International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 8; Issue 04 (B); April 2019; Page No.18125-18130
DOI: http://dx.doi.org/10.24327/ijcar.2019.18130.3456

Research Article

ROLE OF ANTIPLATELET THERAPY IN ISCHEMIC STROKE – A REVIEW

Saikala M[1], Naga jyothi D[1], Sudheer kumar D[2] and Kishore P[1]*

[1]Department of Pharmacy Practice, Care College of Pharmacy, Warangal
[2]Department of Pharmaceutics, Care College of Pharmacy, Warangal

A R T I C L E I N F O

Article History:
Received 6th January, 2019
Received in revised form 15th February, 2019
Accepted 12th March, 2019
Published online 28th April, 2019

Key words:

Stroke, ischemic stroke, antiplatelet therapy, platelet aggregation inhibitors, stroke prevention, bleeding, aspirin

A B S T R A C T

Stroke is one of the leading cause of disability and death. Stroke is of two types ,ischemic stroke and hemorrhagic stroke. Of the two major forms of stroke, ischemic stroke is the most common accounting upto 85% of stroke cases. Ischemic stroke is a sudden loss of blood to the brain which results in deprivation of oxygen and other nutrients. Hemorrhagic stroke results when the blood vessels in the brain becomes weak and ruptures. Each year, about 795,000 people will experience a new or recurrent stroke. It is more common in men when compared to women. Classic signs of stroke are weakness in face, arms & legs, difficulty speaking, vision disturbances, headache, confusion. Antiplatelet therapy remains mainstay in the prevention of stroke. Antiplatelets aim to prevent recuurence and deterioration of stroke. They act by blocking the activation pathways of platelets. Commonly used antiplatelets are aspirin, clopidogrel, aspirin plus dipyridamole, cilostazol. Each of these drugs act through different mechanism and share some common adverse events such as gastrointestinal bleeding and intracranial hemorrhage.

INTRODUCTION

Stroke is defined as inadequate blood flow to the brain that results in cell death. It is a neurological dysfunction that could either be transient episode called "transient ischemic attack", or it could lasts more than 24 hours leading to "infarction of tissues" in central nervous system.

Ischemic stroke is defined as an episode of neurological dysfunction caused by focal, cerebral, spinal, or retinal infarction. It is due to obstruction of blood vessels by thrombi or embolus.

Hemorrhagic stroke occurs due to the rupture of blood vessels that may be due to intracerebral hemorrhage or subarachnoid hemorrhage (SAH).

Intracerebral hemorrhage is a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma. Subarachnoid hemorrhage is bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord).

Incidence & Prevalence(1,3,4,5)

Stroke is the fifth leading cause of death and is the major cause of disability in adults. 80% of cases are ischemic strokes and remaining 20% are hemorrhagic strokes.In United States 800,000 strokes occur every year. In Canada, 62,000 strokes were estimated to occur each year that affect all age groups, from neonates to elderly people, with occurrence rates rising by age. The lifetime risk of overt stroke is estimated at one in four by age 80 years and the lifetime risk of silent or covert stroke is likely closer to 100%. Globally it was reported that in 2013, there were 25.7 million stroke survivors, 6.5 million deaths due to stroke, 113 million disability-adjusted life-years (DALYs) lost because of stroke, and 10.3 million new cases of strokes. Stroke mortality is higher in Asia than in Western Europe, America or Australasia, except in some countries such as Japan. Incidence rate of stroke is lowest in Malaysia (67/100,000 person-years) and highest in Japan (422/100,000 person-years among men and 212/100,000 person-years among women) and Taiwan (330/100,000 person-years). Highest mortality rates were observed in Mongolia (222.6/100,000 person-years) and Indonesia (193.3/100,000 person-years), followed by Myanmar and North Korea, while lowest rates were observed in Japan (43.4/1,000,000 person-years and Singapore (47.9/100,000 person-years), followed by Bangladesh, Papua New Guinea, and Bhutan. Stroke is more common in men younger than 79 years old when compared to women, but the lifetime risk of stroke is high in women due to longer life expectancy in women. Symptoms of stroke are common in blacks compared to whites and also in those with lower economic and educational status.

