Eastern Journal of Medicine 14 (2009) 84-93

Review Article

An update on new anticoagulant drugs

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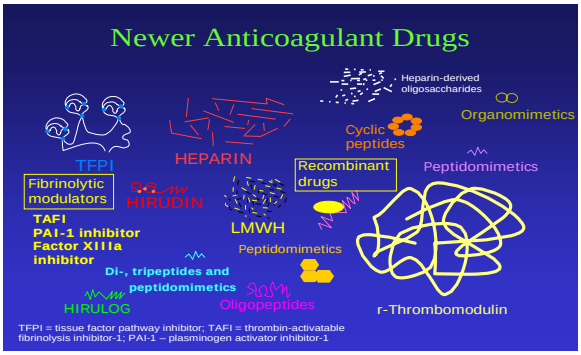
Abstract. The conventional management of thrombotic and cardiovascular disorders is based on the use of heparin, oral anticoagulants and aspirin. Despite remarkable progress in life sciences, these drugs still remain a challenge and mystery to us, and their use is far from optimized. The development of low molecular weight heparins and the synthesis of heparinomimetics, such as the chemically synthesized pentasaccharide, represent a refined use of heparin. Additional drugs from this knowledge will continue to develop; however, none of these drugs will match the polypharmacology of heparin. Aspirin still remains the leading drug in the management of thrombotic and cardiovascular disorders. The newer antiplatelet drugs such as ADP receptor inhibitors, GPIIb/IIIa inhibitors and other specific inhibitors have limited effects and have been tested in patients who have already been treated with aspirin. Warfarin provides a convenient and affordable approach in the long-term outpatient management of thrombotic disorders. The optimized use of these drugs still remains to be the approach of choice to manage thrombotic disorders. The new anticoagulant targets, including specific sites in the hemostatic network such as tissue factor, individual clotting factors (IIa, VIIa, IXa, Xa, XIIa and XIIIa), recombinant forms of serpins (antithrombin, heparin co-factor II and tissue factor pathway inhibitors), recombinant activated protein C, thrombomodulin and site specific serine proteases inhibitors complexes have also been developed. There is a major thrust on the development of orally bioavailable anticoagulant drugs (anti-Xa and IIa agents), which are slated to replace oral anticoagulants. Both the anti-factor Xa (Rivaroxaban and Apixaban) antithrombin (Dabigatran) agents have been developed for oral use and have provided impressive clinical outcomes in sponsor trials for the post surgical prophylaxis of venous thrombosis; however, safety concerns related to liver enzyme elevations and thrombosis rebound have been reported with their use. For these reasons the US FDA did not approve the orally active antithrombin agent Ximelagatran for several indications. More recently the Columbian health authorities reject dabigatran for similar reasons. The synthetic pentasaccharide (Fondaparinux) has undergone an aggressive clinical development. Unexpectedly, Fondaparinux also produced major bleeding problems at minimal dosages. Fondaparinux represents only one of the multiple pharmacologic effects of heparins. Thus, its therapeutic index will be proportionately narrower. The methylated pentasaccharide, namely Idraparinux, is effective for long term prophylaxis, but its use is associated with bleeding. Other forms of pentasaccharide such as the biotinylated form which can be reversed with fucoidin are also developed. The newer antiplatelet drugs have added a new dimension in the management of thrombotic disorders. The favorable clinical outcomes with aspirin and Clopidogrel have validated COX-1 and $P2Y_{12}$ receptors as targets for new drug development. Prasugrel, a novel thienopyridine, Cangrelor and AZD 6140 represent newer $P2Y_{12}$ antagonists. Cangrelor and AZD 6140 are direct inhibitors, whereas Prasugrel requires metabolic activation. While clinically effective, recent results have prompted a closure of a large clinical trial with Prasugrel due to bleeding. The newer anticoagulant and antiplatelet drugs are attractive for several reasons; however, none of these are expected to replace the conventional drugs in poly-therapeutic approaches. Heparins, warfarin and aspirin will continue to play a major role in the management of thrombotic and cardiovascular disorders beyond 2010.

