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Pharma Tab

Department of Pharmacy Practice

C.L. Baid Metha College of Pharmacy

Jyothi Nagar, Rajiv Gandhi Salai, Thorapakkam, Chennai -97. E-mail: dicclbaid@gmail.com

FDA APPROVES VORAPAXAR

TO REDUCE THE RISK OF HEART ATTACKS AND STROKE IN HIGH-RISK PATIENTS

VORAPAXAR SULFATE is the first in a new class of drug, called a protease-activated receptor-1 (PAR-1) antagonist. It is an anti-platelet agent, designed to decrease the tendency of platelets to clump together to form a blood clot. By decreasing the formation of blood clots, Vorapaxar Sulfate decreases the risk of heart attack and stroke.

CLINICAL TRIAL REPORT:

In a clinical trial with over 25,000 participants, Vorapaxar Sulfate was added to other anti-platelet agents (generally aspirin and clopidogrel), and it reduced the rate of a combined endpoint of heart attack, stroke, cardiovascular death, and urgent procedures to improve blood flow to the heart (coronary revascularization) when compared to an inactive pill (placebo).

Drug Name(s)	ZONTIVITY
Active Ingredient(s)	VORAPAXAR SULFATE
Original Approval Date	May 8, 2014
Strength	E Q 2.5 mg Base
Dosage Form/ Route	Tablet/ Oral
Manufacturer	Merck Sharp & Dohme Corp.,

Drug Properties:

Synonyms: Vorapaxar, Vorapaxar Sulfate

Physicochemical Properties

A) Vorapaxar Sulfate - Molecular Weight 590.7

B) Solubility

Freely soluble in methanol and slightly soluble in ethanol, acetone, 2-propanol, and acetonitrile; slightly soluble in aqueous solution of pH 1 with solubility decreasing with increasing pH.

Mechanism of Action

Vorapaxar is a reversible antagonist of the protease-activated receptor-1 (PAR-1) expressed on platelets, but its long half-life makes it effectively irreversible. Vorapaxar inhibits thrombin-induced and thrombin receptor agonist peptide (TRAP)-induced platelet aggregation in in vitro studies. Vorapaxar does not inhibit platelet aggregation induced by adenosine diphosphate (ADP), collagen or a thromboxane mimetic and does not affect coagulation parameters ex vivo. PAR-1 receptors are also expressed in a wide variety of cell types, including endothelial cells, neurons, and smooth muscle cells, but the pharmacodynamic effects of vorapaxar in these cell types have not been assessed.

Adult Dosage

Normal Dosage

Oral route

Thrombosis, History of myocardial infarction or with peripheral arterial disease; Prophylaxis

a) Usual dose: 1 tablet (2.08 mg) orally once daily in addition to aspirin and/or clopidogrel according to their standard of care or indications.

- Dosage in Renal Failure

  In patients with renal impairment, no dose adjustment is necessary..

- Dosage in Hepatic Insufficiency

  Avoid use in patients with severe hepatic impairment. No dose adjustment is necessary in patients with mild or moderate hepatic impairment.

Pediatric Dosage

Normal Dosage

Safety and effectiveness have not been established in pediatric patients

PHARMACOKINETICS

Onset and Duration

Onset

Peak Response

a) Inhibition of Platelet Aggregation: within 1 week.

b) Inhibition of platelet aggregation of 80% or greater is achieved within 1 week of initiation of therapy.

Duration

Multiple Dose

a) Inhibition of Platelet Aggregation: 50% at 4 weeks.

b) Four weeks after stopping daily therapy with vorapaxar, approximately 50% of platelet aggregation inhibition persists. The duration of platelet inhibition is dependent on dose and concentration

Drug Concentration Levels

Time to Peak Concentration (Tmax)

Oral: 1 hour - The Tmax is 1 hour following oral administration of a single vorapaxar dose

CAUTIONS

Black Box Warning

Oral (Tablet) - Antiplatelet agents increase the risk of bleeding, including intracranial hemorrhage (ICH) and fatal bleeding. Do not use vorapaxar in patients with active pathological bleeding or a history of stroke, TIA, or ICH

Contraindications

Active pathological bleeding such as intracranial hemorrhage or peptic ulcer.

History of stroke, TIA, or intracranial hemorrhage (ICH); increased risk of ICH; discontinue with occurrence of stroke, TIA, or ICH

Precautions

A) Black Box Warning:

Increased risk of bleeding proportional to underlying bleeding risk, including intracranial hemorrhage (ICH) and fatal bleeding; risk factors

include low body weight, older age, and reduced renal or hepatic function.

