Direct thrombin inhibitor

Direct thrombin inhibitors (DTIs) are a class of medication that act as anticoagulants (delaying blood clotting) by directly inhibiting the enzyme thrombin (factor II). Some are in clinical use, while others are undergoing clinical development. Several members of the class are expected to replace heparin (and derivatives) and warfarin in various clinical scenarios.

Dabigatran, and the activated factor X inhibitors, Rivaroxaban and Apixaban, are rapidly gaining clinical popularity in North America and Europe following a number of seminal randomised control trials comparing their efficacy to Warfarin and Enoxaparin.

Oral anticoagulation are commonly used in the ageing population and therefore, spine surgeons are increasingly confronted with anticoagulated patients requiring surgical therapy.

In the coming years these agents are set to replace Warfarin use for the primary prevention of stroke in non-valvular atrial fibrillation, post-operative thromboprophylaxis and the treatment of deep vein thrombosis. The main trials have shown superior anti-coagulant effects over warfarin and low-molecular-weight heparin with the added benefits of lower bleeding complications (including intracranial haemorrhages) and no requirement for monitoring. Case reports are now appearing in the literature, highlighting some of the complications of their use, namely the lack of a uniform normalised anticoagulation test and the paucity in clinical experience with reversing the anticoagulant effects when emergent surgery is mandated.

Hospital clinicians will need to understand the pharmacokinetics of drug administration, the laboratory tests to measure the level of anticoagulation and the treatment of patients who are therapeutically anticoagulated and require urgent surgical intervention [1)].

Types

There are three types of DTIs, dependent on their interaction with the thrombin molecule. Bivalent DTIs (hirudin and analogs) bind both to the active site and exosite 1, while univalent DTIs bind only to the active site.

The third class of inhibitors which are gaining importance recently is the allosteric inhibitors.

Hirudin and derivatives were originally discovered in Hirudo medicinalis:

Hirudin

Bivalirudin (transient inhibition - is cleaved by thrombin)

Lepirudin

Desirudin

Univalent DTIs include:

Argatroban

Melagatran (and its prodrug ximelagatran)

Dabigatran

Thrombin demonstrates a high level of allosteric regulation.

Allosterism in thrombin is regulated by the exosites 1 and 2 and the sodium binding site. A recent patent review has shown that the general consensus among researchers is that allosteric inhibitors may provide a more regulatable anticoagulant.

Some of the allosteric inhibitors discovered include DNA aptamers, benzofuran dimers, benzofuran trimers,as well as polymeric lignins.[6] A new sulfated β-O4 lignin (SbO4L) has been discovered which has shown a dual mechanism of action for anti-thrombosis. This SbO4L shows allosteric inhibition of thrombin for fibrinogen, while providing a competitive inhibition of thrombin interaction with platelet glycoprotein Ibα (GPIbα), thereby preventing thrombin mediated platelet aggregation.

However, despite the growing interest and the advances in allosterism, no allosteric thrombin inhibitor has still reached the stage of clinical trials.

Bivalent DTIs enjoy limited use in circumstances where heparin would be indicated such as the acute coronary syndrome (“unstable angina”), but cannot be used. As they are administered by injection (intravenous, intramuscular or subcutaneous), they are less suitable for long-term treatment.

Argatroban (as well as the hirudins) is used for heparin-induced thrombocytopenia, a relatively infrequent yet serious complication of heparin treatment that requires anticoagulation (as it increases both arterial and venous thrombosis risk) but not with the putative agent, heparin.

Ximelagatran showed good efficacy compared with warfarin in several trials in prevention and treatment of deep vein thrombosis and as thromboprophylaxis in atrial fibrillation.

Development was stopped by manufacturer AstraZeneca, however, because of reports of liver enzyme derangements and liver failure.

Recent studies have indicated Dabigatran is slightly more effective for stroke thromboprophylaxis in the setting of atrial fibrillation than coumadin.

There is no therapeutic drug monitoring widely available for DTIs, in contrast with warfarin (INR) and heparin (APTT). The ecarin clotting time, although not in general clinical use, would be the most appropriate monitoring test.

1)
Vakharia VN, Tai D, Marcus H, Vakharia NN, Nandi D. New oral anti-coagulants: Implications for neurosurgery. Br J Neurosurg. 2015 Jan 29:1-7. [Epub ahead of print] PubMed PMID: 25633803.