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Review Article

A REVIEW ON SAFETY AND EFFICACY OF DIRECT THROMBIN INHIBITORS

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ABSTRACT

Direct thrombin inhibitors (DTIs) are a new class of anticoagulants used over other anticoagulants like GP IIa/IIb inhibitors, heparin, warfarin and low molecular weight heparins. The active molecule of direct thrombin inhibitors are derived from the salivary enzymes of a medicinal leech namely *HIRUDO MEDICINALIS*. DTIs have many clinical uses like prevention of coagulation in atrial fibrillation, orthopedic hip replacement surgery, unstable angina, coronary angioplasty, ST-segment elevated myocardial infarction, heparin-induced thrombocytopenia and venous thromboembolism etc., DTIs act by directly inhibiting both free and fibrin-bound thrombin. The present review describes all biochemistry, pharmacokinetic and pharmacodynamic data of various DTIs like bivalirudin, hirudin, lepirudin, argatroban, ximelagtran/melagatran, desirudin with their indications and side effects and comparative study results between the class of drugs and other class of anticoagulants like warfarin, heparin.

Key Words: Direct Thrombin Inhibitors(DTIs), Venous Thromboembolism, Heparin-Induced Thrombocytopenia(HIT), *Hirudo medicinalis*.

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INTRODUCTION

Prothrombin is the precursor of thrombin, which is one of the several coagulation factors containing proteins like γ-carboxyglutamic acid. Thrombin (factor lla) has an important role in thrombosis and haemostasis with its anticoagulant and procoagulant functions. Thrombin converts soluble fibrinogen into insoluble fibrin in blood coagulation. Its activity is regulated by serum inhibitors and by its own. It also stimulates platelet activation (Catherine J. Lee MD, 2011). Thrombin in addition to the above have many biological functions as shown in figure 1., like vasoactive compound, potent mutagen, thrombin mediated secretion of growth factors, chemoattractant, induction of contraction of smooth muscles by increasing the permeability of vascular endothelium (Kenneth G. Mann, PhD, 2003), thus promoting adhesion of endothelial cells, and plays a key role in angiogenesis, bone absorption and muscle development (Chinni C *et al*., 1999).

Direct thrombin inhibitors (DTIs) are the active drug molecules that inhibit the activity of thrombin. DTIs directly bind to both soluble thrombin and fibrin bound thrombin without any cofactors such as antithrombin (Bates SM, Weitz JI, 2008). The main advantage of direct thrombin inhibitors beyond heparin is that they donot cause immune mediated

thrombocytopenia, as they do not bind to other plasma proteins (Alban S., 2008).

Direct thrombin inhibitors are classified into two classes i.e., univalent and bivalent. Univalent drugs include argatroban, inogatran, melanogatran/ ximelagatran, dabigatran. Whereas, hirudins, bivalirudin, lepirudin, desirudin are the bivalent direct thrombin inhibitors. Both oral and parenteral forms of DTIs have in developed and used for both prophylaxis and therapy of an disease in many subjects with various conditions like venous thromboembolism, heparin- induced thrombocytopenia (HIT), acute coronary syndrome, atrial fibrillation (Marcello Di Nisio, M.D, 2005). Parenteral direct thrombin inhibitors include hirudin, lepirdin, bivalirudin, argatroban and desirudin. Whereas, ximelogatran is the first DTIs available as oral formulation (Anonymous 1, 2012).

***Hirudin*:**

Hirudin is a recombinant anticoagulant clinically available for various uses, with an renal elimination of about 60 minutes *Hirudo medicinalis* is the medicinal leech which contains a substance with anticoagulant properties, which is extracted by aqueous and dry preparation from the homogenized heads of medicinal leeches (Walsmann P, Kaiser B., 1989) by gel filtration and ion exchange chromatography techniques. However, there is no antidote available for hirudin toxicity (Koster A *et al*., 1998). Lepirudin and desirudin are the two forms of recombinant hirudins surviving in market.

***Lepirudin*:**

Lepirudin is a recombinant hirudin derived from transfected yeast cells by recombinant technology. It comprises of 65 amino acids, contains leucine instead of isoleucine (Petros S *et al*., 2006), tyrosine residue at position 63(termed as desulfatohirudin). It is well absorbed through the extracellular spaces after intravenous infusion, and does not cross blood brain barrier (Roberts HR *et al*., 2006). It is also assumed lepirudin to have procoagulant activity, but, no evidences exist.

***Desirudin*:**

Desirudin is a subcutaneous thrombin inhibitor. Which is an recombinant hirudin indicated for the use of thrombosis prophylaxis of orthopedic hip replacement surgery(Eriksson BI *et al*., 1997).