B) Concomitant Use:

- Avoid warfarin or other anticoagulants
- Avoid strong CYP3A inhibitors
- Avoid strong CYP3A inducers

ADVERSE REACTIONS

Bleeding, including life-threatening and fatal bleeding, is the most commonly reported adverse reaction.

DRUG INTERACTIONS

Vorapaxar is eliminated primarily by metabolism, with contributions from CYP3A4 and CYP2J2.

Strong CYP3A Inhibitors

Avoid concomitant use of ZONTIVITY with strong inhibitors of CYP3A (e.g., ketoconazole, itraconazole, posaconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, boceprevir, telaprevir, telithromycin and conivaptan)

Strong CYP3A Inducers

Avoid concomitant use of ZONTIVITY with strong inducers of CYP3A (e.g., rifampin, carbamazepine, St. John's Wort and phenytoin)

Storage

- Store at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep the tablets in the bottle they come in.
- Keep the bottle tightly closed.
- The bottle contains a desiccant packet to help keep your medicine dry (protect it from moisture). Keep the desiccant packet in the bottle. Do not throw away the desiccant packet.
- Store blister packs in the original package it comes in.
- Keep this medicine and all other medicines out of the reach of children.

M.Ashok Kumar
Assistant Professor
Department of Pharmacy Practice

Influence of Genetic Variation On Cardiovascular Drug Therapy

Inter-individual variability in drug response

It was long been known that the type of medication, the required dose and response to the drug significantly differ from person to person. Numerous factors that cause variations in drug response, the factors are complex including genetic variation (inherited) environmental and physiological factors. Cardiovascular disease (CVD) persists one of the leading cause of death worldwide, hence CVD remains as a main focus of research and development. There are many class of drugs used to treat CVD conditions such as cardiac arrhythmia, congestive cardiac failure, myocardial infarction, coronary artery disorders, hyperlipidemia and others. However, the patient response to the drugs may vary from one another. This may be overcome by finding the exact cause of inter-individual variations.

Genetic polymorphisms

Genetic variations in genes are inherited and stable over the course of lifetime. Mutations in genes encoding for drug-metabolizing enzymes, drug transporters and drug targets contributes to 25-50% of variation in drug responses. Genetic polymorphism is a variation in the DNA sequence that is present at an allele frequency of 1% or greater in a population. There are two most common types of sequence variation have been associated with variation in human phenotype, single nucleotide polymorphisms (SNPs) and insertions/deletions (indels) polymorphisms. The presence of these variation or polymorphism leads to synthesis of defective enzyme or protein, which leads to altered drug metabolism and drug response. There are several genes responsible for differences in drug metabolism among the major genetic polymorphisms and most common are the cytochrome P450 (CYP). They are encoding the cytochrome P450 class of metabolic enzymes found primarily in the human liver. Many of these enzymes play an important role in the metabolism and excretion of clinically prescribed drugs. Approximately 80% of drugs used to treat CVDs are metabolized by the enzymes namely, CYP2D6, CYP2C19, CYP2C9 and CYP3A4/5. Apart from variation in drug metabolizing enzymes, several other target enzymes for the drugs leads to altered response.

Pharmacogenomics

Pharmacogenomics is a more extensive term referring to multiple genes affecting drug response, whereas Pharmacogenetics represents to a more determined single or combination of genes. However, the two terms are arbitrarily used. Cardiovascular pharmacogenetics has largely focused on genetic variants with implications for already existing therapies. The previous research studies found that the significant trends toward revealing genetic determinants of response to a number of cardiovascular agents (Table 1). At present genetic information is rapidly emerging into the cardiovascular research studies focusing on patient individualization.

Table.1 Recent genotype test and their indication in CVDs

BIOMARKERS/ T EST / GENOTYPING	INDICATIONS
Cytochrome P450 2C9 genotype (CYP2C9)	• Affect the metabolism of warfarin in the liver • Increased bleeding risk for patients carrying either the CYP2C9*2 or CYP2C9*3 alleles
Vitamine K epoxide reductase complex genotype (VKORC1)	• Associated with lower dose requirements for warfarin through leading to differential rates of vitamin K recycling
Cytochrome P450 2C19 genotype (CYP2C19)	• Loss-of-function alleles result in diminished conversion of clopidogrel to its active metabolite
Platelet aggregation assay, Paraoxonase I (PONI) genotype	• Use it for aspirin dose, clopidogrel dose, or need for combination antiplatelet therapy
Bradykinin type I (BKI) receptor Haplotype, Angiotensin II (AT-II) type I receptor haplotype	• Have treatment benefit of angiotensin converting enzyme (ACE) inhibitor

