ELSEVIER

Latest developments in anticoagulant drug discovery

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Thromboembolic diseases have increased in number over the past years. Oral anticoagulants impair the formation and progression of thrombotic processes and are therefore of great importance in the treatment of these diseases. Until recently, vitamin K antagonists were used to block the coagulation system. But these agents display a lot of interactions besides their narrow therapeutic range and have potential risk of hemorrhage complications. Therefore, other factors of the coagulation cascade are currently being explored as therapeutic targets for the development of novel anticoagulants. This review will provide an overview of new drugs promising more effectiveness in the treatment of arterial and venous embolism. Furthermore, pharmacodynamics and drug interactions regarding new anticoagulants will be reported.

Introduction

Arterial and venous thromboembolic diseases are becoming more and more common with an impairment on patient quality of life [1]. Owing to a rising number of older people in the population the rate of thromboembolic disorders is increasing. Nowadays alternative strategies exist for oral anticoagulation next to vitamin K antagonists (VKA; see Glossary for full list of abbreviations used). The commonly used VKAs are warfarin, acenocoumarol or phenprocoumon (Box 1). Warfarin is the most commonly prescribed VKA worldwide [2,3] and has annual prescriptions equaling 0.5–1.5% of the population [4]. VKA limitations are their high rate of drug and food interactions as well as their need of monitoring [5]. In the past five years, the range of available anticoagulant treatment options has evolved substantially [1]. To find new agents appropriate to the ideal anticoagulant profile, different steps in the coagulation cascade have been targeted, including direct thrombin inhibition and inhibition of factor Xa, factor IXa, the factor-VIIa–tissue-factor complex and the factor-Va–factor-VIIIa complex [6] (Fig. 1).

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These new anticoagulant drugs are emerging and have the potential to simplify the long-term treatment of patients [7]. This review will provide an overview regarding pharmacokinetics, interactions and administration on novel anticoagulant drugs. Agents that are currently under clinical investigation will be outlined as well (Tables 1–4).

Clinically approved novel oral anticoagulants

Dabigatran

Dabigatran is a reversible direct thrombin inhibitor with a fast plasma concentration peak [8]. Standard doses have been recommended for dabigatran, depending on the renal function and the age of the patient [9].

Dabigatran and venous embolism

Dabigatran for venous thromboembolism (VTE) prophylaxis is recommended in a dosage of 220 or 150 mg o.a.d. for patients with renal impairment or taking a P-glycoprotein (P-gp) inhibitor [10]. Dabigatran showed in many trials to have safety against deep vein thrombosis (DVT) and pulmonary embolism (PE) in prophylaxis of major orthopedic surgery. More than 10,000 patients have been evaluated in four Phase III trials [11]. Studies compared dabigatran to commonly used heparin, and recorded and equal

