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A STUDY ON COMBINATIONS FOR STATINS AND CLOPIDOGREL; CLINICAL REVIEWS AND ITS RISK AMANGEMENT IN COMBINATION THERAPY

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ABSTRACT

Stroke is a clinically defined syndrome of acute, focal neurologicaldeficit attributed to vascular injury (infarction, haemorrhage) of the central nervous system. Stroke is the second leading cause of death and disability worldwide. Stroke is not a single disease but can be caused by a wide range of risk factors, disease processes and mechanisms. Hypertension is the most important modifiable risk factor for stroke, although its contribution differs for different subtypes. It is caused by when there is a disruption of blood flow to the brain, resulting in damage to brain cells. In this we have focused on drugs interactions of Clopidogrel and atorvastatin drugs are most common drugs in stroke conditions then we found an interaction in that because atorvastatin reduces the ability of Clopidogrel to inhibit platelet aggregation because atorvastatin is metabolized by cytochrome p450(CYP) 3A4 we hypothesized that Clopidogrel might be activated by CYP3A4. So that it get interaction between Clopidogrel and atorvastatin so wehave to alter the drug or we have to reduce the dose of drugs.

Stroke Condition

Stroke is a neurological disorder characterized by blockage of blood vessels. Clots form in the brain and interrupt blood flow, clogging arteries and causing blood vessels to break, leading to bleeding. Rupture of the arteries leading to the brain during stroke results in the sudden death of brain cells owing to a lack of oxygen. Stroke can also lead to depression and dementia.

Pathophysiology of Stroke

Stroke is defined as an abrupt neurological outburst caused by impaired perfusion through the blood vessels to the brain. It is important to understand the neurovascular anatomy to study the clinical manifestation of the stroke. The blood flow to the brain is managed by two internal carotids anteriorly and two vertebral arteries posteriorly (the circle of Willis). Ischemic stroke is caused by deficient blood and oxygen supply to the brain; hemorrhagic stroke is caused by bleeding or leaky blood vessels. Ischemic occlusions contribute to around 85% of casualties in stroke patients, with the remainder due to intracerebral bleeding. Ischemic occlusion generates thrombotic and embolic conditions in the brain. In thrombosis, the blood flow is affected by narrowing of vessels due to atherosclerosis. The build-up of plaque will eventually constrict the vascular chamber and form clots, causing thrombotic stroke. In an embolic stroke, decreased blood flow to the brain region causes an embolism; the blood flow to the brain reduces, causing severe stress and untimely cell death (necrosis). Necrosis is followed by disruption of the plasma membrane, organelle swelling and leaking of cellular contents into extracellular space, and loss of neuronal function. Other key events contributing to stroke pathology are inflammation, energy failure, loss of homeostasis, acidosis, increased intracellular calcium levels, excitotoxicity, free radical-mediated toxicity, cytokine-mediated cytotoxicity, complement activation, impairment of the blood–brain barrier, activation of glial cells, oxidative stress and infiltration of leukocytes Hemorrhagic stroke accounts for approximately 10–15% of all strokes and has a high mortality rate. In this condition, stress in the brain tissue and internal injury cause blood vessels to rupture. It produces toxic effects in the vascular system, resulting in infarction. It is classified into intracerebral and subarachnoid hemorrhage. In ICH, blood vessels rupture and cause abnormal accumulation of blood within the brain. The main reasons for ICH are hypertension, disrupted vasculature, excessive use of anticoagulants and thrombolytic agents. In subarachnoid hemorrhage, blood accumulates in the subarachnoid space of the brain due to a head injury or cerebral aneurysm.

INTRODUCTION

A stroke, a critical medical event, occurs when there is a disruption in blood supply to the brain, leading to damage or death of brain cells. This disruption can

manifest as either an ischemic stroke, resulting from a blocked blood vessel, or a hemorrhagic stroke, caused by bleeding in the brain. The consequences of a stroke extend beyond the initial event, with a dynamic interplay of processes influencing the extent of damage and subsequent recovery. Ischemic strokes often involve atherosclerosis or blood clots, obstructing vessels and triggering a chain reaction of inflammatory responses and cellular damage.

