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STRENGTH AND LIABILITIES OF ASPIRIN IN THE PREVENTION OF CARDIOVASCULAR EVENTS

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ABSTRACT

Cardiovascular diseases are the major cause of death globally, which are a group of disorders of the heart and blood vessels. Myocardial infarction and stroke are the major cause of morbidity and mortality in patients with cardiovascular disease. Aspirin is one of the oldest and most widely used and tested antiplatelet drug in CVD, and it is proven to be the cornerstone of antiplatelet therapy in the treatment and prevention of CVD. The most common side effect of aspirin is gastrointestinal upset ranging from gastritis to gastrointestinal bleeding. The strength of low dose aspirin therapy for the secondary prevention of CVD is clear, but the use of aspirin for the primary prevention of CVD remains challenging due to mixed findings on mortality benefits. Eventually, management decisions in patients requiring antiplatelet therapy for cardiovascular protection will depend on a patient-by-patient assessment of strength and liabilities.

KEYWORDS: Cardiovascular diseases, aspirin, gastro protective agents, acid-suppressive therapy, antiplatelet therapy.

INTRODUCTION

Cardiovasular Diseases (Cvd)

Cardiovascular diseases are the major cause of death globally, which are a group of disorders of the heart and blood vessels.[1] Myocardial infarction and stroke are the major cause of morbidity and mortality in patients with cardiovascular disease.[2] In spite of CVD may directly rise from different etiologies such as emboli in a patient with arterial fibrillation resulting in ischemic stroke, rheumatic fever causing valvular heart disease, among others, addressing risk factors associated to the development of atherosclerosis is most important because it is the common denominator in the pathophysiology of CVD.

During the couple of years, the risk of heart disease remains high with a calculated 50% risk by age 45 in the general residents. The incidence significantly increases with age with some variations between genders higher in men at younger ages. The difference in incidence narrows progressively in the post-menopausal state.[3]

Aspirin

Aspirin is one of the oldest and most widely used and tested antiplatelet drug in CVD, and it is proven to be the cornerstone of antiplatelet therapy in the treatment and prevention of CVD. Aspirin had been introduced as a non-steroidal anti-inflammatory molecule.[4] As further research on aspirin started, other therapeutic effects have been revealed. Now, the molecule has become the polychrest in medical science. Aspirin has served as a drug of choice for the primary prevention of CVD for last few decades.[5] It can be administered via oral, rectal, and intravenous (IV) route. Available in different doses: tablet-325mg, 500mg delayed-released tablet-81mg,325mg,500mg,650mg chewable-81mg suppository-60mg, 120mg, 200mg, 300mg, 600mg intravenous-250mg,500mg.[4]

Mechanism of Action

Aspirin selectively and rapidly acetylates serine residue in the cyclooxygenase (COX) to cause irreversible inhibition. There are two structurally similar COX isoforms namely COX-1 and COX-2, which are encoded by different genes. COX-1 and COX-2 catalyse the conversion of arachidonic acid to the cyclic end peroxides prostaglandin G2 and prostaglandin H2, which are biosynthetic intermediates in the formation of biologically active prostanoids, including thromboxane A2. Covalent acetylation of critical serine residues in COX-1 and COX-2 by aspirin permanently inactivates the COX activity of these enzymes and blocks to a variable extent of this pathway of arachidonic acid mechanism, thereby reducing prostanoide production.[6]

Pharmacokinetics of Aspirin

Acetylsalicylic acid is converted to salicylic acid by hydrolyses and first pass metabolism, peak plasma concentrations is extremely sensitive to minor variations

in solid dosage form dissolution and disintegration after absorption.[2]

Absorption

70% of aspirin reaches to the peripheral circulation intact with maximum serum concentrations observed 25 minutes after the administration. After entering the blood stream, it undergoes enzymatic hydrolyses to yield acetate and salicylic acid.[7] The major enzymes hydrolysing aspirin in plasma are believed to be cholinesterase. Intravenous aspirin has a distribution half-life of above 3 min and inhibits prostaglandin biosynthesis within 5 min of administration, reflecting the rapid onset of inhibition compared to oral dosing.

Distribution

Once absorbed, salicylates are distributed through body fluids. Volume of distribution of salicylate ranges from 9.6 to 12.7 litre in adults with similar values (0.12- 0.14 L/kg) in children.

