Evaluation of Different Protocols for Management of Thrombotic Disorders

Essay

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Summary and Conclusion

Better understanding of the molecular mechanisms underlying thrombogenesis, advances in recombinant DNA technology, isolation and characterization of antithrombotic proteins from hematophagous organisms, and improvements in structure-based drug design have accelerated the pace of drug discovery. With these advances, we now have an array of new antithrombotic drugs.

Limitations of the currently available anticoagulants have fanned the continuing search for new anticoagulants with improved pharmacological and biosafety profile, and equal, if not superior efficacy. Targets of inhibition include the factor VIIa/tissue factor pathway (recombinant nematode anticoagulant peptide c2, tissue factor pathway inhibitor), factor Xa (fondaparinux, idraparinux, razaxaban), factor Va and VIIIa

pathway (recombinant activated protein C, soluble thrombomodulin) and thrombin (hirudin, bivalirudin, argatroban, ximelagatran, dabigatran). Irrespective of their mode of action, bleeding complications are invariable with all anticoagulants. Conventional assessment and measures should remain as first-line responses to bleeding complicating the use of these anticoagulants. Antidotes do not exist for the overwhelming majority of these agents. The role of recombinant activated factor VIIa in controlling bleeding is still investigational. Definitive haemostatic strategies for bleeding

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List of Abbreviations

ACT	Activated clotting time
APC	Activated protein c
APTT	Activated partial thromboplastin time
ATIII	Antithrombin III
BRVO	Branch retinal vein occlusion
CAST	Chinese acute stroke trial
CI	Confidence interval
COX	Cyclooxygenase
CrCl	Creatinine clearance
CS	Cystathionine synthase
CT	Computed tomography
CURE	Clopidogrel in unstable angina to prevent recurrent events
CVT	Cerebral vein thrombosis
Da	Daltons
DNA	Deoxyribonucleic acid
DVT	Deep veinous thrombosis
EFAT	European atrial fibrillation trial
ELT	Euglobuline time
ESPRIT	Enhanced suppression of the platelet IIb/IIIa receptor with integrilin therapy
FRISC	Fragmin and fast revascularisation during instability in coronary artery disease

List of Abbreviations (Cont.)

FV	Factor V
GPIb	Glycoprotein Ib
GUSTO	Global utilization of streptokinase and tissue plasminogen activator for occluded coronary artery
HCII	Heparin cofactor II
HIT	Heparin induced thrombocytopenia
HMWK	High molecular weight kininogen
HRG	Histidine rich glycoprotein
HRT	Hormonal replacement therapy
INR	International normalized ratio
ISAR-CHOICE	Intracoronary stenting and antithrombotic regemin:choose between 3 high doses for immediate clopidogrel effect
ISIS	International study for infarct survival
IV	Intravenous
LMWH	Low molecular weight heparin
Lpa	Lipoprotein a
MEDAL	Multinational etoricoxib and diclofenac arthritis long term
MI	Myocardial infarction
MRI	Magnetic resonance imaging
MTHFR	Methylene tetrahdrofolate reductase
MW	Molecular weight
OR	Odds ratio

List of Abbreviations (Cont.)

PAI	Plasminogen activator inhibitor
PaO_2	Partial pressure of arterial oxygen
PC	Protein C
PCI	Percutaneous coronary intervention
PE	Pulmonary embolism
PF4	Platelet factor 4
PG	Prostaglandin
PNH	Paroxysmal nocturnal hemoglobinuria
PRISM-PLUS	Platelet receptor inhibition in ischemic syndrome management in patients limited by unstable signs and symptoms
PS	Protein S
PT	Prothrombin time
PTT	Partial thromboplastin time
RR	Relative risk
RVO	Retinal vein occlusion
RVT	Retinal vein thrombosis
SALT	Swedish aspirin low dose trial
SBP	Systolic blood pressure
Sc	Subcutaneous
SLE	Systemic lupus erythromatosis
SVT	Splanchnic vein thrombosis
TAFI	Thrombine activatable fibrinolytic inhibitor
TARGET	Therapeutic arthritis research and gastrointestinal event trial

List of Abbreviations (Cont.)