Hemorrhagic strokes arise from the rupture of blood vessels, causing bleeding within the brain and inducing pressure that can lead to further tissue damage. The aftermath of a stroke is marked by the brain's attempt to adapt through neuroplasticity, a process where surviving neurons reorganize to compensate for lost functions. Rehabilitation, including physical and cognitive therapies, plays a pivotal role in maximizing recovery. Understanding the intricacies of stroke, from its origins to the dynamic processes that follow, is crucial for effective prevention, immediate medical response, and long-term rehabilitation strategies.

The complexity of stroke dynamics underscores the importance of a comprehensive approach to minimize its impact on individuals' lives.

Ischemic Stroke Classification
According to the multicenter Trial of Acute Stroke Treatment (TOAST) there are three kinds of ischemic stroke
1. Large vessel stroke
2. Small vessel stroke or Lacunar stroke
3. Cardio embolic stroke

Strokes occur when there is a disruption of blood flow to the brain, resulting in damage to brain cells. The two main types of stroke and their causes are
1. Ischemic Stroke: Caused by a blockage or clot that obstructs blood flow to the brain.

Common causes include
Thrombosis: Formation of a blood clot in an artery supplying the brain. Embolism: Movement of a clot from another part of the body to the brain. 2. Hemorrhagic Stroke: Caused by bleeding within the brain.

Life Style Modifications
- Avoid alcohol consumption and smoking
- Be physically active
- Decrease your stress level and maintain a healthy weight
- Avoid foods like egg yolks fatty meals, butter, cream, which are highin fat and cholesterol
- Eat moderate amount of food and cut down on saturated fat
- Eat fruits, vegetables, whole grains and fat free or low fat dairy foods cereals pasta and brown rice
- Do not eat before bedtime

Etiology
Common causes include
Hypertension (High Blood Pressure): Weakens blood vessel walls, leading to rupture Aneurysm: Weakened area in a blood vessel that can rupture.

Arteriovenous Malformation (AVM): Abnormal tangle of blood vessels prone to bleeding. Risk factors for strokes include hypertension, smoking, diabetes, high cholesterol, age, family history, and a previous history of stroke or transient ischemic attack (TIA).Understanding and managing these risk factors can significantly reduce the likelihood of experiencing a stroke. Regular medical check- ups and adopting a healthy lifestyle are essential preventive measures.

Risk factors
Age is a risk factor, too. A stroke can occur at any age, but the risk is higher for babies under the age of 1 and for adults as they grow older.

Anxiety, depression, and high stress levels, as well as working long hours and not having much contact with family, friends, or others outside the home, may raise your risk for stroke.

Family history and genetic play a role as well. Your risk of having a stroke is higher if a parent or other family member has had a stroke, particularly at a younger age. Certain genes affect your stroke risk, including those that determine your blood type. People with blood type AB (which is not common) have a higher risk.

Living or working in areas with air pollution can also contribute to stroke risk. Other medical conditions, such as sleep apnea, kidney disease, and migraine headaches, are also factors.

Other unhealthy lifestyle habits, including drinking too much alcohol, getting too much sleep (more than 9 hours), and using illegal drugs such as cocaine, may raise stroke risk.

Race and ethnicity is another factor. In the United States, stroke occurs more often in Black, Alaska Native, American Indian, and Hispanic adults than in white adults.

Sex can play a role in risk for stroke. At younger ages, men are more likely than women to have a stroke. But women tend to live longer, so their lifetime risk of having a stroke is higher. Women who take birth control pills or use hormone replacement therapy are at higher risk. Women are also at higher risk during pregnancy and in the weeks after giving birth. High blood pressure during pregnancy — such as from preeclampsia — raises the risk of strokelater in life.