Aspirin and salicylic acid are partially bound to serum proteins. The distribution of aspirin is enhanced by binding to human serum albumin. Albumin is the most abundant protein found in blood and is often used as a plasma shuttle for steroids, hormones, and other small molecules.

Metabolism and Excretion

Aspirin is rapidly converted to salicylic acid with a half-life of only 15 to 20 mints. This hydrolyses is due to known specific esterase's found in many body. The major route of elimination of aspirin is through its hydrolysed product salicylic acid. Salicylic acid is cleared from circulation through the kidney with a serum half-life of approximately 2 hours.

Pharmacodynamics

Almost 90% of COX inhibition can be achieved with administration of 160 to325mg of aspirin. These effects last 7 to 10 days which usually corresponds with the lifespan of a platelet. Prostacyclin inhibition can be achieved with the use of higher doses.[6] This inhibition occurs in the endothelial cells of blood vessels. The bioavailability of aspirin tablets is approximately 40 to 50% over a wide range of doses. However considerably lower bioavailability aspirin reported for some aspirin preparations designed to delay absorption until the drug reaches the small intestine. The efficacy and safety of an optimized, twice daily, low dose aspirin regimen is currently under investigation. As a result of its unique pharmacokinetics and pharmacodynamics features, aspirin has a lower inhibitory effect on prostaglandin (PG) I2 biosynthesis in vascular cells than on platelet TXA2 biosynthesis at all doses, reaching a ceiling effect on inhibition of PGI2 biosynthesis at a dose of 650-11300 mg daily. Aspirin has effects on haemostasis that are not related to the inactivation of platelet COX1. These effects include dose-dependent inhibition of platelet function, increase of fibrinolysis and suppression of plasma coagulation.[7]

ADVERSE EVENTS WITH ASPIRIN

The most common side effect of aspirin is gastrointestinal upset ranging from gastritis to gastrointestinal bleeding.[6] The antithrombotic trialists' collaboration (ATTC) meta-analysis revealed that aspirin use increased the risk of major gastrointestinal and other extra cranial bleeding by about 50%. Following are the other adverse effects.[8]

1: Hypersensitivity

Excessive sensitivity to NSAIDS is normal among everyone. The rate is about 1-2 %. The unwanted effects could be as gentle as a simple rash to angioedema and hypersensitivity. The new term related with the disorder NSAID exacerbated respiratory malady (NERD) is because of upper just as lower respiratory mucosal inflammation.[6]

2: Reye Syndrome

It is a metabolic non inflammatory encephalopathy associated with fatty degeneration of the liver. This syndrome is typically preceded by a viral illness, and generally presents with severe protracted vomiting, followed by encephalopathy that may progress to coma or death, or may spontaneously resolve.[9] Aspirin or similar medicine gives the subsequent hit finishing the disorder. The occurrence has significantly reduced because of better mindfulness and utilization of acetaminophen for the treatment of fever in kids rather than aspirin. Infact that the relationship between aspirin and Reye condition exists, a few authors content that during diagnosis, salicylate levels were not routinely checked, biopsies were not acquired, and hereditary/ intrinsic blunders of metabolism were not precluded.

3: Intracerebral Hemorrhage

Aspirin versus placebo, aspirin increases the risk of intracranial bleeding.

4: Nephrotoxicity

Some of the studies have shown that the use of aspirin is associated with chronic kidney disease. A study in healthy people did not find any association between aspirin and nephrotoxicity.[6]

5: Bleeding

Aspirin has been associated with the increased risk of bleeding in general population. Aspirin makes an increment in the danger of dose related peptic ulcer bleeding.[10] In a study they have demonstrated that among people who had peptic ulcer blood loss, constant low dose aspirin utilize expanded the danger of repetitive bleeding yet brought about lower overall cardiovascular and cerebrovascular mortality rates.

Strength of Aspirin

Efforts were being done for years to prevent and treat CVD. By the 20th century, CVD had become a major cause of mortality and morbidity, and many efforts were being made to prevent it globally. Several strategies were considered for CVD including lifestyle changes and traditional methods. Along with this some exploiters have used aspirin for the prevention of CVD. With some controversy, it is believed that aspirin is beneficial in the primary prevention of CVD.[6] Thrombotic and thromboembolic occlusions of atherosclerotic blood vessels play a major role in ischemic events, and platelet activation and aggregation are central to thrombus formation. For this reason antiplatelet agents like aspirin are widely used for the prevention and management of CVD.[2]

1: Aspirin in Secondary Prevention

Patients who suffer from one or more CVD events, like myocardial infarction or ischemic stroke, are at very high risk for another CVD event.[7] The benefits of aspirin therapy in secondary prevention of ischemic events are well reputable. A study has shown that aspirin reduces the risk of major coronary events, in patients with a history of such events, to a similar degree in men and women.[2] Aspirin use as a secondary prevention measure for serious CVD events is well accepted and recommended by several major establishments.

