IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

The Willow Wonder Drug Aspirin and It's Drug-Drug Interactions

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ABSTRACT:

Aspirin invented by Dr. Felix Hoffman in 1897 as a pain killer, was the first synthetic drug when drugs were made from the extracts of the plants, and the new pharmaceutical business evolved. Later, it was found that it could be used for cardiovascular events as an antiplatelet agent in the 1960s. Aspirin is synthetically prepared from salicylic acid and acetic anhydride. It is a nonselective cyclooxygenase receptor antagonist. Aspirin is used as over-the-counter medication as pain killer as well as prescription medication for cardiovascular events worldwide. The common side effects of aspirin are nausea, vomiting, heartburn, and stomach pain. The other worst side effects are bleeding from the stomach, black-tarry stools, and hemoptysis. This article discusses some of the drug-drug effects of aspirin and drug-drug interactions with which it is commonly prescribed.

Key Words:

Aspirin, bleeding, adverse effects, drug-drug interactions.

INTRODUCTION:

Aspirin is a nonsteroidal anti-inflammatory drug, used for relieving pain and lowering inflammation in higher doses and managing various conditions like cardiovascular events in lower doses in people with high risk. It has well-known interactions with other drugs. This article discusses some of the drug-drug interactions of aspirin with which it is administered commonly.

Some of the class of drugs, which interact with aspirin are:

1. Anti-inflammatory pain killers like diclofenac, ibuprofen, and naproxen, when combined with aspirin can increase the risks of bleeding.
2. Selective serotonin reuptake inhibitors and atypical antidepressants like citalopram, paroxetine, fluoxetine, venlafaxine, and sertraline, when combined with aspirin increases the risk of bleeding.
3. Blood thinners including Apixaban, Dabigatran, Enoxaparin, Heparin, Rivaroxaban, and warfarin with aspirin the risk of bleeding increases.

4. Methotrexate, a drug used for autoimmune diseases, when combined with aspirin increases the level of methotrexate, which is toxic.
5. Amlodipine when combined with Aspirin increases the risk of bleeding.
6. Amphotericin B is commonly used to treat potentially life-threatening fungal infections when combined with aspirin increases the risk of nephrotoxicity.
7. Phenytoin and Sodium Valproate when combined with aspirin increases the concentration of valproic acid and phenytoin (in higher doses), which leads to toxicity and increased side effects.
8. Penicillin when combined with aspirin may make the aspirin less effective.
9. Clopidogrel and aspirin taken together may cause unusual bleeding, severe abdominal pain, weakness, and appearance of black-tarry stools.
10. Corticosteroids may increase the risk of developing ulcers and gastrointestinal bleeding, inflammation, ulceration, rarely cause perforation when taken with aspirin.

MECHANISM OF ACTION OF ASPIRIN:

Acetyl salicylic acid is a nonselective cox inhibitor. Cyclooxygenase enzyme produces prostaglandin, which induces pain. When given in lower doses 75/81 mg, Aspirin inhibits Cox 1 enzyme and acts as antiplatelet. When given in higher doses, 650 mg to 4 g, it inhibits both cyclooxygenase enzyme 1 and cyclooxygenase 2 enzymes, which relieves pain and fever. The average life span of platelets is seven to ten days. Aspirin acts on the platelets. The acetyl group irreversibly combines with the serine residue 530 of Cox 1 enzyme and blocks the production of prostaglandin, which through a series of reactions converted to thromboxane A2. Thromboxane A2 is a potent inducer of platelet aggregation. In higher doses, it also blocks cyclooxygenase 2 enzyme, thereby relieving pain.

DRUG-DRUG INTERACTIONS:

1. **NSAIDS and aspirin**: As both drugs act on the same pathway, the cyclooxygenase pathway, both when combined increases the risk of bleeding. Both inhibit production of thromboxane A2 and platelet aggregation and produce excessive bleeding and stomach-ache. The common symptoms include indigestion, nausea, and vomiting and other serious symptoms include coughing up blood, blood in urine, stool, or vomiting, yellow skin or eyes, red blistered peeled skin, painful joints, swollen hands, or feet.

Prevention**:** Concomitant use of both drugs should be avoided, instead they can use acetaminophen.

2. Selective serotonin reuptake inhibitors and aspirin:

Mechanism of action: Serotonin or 5-hydroxy tryptamine is a neurotransmitter, 95% of serotonin is produced in the intestine where it is doing its paracrine, autocrine, and endocrine actions. Platelet stores huge amounts of serotonin. They release them during acute inflammation or thrombus formation. This serotonin impels both platelet aggregation and coronary vasoconstriction

to reduce blood loss. Selective serotonin reuptake inhibitors inhibit the reuptake of serotonin, thereby inhibiting platelet aggregation and causing bleeding. When combined with aspirin increases the risk of bleeding.