Etiology and Classification of Stroke *(6)*

Stroke can either be ischemic or hemorrhagic (88% and 12%, respectively, of all strokes in the 2006 American Heart Association report).Subarachnoid hemorrhage occurs when blood enters the subarachnoid space (where cerebrospinal fluid is housed) owing to either trauma, rupture of an intracranial

Corresponding author:* **Kishore P
Department of Pharmacy Practice, Care College of Pharmacy, Warangal

aneurysm, or rupture of an arteriovenous malformation (AVM). By contrast, intracerebral hemorrhage occurs when a blood vessel ruptures within the brain parenchyma itself, resulting in the formation of a hematoma. These types of hemorrhages very often are associated with uncontrolled high blood pressure and sometimes antithrombotic or thrombolytic therapy. Subdural hematomas refer to collections of blood below the dura (covering of the brain), and they are caused most often by trauma. Hemorrhagic stroke, although less common, is significantly more lethal than ischemic stroke, with 30-day case-fatality rates that are two to six times higher. Ischemic strokes are caused either by local thrombus formation or by embolic phenomenon, resulting in occlusion of a cerebral artery. Atherosclerosis, particularly of the cerebral vasculature, is a causative factor in most cases of ischemic stroke, although 30% are cryptogenic. Emboli can arise either from intra- or extracranial arteries (including the aortic arch) or, as is the case in 20% of all ischemic strokes. Cardiogenic embolism is presumed to have occurred if the patient has concomitant atrial fibrillation, valvular heart disease, or any other condition of the heart that can lead to clot formation. Distinguishing between cardiogenic embolism and other causes of ischemic stroke is important in determining long-term pharmacotherapy in a given patient.

Different ischemic and Hemorrhagic stroke Causes Includes the following: (7)

Atherosclerosis

Atherosclerosis is a progressive disease that damages the arteries and affects how well they function. In atherosclerosis, cholesterol and other substances are deposited within the arterial wall, and certain types of cells begin to grow and divide, forming plaques. Plaque promotes local clot formation, and if the clot grows so large that it halts blood flow, the result is a thrombotic stroke. If it breaks apart, pieces of plaque and blood clot may flow into the bloodstream as emboli. When emboli lodge in a smaller artery and obstruct blood flow, an embolic stroke occurs.

Aortic Arch Atheroma

In patients with atherosclerosis, the aortic arch can be a source of blood clots. This is known as aortic arch atheroma, and it tends to affect older patients with high blood pressure. Although the arch itself is large and not likely to become blocked with plaque, atherosclerotic plaques that form in this region are prone to breaking off and traveling towards the brain.

Heart Valve Disease

Diseases of the mitral valve, which connects the left atrium and left ventricle, are associated with increased risk of ischemic stroke. A bacterial infection known as infective endocarditis can cause plaque and other debris to slough off, resulting in an embolic stroke.

Atrial Fibrillation

Atrial fibrillation is a heart rhythm disturbance (arrhythmia) originating in the upper chambers of the heart (atria). Untreated atrial fibrillation increases the risk for ischemic stroke five-fold.

Hypertension

Hypertension greatly increases the risk of stroke, heart attack, heart failure, and kidney failure. It also increases the risk of second stroke among stroke survivors. Widely fluctuating blood pressure may be an even greater danger.Hypertension is dangerous because increased pressure and stress on the blood vessels causes arteries to age faster, making them more likely to rupture and cause hemorrhagic stroke or develop fatty plaques, which increases the risk of ischemic stroke.

Aneurysms

Aneurysms form in weakened areas of an artery wall. As the wall weakens, even normal blood pressure can cause it to balloon out. A burst aneurysm is the most common cause of a spontaneous subarachnoid hemorrhagic stroke.