Key word: New anticoagulant drugi

1. Introduction

Over the past twenty five years interest in anticoagulant drugs has grown dramatically as evidenced by a continual increase in the number of drugs introduced for both pre-clinical and clinical development (1-6). Technologic advances have contributed to the development of rationale design of anticoagulant drugs with specific targets. As shown in Figure 1, the newer anticoagulants represent a diversed variety of agents with structural and functional heterogeneity. Many new drugs such as new heparin derivatives such as the low molecular weight heparins (LMWHs), synthetic heparinomimetic agents such as the heparin pentasaccharide (Arixtra), antithrombin agents, anti-factor-Xa agents, and biotechnology derived antithrombotic proteins, such as the antithrombin III and activated protein C have been described. The scientific research and development activities in academic centers and pharmaceutical industry have resulted in a steady flow of many new products from various groups. Additional validation of developed products and extensive clinical trials have been carried out globally to validate claims of the safety and efficacy of these newer drugs. Through their fast track policies, regulatory bodies such as the EMEA (European Medicine Evaluation Agency), US FDA (US Food and Drug Administration), and other regulatory agencies, have continually contributed to the timely evaluation and approval of new drugs by providing valuable input at various stages of drug development. Such close interactions have facilitated clarification of various issues related to drug development and in fact have accelerated the approval process of many new drugs such as LMWHs, synthetic heparin pentasaccharide (fondaparinux, Arixtra®), newer parental antithrombin agents (bivalirudin, Angiomax®; lepirudin, Refludan®;



argatroban, Novastan®) and activated protein C (drotrecogin alfa, Xigris®). A focused interest in the development of oral anti-Xa and anti-IIa drugs to replace oral anticoagulant drugs such as warfarin, has resulted in the development of Rivaroxaban (Xeralto) and Dabigatran (Pradaxa). Both agents are approved in the EMEA and Canada for the prophylaxis of DVT in orthopedic surgical patients. Rivaroxiban has been reviewed by the US FDA advisory committee who has recommended approval of this drug in March 2009. The US FDA has required some additional data on the safety issues. It is likely that both the rivaroxiban and dabigatran will be approved in the US in due time.

Despite their limitations, unfractionated and LMW heparins are still the most widely used anticoagulants in the United States. Several oral formulations of heparin have been developed and tested in clinical trials. Although effective, the oral formulations of heparin failed to exhibit comparable efficacy in the management of deep vein thrombosis (DVT). It may be that the oral formulations exhibit efficacy in other indications. Additional studies on modified and improved formulations are in progress at this time. In addition, several other chemically modified forms of heparin did not exhibit the expected pharmacologic effects in either pre-clinical and clinical settings.

2. Low molecular weight heparins

While heparin remains the primary anticoagulant used during cardiovascular and several surgical procedures, the continual expansion of applications of LMWH has added a new dimension to the overall management of thrombotic disorders (5,6). The LMWHs have achieved gold standard status in the management of thromboembolic disorders and now challenge other treatments, such as oral anticoagulants, for various other indications. Several recent clinical trials have provided supportive data for the polytherapeutic use of LMWHs in the

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management of acute coronary syndromes, thrombotic stroke, and malignancy associated with thrombotic events (7-9). LMWHs have also shown efficacy as surgical and interventional anticoagulants. Compared to heparin, these drugs exhibit a better therapeutic index in these indications. LMWHs have also been evaluated in atrial fibrillation and cardiac transplantation, treatment of pulmonary embolism (PE) and home therapy. The LMWHs have multiple sites of action that extend to profound actions on endothelial sites and blood cells. This understanding has led to the development of non-anticoagulant forms of LMWHs (7-10).

LMWHs are now globally regarded as drugs of choice for post-surgical prophylaxis of DVT and the management of acute coronary syndromes. [6] Several products are currently available for clinical use worldwide. Because of manufacturing differences, each of the LMWHs exhibits distinct pharmacologic and biochemical profiles (5). Studies that compare the antithrombotic and hemorrhagic profile of some of the available LMWHs have been reported. Product individuality in terms of relative potency in different assays and the failure of standardization protocols to provide any guidelines for product substitution and prediction of the clinical effects have remained major considerations (5,6).

Only two of the LMWHs have been approved for multiple indications. In addition, these drugs are also used in several other off-label indications. At this time, LMWHs are being evaluated in newer indications such as the management of atrial fibrillation, ischemic and thrombotic stroke, transplantation, inflammatory bowel disease, cancer and sepsis. In addition LMWHs have been evaluated for the anticoagulant use in percutaneous interventions and surgical procedures (9,10).