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GLOSSARY

AF atrial fibrillation
NOAC new oral anticoagulation
VKA vitamin K antagonist
PFO patent foramen ovale
TTR time in therapeutic range
LMWH low molecular weight heparin
VTE venous thromboembolism
DVT deep venous thrombosis
MI myocardial infarction
PE pulmonary embolism
CrCl creatinine clearance
C_{max} peak plasma concentration
b.i.d. twice daily
o.a.d. once daily
ECT eucerin clotting time
TCT thrombin clotting time
aPTT activated partial thromboplastin time
PT prothrombin time
TKR total knee replacement
THR total hip replacement
PL platelet count
F factor
INR international normalized ratio
CNS central nervous system
CHADS2 C, congestive heart failure; H, hypertension; A, age $\geq$ 75 y; D, diabetes; S2, prior stroke or transient ischemic attack
P-gp P-glycoprotein
EMA European Medicines Agency
four factor PCC prothrombin complex concentrate
PETRO The Prevention of Embolic and Thrombotic Events in Patients With Persistent Atrial Fibrillation Trial
RE-LY Randomized Evaluation of Long-Term Anticoagulation Therapy Trial
RE-MEDY Secondary Prevention of Venous Thrombo Embolism
RECORD Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism
EINSTEIN Oral Rivaroxaban for Symptomatic Venous Thromboembolism
ROCKET A Prospective, Randomized, Double-Blind, Parallel-Group, Multicenter, Noninferiority Study Comparing the Efficacy and Safety of Rivaroxaban with Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Subjects With Nonvalvular Atrial Fibrillation
ATLAS ACS 2-TIMI 51 trial Randomized, Double-Blind, Placebo-Controlled, Event-Driven Multicenter Study to Evaluate the Efficacy and Safety of Rivaroxaban in Subjects with a Recent Acute Coronary Syndrome
ADOPT Alternative Dosing for Outpatient Treatment
APRAISE Safety Study of Apixaban in Recent Acute Coronary Syndrome
ARISTOTLE Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation Trial
DARINA The Direct Treatment Comparison of Dabigatran and Rivaroxaban Versus Nadroparin in the Prevention of Venous Thromboembolism After Total Knee Arthroplasty
Surgery Design of a Randomized Pilot Study
ASA Aspirin
PT Prothrombin time
CrCl Creatinine clearance
eGFR estimated Glomerular Filtration Rate
ECT Ecarin Clotting Time
TCT Thrombin Clotting Time
aPTT activated partial thromboplastin time

BOX 1

Why anticoagulation? [4,74,75]

- Patients with pacemakers
- Acute myocardial infarction
- Congestive heart failure
- Persistent foramen ovale
- Rheumatic valve disease
- Mechanical valves
- Infective endocarditis
- Atrial fibrillation
- Hypercoagulable state
- Vessel arteritis
- Dissection of a vessel wall
- Primary prothrombotic states (antithrombins, heparin cofactor II, proteins C and S and fibrinolytic system derangements)
- Deep vein thrombosis
- Pulmonary embolism

effect for thrombosis prevention and bleeding in major orthopedic surgery [10,12–15] (Table 1).

For perioperative anticoagulation in patients with knee and hip total endoprothesis dabigatran reduced the risk of thrombus formation in deep veins and therefore dabigatran was approved in 2008 by the European Medicines Agency (EMA; http://www.ema.europa.eu/ema/) [14,16].

Regarding acute VTE, dabigatran demonstrated in a fixed dose efficacy in thrombosis prevention significantly less minor bleeding and similar major bleeding in comparison to warfarin [14,17]. However, dabigatran demonstrated noninferiority to warfarin, with fewer bleeding complications, but in one trial there were more acute coronary syndrome events in the dabigatran group, although after further analysis of the data this difference was no longer significant [18–20]. The reason for the increase in myocardial infarction (MI) is yet to be resolved. One theory is that, rather than promoting MI, dabigatran provides less protection from myocardial infarction than warfarin [20].

Dabigatran and arterial embolism

Dabigatran etexilate was approved by the FDA in 2010 as anticoagulant prophylaxis for patients with nonvalvular atrial fibrillation (AF) [21]. Two doses are recommended: either 150 mg b.i.d. (twice a day) or 110 mg b.i.d., which enables tailored dosing [21–23]. Dabigatran 150 mg b.i.d. dose showed a superior efficacy in stroke prevention and systemic embolism with a similar major bleeding rate compared to warfarin. The 110 mg b.i.d. dose had a significantly lower major bleeding rate and the same efficacy as warfarin regarding rates of stroke and systemic embolism. Both doses showed a significant (up to 70%) reduction of intracranial hemorrhage and a reduction in life-threatening bleeding [22]. Interestingly, these effects seen under both doses were independent from gender, weight, ethnicity, renal impairment grade, CHADS2 scores [24], concomitant diseases (e.g. hypertension, diabetes, heart failure) and treatments [22]. Studies registered gastrointestinal bleeding complications as more common especially in patients above 75 years. A RE-LY trial subgroup analysis concerning age and bleeding complications revealed dabigatran 110 mg b.i.d. to improve safety profile in patients above 80 years in comparison to the 150 mg b.i.d. dosage [23].

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