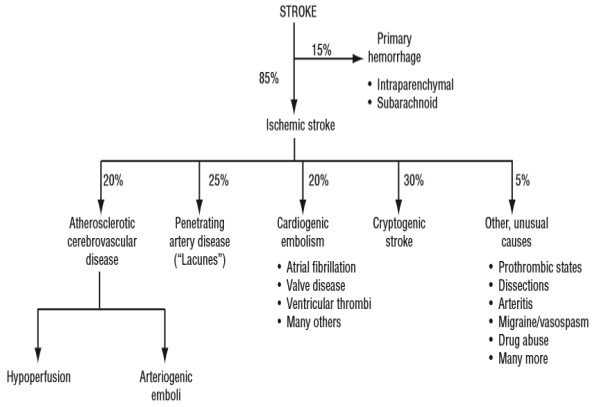

Figure 1 A classification of stroke by mechanism with estimates of the frequency of various categories of abnormalities. Approximately 30% of ischemic strokes are cryptogenic.(6)

Risk Factors (8)

Risk factors of stroke can be classified as non-modifiable and modifiable.

Non- modifiable risk Factors include

- Age
- Gender
- Race/ Ethnicity
- Family history of stroke
- Previous vascular events
- Low birth weight

Modifiable risk factors include

- Hypertension
- Cardiovascular disease (Coronary heart disease, heart failure, peripheral arterial disease)
- Diabetes
- Atrial fibrillation
- Hyperlipidemia
- Postmenopausal hormonal therapy
- Alcohol consumption
- Diet
- Physical inactivity
- Obesity
- Smoking
- Sickle cell disease

Pathophysiology (6,9,10)

Cerebral ischemia results in a number of hemodynamic, biochemical and neurophysiology alterations. After the incidence of stroke and reperfusion, a series of complex acute, subacute and chronic events occur.Ischemic stroke may be categorized as embolism and thrombosis. *Thrombotic stroke* occurs when a clot forms in a vessel and reduces blood flow to the brain from the area where the clot originates. In *embolic stroke*, the clot forms in an area apart from the brain, loosens, and travels until it reaches a blood vessel that is too narrow to allow it to pass. This occlusion impedes the flow of blood to the brain. Normal cerebral blood flow averages 50 mL/100 g per minute. Irreversible damage to brain which is called infarction occurs when blood flow is reduced below 12 mL/100 g per minute. Ischemia causes brain damage by activating the ischemic cascade, which leads to local depletion of oxygen or glucose, causing failure of production of high energy phosphate compounds, like adenine triphosphate (ATP). This affects energy-dependent processes which is essential for tissue cell survival, and sets off a series of interrelated events resulting in cellular injury and death. Inadequate energy supply leads to efflux of K^+ ions and influx of Na^+ , Cl^-, Ca^{2+} which is accompanied by influx of water resulting in cell swelling and lysis. Depolarisation of neuron leads to release of excitatory amino acids, such as glutamate and aspartate,which results in neuronal damage when released in excess. Influx of calcium is responsible for the activation of destructive enzymes such as proteases, endonucleases and lipases which leads to release of cytokines and other inflammatory mediators, resulting in the loss of cellular integrity. Leukocytes recruited to the ischemic area activate mediators of inflammation such as oxygen free radicals, cytokines, and nitric acid. All these events occur within 2 to 3 hours of the onset of ischemia and contribute to the ultimate cell death.In contrast to necrosis causing cell death in the ischemic core, apoptosis (programmed cell death) occurs in the peripheral neurons and can interfere with recovery and repair of brain tissue. Tissue that is ischemic but maintains membrane integrity is referred to as the ischemic *penumbra* because it usually surrounds the infarctcore which can be retrieved by timely therapeutic intervention.

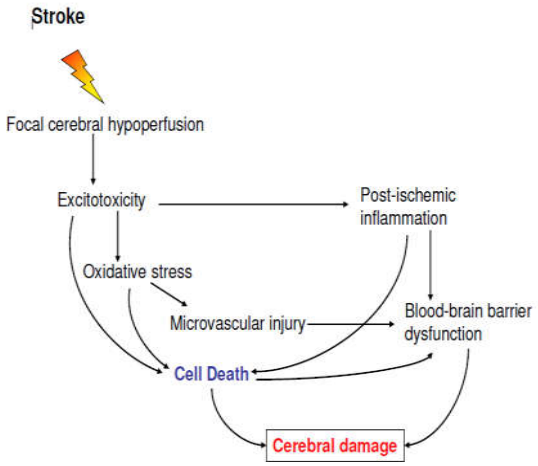

Figure 2 Ischemic Cascade leading to cerebral damage (10)

Clinical Manifestations

Warning signs of stroke established by the (American) National Institute of Neurological Disorders and Stroke (NINDS 2005): (11)

- numbness or weakness in the face, arms, or legs (especially on one side of the body);
- confusion, difficulty speaking or understanding speech;
- vision disturbances in one or both eyes;
- dizziness, trouble walking, loss of balance or coordination;
- severe headache with no known cause.