Viral infections or conditions, such as lupus or rheumatoid arthritis, can cause inflammation

Pharmacokinetics of drugs

Clopidogrel Kinetics
Absorption: Clopidogrel is administered orally and undergoes extensive absorption in the small intestine. It is a prodrug that requires biotransformation to its active form through a two-step process, primarily in the liver.

Activation: Hepatic enzymes, including CYP2C19, convert Clopidogrel into its active metabolite. Genetic variations in CYP2C19 can affect the rate of conversion, leading to variations in the drug's efficacy among individuals.

Metabolism: The active metabolite of Clopidogrel inhibits platelet aggregation by irreversibly binding to the P2Y12 receptor on platelets. This effect lasts for the lifespan of the platelet, about 7 to 10 days. Elimination: Clopidogrel and its metabolites are mainly eliminated through the bile. The drug's half-life is approximately 6 hours, but due to its irreversible platelet inhibition, the antiplatelet effect persists even after the drug has been cleared from the system. Genetic Variability: Genetic polymorphisms in CYP2C19 can result in poor metabolizers, intermediate metabolizers, extensive metabolizers, or ultra-rapid metabolizers. This variability can impact the effectiveness of Clopidogrel, with poor metabolizers being less responsive. Drug Interactions: Clopidogrel can interact with medications that affect its metabolism, particularly those that inhibit or induce CYP2C19. Such interactions may influence the drug's antiplatelet effects.

Understanding these pharmacokinetic aspects is crucial for tailoring Clopidogrel therapy to individual patients and avoiding potential complications. Patients are often tested for CYP2C19 genotype to guide dosing strategies. Always consult with healthcare professionals for personalized advice.

Atorvastatin Kinetics
Absorption: Atorvastatin is well-absorbed in the small intestine after oral administration. Its absorption can be influenced by food intake, with maximum concentrations observed around 1-2 hours post-dose.

Metabolism: The liver plays a crucial role in metabolizing Atorvastatin, primarily through the cytochrome P450 enzyme CYP3A4. This metabolism transforms Atorvastatin into active and inactive metabolites.

Distribution: Atorvastatin and its metabolites are extensively distributed to tissues, including the liver. Plasma protein binding is high, primarily to albumin.

Elimination: The elimination half-life of Atorvastatin is approximately 14 hours, reflecting its extended duration of action. Elimination occurs mainly through bile, with minimal renal excretion.

Genetic Variability: Individual variations in the genes encoding drug-metabolizing enzymes, especially CYP3A4, can influence Atorvastatin's pharmacokinetics.

Genetic factors may contribute to variability in response and potential side effects. Drug Interactions: Atorvastatin can interact with other medications that affect the same metabolic pathways, potentially leading to increased or decreased concentrations in the bloodstream. Understanding these kinetic aspects is essential for optimizing Atorvastatin therapy and minimizing potential adverse effects. Always follow healthcare provider recommendations and discuss any concerns with them.

Explanation of drugs
Clopidogrel is an antiplatelet medicine. It prevents platelets (a type of blood cell) from sticking together and forming a dangerous blood clot. Taking clopidogrel helps prevent blood clots if you have an increased risk of having them.

Common side effects include headache, nausea, easy bruising, itching, and heartburn. More severe side effects include bleeding and thrombotic thrombocytopenic purpura. While there is no evidence of harm from use during pregnancy, such use has not been well studied. Clopidogrel is in the thienopyridine- class of antiplatelet works by irreversibly inhibiting a receptor called P2Y12 on platelets.

Clopidogrel was patented in 1982, and approved for medical use in 1997. It is on the World Health Organization's List of Essential Medicines. In 2021, it was the 37TH most commonly prescribed medication in the United States, with more than 16 million prescriptions. It is available as a generic medication.