TCT	Thrombin clotting time
TEG	Thromboelastography
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
TIMI	Thrombolysis and thrombin inhibition in myocardial infarction
TM	Thrombomodulin
TTP	Thrombotic thrombocytopenic purpura
TX	Thromboxane
U/d	Unit per day
UA	Unstable angina
UFH	Unfractionated heparin
US FDA	United States Food and Drug Administration
V/Q	Ventilation-perfusion
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
vWF	von Willebrand factor
WHO	World health organization
WRIGHT	WHO Research into global hazards of travel

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Introduction

Thrombosis is the formation of a blood clot (thrombous) inside a blood vessel, obstructing the flow of blood through the circulatory system. When a blood vessel is injured, the body uses platelets and fibrin to form a blood clot, as the first step in repairing it (hemostasis) to prevent loss of blood. If that mechanism causes too much clotting, and the clot breaks free, a thrombous is formed ***(Furie and Furie, 2008).***

Intravascular thrombous formation present the greatest challenge in the field of cardiovascular disease. Within the arterial tree, it is the culprit including clinical presentation in the majority of patients presenting with acute coronary syndrome (ACS). Thrombous formation within the venous circuit also results in substantial morbidity and mortality. Despite significant advances in prevention and treatment of venous thromboembolism (VTE), pulmonary embolism (PE) remains a common preventable cause of hospital death ***(Horlander et al., 2003).***

Concepts of hemostasis and thrombosis emphasize the endothelial cells as a regulatory interface between blood and tissues. The endothelium constitutes an immense surface area ideally suited to control biologic events at the vessel surface. These include expression of membrane surface receptors for assembly of zymogens, localization of enzyme activity, orientation of adhesive glycoprotein interactions, and binding of

signals transducing ligands. In health, surface oriented interactions of endothelium serve primarly to maintain blood fluidity. In disease, disordered thromboregulation may acutely culminate in arterial and venous thrombosis ***(Nachman, 1992).***

Of the three mechanisms of thrombosis defined by Virchow in the 19th centuary, vessel wall injury, stasis,and change in the composition of blood (hypercoagulability). Hypercoacgulability can be inherited or acquired.The inherited type which is also called inherited thrombophilia, should be suspected when a patient has recurrent or life threatening venous thromboembolism, has a family history of venous thrombosis, is younger than 45 years of age, or has no apparent acquired risk factors, or if the patient is a woman who has a history of multiple abortions, stillbirth, or both. Acquired and genetic causes frequently interact ***(Seligohn et al., 2001).***

By targeting the three essential components of the arterial thrombous, platelets, fibrin and thrombin, various regimens, combining antiplatelet agents (e.g. aspirin. Clopidogrel, GP IIb/IIIa inhibitors), antithrombotics (e.g. heparin, LMWH (enoxaparin), DTI(Bivalirudin)), and either fibrinolysis have improved outcomes following acute ischemic syndromes ***(de Lemos et al., 2000).***

Anticoagulant therapy remains the cornerstone of VTE treatment. Such treatment is usually divided into 2 stages. Rapid initial anticoagulation is givin to minimize the risk of thrombous extention and subsequent fatal PE, wherase extended

anticoagulation is administered to prevent recurrent VTE, thereby reducing the risk of postphlebitic syndrome. With currently available drugs, immediate anticoagulation can only be effected with parenteral anticoagulants, such as heparin (UFH), low molecular weight heparin (LMWH) or fondaparinux. Extended therapy usually involves the administration of an oral anticoagulant. Currently, the orally available anticoagulants are the vitamin K antagonists such as warfarin.LMWH and fondaparinux have simplified the intial treatment of VTE. Both agents have better bioavailability after subcutaneous injection and longer have life than heparin. In addition, they produce a more predictable anticoagulant response. These features permit once daily subcutaneous dosing without coagulation monitoring. Consequently the majority of patients with VTE can now be treated with LMWH or fondaparinux as outpatients, an approach that reduces the health care costs and enhances the patient satisfaction ***(Peter et al., 2008).***

Although LMWH and fondaparinux are important advances in VTE treatment, some difficulties persist. The need for once daily subcutaneous injections renders treatment problematic for some patients. This has prompted the introduction of longer acting parenteral anticoagulants that can be given subcutaneously on a once-weekly basis, and the development of novel oral anticoagulants with a rapid onset of action.Warfarin also problematic in the setting of VTE. Its slow onset of action necessitates overlap with a parenteral

anticoagulant for at least 5 days. The therapeutic dose of warfarin varies from patient to patient reflecting, at least in part, differences in dietary vitamin K intake, genetic polymorphisms in the enzymes involved in warfarin metabolism, and administration of concomitant medications that suppress or potentiate the anticoagulant effects of warfarin. Frequent coagulation monitoring is necessary to ensure that a therapeutic anticoagulant response is achieved with warfarin ***(Ansell et al., 2004).***

The requirement of frequent coagulation monitoring is burdensome for patients and physicians and costly for the healthcare system. The difficulties surrounding warfarin administration have spurred the development of new oral anticoagulants that can be given in fixed doses with little or no coagulation monitoring. The need for such agents has increased in the recent years with emerging evidence that patients with unprovoked VTE require anticoagulation therapy for at least 6 months and possibly longer ***(Kearon, 2004).***