Common symptoms of stroke(4)

- Symptoms in left hemisphere include aphasia, right hemiparesis and right hemianopia.
- Symptoms in the right hemisphere include left hemispatial neglect, left hemiparesis and left hemianopia.
- Altered levels of consciousness
- Ataxia
- Seizures
- Coma

D*iagnosis* (6, 12)

Basic laboratory and diagnostic tests should be quickly performed to exclude noncerebrovascular causes, such as metabolic or toxicologic derangement,or infections. These tests include a routine serum chemistry profile (electrolytes, blood urea nitrogen [BUN], serum creatinine [SrCr], hepatic enzymes, calcium, phosphorus, magnesium, albumin), complete blood count, and toxicology screen.

Laboratory Tests

- Tests for hypercoagulable states (protein C deficiency, antiphospholipid antibody) should be done only when the cause of the stroke cannot be determined based on the presence of well-known risk factors for stroke.
- Protein C, protein S, and antithrombin III are best measured in the "steady state," not in the acute stage.
- Antiphospholipid antibodies as measured by anticardiolipin antibodies, ß 2-glycoprotein I, and lupus anticoagulant screen are of higher yield than protein C, protein S, and antithrombin III but should be reserved for patients who are young (<50 years of age), have had multiple venous/arterial thrombotic events, or have livedo reticularis (a skin rash).

Other Diagnostic Tests

- CT scan of the head will reveal an area of hyperintensity (white) in the area of hemorrhage and will be normal or hypointense (dark) in the area of infarction.
- MRI of the head will reveal areas of ischemia with higher resolution and earlier than the CT scan.
- Carotid Doppler (CD) studies will determine whether the patient has a high degree of stenosis in the carotid arteries supplying blood to the brain (extracranial disease).
- An electrocardiogram (ECG) will determine whether the patient has atrial fibrillation, a potent etiologic factor for stroke.

- Transthoracic echocardiography (TTE) will determine whether valve abnormalities or wall-motion abnormalities are sources of emboli to the brain. A "bubble test" can be done to look for an intraatrial shunt indicating an atrial septal defect or a patent foramen ovale.
- Transesophageal echocardiography (TEE) is a more sensitive test for thrombus in the left atrium. It is effective at examining the aortic arch for atheroma, a potential source of emboli.
- Transcranial Doppler (TCD) will determine whether the patient is likely to have intracranial stenosis (e.g., middle cerebral artery stenosis).

Treatment

Goals of Treatment (6)

- To reduce the ongoing neurologic injury and decrease mortality and long-term disability
- Prevent complications secondary to immobility and neurologic dysfunction
- Prevent stroke recurrence

Management

Three areas require adequate attention while managing a case of acute stroke :(13)

1. General therapy to maintain the physiology of patient
2. Specific therapy focussing on reperfusion and neuroprotection and finally
3. Complication prevention like subarachnoid hemorrhage, cerebral or cerebellar swelling, post stroke infection, etc.

General therapy comprises of respiratory and cardiac care, fluid and metabolic management, control of Blood Pressure, prophylactic measures against DVT, aspiration pneumonia and decubitus ulcer. Approximately 2-4 liters of Oxygen per minute administered per-nasally helps attain adequate oxygenation of the penumbra.

