Vorapaxar: The missing link in antiplatelet therapy!

Sir,

Patients with atherosclerotic disease (coronary, cerebrovascular, and peripheral vascular) are prescribed with dual antiplatelets (DAPs) along with statins. DAP constitutes aspirin along with thienopyridine derivative (clopidogrel, prasugrel, and ticagrelor). Aspirin inhibits cyclooxygenase-I irreversibly that prevents generation of thromboxane A2 by platelets leading to antithrombotic effect. Thienopyridines inhibit P2Y12 receptors irreversibly that prevent adenosine diphosphate-induced platelet aggregation, thus preventing thrombosis.

In spite of regular use of DAP by patients, recurrent cardiovascular events still occur. Researchers realized that there is some other mechanism leading to thrombosis which is not addressed by conventional DAP. This led to the development of agents that act at the thrombin-mediated pathway.[1]

Vorapaxar belongs to protease-activated receptor-1 (PAR-1) inhibitor group. It is the first PAR-1 inhibitor approved by the United States Food and Drug Administration in coronary and peripheral vascular disease in May 2014. It was approved after the results of thrombin receptor antagonist in secondary prevention of atherothrombotic ischemic events-thrombolysis in myocardial infarction 50 trial were released.[2] The results revealed that vorapaxar reduced the rate of the combined endpoint of cardiovascular death, myocardial infarction, stroke, and urgent coronary revascularization when used along with aspirin and/or clopidogrel in patients without previous history of stroke. However, patients with history of stroke suffered with intracranial hemorrhage 2 years after starting vorapaxar. Therefore, the drug is not recommended in patients with history of stroke, transient ischemic attack, or a previous intracranial hemorrhage.[3]

PAR receptors are a super-family of G-protein-coupled receptors which are expressed throughout the body and are involved in platelet activation along with thromboxane A2 and P2Y12 through a different pathway. PAR receptors have a significant contribution to the pro-inflammatory response occurring due to atherosclerosis and thrombotic events. Vorapaxar is a competitive, reversible antagonist of PAR-1 receptor that acts by blocking thrombin-induced platelet activation. Vorapaxar binds to PAR-1 reversibly, but due to a long half-life (terminal half-life of approximately days), the final effect is irreversible.[4]

Vorapaxar is completely absorbed when consumed orally and attains a peak plasma concentration within 1–2 h. Oral bioavailability is not affected when consumed with food. The mean

volume of distribution of vorapaxar is around 424 L. Vorapaxar is primarily metabolized to an inactive metabolite (M19) and an equally potent active metabolite M20 by CYP3A4 and CYP2J2. Vorapaxar and M20 are extensively bound to albumin. The metabolites are eventually eliminated by kidneys.[5]

The recommended dose of vorapaxar for secondary prevention is 2.5 mg once daily.

There is no antidote available at present for Vorapaxar-induced bleeding. At present, there are no recommendations which mentions for how long vorapaxar needs to be stopped for performing central neuraxial blockade required for a noncardiac surgery safely.

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Conflicts of interest
There are no conflicts of interest.

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