In the coming years the role of LMWHs will be expanded in both the thrombotic and non-thrombotic indications. Newer formulations, drug combinations, extended use and long term effects of these drugs will be important in the optimization of these drugs. With the continued pressure to reduce healthcare costs, pharmacoeconomics will play a key role in the expanded and optimized usage of these drugs in years to come. Selection of a proper agent for a given indication, dosing, management of adverse reactions and substitution therapy represent some of the areas where valid clinical trials are needed.

3. Ultra low molecular weight heparins

Additional depolymerization of LMWHs has resulted in the development of ultra low LMWHs. Several ultra-LMWHs have recently become available and are currently in development for specific indications. Bemiparin (Rovi, Madrid, Spain) is one such product that is efficacious in the management of DVT. Bemiparin represents a lower low molecular weight heparin which is derived from the same depolymerization process as enoxaparin (11). Bemiparin has been evaluated in the management of venous thrombosis in both the medical and surgical settings. Additional clinical development of bemiparin is planned in both arterial and venous thrombosis. Several other agents are clinically tested in vascular dementia, inflammatory bowel disease and acute coronary syndromes.

Semuloparin represents an ultra low molecular weight heparin with a higher anti-Xa activity than enoxaparin and much lower anti-IIa activity. The molecular weight of octaparin is 2.4 KDA which is nearly half of enoxaparin, while the specific anti-Xa activity is 140 U/mg (12). This anti-Xa enriched ultra LMWH is currently developed for multiple clinical indications including cancer associated thrombosis.

4. Antithrombin agents

Understanding the coagulation process has led to the identification of thrombin as a key enzyme in the thrombogenic processes. As shown on Table1, several direct thrombin inhibitors have been developed over the past few years including; Argatroban(Novastan®),bivalirudin(Angiomax®) and lepirudin (Refludan®) (13). More recently, an oral antithrombin agent, dabigatran has been developed for the management of DVT and atrial fibrilation (13). The recognition of heparin induced thrombocytopenia as the most adverse effect of heparin has spurred the development of alternate anticoagulants. The parenteral antithrombin agents are most useful in this indication and have been specifically developed for heparin induced thrombocytopenia(HIT).

Two agents, lepirudin and argatroban are approved in the US for HIT (13).The data on the safety and efficacy of these two agents in HIT came from prospective cohort studies that used historical controls (14-16). Thus, both these agents were effective in HIT, but drawbacks included bleeding and with lepuridin, antibody formation (13-16).

Table 1. Antithrombin inhibitors

Agent	Originator	Developmental Status
Argatroban	Mitsubishi Pharma	FDA approved as alternate anticoagulant for HIT and anticoagulation during PCI.
Lepirudin	Bayer Healthcare	FDA approved as alternate anticoagulant for HIT
Bivalirudin	Medicines Co.	FDA approved for patients undergoing PCI and in ACS patients undergoing PCI
Ximelagatran,*	AstraZeneca	Off the market
melagatran		
Dabigatran*	Boehringer ingelheim	Clinical trials

*Oral antithrombotic agents

Table 2. Factor Xa inhibitors

Agent	Originator	Source	Developmental Status
Direct Inhibitors			
Antistasin*	Merck	Recombinant	Terminated
Yagin*	Bio-Technology General	Animal derived	Terminated
TAP*	Merck	Recombinant	Preclinical
NAPc2*	Corvas	Recombinant	Clinical Trial
TFPI*	Chiron/Pfizer	Recombinant	Clinical Trial
DU-176b*	Daiichi-Sankyo	Synthetic	Clinical Trial
SEL 2711*	Selectide	Synthetic	Preclinical
YM-150*	Yamanouchi (Astellas)	Synthetic	Clinical Trial
Betrixaban*	Portola	Synthetic	Clinical Trial
KFA 1411*	Kissei	Synthetic	Preclinical
RPR 12084*4	Rhone-Poulenc Rorer	Synthetic	Preclinical
Otamixaban*	Sanofi-Aventis	Synthetic	Clinical Trials
Rivaroxaban (BAY 59-7939)**	Bayer	Non-peptidic	Clinical Trials
Apixaban**	Bristol-Myers Squibb	Synthetic	Clinical Trials
Indirect Inhibitors			
Heparin pentasaccharide (fondaparinux, Arixtra®)*	Sanofi-Aventis	Synthetic	Approved for prevention and treatment of VTE, being tested in additional clinical trials
Idraparinux*	Sanofi-Aventis	Synthetic	Clinical trials