Dr. Krishna Kumar D
Professor & Head, Department of Pharmacy Practice

Cardiac Drugs and Nutritional Interaction

Drug-Nutrient Interactions with Commonly Used Cardiac Medications

Drug Class & Common Names	Common Use / Indications	Interaction/Councelling
Beta Blockers (Antihypertensive) Atenolol , Carvedilol , Metoprolol	Decreases heart rate and cardiac output, lowers blood pressure and makes the heart beat more slowly and with less force.	-Decrease sodium and calcium intake. -Avoid natural licorice. -Take beta blockers 2 hours before or 6 hours after intake of antacids or calcium supplement. -Ca salts and orange juice may decrease absorption.
Statins, HMG-CoA Reductase Inhibitors (Antihyperlipidemic) Simvastatin , Rosuvastatin, Atorvastatin	Used to lower LDL cholesterol and triglycerides and raise HDL cholesterol.	-Decrease fat, cholesterol -Avoid alcohol, grapefruit juice and citrus. -Do not take with high doses of niacin. If fiber, pectin and oat bran is taken, give several hours before taking the medication.
Vasodilators, also known as nitrates (Antihypertensive) Isosorbide dinitrate, Nesiritide , Hydralazine, Nitrates & Minoxidil	Used to ease chest pain (angina) by relaxing blood vessels and increasing blood supply to the heart to help decrease its workload.	-Limit alcohol. -Decreased sodium and calcium intake. Avoid natural licorice.
Anticoagulants Warfarin, Enoxaparin Heparin	Also referred to as blood thinners. Helps to prevent blood clotting in blood vessels and may prevent clots from becoming larger in size	-Interacts with vitamin K; -Avoid or limit garlic, ginger, ginkgo, ginseng, saw palmetto, green tea and avocado. -Caution with quinine, papaya and mango. -Caution with alcohol. -Caution with onions.
Antiplatelet Agents Aspirin, Ticlopidine, Clopidogrel, Dipyridamole	Decreases the heart rate and cardiac output, which lowers blood pressure and makes the heart beat more slowly and with less force.	-Avoid alcohol. -Limit ca□eine. -Avoid or limit natural products which a□ects coagulation such as garlic, ginger, ginkgo, ginseng
Agiotensin Converting Enzyme (ACE) Inhibitors (Antihypertensive) Benazepril, Enalapril, Fosinopril, Lisinopril	Used to treat high blood pressure and heart failure by expanding lood vessels and decreases resistance.	-Avoid salt substitutes. Caution with potassium (K) and magnesium (Mg) supplements. Limit alcohol.
Angiotensin II Blockers (or Inhibitors) Irbesartan , Losartan , Telmisartan, Valsartan	Used to treat high blood pressure and heart failure by preventing Angiotensin II from having any e□ect on the heart and blood vessels.	-Caution with potassium (K) supplements and salt substitutes. -Decreased calcium and sodium intake. -Avoid natural licorice. -Losartan only: Caution with grapefruit juice.
Calcium Channel Blockers (Antihypertensive) Amlodipine, Bepridil , Felodipine	Used to treat high blood pressure and chest pain and may relax blood vessels and decrease the heart's pumping strength.	-Avoid natural licorice. Limit ca□eine. -Decrease sodium and calcium intake.
Antiarrhythmic Digoxin (Lanoxin) Amiodarone	Used to help relieve heart failure ymptoms and irregular heartbeats by increasing the force of the heart's contractions.	-Maintain diet with high vitamin K, low sodium and adequate Mg and Ca. Take the medication 2 hours before antacids or Mg supplement. -Caution with some herbal products (aloe, hawthorn & others) and vitamin D &/or calcium supplementation. Avoid natural licorice.
Diuretics (Antihypertensive) Chlorothiazide, Furosemide , Hydro-chlorothiazide	Used to help reduce swelling (edema), caused by excess fluid buildup in the body, through urination of sodium and excess fluids.	-Limit alcohol. -It increases excretion of electrolytes (potassium,magnesium). May need to supplement losses. -Avoid natural licorice. -Caution with calcium &/or vitamin D supplement. -Decreased Na and Ca intake may be recommended.