Specific Therapy includes thrombolysis with recombinant-tissue plasminogen activator (rt-PA) 0.9mg/kg administered within 3 hours of acute ischaemic stroke. Aspirin may be administered 100-300 mg as a preventive measure in patients with positive symptoms even without CT scan but the diagnosis must be confirmed with radio imaging. Ischemic Brain edema should be managed with mannitol.
Prevention of stroke before or after TIA or stroke can be done by drug therapy, surgery and life style changes. Drugs include antiplatelets (Aspirin, clopidogrel etc), oral anticoagulants(warfarin), Cholesterol lowering agents like statins (Atorvastatin), Antihypertensive agents(Diuretics, ACE-I).

Surgical treatment is carotid endarterectomy Lifestyle changes include smoking cessation, moderate alcohol consumption, physical activity, weight reduction (14).

Table 1 Drug Therapy in Stroke

S.no	Category	Examples
1.	t-PA	• Alteplase(0.9 mg/kg) Max: 90 mg
2.	Antiplatelets	• Aspirin 50–325 mg • Clopidogrel 75 mg • Cilostazol 100 mg • Aspirin 25 mg + extendedrelease • dipyridamole 200 mg • Abiciximab 0.25 mg/kg • Tirofiban 0.4 mcg/kg/min infusion
3.	Anticoagulants	• Warfarin (INR: 2-3) • Dabigatran 150 mg • Rivaroxaban 20 mg
4.	Statins	• Atorvastatin 20 mg

Antiplatelet Therapy

Antiplatelet agents play an important role in the treatment of stroke and its prevention. They mainly reduce the risk of blood clots or prevent already existing clots by inhibiting or blocking different receptors present on platelets. Antiplatelets are mainly indicated for prevention of non cardioembolic stroke whereas, for cardioembolic stroke anticoagulants are recommended. Oral antiplatelet agents decreases vascular death by 15% and serious cardiovascular events by 20 % in high risk patients (15,16).

Commonly used antiplatelet drugs are Aspirin, Clopidogrel, Dipyridamole, Prasugrel, Abciximab, Ticlopidine, Cilostazol.

Aspirin

Aspirin is the frequently used agent in the prevention and treatment of stroke. It is a cyclooxygenase (COX) inhibitor which inhibits COX- 1 irreversibly and also inhibits COX -2 in higher doses. Inhibition of COX-2 leads to decreased production of thromboxane A2 which stimulates platelet aggregation (17,18).

Orally aspirin is administered once a day at different doses for prevention of stroke and myocardial infarction (19). Effect of aspirin on platelets is irreversible which causes inhibition of the lifespan of a platelet, upto 7-10 days. Platelet function can be increased by 10-15% per day due to the formation of new platelet, after the discontinuation of aspirin intake by patient. It's bioavailability is 68% and peak plasma concentration is 30-40 minutes. Its half life ranges between 15-30 minutes (17). Aspirin has rapid absorption which may lasts for 46 hours(19).Dose of aspirin ranges from 81-325 mg/day. Common side effects of aspirin include gastrointestinal bleeding and dyspepsia. Others include vertigo, tinnitus, headache, nausea. Aspirin in combination with warfarin increases the risk of intracranial hemorrhage, which is a serious adverse effect. It is contraindicated in asthma, rhinitis, angioedema, nasal polyps. It is also contraindicated in children and young adults due to the chance of developing Reye's syndrome. Administration of aspirin along with non-selective COX-1 inhibitors should be avoided, as they impair the efficacy of aspirin (16).

Clopidogrel

Clopidogrel is another widely used antiplatelet drug. It is a second generation oral thienopyridine. Clopidogrel is a

prodrug which converts into active metabolite. 85% of absorbed is hydrolyzed into its active metabolite and 15 % into active metabolite (19). It is mostly indicated for patients who do not tolerate aspirin. Clopidogrel acts through different mechanism when compared to aspirin, as it is a prodrug which is inactive until it gets hydrolyzed by cytochrome P450 in liver via an nicotinamide adenine dinucleotide phosphate (NADPH) dependent mechanism. After activation, it acts by binding irreversibly to ADP receptor P2Y12 which is present on the membrane of platelets which prevents ADP binding to platelets & inhibits platelet activation and thrombus formation. Dose of clopidogrel is 75 mg per day. In contrast to aspirin it shows slower onset where peak platelet inhibition is observed within 3-7 days. Its bioavailability is50%, half life is 6-8 hours (20).Gastrointestinal bleeding is the common side effect seen with clopidogrel. Other side effects include rash, neutropenia, joint pain. Intracranial hemorrhage is less associated with clopidogrel alone. Proton pump inhibitors reduce its effect by inactivating the enzyme cytochrome P450 2C19 (16).