* Parenteral
** Oral

Hirudin, the leech-derived protein, has been compared with heparin for various indications in numerous clinical settings, including treatment and prophylaxis of venous and arterial thrombotic disorders. The use of hirudin has been reported to be associated with increased risk of bleeding, indicating that better monitoring and dose-adjustment protocols are needed as are effective antidotes. In addition, hirudin has been reported to produce nonneutralizing antibodies in patients which can influence its anticoagulant effect. In HIT patients treated with lepirudin, 4% versus 15% (historical controls) developed a thrombotic event, however bleeding complications (14%) were associated with lepirudin (14). In clinical trials comparing hirudin and heparin as adjuncts in thrombolytic therapy in myocardial infarction (TIMI 9B) and acute coronary syndromes (GUSTO IIb) have shown hirudin to be marginally (if at all) superior to heparin. In two different studies comparing heparin or enoxaparin with recombinant hirudin for the prophylaxis of deep venous thrombosis (DVT) in hip replacement, the incidence of deep vein thrombosis was lower in hirudin treated patients with a similar bleeding risk. (17,18). In established DVT, LMWH was compared with hirudin and similar safety and efficacy was achieved in both groups (17). Both studies emphasized the importance of understanding that the efficacy and safety of a new drug may not be determined by trials for a single indication. Therefore, additional clinical trials are needed for various specific indications.

Bivalirudin is a bivalent reversible direct thrombin inhibitor that has been approved by the FDA for use in patients undergoing routine PCI and in acute coronary syndrome patients undergoing PCI (19-21). In controlled clinical trials, bivalirudin has been shown to reduce major bleeding by approximately 50% in comparison to heparin, LMWHs and GPIIb/IIIa inhibitors while exhibiting similar efficacy in terms of incidence of death and MI (19-21). In addition, there have been several reports on the successful use of bivalirudin for cardiopulmonary bypass surgery in patients with HIT and heparin allergies (22,23). Several additional clinical trials are ongoing using bivalirudin in different clinical indications.

Argatroban, a small molecule, peptidomimetic reversible thrombin inhibitor, is also approved by the US FDA as an alternate anticoagulant for patients with HIT and for anticoagulation during PCI (24,25). It represents the first clinically used antithrombin agent as it has been used successfully in Japan for over a decade in the treatment of thrombotic disorders. Several clinical trials in both Europe and the United States have been designed to investigate its use as alternative to heparin in heparin-compromised patients and as a prophylactic agent to reduce late restenosis after PTCA and coronary directional atherectomy (CDA) (15,16). In patients with proven HIT who were treated with argatroban, the incidence of a new thrombotic event was 13% compared to 35% (historical controls), with a bleeding rate of 6% (15,16). Argatroban also exhibits additional actions on blood vessels and may exert its clinical effects via multiple mechanisms. More recently, in a Phase II study, argatroban has been tested in acute stroke, however this study included a small number of patients (26).

Another area of aggressive basic and clinical research is the development of oral thrombin inhibitors. Ximelagatran represents a prodrug version of a direct thrombin inhibitor, melagatran. This antithrombin drug has been evaluated in various thrombotic indications. Although this orally administered drug is effective, there are several safety issues related to its use. Therefore the regulatory agencies in North America and Europe took this product off the market.

Dabigatran etexilate is also an oral prodrug that is in advanced stages of clinical development (12). Dabigatran has been studied in clincial trials for the prophylaxis of DVT in total hip (RE-NOVATE trial) and total knee (RE-MODEL, RE-MOBILIZE trials) replacement (24,25). In the BISTRO II trial, oral dabigatran was compared to enoxaparin after orthopedic surgery. In this study VTE was decreased but bleeding increased with an increase in dosage (27). Dabigatran is currently being evaluated for treatment of VTE and for the prevention of stroke in atrial fibrillation (25). Dabigatran is now approved in Canada and EMEA for the prophylactic management of DVT in patients undergoing orthopedic surgery and atrial fibrilation.

