Review Article [Rajan *et al.*, 5(8): Aug., 2014:3725-3726]
CODEN (USA): IJPLCP ISSN: 0976-7126

INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES
(Int. J. of Pharm. Life Sci.)

Vorapaxar: A new class of drug

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Abstract

Antiplatelet therapy is the major concern in secondary prevention of ischemic cardiovascular complications. But the failure of combined antiplatelet therapy led to the development of new class of antiplatelet drugs. Vorapaxar is a novel, competitive PAR-1 inhibitor. This present review summarizes the pharmacology of vorapaxar.

Key-Words: Anti-platelet, CVD, Vorapaxar

Introduction

Patients with atherothrombosis have a high risk of recurrent ischemic attacks including myocardial infarction (MI), stroke, and cardiovascular death and require a secondary preventive therapy. Even when patients with Peripheral Artery Disease (PAD) do not clinically manifest disease in the coronary or cerebrovascular circulation, subclinical atherosclerosis is often present and puts them at risk for adverse cardiovascular manifestations. [1-2]Since platelets play a major l role in atherothrombosis, hence antiplatelet therapy should be considered as secondary preventive therapy. [1,3]Combination of antiplatelet agents with different mechanism have shown to be beneficial over mono therapy. The dual therapy with aspirin and clopidogrel reduces the incidence of ischemic complications in patients with non-ST Elevate Acute Coronary Syndromes (NSTEACS) by 20% and by 25-30% the frequency of acute ischemic events at 30 days and 12 months post placement of a coronary stent.

Furthermore, it reduces by 20% the risk of mortality, re infarction and recurrent myocardial ischemia in patients with acute myocardial infarction (AMI) treated with thrombolysis, and by 7% the overall mortality of patients with AMI, even in old age. However, the risk of recurrent cardiac events remains high after dual antiplatelet regimen. The failure of antithrombotic therapy have been the subject of intensive investigation in recent years and led to the development of newer class of antiplatelet agents i.e. thrombin receptor antagonists.[1-5]

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Vorapaxar is an antagonist of protease-activated receptor-1 (PAR-1) that blocks thrombin mediated platelet activation.[2] Vorapaxar got approval by US Food and Drug Administration in May 2014 for the treatment of ischemic stroke.[6]The PAR-1 receptor is the target of drug therapy since PAR-1 blockade may produce potent antiplatelet activity without affecting the ability of thrombin to generate fibrin and without inhibiting platelet activation by collagen. Theoretically, this alternate pathway would block platelet activation during clot formation while preserving essential vascular repair and protective haemostatic function.[5] The Preventing Heart Attack and Stroke in Patients with Atherosclerosis trial demonstrated the efficacy and safety of vorapaxar for secondary prevention in patients with atherosclerosis manifest as a prior MI, ischemic stroke, or PAD and revealed an overall 13% reduction in major cardiovascular manifestations with vorapaxar.[2]

Mechanism of action: Vorapaxar is a novel, orally active, non-protein, potentially selective, competitive PAR-1 inhibitor. It is a Thrombin Receptor Antagonist (TRA) that inhibits thrombin receptor-activating peptide (TRAP)–induced platelet aggregation in a dose dependent manner. In preclinical studies, vorapaxar did not affect the platelet aggregation. Although platelet aggregation have a major role in thrombosis, it doesnot affect prothrombin time or activated partial thromboplastin time.[4-5]

Pharmacokinetics

Absorption: Voraparax is completely absorbed, with absolute bioavailability of 100 %. Peak plasma concentration reaches in 1 hour. Concomitant ingestion of vorapaxar with a high-fat meal resulted in no marked change in AUC with a small (21%) decrease in

peak plasma concentration and delayed time to peak concentration (45 minutes).

Distribution: The apparent volume of distribution of vorapaxar is approximately 424 litres. Vorapaxar and its active metabolite are highly protein bound (90%). High affinity towards human serum albumin and distributed less in to red blood cells.