Atorvastatin is used together with a proper diet to lower cholesterol and triglyceride (fats) levels in the blood. This medicine may help prevent medical problems (eg, chest pain, heart attack, or stroke) that are caused by fats clogging the blood vessels.

Common side effects include joint pain, diarrhea, heartburn, nausea, and muscle pains. Serious side effects may include rhabdomyolysis, liver problems, and diabetes. Use during pregnancy may harm the fetus. Like all statins, atorvastatin works by inhibiting HMG-CoA reductase, an enzyme found in the liver that plays a role in producing cholesterol.

Atorvastatin was patented in 1986, and approved for medical use in the United States in 1996. It is on the World Health Organization's List of Essential Medicines. It is available as a generic medication. In 2021, it was the most commonly prescribed medication in the United States, with more than 116 million.

Drug Interactions

Clopidogrel inhibits platelet aggregation. It decreases the incidence of coronary artery stent thrombosis and is approved for reduction of myocardial infarction, stroke, and vascular death in patients with atherosclerotic vascular disease.2–4 Clopidogrel is an inactive thienopyridine prodrug that requires in vivo conversion in the liver to an active metabolite that exerts its antiplatelet effect by forming an inactivating disulfide bond with the platelet P2Yac (P2Y12) adenosine diphosphate (ADP) receptor.5–8 The P2Yac ADP receptor is a guanosine triphosphate (GTP)- coupled 7 transmembrane protein that mediates platelet aggregation by inhibiting adenyl cyclase.8 In rats, it has been suggested that clopidogrel is activated by cytochrome P450 1A2,6 whereas an analogue of clopidogrel, CS-747, is speculated to be activated by human cytochrome P450 3A4 (CYP3A4).[9] In humans, it is not known how clopidogrel is activated. Atorvastatin is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor widely used to treat hypercholesteremia. It is metabolized by CYP[3A4,10] the most abundant cytochrome P450 in human liver. Patients with atherosclerotic disease are frequently treated for hypercholesteremia with both clopidogrel and atorvastatin or another statin. During the course of evaluating the effect of clopidogrel on platelet function using a novel bedside platelet aggregometer, it was noted that the antiplatelet activity of clopidogrel was diminished significantly when patients were also taking atorvastatin. This prompted prospective studies to test the hypothesis that atorvastatin was inhibiting clopidogrel activation by CYP3A4

CASE STUDY

A 50 years old male patient was admitted in hospital with chief complaints Forgetting incidence, left hand weakness, deviation of angle of mouth since 1 day c/o slurred speech since 2days, fall from the bed, Incontinence of urine and he has past medical history Hypertension from 20 years treating by using losartan 25 mg And CVA from 5 years by using amlodipine 10 mg and Clopidogrel 25 mg And diagnosed with CEREBROVASCULAR ACCIDENT (CVA) and treating with.

Inj. Heparin (5000U), Inj STROCIT(250mg/ml),T. Colihen (500mg), Inj. Levipil (500mg), T. Atorvastatin (20mg),T. Betalo(25mg), T. PAN (40mg), Inj ecosprin (150 mg) and patient improved symptomatically and discharged on following advise T DEPLATT _75mg, T ATORVA_ 20mg, T PAN_ 40mg.

CONCLUSION

In Cerebrovascular case they have been treating with Clopidogrel used as antiplatelet drug in case of Cerebrovascular, Heartattack, Stroke etc to reduce platelet and atorvastatin is use as HMG- COA reductase inhibitors mevalonate that lower cholesterol and triglyceride (fats) levels in the blood then we found an interaction in that because atorvastatin reduces the ability of Clopidogrel to inhibit platelet aggregation because atorvastatin is metabolized by cytochrome p450(CYP) 3A4 we hypothesized that Clopidogrel might be activated by CYP3A4. So that it get interaction between Clopidogrel and atorvastatin so we have to alter the drug or we have to reduce the dose of drugs.

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