Prasugrel

It is a 3rd generation oral thienopyridine. Prasugrel is also related to clopidogrel,with more efficient platelet inhibition (15). Prasugrel is also a prodrug which is converted to its active metabolite by cyp450. It shows more reliable conversion. It is metabolized more efficiently and shows high level of inhibition when compared to clopidogrel. It acts by binding irreversibly to P2Y12, thereby inhibiting platelet function for the lifespan of the affected platelets (17,19).Dose is 10 mg once daily. It's half life is 8 hours and bioavailability is 80%. Side effects include bleeding (20).

Ticagrelor

It is an oral cyclopentyl – triazolo- pyrimidine analog. Unlike other thienopyridines, it is a direct and reversible inhibitor of P2Y12 receptors that is activated from its prodrug by CYP3 A. CYP3 A4 & CYP3 A5 are the enzymes involved in hepatic metabolism of ticagrelor. It shows its action by binding to P2Y12 receptor at a site different from ADP binding site, making it an allosteric inhibitor. It has rapid onset of action, safety profile and effectiveness. Its bioavailability is 36% and half life is 6-12 hours. Dose is 90 mg taken twice daily. Common side effect is dyspnea. Digoxin concentration should be monitored in case of concomitant use. Serum concentration of lovastatin and simvastatin are increased. Concomitant use of CYP3A4 inhibitors(Ketoconazole,Ritonavir) or inducers (Rifampicin, Phenytoin) should be avoided (17,20).

Cilostazol

Cilostazol is a type 3 (PDE 3) selective oral inhibitor. It acts by inhibiting phosphodiesterase III, which leads to increase in cycle AMP and irreversibly inhibits platelets. Its onset of action can take upto 2-4 weeks. Half life is 11-13 hours. Dose is 100 mg two times per day. Side effects include; headache, dizziness, hypotension, flushing, abdominal pain, skin rash, leucopenia.This is mostly used for the treatment of intermittent claudication (19,20).

Ticlopidine

Ticlopidine is a first generation thienopyridine with a chemical structure and mechanism of action similar to clopidogrel. It requires cytochrome P450 (CYP) 1A metabolism prior to irreversible antagonistic effects on platelet reactivity via P2Y12 receptor. Inhibition of platelet aggregation is seen 3-5 days after its administration. Its half life is 12 hours. Hemorrhagic events are less commonly seen. Its use has been decreased because of its secondary adverse events which include diarrohea, skin rash, neutropenia. Dose: 500 mg once daily (20).

Glycoprotein Antagonists (15,20)

Abiciximab

It is a glycoprotein antagonist. Its target is integrin αIIbβ3 and prevents it from binding to fibrinogen, Von Willebrand factor, Vitronectin. The binding of abciximab to platelet glycoprotein IIb/IIIa receptor is a rapid high-affinity interaction, and the inhibitory effects are immediate (within minutes). Abiciximab has short half life, as a result aggregation of platelets returns to baseline levels within 12-24 hours after discontinuation of therapy. Its half life is 10-15 minutes. Bleeding and thrombocytopenia are the side effects. It blocks the receptors within 15 minutes with a bolus dose 0.25 mg/kg. It will prolong the activated clotting time (ACT) by 30-80 seconds.

Tirofiban

It is a tyrosine derivative non peptide reversible inhibitor of αIIbβ3 and it dissociates rapidly (10-15 seconds) from the GpIIb/III a receptor. Its plasma half life is 2 hours. It adheres to the binding site on glycoprotein IIb/IIIa receptor and inhibits platelet aggregation mediated by fibrinogen and Von Willebrand factor. Dose is 0.4 mcg/kg/min infusion. Its plasma clearance is decreased ≥

50% in patients with creatinine clearance is less than 30 ml/min. Activated clotting time (ACT) is prolonged by 40-50 seconds.