Metabolism: Vorapaxar is metabolized by CYP3A4 and CYP2J2 enzymes. The chief active circulating metabolite is monohydroxy metabolite and the predominant metabolite identified in excreta is amine metabolite.

Excretion: Mainly excreted as metabolite through faeces and partially through urine. Vorapaxar possesses multi-exponential disposition with an effective half-life of 3-4 days and an apparent terminal elimination half-life of 8 days.[4,7]

Indications: Patients with History of Myocardial Infarction (MI) or with PAD. Voraxapar has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization (UCR). However, some clinical studies demonstrate that there were no significant differences in the effect of vorapaxar in reducing MI. [78]

Dosage: It can be given at a dose of 2.08 mg once daily.

Contraindications: Contraindicated in patients those with active peptic ulcer and Intra cranial Haemorrhage.[7]

Drug interactions

Enzyme inhibitors: Concomitant use of vorapaxar with strong inhibitors of CYP3A such as ketoconazole, Itraconazole, posaconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, boceprevir, telaprevir, telithromycin and conivaptan may result in decrease in plasma concentration of vorapaxar. Vorapaxar (2.5 mg/day or 40 mg) has no marked effect on the pharmacokinetics or pharmacodynamics of warfarin, recommending that the co-administration of vorapaxar with other CYP2C9/ CYP2C19 substrates is unlikely to cause a clinically significant pharmacokinetic drug interaction.[4,7]

Adverse drug reactions: In general voraparax is well tolerated. In dose ranging studies mild to moderate adverse events were reported they include headache, upper respiratory infection, and fatigue, none of which were dose-related. [5]

Use in special poulation

Pregnancy: There is inadequate data on its safety use in pregnant.

Paediatrics: There is limited data on its safety and efficacy in paediatrics.

Renal and Hepatic impairment: Dosage adjustment is not necessary in both renal and hepatic impaired patients.[7]

Conclusion

Although vorapaxar got approval by FDA for the atherothrombotic disorders, its safety and efficacy profile was still unclear, hence its antithrombotic effectiveness and side effects in association with other antiplatelet agents remain major concerns.

References

1. Raewyn M.P. and Shelley E. (2014).Vorapaxar: First Global Approval, Drugs, 74: (10): 1153-1163.
2. Marc P.B., Benjamin M.S., Mark A.C., Jeffrey O., Henri B., Mikael D., et al. (2013).Vorapaxar in Patients With Peripheral Artery Disease: Results From TRA2°P-TIMI 50, Circulation,127: 1522-1529.
3. David A.M., Eugene B., Marc P.B., Sebastian F.A., Anthony J.D., Mary P.F., et al. (2012).Vorapaxar in the Secondary Prevention of Atherothrombotic Events, N Engl J Med, 366:1404-13.
4. Gianluca A. andMauro C. (2013).Vorapaxar, Italian Journal of Medicine, volume 7:88-95.
5. Younos A., Theologia T. and Danielle G. (2011).Vorapaxar: Targeting a Novel Antiplatelet Pathway, Drug Forecast, 36: (9): 564-568.
6. http://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/default.htm
7. http://www.merck.com/product/usa/pi_circulars/z/zontivity/zontivity_pi.pdf
8. David A.M., Mark J.A., Jay P.M., Sebastian F.A., Marc P.B., Shinya G., Graeme J.H. et al. (2013)Efficacy and Safety of Vorapaxar in Patients With Prior Ischemic Stroke, Stroke, 44: 691-698.

How to cite this article

Rajan K.R.N., Sreenivas P.S., Devi P.S.S.D., Vineela P., Kalluri S. and Raj P.S. (2014). Vorapaxar: A new class of drug. *Int. J. Pharm. Life Sci.*, 5(8):3725-3726.

Source of Support: Nil; Conflict of Interest: None declared

Received: 27.07.14; Revised: 03.08.14; Accepted:10.08.14