Prevention: Using gastroprotective medications when combined with SSRI. Avoiding SSRI and aspirin at the same frequency.

3. Aspirin and blood thinners including Apixaban, Dabigatran, Enoxaparin, Heparin, Rivaroxaban, and warfarin:

A) Mechanism of Action of Warfarin: Warfarin is an anticoagulant that prevents clot formation and migration. Warfarin antagonizes vitamin K. It binds to vitamin K epoxide reductase complex. This complex irreversibly inhibits the vitamin K reductase enzyme. This process prevents the recycling of vitamin K. Vitamin K is required for coagulation factors VII, IX, X, and thrombin to convert into active form.

B) Mechanism of Action of Apixaban: Apixaban prevents thrombus formation by selectively antagonizing factor Xa in its free and bound forms independent of antithrombin III and prothrombinase.

C) Mechanism of Action of Dabigatran: Dabigatran is a direct thrombin inhibitor that competitively inhibits the thrombin of fibrinogen to fibrin, and it inhibits platelet aggregation.

D) Mechanism of Action of Enoxaparin: Enoxaparin binds to antithrombin III forming a complex. This complex irreversibly inactivates the factor Xa, following that enoxaparin binds to other antithrombin molecules. Factor IIa is directly inhibited by enoxaparin, because of this fibrin formation is prevented.

E) Mechanism of Action of Heparin: Under normal circumstances, antithrombin III inactivates thrombin and factor Xa. This event is a slow process. When combined with heparin, this process becomes instantaneous. Heparin is not thrombolytic or fibrinolytic. It prevents the progression of existing clots by inhibiting further clotting.

F) Mechanism of Action Rivaroxaban: Rivaroxaban competitively inhibits free, and clot bound factor Xa. Factor Xa is needed to activate prothrombin to thrombin. Thrombin is required for the conversion of fibrinogen to fibrin. It is the last step of the clotting process. It is a reversible reaction.

When blood thinners are combined with aspirin, the risk of bleeding increases.

Prevention: Avoiding combination with of these drugs.

4. Methotrexate and Aspirin:

Mechanism of Action of Methotrexate: Methotrexate is converted to methotrexate polyglutamate by folylpolyglutamate. The mechanism of action includes its inhibition of dihydrofolate reductase, thymidylate synthetase, and aminoimidazole carboxamide ribonucleotide transformylase (AICRT). This prevents the synthesis of nucleotide. Inhibition of nucleotide synthesis prevents cell division. When it is combined with aspirin, it affects glomerular filtration rate and tubular function and increases concentration of

Methotrexate. This combination may cause vomiting, diarrhea, sore throat, chills, fever, rash, unusual bleeding and bruising, shortness of breath, swelling of the extremities.

Prevention: Avoid combinations of Methotrexate with aspirin.

5. Amlodipine and Aspirin:

Mechanism of Action of Amlodipine: Amlodipine is a dihydropyridine type calcium antagonist. It inhibits the influx of calcium ions in both vascular smooth muscle and cardiac muscles. Amlodipine combines with both dihydropyridine and non-dihydropyridine binding sites located on the cell membrane. The contraction of smooth muscle and cardiac muscle depends on the movement of extracellular calcium ions into the cells by specific ion channels. Amlodipine blocks calcium ion influx across the cell membranes with selectivity. There is a moderate interaction occurring between aspirin and amlodipine. The metabolism of aspirin decreased when combined with amlodipine, which increases the bleeding.

Prevention: Avoid using combination or frequency.

6. Amphotericin B and Aspirin:

Mechanism of Action of Amphotericin: The drug acts on binding to the ergosterol of the cell membrane of susceptible fungi. This occurrence creates pores across the transmembrane channel and leakage of intracellular components and death of cells. When combined with aspirin, it increases the risk of nephrotoxicity. Aspirin reduces blood supply to the kidney and glomerular filtration rate. Amphotericin B induced nephrotoxicity manifested as azotemia, renal tubular acidosis, impaired renal concentrating capacity, and electrolyte abnormalities like hypokalemia and sodium and magnesium wasting. These effects are secondary to the activation of intrarenal mechanism and or release of mediators, thromboxane A2. These effects decrease renal blood flow and filtration rate.

Prevention: Concomitant use of these drugs may be avoided.

7. Phenytoin and Sodium Valproate with Aspirin:

A) Mechanism of Action of Phenytoin: Phenytoin is a nonspecific sodium channel blocker and targets almost all voltage-gated sodium channel subtypes.

B) Mechanism of action of Sodium Valproate:

(1) Sodium valproate is known to inhibit succinic semialdehyde dehydrogenase, which results in increase in succinic semialdehyde in the neurotransmitter. Succinic semialdehyde inhibits GABA transaminase. GABA transaminase is GABA metabolizer, which results in increased levels of GABA in the nerve terminal. GABA is an inhibitory neurotransmitter. (2) It also directly suppresses voltage-gated sodium channels.

