Thrombosis Research 133 S2 (2014) S158–S166

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thomres

Potential antidotes for reversal of old and new oral anticoagulants

Deepa Suryanarayan[a,b], Sam Schulman*[a]

[a]Department of Medicine and Thrombosis and Atherosclerosis Research Institute, McMaster University, Hamilton, ON, Canada
[b]Department of Medicine, University of Calgary, AB, Canada

ARTICLE INFO

Keywords:
Bleeding
Antidote
Direct thrombin inhibitors
Factor Xa inhibitors
Warfarin
Heparin

ABSTRACT

The prescription of new oral anticoagulants is on the rise. As opposed to vitamin K antagonists and heparins the new agents have single targets in the coagulation cascade, more predictable pharmacokinetics and they lack validated and available antidotes. In general, the new agents have similar or lower bleeding risk than vitamin K antagonists, especially risk of intracranial bleeding. Risk factors for bleeding are typically the same for old and new anticoagulants. Old age, renal dysfunction and concomitant antiplatelet agents seem to be recurring risk factors. Adequate supportive care and temporary removal of all antithrombotic agents constitute the basis for management of serious bleeding complications. With the exception of vitamin K (for vitamin K antagonists) and protamine (for heparin) the same array of prohemostatic agents – unactivated or activated prothrombin complex concentrate, and activated factor VIIa – have been tried for almost all anticocoagulants in different models, and for some agents also in patients, with varying success. Hemodialysis can reduce the level of dabigatran efficiently and activated charcoal may be used for very recent oral ingestion of lipophilic agents. In view of the shorter half life of the new agents compared to warfarin the need for reversal agents may be less critical. Nevertheless, highly specific reversal agents for the thrombin- and factor Xa-inhibitors are under development and might be available within two years.

Introduction

Vitamin K antagonists (VKA) have been widely used for the prevention and treatment of arterial and venous thromboembolism for more than 50 years. During the last ten years the clinical armamentarium has expanded to include several new oral anticoagulants (NOACs) based on high quality evidence from large randomized clinical trials [1]. These agents have several advantages over the VKA with more predictable pharmacokinetics and pharmacodynamics, fewer drug and food interactions allowing fixed dose regimens and eliminating the need for regular monitoring. However unlike for warfarin there are no specific antidotes available for urgent reversal and there is little to no evidence to guide practical management when patients present with bleeding complications or need reversal for urgent interventional procedures. A recent population based review noted rapid growth in the uptake of NOACs, in particular dabigatran, within the 2 years of its approval in Ontario, Canada, specifically in patients aged 85 years and older [2]. There was also a 14% decline observed in warfarin prescriptions. This highlights the need for evaluation of therapeutic strategies to reverse the anticoagulant state. Our review will focus on the available literature and suggest practical strategies for reversal and management of both the older and newer anticoagulants.

Mechanisms of action of antithrombotic agents

Vitamin K antagonists

These agents inhibit the regeneration of vitamin K, a cofactor in the gamma carboxylation of coagulation factors II, VII, IX and X as well as protein C, S and Z. The pharmacodynamics and pharmacokinetics of the most widely used VKA, warfarin, are well described elsewhere [3]. The anticoagulant effects of warfarin are affected by genetic variability of involved cytochrome P450 and vitamin K epoxide reductase enzymes, multiple drugs and dietary supplements. Due to these interactions constant monitoring is required to maintain therapeutic international normalized ratio (INR). Whether genotyping would improve warfarin dose prediction and optimization was studied in three recently published randomized trials [4-6]. One trial showed that genotype based dosing was similar to clinically guided dosing of warfarin in the initial 4 weeks of anticoagulation and the second trial showed similar results for acenocoumarol or phenprocoumon during 12 weeks of initiation therapy. The third trial showed that pharmacogenetic based dosing was associated with a higher percentage of time in therapeutic range versus standard dosing during the first 12 weeks of warfarin initiation but none of the trials demonstrated a benefit in clinically important outcomes.

* Corresponding author at: Thrombosis Service, HHS-General Hospital, 237 Barton Street East, Hamilton, ON, L8L 2X2, Canada. Tel.: 1-905-5270271, ext 44479; fax: 1-905-5270271.
E-mail address: schulms@mcmaster.ca (S. Schulman).

0049-3848/$ – see front matter

Heparins

Unfractionated heparin (UFH) is a mixture of sulfated glycoaminoglycans of varying molecular weight and inhibits several coagulation factors by binding to antithrombin causing a conformational change and augmenting its inhibition 1000 fold. Low molecular weight heparin (LMWH) is obtained by depolymerization and/or fractionation of UFH and has predominant factor Xa inhibiting effect. Fondaparinux is a pentasaccharide that effectively binds and potentiates antithrombin to block factor Xa. The half life of UFH following intravenous injection is 1 to 2 hours and the half life of different LMWHs ranges from 3 to 12 hours. The limitations of heparin are based on its pharmacokinetic and biophysical properties [7]. Pharmacokinetic limitations result in variable anticoagulant response to heparin and are caused by antithrombin independent binding of heparin to plasma proteins and proteins released from platelets and endothelial cells. Biophysical limitations include osteopenia and heparin induced thrombocytopenia. These limitations are less evident with LMWH.