***Bivalirudin*:**

Bivalirudin is the most widely used and assumed to be safe among all the direct thrombin inhibitors due to its high affinity to thrombin, which is a semi-synthetic derivative of hirudin. Indicated in coronary angioplasty, unstable angina and myocardial infarction (Lidón R-M *et al*., 1993).

Argatrobatran:

Argatroban is a univalent small- molecule direct thrombin inhibitor, structurally which contains arginine residue. It is highly selective and reversible in its mechanism of binding. It is highly selective for thrombin and has a little or no effect on trypsin, factor Xa, kallilrein and plasmin. These characteristics make argatroban more preferable to hirudin and heparin (Berry CN *et al*., 1994).

***Ximelagatran / Melagatran*:**

Melagatran is the active metabolite, whereas, ximelagatran is the oral prodrug of melagatran, which is a direct thrombin inhibitor (Lenka Hrebickova *et al*., 2003). Ximelagatran rapidly converts to melagatran on oral administration. Ximelagatran widely recommended to warfarin in myocardial infarction and other cardiac diseases like atrial fibrillation due to its minimal drug-drug interactions and unobserved drug-food interactions (Johansson LC *et al*., 2003).

***Mechanism of Action of Direct Thrombin Inhibitors*:**

Direct thrombin inhibitors act by blocking the interaction of thrombin with its substrate. DTIs directly block the thrombin unlike indirect thrombin inhibitors which require an antithrombin mediation for blocking the thrombin activity.

Damage to the blood vessel results in the exposure of tissue factor on the surface of the damaged endothelium. On exposure of the tissue factor to coagulation factor VII, it activates the coagulation cascade producing thrombin which is the central factor of coagulation cascade which further activates other coagulation factors namely factors V, VII, XI and XIII. Thus, thrombin stabilizes the clots by favoring the formation of cross linked bonds among the fibrin molecules (Bates SM, Weitz JI., 2000), it is better explained in figure 8.

Pharmacokinetics of Direct Thrombin Inhibitors:

Lepirudin and desirudin are the derivatives of hirudin which act by direct thrombin inhibition. Both the drugs are metabolized in the liver having varying rates of real elimination. Dabigatran which is found to have less absorption, it is available in its prodrug form namely dabigatran etixelate to merely increase the bioavailability. Ximelagatran is the prodrug of melagatran (Rosenberg RD *et al*., 1996).

Dabigatran is the long acting DTI with its highest half-life of about 7-17hrs. whereas, bivalirudin is the short acting DTI with its lowest half life of about 10-

25mints. Desirudin irreversibly binds to the free and plasma bound thrombin unlike other drugs which reversibly bind to the thrombin. The mere drawback of direct thrombin inhibitors is that, there is no antidote available for over dose of DTIs (Gustafsson D *et al*., 2001) (Eriksson UG *et al*., 1998).

Indications/uses of direct thrombin inhibitors:

Direct thrombin inhibitors have many clinically proven indications which include coronary angioplasty, ST-segment elevated myocardial infarction, unstable angina, heparin-induced thrombocytopenia, acute coronary syndrome, atrial fibrillation, prevention of venous thromboembolism (Schulman S *et al*., 2003) (Geerts WH *et al*., 2004) orthopedic hip surgery.

Both hirudin and bivalirudin are found to be safe and effective in treating coronary angiography in comparison with other indirect thrombin inhibitors like heparin and warfarin (Zoldhelyi P *et al*., 1993). Bivalirudin with its minimal drug- food and drug-drug interactions is mostly widely used in treatment of various conditions like unstable angina, coronary angioplasty, heparin induced thrombocytopenia, venous thromboembolism, however, the major drawback of bivalirudin is its short acting nature, which makes other drugs like hirudin or dabigatran as drug of choice (Jeffrey Lefkovits, MBBS; Eric J. Topol, MD., 1994).

Melagatran an active metabolite of ximelagatran is indicative in ST-elevated myocardial infarction as it donot have an increased risk of bleeding in subjects with use of higher doses (Lars Wallentin *et al*., 2003). It is mainly used as a secondary prophylaxis after myocardial infarction. In addition ximelagatran does not require any coagulation monitoring in long term use as in warfarin. Thus, ximelagatran is used to prevent thromboembolism in patients with atrial fibrillation(Jonathan L. Halperin, 2005).

Desirudin which is a derivative of hirudin is effective for prophylaxis of orthopedic hip replacement therapy to prevent thromboembolism. Dabigatran is the another DTI used for long term prevention of venous thromboembolism over warfarin with a minimal side effects like stomach upset(Eriksson BI *et al*., 1996).