(3) It has also been suggested that valproate impacts the extracellular signal-related kinase pathway. These effects appear to be dependent on mitogen-activated protein kinase and result in phosphorylation of extracellular signal-related kinase 1 and 2. This activation increases expression of several downstream targets including ELK-1 with subsequent increase in c-fos, growth cone-

associated protein-43, which contributes to neural plasticity, B-cell lymphoma/leukemia-2, which is an antiapoptotic protein, and brain-derived neurotrophic factor (BDNF), which is also involved in neural plasticity and growth. Increased neurogenesis and neurite growth due to valproate are attributed to the effect of this pathway. An additional effect is increased BDNF increases GABA receptors, which contributes to further increase in GABAminergic activity.

(4) Valproate has been found to be non-competitive direct inhibitor of brain microsomal long-chain fatty acyl-CoA synthetase. Inhibition of this enzyme decreases the available arachidonoyl-CoA, a substrate in the production of inflammatory prostaglandins. (5) Valproate acts as a direct histone deacetylase (HDAC) inhibitor. Hyperacetylation of lysine residue on histone promotes DNA relaxation and allows for increased transcription. Histone hyperacetylation at the BDNF gene, increasing expression. Its neuroprotective effects enhanced with reduction in glyceraldehyde-3-phosphate dehydrogenase, a proapoptotic enzyme. Valproic acid and aspirin both are highly bound to plasma proteins. Thus, when they are co-administered at sufficient doses, there is mutual displacement and rise in the free fraction of each drug.

Prevention: The patient may need dose adjustments or special tests to safely take both medications.

8. Penicillin and Aspirin:

Mechanism of Action: Penicillin is a beta-lactam antibiotic used to treat bacterial infections caused by susceptible gram-positive organisms. By binding to specific penicillin-binding proteins located inside the cell wall, penicillin inhibits the third and last stage of bacterial cell wall synthesis. Taking aspirin with penicillin can alter the gut bacteria levels, this event may make bacterial infection get worse. This combination may make aspirin less effective.

Prevention: Concomitant use may be avoided.

9. Clopidogrel:

Mechanism of Action: Clopidogrel is metabolized to its active form by carboxyestrase-1. The active form is a platelet inhibitor that irreversibly binds to P2Y12 ADP receptors on the platelets. This binding prevents ADP binding to P2Y12 receptors, activation of glycoprotein GPIIb/IIIa complex and platelet aggregation. When combined with aspirin, it increases the risk of bleeding.

Prevention: Combination pills are available; the benefit outweighs the risk of bleeding, and the combination uses only low doses.

10. Corticosteroids: Examples are prednisone, prednisolone, dexamethasone, hydrocortisone.

Prednisone and prednisolone mechanism of action: Prednisone first metabolized in the liver to its active form prednisolone. The short-term effects of corticosteroids are decreased vasodilation and permeability of capillaries as well as decreased leukocyte migration to sites of inflammation. Corticosteroids binding to the glucocorticoid receptor mediates changes in gene expression that lead to multiple downstream effects over the hours to days.

Glucocorticoids inhibit neutrophil apoptosis and demargination. They inhibit phospholipase A2, which decreases the formation of arachidonic acid derivatives. They inhibit NF-kappa B and other inflammatory transcription factors; they promote anti-inflammatory genes like interleukin-10. Lower doses of corticosteroids provide an anti-inflammatory effect, while higher doses

are immunosuppressive. Higher doses of glucocorticoids for an extended period bind to the mineralocorticoid receptor, raising sodium levels and decreasing potassium levels.

Prevention: Use cautiously.

CONCLUSION:

Aspirin is widely used in cardiovascular and stroke prevention. Platelet activation and aggregation with subsequent activation of clotting cascade play a crucial role int the onset of acute occlusive vascular events such as myocardial infarction and cerebrovascular accidents. Because platelets do not have nucleus and cannot regenerate Cox, they become excellent therapy. Attempts have been made to decrease the gastrointestinal toxicity of aspirin by pharmacological manipulation. Sustained release and topical preparations have been demonstrated to produce relatively selective inhibition of platelet thromboxane A2 production with minimal side effects on vascular and gastric prostanoids production and thus may have less gastro toxicity. Aspirin is also now proven to be useful in preventing prostate cancer. The dose and length of treatment depends on the medical condition and response to treatment. Low dose aspirin has been used during pregnancy most commonly to prevent or delay the onset of preeclampsia. It is also used for the prevention of stillbirth, fetal growth restriction, preterm birth, and even pregnancy loss as it increases the blood supply to the fetus. Despite adverse effects, the benefits outweigh the adverse effects. It remains the cornerstone of antiplatelet therapy in patients with cardiovascular disease.

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