5. Factor Xa inhibitors

The serine protease factor Xa has a central role in the process of coagulation and platelet activation. Factor Xa is an essential component of the prothrombinase complex and leads to the formation of thrombin. Thus, the inhibition of factor Xa and its generation represent an important strategy in the development of new antithrombotic drugs (28-30). Because of their different mechanisms of action, factor Xa inhibitors are expected to be safer than thrombin

inhibitors, yet be effective antithrombotic agents. Today there is a major move within the pharmaceutical sector for the development of more efficient factor Xa inhibitors. These agents represent a wide array of organic/synthetic compounds with varying structural and functional diversity. Factor Xa inhibitors that are in drug development today are structurally diverse ranging from peptides and proteins to heparin saccharidic sequences (4,24,25,28). They can be naturally derived, recombinant or synthetic. Molecular size, specificity and kinetics of factor Xa inhibition differ between inhibitors. They can be direct binding to factor Xa or indirect via a cofactor such as antithrombin (AT) III, and binding can be reversible or irreversible (4,30).

Factor Xa inhibitors may be particularly effective in less severe indications where there is not a high degree of pre-formed thrombin. Factor Xa inhibitors can potentially be used for clinical indications where heparin or LMW heparins are used, such as for prophylaxis of venous thrombosis.(4,28,30). Other clinical developments that pharmaceutical industry is considering include arterial thrombosis, thrombotic stroke and cancer. Factor Xa inhibitors may also be useful in DIC, sepsis, inflammatory disorders, and as adjunct drugs for the new antiplatelet agents and thrombolytic therapy. The limited data available on factor Xa inhibitors is favorable and warrants additional investigations to demonstrate the efficacy of these agents in thrombotic and cardiovascular indications and to validate their true clinical potential. The number of clinical studies published on factor Xa inhibitors is limited (24,25,30). Table 2 shows both the indirect and direct anti-Xa agents currently under development.

The clinically available indirect factor Xa inhibitor is the synthetic heparin pentasaccharide (24,25). This is a novel antithrombotic agent that, although based on the structure of heparin, is different from both heparin and LMW heparin. Pentasaccharide is a selective, reversible inhibitor of factor Xa.

Pentasaccharide (SR90107a, ORG31540, fondaparinux, Arixtra®) is developed for the prevention and treatment of DVT. Four phase III clinical trials (EPHESUS, PENTATHLON 2000, PENTHIFRA and PENTAMAKS) for the prophylaxis of venous thrombosis have been completed (31-34). In EPHESUS, PENTATHLON 2000, PENTHIFRA there was no difference between LMWH and fondarinux (31,32,34) However, in the PENTAMAKS trial fondaparinux was superior to LMWH (33) In addition two trials for the treatment of acute DVT or PE also showed that fondaparinux was at least as effective as LMWH or heparin (35,36). These were multi-center clinical trials, conducted globally and included total hip replacement, hip fracture and total knee replacement surgical patients. The US FDA granted approval of fondaparinux for prophylaxis following hip fracture surgery, total hip and knee replacement, major abdominal surgery and the initial treatment of DVT and PE. Fondaparinux is contraindicated in patients with severe renal impairment and there are warnings against increased risk of bleeding with age, with the use of spinal puncture and epidural/spinal anesthesia. Fondaparinux has also been studied in unstable angina and in acute coronary syndromes (37,38). However, catheter thrombois was noted with fondaparinux (25).

Idraparinux (SANORG-34006) is a more potent and longer-acting pentasaccharide than the fondaparinux (39). This agent is a hypermethylated analogue of fondaparinux that binds to AT with high affinity. This agent has been studied in the treatment of VTE and in long-term stroke prevention in patients with atrial fibrillation (25,40). One drawback of fondaparinux and idraparinux is that there is no specific antidote. However, a biotinylated form of the idraparinux, namely idrabiotaparinux is developed. The derivative of idraparinux can be neutralized by avidin, an egg protein which tightly binds to biotin moiety. Both the idraparinux and idrabiotaparinux exhibit similar antithrombotic efficacy in a long term clinical trial (41). Avidin infusion after the last injection was found to reverse the anti-Xa activity of idrabiotaparinux. Additional clinical trials are ongoing at this time to investigate the clinical efficacy of idrabiotaparinux.