Argatroban is used in preventing coagulation during haemodialysis in patients with antithrombin III deficient. As in these subjects heparin and other indirect thrombin inhibitors cannot be used as antithrombin in the binding of these drugs. Thus, argatroban is the drug of choice (Kazuo Ota *et al*., 2003) (Vance G. Nielsen *et al*., 2006).

***Side Effects of* DTIs:**

DTIs do also possess some side effects, however no lethal side effects or adverse have not been yet reported by FDA. Some of the side effects of DTIs are hypotension, fever with argatroban, hypotension (Bengt I. Eriksson *et al*., 2009), backpain and insomnia with bivalirudin., as by class they are anticoagulants in subjects bleeding has been observed, but, clear evidence does not exist.

Figure 1. Various biological functions of thrombin

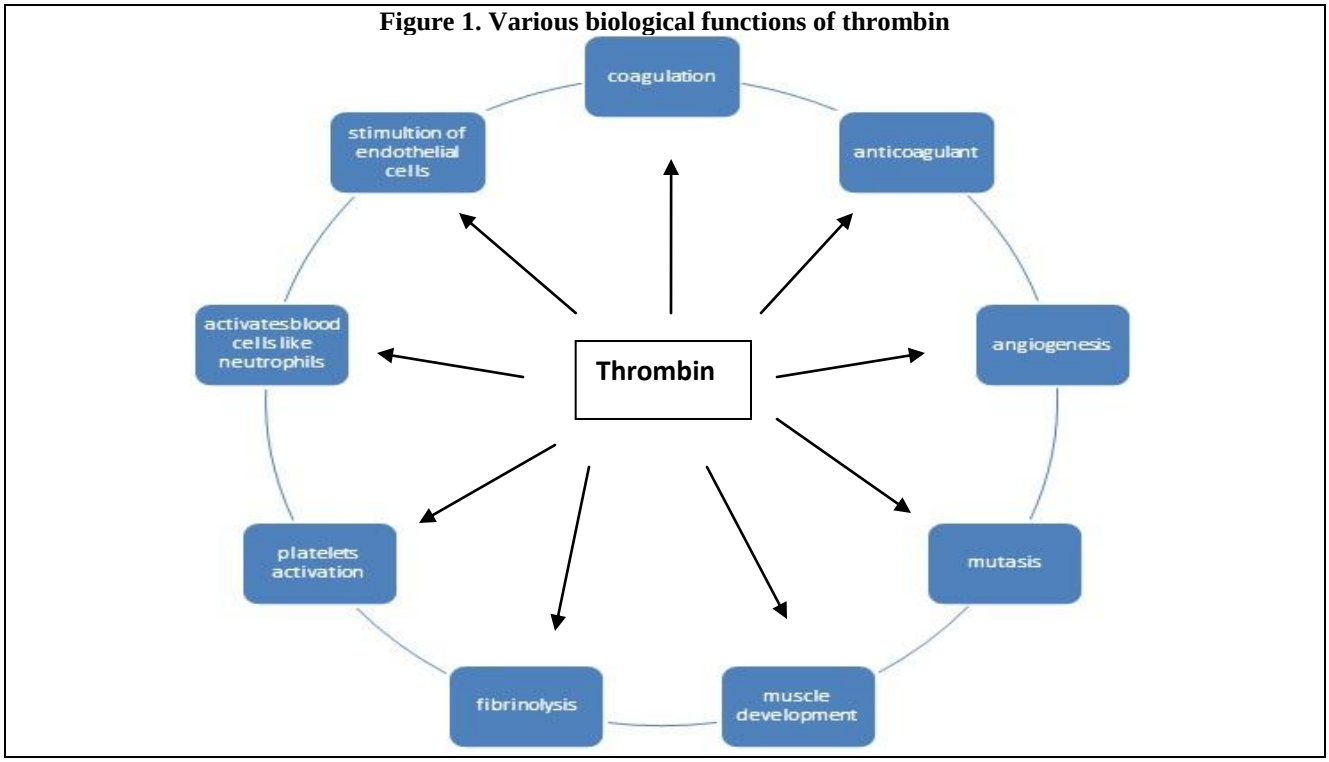

Figure 2. Chemical structure of hirudin

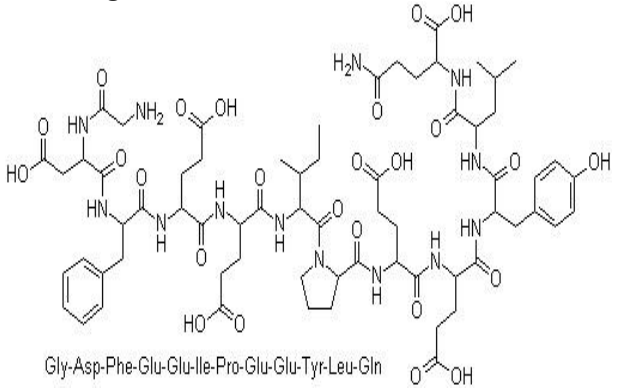

Figure 3. Chemical structure of lepirudin

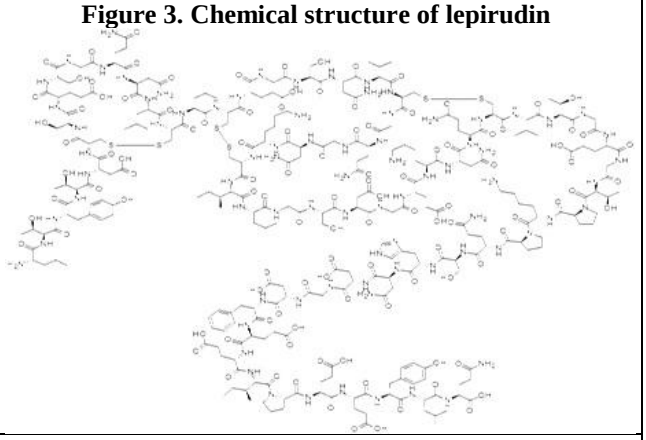

Figure 4. Chemical structure of desirudin

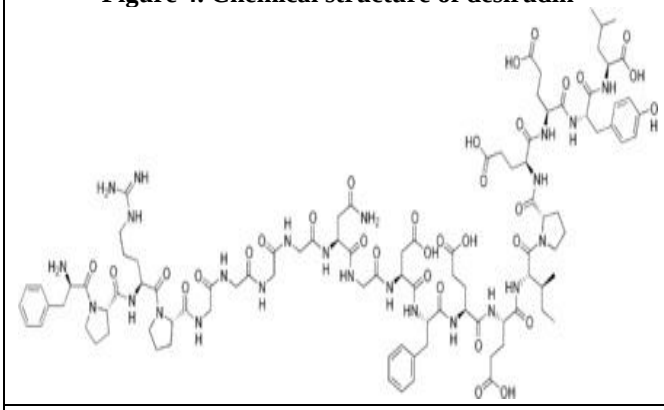

Figure 5. Chemical structure of bivalirudin

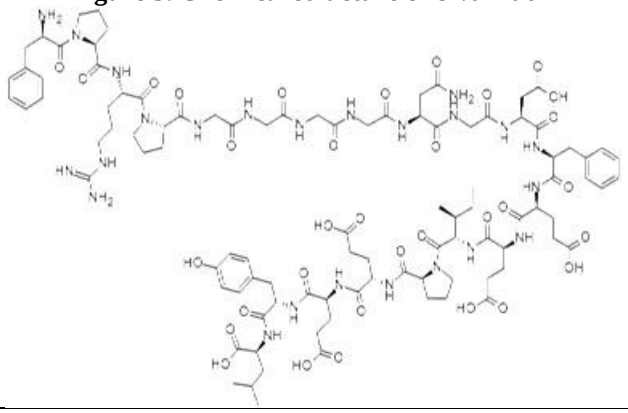

Figure 6. Chemical structure of argatroban

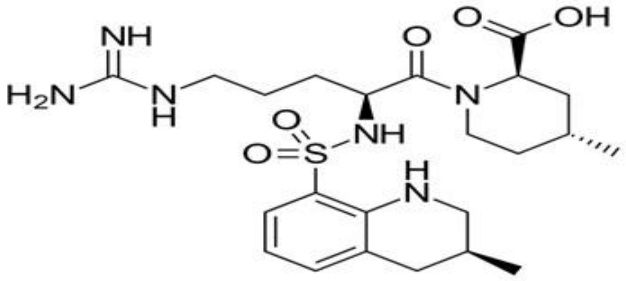

Figure 7. Chemical structure of ximelagatran.