K.Bharathi Priya
Assistant Professor
Department of Pharmacy Practice

Women And Heart Disease

Heart disease is the number one killer of women and more than 8.6 million women die of cardiovascular disease (CVD) (including heart disease and stroke) around the world each year. This is more than the total number of women who die from all cancers, tuberculosis, HIV/AIDs and malaria combined and represents one-third of all deaths among women.

The risk of dying or becoming seriously unwell due to heart disease and stroke is largely underestimated in women.

Heart attacks claim the lives of 3.3 million women every year, with another 3.2 million women dying from stroke and the remaining 2.1 million women succumbing to rheumatic heart disease, heart failure, hypertensive heart disease, inflammatory heart disease, and other CVD.

Cardiovascular disease: not just a man's disease

CVD does not just affect men, and in some instances its effects can be worse in women.

- Younger women who have a heart attack have higher mortality than men of the same age.
- Women are more likely than men to become disabled by stroke.
- Women with diabetes have higher CVD mortality rates than men with diabetes.
- Women in low- and middle-income countries fare worse than men, experiencing a higher proportion of CVD deaths than men.

Under-recognition of the risk in women and under-treatment

Women do not perceive CVD as the greatest threat to their health.

- Young women still feel more threatened by cancer than they do by CVD.
- Some of the symptoms in women can be different to that in men and as a result they are often under-diagnosed and under-treated when compared to men.

Risk factors in women

Risk factors for heart disease and stroke are largely the same for men and women. Factors such as age and family history play a role, but it is estimated that the majority of CVD deaths are due to modifiable risk factors such as smoking, high cholesterol, unhealthy diet, high blood pressure, obesity, or diabetes.

- Women who smoke double the risk of stroke. The more cigarettes smoked, the higher the risk.
- Exposure to second-hand smoke increases the risk of dying from heart disease by 15 per cent in women.
- Women with high blood pressure have 3.5 times the risk of developing coronary heart disease compared to women with normal blood pressure.

Prevention of cardiovascular disease in women

Women, like men, need to take preventive action to manage their risk factors. This includes monitoring their blood pressure and taking appropriate steps to control high blood pressure; monitoring blood glucose levels; eating healthily; avoiding tobacco; and participating in regular physical activity. Indeed:

- Physical activity can reduce the risk of CVD among women in a dose-response fashion. Inactive women would benefit by even slightly increasing their physical activity – for example by walking one hour per week or possibly less – and would benefit more from additional activity.
- Young women can significantly reduce their risk of developing CVD by consuming more fish; researchers found that the risk of CVD was three times lower in women of child-bearing age who frequently ate fish one or more times per week compared with women who never ate fish.

Go Red for Women campaign

Go Red for Women is an international awareness campaign dedicated to the prevention, diagnosis and control of CVD in women. The American Heart Association created the Go Red for Women campaign in 2004 to empower women with the knowledge and tools to take charge of their heart health. The World Heart Federation, together with more than 40 of its member organizations, has taken the campaign global to bring attention to the fact that CVD is the number one killer of women and the steps that can be taken to prevent it.

Reference: www.worldheart.org/grfw

Lavanya,
Assistant Professor,
Dept. of Pharmacy Practice

ACTIVE PARTICIPATION

Faculty members Dr.M.Sudaroli, Dr.G.Praveen Kumar, S.Lavanya and Pharm.D students participated and presented posters on clinical pharmacy services in the "Indian Congress of Pharmacy Practice 2014 & Inaugural Convention of the Indian Association of Colleges of Pharmacy Advancing Pharmacy Practice in India: The Next Generation Pharmacist held on 21 - 22 Feb 2014" organized by Indian Association of Colleges of Pharmacy at Sheraton hotel, Bangalore.

Students presented posters on following topics:

- SELF MEDICATION PATTERN IN SOCIETY
  – by S.Persis Flora
- PRESCRIBING PATTERNS OF DRUGS IN OUTPATIENT DEPARTMENT OF PAEDIATRICS IN TERTIARY CARE HOSPITAL
  – by Lita Susan Thomas
- A STUDY ON THE CANCER CHEMOTHERAPEUTIC AGENTS AND ASSOCIATED RENAL FAILURE
  – by Aswathy Sathyan

For details and feedback contact:
Department of Pharmacy Practice
C.L. BAID METHA COLLEGE OF PHARMACY
Rajiv Gandhi Salai, Jyothi Nagar, Thorapakkam, Chennai – 600097.
Phone: 044-24960151, 24960425, 24962492 (DIC: Extn-37) Mail: dicclbaid@gmail.com