Eptifibatide

This is a small molecule compared with abciximab which binds to the glycoprotein IIb/IIIa receptor and prevents binding of fibrinogen. It shows rapid onset of action and rapid reversibility of platelet inhibition with a plasma half life of 2.5 hours. Bolus dose ranges from 90-250 mcg/kg and infusion rates from 0.5-3 mcg/kg/min. Dose should be decreased in renal impaired patients as most of the drug is renally excreted. It prolongs Activated clotting time (ACT) by 40-50 seconds.

Aspirin plus Dipyridamole

Aspirin with dipyridamole is a dual medication with composition of 25 mg of aspirin and 200 mg of extended release dipyridamole taken twice daily.
It has three different effects that will contribute to antiplatelet activity

- Primarily it acts by blocking the activity of platelet cyclic adenosine monophosphate (cAMP)-phosphodiestaerase(PDEs) thereby preventing activation of PDEs which leads to increase in intracellular cAMP levels and prevents Ca^{2+} release and G protein linked activation which are involved in platelet aggregation.
- Second, it acts by preventing the breakdown of adenosine.
- Third, it amplifies synthesis of prostacyclines, which are involved in cAMP production and thus functions to inhibit platelet activation.

Its half life is 10-12 hours and time to peak is 2-2.5 hours. Dual therapy of aspirin with dipyridamole is superior in preventing vascular events when compared to aspirin alone. This drug is discontinued due to its secondary side effects, commonly head ache, when compared with clopidogrel alone (16,19).

Table 2 Dose, side effects and cost of Antiplatelet drugs

S.no	Drug	Dose	Side effects	Cost
1	Aspirin	81-325 mg	GIbleeding and dyspepsia, vertigo, tinnitus, headache, nausea.	Rs.3.50/10 tablets
2	Clopidogrel	75 mg	GI bleeding, rash, neutropenia, joint pain.	Rs.26/10 tablets
3	Aspirin+ Dipyridamole	25 mg +200 mg	Bleeding, headache, palpitations, rash	Rs.35/10 tablets
4	Prasugrel	10 mg	Bleeding	Rs.124/10 tablets
5	Cilostazol	100 mg	Headache, dizziness, hypotension, flushing, abdominal pain, skin rash, leucopenia	Rs.99/10 tablets
6	Ticagrelor	90 mg	Dyspnea	Rs.549/10 tablets
7	Ticlopidine	500 mg	Bleeding, rash, neutropenia, heartburn, indigestion.	Rs.48/10 tablets
8	Abiciximab	0.25 mg/kg	Bleeding and thrombocytopenia	Rs,19,740/5 ml injection
9	Tirofiban	0.4 mcg/kg/min	Bleeding and thrombocytopenia	Rs.3,718.50/100 ml infusion
10	Eptifibatide	90-250 mcg/kg	Bleeding and thrombocytopenia	Rs.7000/100 ml infusion

CONCLUSION

Stroke is a debilitating disease, as it is one of the leading causes of death. Antiplatelet therapy is most effective in the treatment and prevention of stroke. Aspirin, clopidogrel, aspirin plus dipyridamole, cilostazole are commonly used antiplatelet drugs. Aspirin is standard drug of choice for the secondary prevention of stroke. Selection of antiplatelet therapy for stroke must be according to patient needs and bleeding risks associated from existing comorbidities.

Abbrevations

SAH-Subarachnoid Hemorrhage
DALYs-Disability Adjusted Life Years
AVM- Arteriovenous Malformation
ATP- Adenosine Triphosphate
BUN- Blood Urea Nitrogen
S Cr- Serum Creatinine
CT- Computer Tomography
CD- Carotid Doppler
ECG- Electrocardiogram
TEE- Transesophageal Echocardiography
TCD-Transcranial Doppler
DVT- Deep Venous Thrombosis
Rt-PA- Recombinant tissue plasminogen activator
TIA- Transient ischemic attack
ACE-I- Angiotensin Converting Enzyme Inhibitors
COX- Cyclooxygenase
NADPH- Nicotinamide Adenine Dinucleotide Phosphate
ADP- Adenine Diphosphate
Cyp- Cytochrome
PDE- Phosphodiesterase
cAMP- Cyclic Adenosine Monophosphate
ACT- Activated Clotting Time
GP- Glycoprotein
GI- Gastrointestinal

