Ximelagatran: An oral direct thrombin inhibitor

Anticoagulants have been in use for more than 50 years for the prevention and treatment of thromboembolic disorders. Vitamin K antagonists such as warfarin are widely used for the prevention of arterial and venous thromboembolism in patients with atrial fibrillation, coronary artery disease and following some orthopedic procedures. The drawbacks of using warfarin are the slow onset and offset of its antithrombotic action, an unpredictable and variable pharmacological response, a narrow margin of safety and numerous food and drug interactions. The need for intensive laboratory monitoring to control its anticoagulant effects and the risk of bleeding has reduced the compliance of the patients. So there is a need for well-tolerated, convenient, and effective alternatives to oral warfarin to improve the management of patients requiring anticoagulation therapy.

Ximelagatran is an orally active direct thrombin inhibitor. After absorption, ximelagatran is rapidly converted into its active form melagatran, a potent inhibitor of thrombin that prevents both thrombin activity and generation. Melagatran has a very poor oral absorption due to the presence of a carboxylic acid, a secondary amine and an amide residue resulting in a charged molecule at physiological pH. Concomitant food intake further reduces its bioavailability. So, ximelagatran, a prodrug of melagatran was developed which has better oral absorption due to better lipophilicity and uncharged nature at intestinal pH.

Pharmacokinetics

Ximelagatran, after oral ingestion is absorbed from the small intestine and undergoes rapid biotransformation, via two intermediates, ethyl melagatran and hydroxy melagatran, to melagatran. About 20% of an oral dose is absorbed. The maximum plasma concentration of melagatran is achieved 2-3 h after the oral administration with a plasma half-life of 4-5 h. The drug is excreted entirely by the kidney with a mean elimination half-life of 3 h. Studies have shown that body weight, sex and ethnicity do not affect the pharmacokinetic profile of ximelagatran. There is no dose adjustment required in patients with mild to moderate hepatic impairment. But dose reduction or prolongation of dose interval is necessary in patients with renal disease.

Pharmacodynamics

Thrombin is a serine protease involved in the formation of a stable insoluble clot. It is also involved in the activation of platelets and factors V and VIII. Ximelagatran is a potent, rapidly binding, competitive and reversible direct inhibitor of thrombin. It causes inhibition of thrombin activity, thrombin generation, platelet activation and thrombus formation. It acts on both soluble and clot-bound thrombin resulting in the prolongation of prothrombin time, partial thromboplastin time and thrombin time. It does not inhibit other serine proteases except trypsin.

Adverse effects

Hepatotoxicity is a major side effect noticed in patients taking ximelagatran. An elevation in alanine transferase values was observed within 6 weeks to 6 months of treatment with ximelagatran. In most of the cases, it was asymptomatic and reversible even on continuation of ximelagatran. But this warrants monitoring of liver function tests at least once a month.

Interactions

The metabolism of ximelagatran is independent of the hepatic P450 system, and has no affinity to bind to plasma proteins or platelets. Hence a lower propensity to cause drug interactions. Food-drug interactions have not been reported either.

Uses

- Treatment and prevention of venous thromboembolism – 24 mg b.d.
- Prevention of stroke in atrial fibrillation - 36 mg b.d.

Advantages

- Administered orally at fixed doses without coagulation monitoring.
- Offers more predictable anticoagulant response as it is not protein cofactor-dependent.
- Wider therapeutic index.
- Anticoagulant action develops immediately.
- No inter-subject variability.
- No drug-drug and drug-food interactions.

Disadvantages

- Hepatotoxicity.
- No antidote available (but dialysis can help in reversal)

Clinical trials

An open-label SPORTIF III treatment trial found ximelagatran to be as effective as warfarin for stroke prevention in non-valvular atrial fibrillation. The results of SPORTIF V study showed the efficacy of fixed dose oral ximelagatran with well controlled warfarin for prevention of thromboembolism in patients with atrial fibrillation requiring chronic anticoagulant therapy. THRIVE treatment study indicated that ximelagatran was as effective as enoxaparin/warfarin for the treatment of deep vein thrombosis with similar or low rates of bleeding.

In Europe, ximelagatran has been recently approved for short-term use and results of post-marketing surveillance are awaited in the near future. US FDA has not yet approved
ximelagatran for concerns about hepatotoxicity.[14]

Conclusion

The novel oral anticoagulant ximelagatran has a favorable pharmacokinetic and dynamic profile as compared to warfarin. It has the potential to initiate the beginning of the end of warfarin. But the propensity to cause hepatotoxicity and the non-availability of an antidote causes concern. So the therapeutic benefits should be weighed against the risks before prescribing it to patients.

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References


Ghrelin: A potential drug target for obesity

The suffix “ghre” means “to grow”. Ghrelin (pronounced GREL-in) was discovered in 1999 as a peptide hormone that potently stimulates the release of growth hormone from the anterior pituitary. It was subsequently determined that ghrelin, along with several other hormones, has significant effects on appetite and energy balance.

Synthesis and receptor

Ghrelin is synthesized as a pre-prohormone, and then proteolytically processed to yield a 28-amino acid peptide. A modification necessary for biological activity is the binding of n-octanoic acid to one of its amino acids, carried out during its synthesis. Synthesis of ghrelin occurs predominantly in the epithelial cells lining the fundus of the stomach, with smaller amounts produced in the placenta, kidney, pituitary and hypothalamus.

The ghrelin receptor was known well before ghrelin was discovered. Cells within the anterior pituitary have a receptor that, when activated, potently stimulates the secretion of the growth hormone. The receptor was named the growth hormone secretagogue receptor (GHS-R). The natural ligand for the GHS-R is ghrelin. The receptors are present on the cells in the pituitary that secrete the growth hormone and also have been identified in the hypothalamus, heart and adipose tissue.[11]

Control and physiological effects of ghrelin

At least two major biological activities have been ascribed to ghrelin

1. Stimulation of growth hormone secretion: Ghrelin, as the ligand for the growth hormone secretagogue receptor, potently stimulates the secretion of the growth hormone. The ghrelin signal is integrated with that of the growth hormone-releasing hormone and somatostatin to control the timing and magnitude of growth hormone secretion.[21]

2. Regulation of energy balance: In rodents and humans, ghrelin functions to increase hunger through its action on the hypothalamic feeding centers. The plasma ghrelin concentrations increase during fasting.[3] Humans injected with ghrelin reported sensations of intense hunger.[11] Ghrelin also appears to suppress fat utilization in the adipose tissue, which is somewhat paradoxical considering that the growth hormone has the opposite effect. Overall, ghrelin seems to be one of