information on the use of clopidogrel in pregnant or lactating women. There are several limitations to clopidogrel. Prasugrel, a third-generation oral thienopyridine, overcomes some of these limitations, although this was associated with a greater risk of bleeding.

With the clinical trials of the thienopyridine drugs under way, it is likely that the number of patients receiving these drugs will increase. An understanding of the pharmacology of the thienopyridine derivatives is essential for the anesthetist so that the peri-operative management surgical patients can be optimized.

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