DIAGNOSIS AND MANAGEMENT OF THROMBOSIS

New development in anticoagulant and antithrombotic therapy: Are we on the right track?

JAWED FAREED

Anticoagulant and antithrombotic drugs have played a key role in the prophylaxis, treatment and surgical/interventional anticoagulant management of thrombotic and cardiovascular disorders. In particular, these drugs have played a crucial role in the management of venous thrombosis and pulmonary embolism. There are several newer drugs which have currently been developed for the management of venous thromboembolic disorders. These include the low molecular weight heparins (LMWHs), antithrombin agents such as the hirudin, hirulog and argatroban and indirect and direct anti-Xa drugs, represented by pentasaccharide (fondaparinux®) and BAY 59-7939, respectively. The oral heparins, anti-IIa and anti-Xa drugs are also in different phases of clinical development. Of these, one oral antithrombin agent, namely, Exanta, is approved in Europe, for qualified indications. However, the US FDA has not approved this drug for any indication. Several other agents such as the natural and recombinant anti-Xa drugs and anti-tissue factor agents are also under development. For subcutaneous indications, unfractionated heparin is gradually being replaced by LMWHs. Such LMWHs as the enoxaparin and dalteparin are commonly used for the management of venous thromboembolic disorders. However, there are eight additional commercially available LMWHs which can be used for this disorder. It is now clear that different LMWHs are clinically none interchangeable. Moreover, the generic versions of the braned product such as enoxaparin may exhibit different properties than the innovator product and therefore do not qualify for generic interchangeability. Fondaparinux® is also being developed for various subcutaneous indications. However, it exhibits lower anticoagulant effects and may not be optimal for intravenous indications. At a higher dosage when administered intravenously the LMWHs produce varying degrees of anticoagulation at relatively lower activated clotting times (ACT;150–200 sec). Several studies in vascular and cardiovascular interventions have shown that even at a relatively low anticoagulant level the LMWHs are as effective as unfractionated heparin at the recommended dosages which produce a relatively higher level of anticoagulation (ACT >200 secs.). Thus, these agents are currently being developed for several interventional/hematologic indications such as bone marrow transplantation and blood cancers. It should be emphasized that different LMWHs produce different degrees of anticoagulation and should therefore be individually optimized for a specific hematologic indication. At a relatively high dosage the levels of LMWHs can be measured by using the ACT and APTT. LMWHs will find expanded indications in both the medical and surgical management of patients with hematologic and oncologic disorders. The LMWHs are also useful in the management of cancer patients. Recent trials have clearly shown that these drugs reduce the mortality outcome in cancer patients. The only approved anti-Xa drug is represented by a synthetic heparinomimetic, namely, fondaparinux®. This drug is given for the prophylaxis of post orthopedic indications. This agent is undergoing additional clinical trials in the management of several other indications. Because of the dependence on antithrombin (AT) and the sole anti-Xa effects, it has a narrow therapeutic index and its efficacy in this indication may be limited. Additional clinical trials are needed at this time to validate the clinical potential of this drug. The long lasting methylated pentasaccharide derivative, namely idraparinux, is also being optimally developed; however, there is no antidote for this agent. The antithrombin agents (hirudin, hirulog and argatroban) were initially developed for arterial indications. However, these agents are approved as a substitute anticoagulant in patients with heparin induced thrombocytopenia (HIT) and PCI. Different antithrombin agents produce their therapeutic effects by distinct mechanisms and should be considered equivalent on the basis of their antic-
oagulant effects. Currently all of these agents are being developed for surgical and interventional use. However, since there is no available antidote at this time, the development is somewhat limited. The antithrombin agents may be useful in patients with HIT which require further clinical validation. Many other anti-Xa agents are also developed. Most of these can be given parenterally. However, the clinical data is somewhat limited. Since most of these newer anticoagulant and antithrombotic drugs are mono-therapeutic their therapeutic index is rather limited. Only in combination these agents can mimic heparins. At this time it is safe to state that heparin and its LMWH derivatives will remain the anticoagulant of choice for the management of thrombosis until these newer agents have been validated in extended clinical trials in polytherapeutic settings. Polytherapeutic approaches including the targeting of adhesion molecule and cellular receptors, modulation of inflammatory process, targeting procoagulant proteins such as the coagulation factors, TF and VWF and bifunctional antiplatelet/antiprotease drugs will be the focus of future targets in this field. Another important development in the field of antithrombotic drugs is the potential impact of generic versions of warfarin, low molecular weight heparins such as enoxaparin and dalteparin. The antithrombotic drugs are used in many of the critical indications and represent a diverse chemical, natural, hybrid agents for which the approval guidelines from the current regulatory agencies are not adequate, thus at this time the generic interchange for antithrombotic drugs is not recommended. Moreover, for such classes of drug as LMWHs and antithrombins therapeutic interchange is not recommended as well. Objective and unbiased clinical trials and group consensus are warranted for the optimal use of these agents.

References