References

1. Ibar Anjum, Tooba Kashif, *et al*. Dual or Mono Antiplatelet Therapy for the Prevention of Ischemic Stroke: A Literature Review. 2018. Cureus., 10(6):2.
2. Sacco RL, Kasner SE, Broderick JP *et al*. An updated definition of stroke for the 21st century. 2013. American Heart Association., (44): 2065.
3. Shilpa Haldal, Jonathan Beary *et al*. Acute Ischemic Stroke Management Review for the Hospitalist.2018. AJHM., 2(1): 1-2.
4. Tapuwa D. Musuka MBChB, Stephen B. Wilton MD *et al*.Diagnosis and management of acute ischemic stroke: speed is critical. 2015. CMAJ.,187(12): 887.
5. Narayanaswamy Venketasubramanian, Byung Woo Yoon *et al*. Stroke Epidemiology in South, East, and South-East Asia: A Review. 2017. Journal of Stroke.,19(3): 286-287.
6. Joseph T. DiPiro, Robert L. Talbert *et al*. Pharmacotherapy A Pathophysiologic Approach (United States of America, McGraw-Hill.),2008. https://universityhealthnews.com
7. Amelia K. Boehme, Charles Esenwa, Mitchell S.V. Elkind. Stroke Risk Factors, Genetics, and Prevention.2017. Circulation Research.,120: 473-474.
8. Shari N, DeAna Augustus Pharmacologic Management of Stroke. 2012. US Pharm. 37(2):1-2.
9. *Manzoor A. Mir, Raid S. Al-Baradie, Malik D. Alhussainawi.*Pathophysiology Of Stroke.2015.Recent Advances in Stroke Therapeutics ., 2-4
10. Marcus B Nicol,Amanda G Thrift. Knowledge of risk factors and warning signs
11. of stroke. 2005. Vascular Health and Risk Management., I(2): 139-140.
12. Nishio Y, Koda M *et al*.Deletion of macrophage migration inhibitory factor attenuates neuronal feath and promotes functional recovery after compression-induced spinal cord injury in mice.2009.*Acta Neuropathologica.*, 117(3): 321-328.
13. NK Mishra, H Patel, SM Hastak. Comprehensive Stroke Care: An Overview.2006. JAPI., 54:37-38.
14. Ralph L.Sacco, Mitchell S.Elkind. Update on Antiplatelet Therapy for Stroke Prevention.2000. ARCH INTERN MED., 160:1579-1581.
14. Jhansi Konduru, Vanita P. A Review on Antiplatelet Drugs and Anticoagulants.2014. Advances in Pharmacoepidemiology & Drug safety., 3(3): 1-2.
15. Nikhil Kapil, Yvonne H. Datta *et al*. Antiplatelet and Anticoagulant Therapies for Prevention of Ischemic Stroke. 2017. SAGE.,23(4): 302-311.
16. V. Koenig-Oberhuber, M. Filipovic. New antiplatelet drugs and new oral anticoagulants. 2016. British Journal of Anarsthesia., 117(S2): ii74-ii76.
17. Bhargava M Vyasa, RD Dave *et al*. A View on Combination Antiplatelet Agents in Ischemic Stroke. 2013. Indian Journal of Clinical Practice., 23(11): 701-702.
18. Julia M Rothlisberger & Bruce Ovbiagele. Antiplatelet therapies for secondary stroke prevention :an update on clinical and cost- effectiveness. 2015. Journal of Comparative Effectiveness Research., 4(4): 377-380.
19. Jennifer Yeung, Michael Holinstat. Newer agents in antiplatelet therapy: A review.2012. Journal of Blood Medicine., 3: 34-36.
20. *Peter C. A. Kam, Mark K. Egan.Platelet Glycoprotein IIb/IIIa Antagonists. 2002.* Anesthesiology., 96(5): 1238-1240.
21. https://www.medindia.net/drug-price.htm