Otamixaban represents a parenteral anti-Xa agent that is also being developed as a potential anticoagulant for acute coronary syndromes.(13). This anti-Xa inhibitor has been evaluated in patients undergoing elective percutaneous intervention. In comparison to heparin this agent provided stronger anticoagulation without causing bleeding.

Currently, there are several oral direct Factor Xa inhibitors in clinical development. These include YM 150 (Astellas), DU-176b (Daiichi/Sankyo), LY517717 (Lilly), Bextrixaban (Portola/Merck), Apixaban (BMS/Pfizer), TAK 442 (Takeda) and the most advanced clinical development program is on the rivaroxaban (BAY 59-7939) (25). Rivaroxaban is a non-peptide,

orally available Xa inhibitor. This agent has been studies in a dose-ranging study (ODIXA-Hip), (ODIXA-Knee) and is currently undergoing evaluation in two studies in hip replacement and two in total knee replacement (42,43). In addition, studies in the treatment of VTE have been completed. Currently studies in prevention of stroke in patients with atrial fibrillation are ongoing. Another oral anti-Xa agent, apixaban is also undergoing clinical trials (13). These agents may be useful for the prophylaxis of both arterial and venous thrombotic disorders. Questions about monitoring and effective antidotes / antagonism will have to be answered before direct factor Xa inhibitors can be widely explored in clinical settings. They may be used as adjuncts with other classes of drugs.

The clinical safety profile of one oral direct thrombin inhibitor, Ximelagatran has prompted additional scrutiny on peptidomimetic anti-IIa and anti-Xa agents (44). Because of the liver enzyme elevation and thrombin rebound observed with ximelagatran it was not approved by the FDA. Similar consensus have been expressed on the potential elevation of liver enzymes by dabigatran and rivaroxaban. These serious outcomes have underscored the concerns about the potential hepatotoxicity of these agents. They also point to the necessity for large scale Phase III trials to rule out potential side effects in causing mortality. For both dabigatran and rivaroxaban, until additional Phase III data are available, a moderate risk for the toxic effects including liver enzyme elevation appears real.

In a recent Phase III trial, an oral factor Xa inhibitor, apixaban was compared with enoxaparin for preventing venous thromboembolism after total knee replacement (45). Both agents produced similar efficacy. However, apixaban regimen resulted in less clinically relevant bleeding than enoxaprin. Apixaban is also developed in the management of cancer associated thrombosis and other medical indications.

Du 176 represents an oral anti-Xa drug developed by Diachi/Sankyo Pharmaceutical Company. This drug is also undergoing advanced clinical development. A Phase II study to assess the safety of different dose regimens of DU 176 in patients with atrial fibrillation is recently reported (46). Du 176b at 30 mg and 60 mg once a day dose was found to exhibit similar safety profile as standard dosage of warfarin. It has been suggested that DU 176b may potentially replace warfarin in the atrial fibrillation. Another study also assessed the safety /efficacy and does response relationship of DU 176b for the prevention of venous thromboembolism in Japanese patients undergoing total knee replacement (47). This study was coarried out with a placebo control group. Patients treated with DU 176b demonstrated significant dose dependent reductions in VTE after total knee replacement with major bleeding complications.

In a recent reported study, 10 mg/once a day, rivaroxaban was compared with the US dosage of enoxaparin (30 mg BID) to determine the relative efficacy and safety of these agents undergoing total knee replacement (48). The results of this study showed that it has superior efficacy to enoxaparin or the prevention of venous thromboembolism after total knee replacement without surgical risk of bleeding.

A pooled data analysis of four multinational double blind Phase III trials (record 1-4) was recently reported (49). A total of 12,729 patients were randomized to receive a fixed dose of rivaroxiban once daily 6-8 hours before surgery and compared with standard European and North American dosage for enoxaparin. The pooled data analysis demonstrated that rivaroxiban reduced the composite of major clinical outcomes compared with enoxaparin regimen with no significant increase in the risk of major bleeding in patients undergoing major orthopedic surgery.