Oral direct thrombin inhibitors

Thrombin plays a key role in the coagulation cascade by mediating the conversion of fibrinogen to fibrin as well as physiologically activating platelets, several other coagulation factors, the protein C-pathway and endothelial receptors. Ximelagatran was the prototype oral drug that was first developed in this family but was subsequently withdrawn from the market due to serious hepatic side effects [8]. Dabigatran etexilate is a prodrug that does not have the risk profile of its predecessor, with a bioavailability of 6.5%. Its half life is 12-17 h in patients with normal renal function and it reaches the maximum serum concentration within 1.5-3 h after ingestion. It is 80% eliminated by the renal route and 35% protein bound [9].

Dabigatran demonstrated similar efficacy as enoxaparin for prophylaxis after hip [10,11] and knee arthroplasty [12] and was as effective as warfarin for acute management [13] and extended maintenance therapy for venous thromboembolism (VTE) [14]. It was non-inferior to warfarin (110 mg bid) and superior to warfarin (150mg bid) for stroke prevention in atrial fibrillation [15]. Based on these clinical trials dabigatran is currently approved for stroke prophylaxis in atrial fibrillation (SPAF) (Europe, North America) and for VTE prevention after major orthopedic surgery (not in the United States).

Oral factor Xa inhibitors

Rivaroxaban and apixaban are the first agents approved from this class of drugs. They act by reversibly blocking factor Xa at the active site. Their bioavailability is higher compared to that of dabigatran (rivaroxaban-80%, apixaban-60% and edoxaban-50%). Peak concentration is achieved within 1-4 h. They are less dependent on renal excretion (rivaroxaban-33% [active drug], apixaban- 25% and edoxaban-35%) [16].

Rivaroxaban was evaluated in a series of clinical trials in patients undergoing major orthopedic surgery for thromboprophylaxis and demonstrated higher efficacy compared to enoxaparin with similar bleeding rates [17-20]. It was non-inferior to warfarin in patients with atrial fibrillation [21] and for acute and extended management of VTE [22,23]. This has led to its approval for thromboprophylaxis after major orthopedic surgery, SPAF and VTE treatment.

Apixaban was also compared to enoxaparin in patients undergoing knee [24,25] and hip replacement surgery [26] and was shown to be equally effective with significantly fewer bleeding complications. Two phase III trials found that apixaban was more effective for stroke prevention than either aspirin or warfarin in patients with atrial fibrillation, with a similar (versus aspirin) [27] or improved (versus warfarin) [28] safety profile. It was non-inferior to warfarin in treatment of VTE and was associated with significantly lower bleeding rates [29]. Based on these studies it also has been approved for SPAF (North America, Europe) and VTE prevention after major orthopedic surgery.

Edoxaban has also recently been evaluated as an alternative to warfarin in phase III trials for VTE [30] and atrial fibrillation [31] demonstrating non-inferiority in both patient populations with significantly lower rates of bleeding.

Bleeding rates and risk factors for bleeding on anticoagulants

Vitamin K antagonists and heparins

Regardless of the choice of anticoagulant the risk of bleeding remains a threat even when maintained within therapeutic ranges.

The use of VKA increases the risk of major bleeding by 2-3% per year and the risk of intracranial hemorrhage by approximately 0.2% per year [32]. Some of the determinants of major bleeding have been identified and include the intensity of anticoagulation, concomitant use of drugs that interfere with hemostasis like antiplatelet, non-steroidal anti-inflammatory drugs or cyclooxygenase inhibitors, patient characteristics (age, comorbidities like hypertension, diabetes mellitus, cerebrovascular disease, ischemic stroke, cardiovascular disease, renal insufficiency, liver disease, malignancy and alcoholism) and the length of therapy [33].

The incremental risk of major hemorrhage with heparins varies between 0% and 2% [33]. The risk is dependent upon the intensity of anticoagulation, underlying disease and concomitant medications similar to VKAs. Renal failure, patient age, and sex have also been implicated as risk factors for heparin-induced bleeding in case series [33]. LMWH should be used with caution in patients with impaired renal function and evidence exists that the resultant bioaccumulation may cause bleeding [34]. Prophylaxis with fondaparinux at a daily dose of 2.5 mg is associated with less bleeding than a therapeutic dose of LMWH [35] but similar bleeding as UFH [36] and prophylactic LMWH [37]. Time of first injection was inversely related to risk of major bleeding as well as overt bleeding in one meta-analysis of studies with fondaparinux and age has also been determined as a risk factor [37].

The new anticoagulants

The NOACs have shorter half-life and wider therapeutic window and are speculated to have lower rates of bleeding. Theoretically the same determinants or factors considered being predictive risk factors for increased bleeding risk for VKAs are applicable to the NOACs. Renal impairement is an important risk factor given that the agents are renally excreted. In a *post hoc* analysis of the major bleeding events in the RE-LY study only age was determined to be an independent risk factor [38]. In a recent prespecified analysis of the RE-LY study age was also found to be the most important covariate and bleeding outcomes were correlated with dabigatran plasma concentrations [39]. In a long-term follow-up study of cohorts from the randomized trial in atrial fibrillation dabigatran was associated with higher bleeding rates at the 150 mg twice daily dose in comparison with 110 mg twice daily [40]. Rates of major hemorrhage were 3.74% and 2.99% per year on dabigatran 150 mg and 110 mg, respectively (hazard ratio, 1.26; 95% confidence interval, 1.04-1.53). In another subgroup