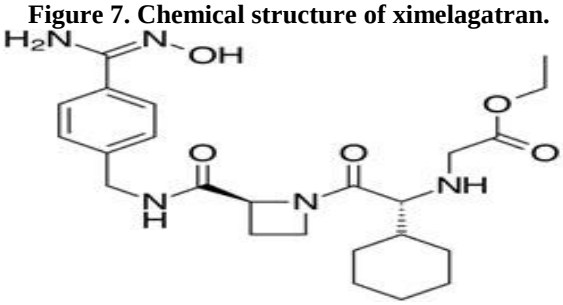

Figure 8. Mechanism of action of direct thrombin inhibitors

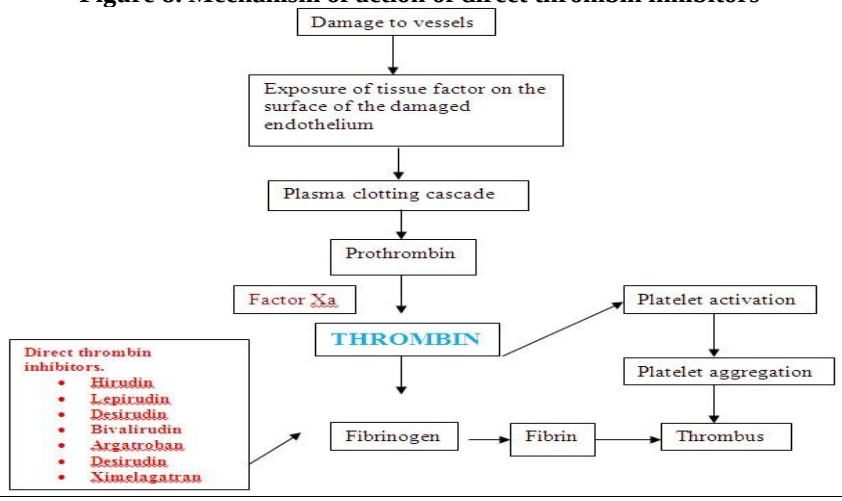

Table 1. Pharmacokinetics of direct thrombin inhibitors

Direct thrombin inhibitors	Source	Mechanism of action	Route	Half – life($T_{1/2}$)	metabolism	Elimination	Antidote
Argatroban	Synthetic hirudin	Reversible Direct thrombin inhibition	IV	40-50min	liver	Hepatobiliary	None
Bivalirudin	Semi-synthetic	Reversible DTI inhibiting circulating and clot bound thrombin	IV	10-25min	Renal and proteolytic cleavage	Enzymatic(liver, kidney and other sites)	None
Desirudin	Synthetic	Irreversible DTI binding to circulating and clot bound thrombin	IV	120-180min	liver	Renal (40%), 50% unchanged	None
Dabigatran	synthetic	Direct thrombin inhibition	IV,PO	7-17hrs	Liver	Renal (80-85%)	None
Ximelagatran/melagatran	synthetic	Direct thrombin inhibition	PO	2.6-4.8hrs	Liver	Renal	None
lepirudin	Hirudin derivative	Direct thrombin inhibition	IV	10min	Liver	Renal (48%), 35% unchanged	None

COMMENTS:

***Bivalirudin vs heparin*:**

In an comparative studies between bivallirudin and hirudin in patients with coronary angioplasty and myocardial infarction, it was proven that bivalirudin reduces the risk of bleeding even in long term use compared to heparin, however the incidence of myocardial infarction was same in both the cases(Ramin Ebrahimi *et al*, 2005).

***Dabigatran vs warfarin*:**

Anticoagulants have their indication in cardiac disorders in which most of the cases are emergency. Hence, as warfarin and other GP IIa/IIb anticoagulants do not show immediate action, dabigatran is the drug of choice ver warfarin in cardiac patient, even safe in chronic use. These factors make dabigatran more preferable over warfarin and heparin (Rangadham Nagarakanti *et al*., 2011).

***Bivalirudin vs argatroban*:**

In a study conducting in patients with heparin-induced thromb ocytopenia, both bivalirudin and argatroban were found to be similarly effective. Thus, both bivalirudin and argatroban can be used as an alternative to each other in unavailability of other (Lee P. Skrupky *et al*., 2010).

CONCLUSION

From all the studies and pharmacokinetic and pharmacodynamic data of direct thrombin inhibitors (DTIs), it is clear that the efficacy of indirect thrombin inhibitors and direct thrombin inhibitors are similar with many drugs. But, the time of onset of action and selective both reversible and irreversible inhibition of DTIs with their lower side effects and drug-drug interactions and drug-food interaction make them more preferable over other classes of anticoagulants. DTIs are more preferable in case of long term use and emergency anticoagulant effects in cardiac patient's due to their faster onset of action(dabigatran). An orally available anticoagulant like ximelagatran is also available however, a predictable hepatotoxicity exist with minimal evidences.

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