The oral anti-Xa and anti-IIa drugs have been extensively developed to replace oral anticoagulant drugs such as warfarin. The initial results in qualified clinical trials are promising, however, bleeding issues and recurrent thrombosis require additional studies to validate the claims for the superiority of the currently available drugs.

6. New anticoagulants for interventional usage

Despite major developments in introducing newer anticoagulants for the management of thrombotic disorders, heparin has remained the anticoagulant of choice for cardiovascular surgical/interventional and neurovascular interventional procedures. While parenteral antithrombin agents such as argatroban, hirudin and hirulog have been used in patients with heparin induced thrombocytopenia, none of these agents are currently approved for cardiovascular surgical procedures due to their pharmacokinetic profile and lack of antidote. Argatroban and hirulog have been approved for anticoagulation during percutaneous intervention in patients

with heparin induced thrombocytopenia. Of the three parenteral antithrombin drugs, namely argatroban, hirulog and hirudin, none of these agents are developed for other routes of administration subcutaneous or oral administration. On the other hand, the only parenteral anti-Xa agent, namely otamixaban, represents a strong anticoagulant drug which has been evaluated in percutaneous interventional settings.

However, it's clinical development is somewhat slow and there are concerns over it's safety in terms of bleeding complications.

The orally bioavailable anti-Xa and anti-IIa agents such as the rivaroxaban, apixaban and dabigatran are clinically validated for the management of DVT after orthopedic surgery and cannot be used parenterally. Relatively larger dosages may be needed to achieve desirable anticoagulant levels needed for each of the drugs for interventional cardiovascular and neurovascular procedures. Moreover, the pharmacokinetic profile of these agents is not suitable for the interventional procedures. There are no studies available on the interventional use of these agents at this time. Therefore, none of the orally available drugs will be of any value for interventional procedures. Furthermore, interventional procedures on patients with the newer anti-Xa and anti-II agents on board may require antidote due to potential bleeding in these patients.

Rivaroxaban and dabigatran are also developed in the long term management of atrial fibrillation and embolic stroke. In this indication the orally available anticoagulants are projected to replace warfarin and related oral anticoagulants.

The mechanism by which these agents produce their anticoagulant effects are not only different from warfarin, but these also have very different pharmacokinetic and pharmacodynamic profiles. Drug interactions, population variations, rebound and pharmacogenomic considerations are some of the important areas which require additional studies to establish the relative safety and efficacy of these new anticoagulant drugs.

More recently the newly developed anti-Xa and anti-IIa agents have also been evaluated in the management of acute coronary syndrome.

As the acute coronary patients are also treated with anticoagulant drugs such as aspirin and clopidogrel, it is likely that the oral anti-Xa and anti-IIa drugs exert interactions which may have input on the safety and efficacy profile. A recent study on the use of rivaroxaban in acute coronary syndrome has provided data on the relative safety and efficacy of this agent (50). It is quite likely that newly developed anti-Xa and anti-IIa agents will exhibit varying degrees of drug interactions with not only the other anticoagulants and antiplatelet agents, but other drugs such as the statins, antihypertensives antidiabetic and other widely used drugs. Therefore, the safety and efficacy profile require clinical validation in specific trials.

7. Future perspectives

UFH will continue to be used for interventional, surgical and procedural indications until the newly developed anticoagulants are shown to have clinical superiority over this drug. Moreover, for these indications these drugs may be of limited value since there is no antidote available at this time. LMWHs and related drugs will replace UFH for most of the subcutaneous indications and can be developed for interventional use however for surgical indications these agents may not be optimal until an antidote is developed. The parenteral antithrombin agents such as argatroban, hirudin and hirulog may be useful in the anticoagulant management of heparin compromised patients, however because of the non-availability of an antidote these agents may not be useful for cardiopulmonary bypass surgery. The newly developed orally bioavailable anti-Xa and anti-IIa agents such as the rivaroxaban, apixaban and dabigatran may be useful for long term management of DVT and atrial fibrillation and acute coronary syndrome, however additional data on bleeding and rebound thrombosis is needed. Moreover, unlike heparins, these agents also cross the placental barrier which may also limited their usage in specific populations. While the newly developed anticoagulants are structurally and biologically well defined, it is unlikely that these drugs can replace heparin for all indications. However, these drugs may be of value in qualified indications where the conventional anticoagulants are not useful.

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