2: Aspirin IN Primary Prevention

The notion that aspirin could be use for primary CVD prevention existed before it's well established use for secondary prevention. Several groups have investigated possible solution for maintaining the benefits of aspirin therapy while reducing the risk for bleeding. In a meta-analysis they found that the main risk factors for CVD were similar to those for major bleeding. To reduce the risk of gastrointestinal bleeding, several groups demonstrated the utility of co-administration of a proton pump inhibitor which was later recommended concurrent with aspirin in those at high risk for ulcer bleeding. In another study demonstrated that combination of aspirin and esomeprazole was higher to clopidogrel for the prevention of recurrent ulcer bleeding. A few organizations, including the American Heart Association (AHA), the American College of Chest Physicians, and the European Society of Cardiology (ESC), have concluded that aspirin is beneficial and safe for primary CVD prevention when it is used properly.

3: Aspirin In Diabetes

Individuals with diabetes have 2- 4 times increased risk for serious cardiovascular events as a result of increased coronary thrombus formation, increased platelet reactivity, and worsened endothelial dysfunction. The early treatment Diabetic Retinopathy Study included patients with type 1 and type 2 diabetes mellitus and some degree of retinopathy. Cardiovascular outcomes were compared in patients given 650mg of aspirin daily versus placebo as a secondary study outcome. A significant reduction in fatal and nonfatal MI was observed in aspirin group. In light of these findings, the American Diabetes Association now recommends the low dose aspirin be prescribed primarily for men over age 50 and women over age 60 who have diabetes and at least moderate CVD risk or who have had a previous MI or stroke.[7]

LIABILITIES OF ASPIRIN

People with the following conditions should be cautious about aspirin:

1: Bleeding disorders such as haemophilia
2: Uncontrolled high blood pressure
3: Asthma
4: Peptic or stomach ulcers

In a study of individuals aged 40-79 years in UK, the incidence of symptomatic, uncomplicated ulcers was found to be 1.03 cases per 1000 person – years in nonusers of aspirin or other NSAIDS, while it was 2.9 for users of aspirin. A significant proportion of patients can experience upper gastrointestinal (GI) discomfort because of aspirin treatment that decreases the already impaired health status of patients with CVD. In a meta-analysis, found that long-term use of aspirin therapy led to an increased incidence of haemorrhagic stroke in individuals both with and without manifest vascular disease. This study also found an increased risk major bleeding with aspirin therapy.

Choices To Manage The Strength and Liabilitites of Aspirin

- Prescribing aspirin only to patients at high-cardiovascular risk
- Prescribing aspirin only to patients at low-GI risk
- Reducing the dose of aspirin
- Reducing the duration of aspirin therapy
- Acid suppressive co-therapy
- Other gastro protective agents
- Avoiding the co-prescription of drugs with similar effects
- Using an enteric-coated formulation of aspirin[11]

CONCLUSION

The strength of low dose aspirin therapy for the secondary prevention of CVD is clear, but the use of aspirin for the primary prevention of CVD remains challenging due to mixed findings on mortality benefits.[7] It has been suggested that in primary prevention, risk reductions for non-fatal MI appear to be limited to men than women. Reasons for these differences are not clear. There is an increased risk of GI complications and haemorrhagic events when taking aspirin. In summary both benefits and risk need to be taken into careful consideration when recommending aspirin, particularly when it is used for primary prevention. Several reasonable options are available to manage these risk. Eventually, management decisions in patients requiring antiplatelet therapy for cardiovascular

protection will depend on a patient-by-patient assessment of strength and liabilities.[2]

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CONFLICT OF INTEREST
There is no conflict of interest between the authors**.**

ABBREVATIONS
CVD-Cardiovascular diseases
IV-Intravenous
COX-Cyclooxygenase
PG-Prostaglandin
ATTC-Anti-thrombotic trialists collaboration
NSAIDs-Non-steroidal anti-inflammatory drugs
NERD- NSAID Exacerbated respiratory malady
AHA-American heart association
ESC-European society of cardiology

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