Thrombosis Research 133 (2014) 705–713

Contents lists available at ScienceDirect

Thrombosis Research

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

Review Article

# Reversal of New, Factor-specific Oral Anticoagulants by rFVIIa, Prothrombin Complex Concentrate and Activated Prothrombin Complex Concentrate: A Review of Animal and Human Studies

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ARTICLE INFO

*Article history:*
Received 24 November 2013
Received in revised form 23 January 2014
Accepted 26 January 2014
Available online 31 January 2014

*Keywords:*
anticoagulant
coagulation factor
factor VIIa
prothrombin complex concentrates

ABSTRACT

*Introduction:* Recombinant activated factor VII (rFVIIa), prothrombin complex concentrate (PCC) and activated PCC (aPCC) are three non-specific haemostatic agents sometimes employed to reverse new, factor-specific oral anticoagulants.
*Methods:* We conducted a review in the literature to compare the abilities of rFVIIa, PCC and aPCC to reverse factor-specific anticoagulants. MEDLINE and EMBASE databases were searched up to Oct 2013.
*Results:* Eleven animal studies and two human trials met predefined inclusion criteria. To account for dosing variations of anticoagulants among studies, data were interpreted based on standards referenced from human trials at therapeutic doses. In animal studies, inconsistencies in the reversal abilities of rFVIIa, PCC and aPCC can be partly attributed to inter-species differences in the affinity among various clotting factors and tissue factors. Moreover, the differences in the affinity between species-specific clotting factors and anticoagulants that were initially designed to inhibit human factor may impose additional obstacles when comparing single factor rFVIIa with agents that contained multiple clotting factors. In the absence of a common clinical indication for the utilization of rFVIIa, PCC and aPCC, it is difficult, if not impossible, to establish an equivalent dose among these haemostatic agents when comparing their effectiveness in reversing factor-specific oral anticoagulants. Human trials were too few and sub-optimally designed to draw definite conclusions.
*Conclusion:* While preclinical studies may hint at a role for these haemostatic agents in reversing the anticoagulant effects of oral, factor-specific anticoagulants, existing trials offer inconclusive evidence to guide a clinical decision among individual agents with respect to potency and thrombosis risk. The mechanistic differences of these hemostatic agents in terms of their interactions with other coagulation factors impose major obstacles for the scientists using animal models to compare the efficacy of these reversal agents.


**Contents**



*Abbreviations:* AF, atrial fibrillation; aPCC, activated prothrombin complex concentrates; BID, twice daily; $C_{max}$, maximal plasma concentration; F, coagulation factor; FEIBA, factor eight inhibitor bypass activity; PCC, prothrombin complex concentrates; rFVIIa, activated recombinant factor VII; TF, tissue factor; VTE, venous thromboembolism.

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0049-3848/$ – see front matter 
http://dx.doi.org/10.1016/j.thromres.2014.01.031

## Introduction

New factor-specific oral anticoagulants have shown tremendous potential in the management of thrombotic disorders. Many large randomized clinical trials have confirmed the effectiveness of these target-specific anticoagulants in the treatment of venous thromboembolism (VTE) [1], prevention of cerebrovascular embolism in patients with atrial fibrillation (AF) [2,4] and thromboprophylaxis in patients undergoing orthopaedic surgery [5-8]. Compared with traditional anticoagulants, these new anticoagulants have several advantages: predictable pharmacokinetics following oral administration so that patients require minimal to no monitoring, a rapid onset but sustained anticoagulant effect, and less drug-drug and drug-diet interactions than traditional vitamin K antagonist. These new anticoagulants either target activated clotting factor X (FXa) or II (FIIa), both of which are involved in the propagation and amplification of thrombosis. All anticoagulants, however, are imbued with the risk of bleeding complications.

When patients on factor-specific oral anticoagulants develop clinically significant bleeding requiring immediate reversal of anticoagulation, the lack of a specific antidote presents a major hurdle for clinicians. Although the development of specific antidotes such as recombinant Xa and monoclonal antibodies against dabigatran etexilate is promising, nothing yet has been approved for clinical use [9-11]. When such patients require reversal, presumptive options are haemostatic agents such as recombinant FVIIa (rFVIIa) and Factor Eight Inhibitor Bypass Activity (FEIBA), an activated prothrombin complex concentrate (aPCC), developed for the treatment of haemophilia patients with inhibitors. Prothrombin complex concentrate (PCC) that was used for decades as the treatment for FIX replacement in haemophilia B patients, and now commonly used to reverse warfarin therapy, may also have the potential to reverse these new oral anticoagulants.

Yet, these non-specific antidotes, particularly rFVIIa and aPCC are double-edged swords because they can potentially aggravate the underlying thrombotic condition. The prothrombotic potential of rFVIIa, PCC and aPCC has been studied in other clinical contexts. The use of rFVIIa increased the risk of arterial thromboembolism with an odd ratio of 1.68 although there was no significant increase in the incidence of venous thrombosis in a meta-analysis of non-hemophilic clinical trials [12]. For patients receiving PCCs and FEIBA for the reversal of warfarin-induced coagulopathy, the risks of thromboembolism were 3.8% and 13.9%, respectively [13,14].

In the absence of high-quality clinical studies comparing the reversal agents for factor-specific anticoagulants using morbidity or mortality as analytic endpoints, managing physicians are left to extrapolate results from preclinical studies. This review will summarize and evaluate the available evidence relating to the abilities of rFVIIa, PCC and aPCC to reverse oral factor-specific anticoagulants.

## Methods

### *Search Strategy*

The databases OVID MEDLINE (1946 – Oct 2013) and EMBASE (1974 – Oct 2013) were searched using the keywords: anticoagulant and reversal. The search strategy was determined *a priori* and conducted in duplicate by two reviewers (FL and HC).

### *Study Selection*

This review focuses on the current evidence relating to the potential roles of rFVIIa, PCC and aPCC as viable reversal agents for the oral, factor-specific anticoagulants. We were interested in primary animal studies using mortality or other clinically relevant surrogate markers defined *a priori* to investigate the efficacy of these reversal agents. The information regarding *in vivo* bleeding end-point was considered more important than *in vitro* or *ex vivo* parameters. We also elected to include two human trials using *ex vivo* parameters as experimental endpoints to assess the potency of these haemostatic agents.

### *Data Collection*

The information gathered was evaluated independently by two reviewers (FL and HC). The selected data included study subjects, method of inducing hemorrhage, experimental endpoints, the dosing of anticoagulants and reversal agents, as well as the key results of the studies (Table 1).

### *Method Used to Standardize the Evaluation*

Anticoagulants were dosed variably among studies. To standardize the doses of anticoagulants for comparison, we preferred plasma concentrations instead of actual doses. Plasma concentrations were most reflective of actual drug availability systematically, which offered the best correlation when the data were extrapolated from animal to human studies. When evaluating animal studies, we compared maximal plasma concentrations of dosing regimens used in animals with our predefined $C_{max}$ levels obtained from human trials. When plasma concentration of anticoagulant was not available, conversion from a human dose was based on a standard body weight of 70 kg to compare with the weight-based dosing regimen in animal studies.

Dabigatran etexilate at 150 mg twice daily (BID) was used as our dosing standard, retrieved from landmark trials studying the treatment of AF and VTE [2,15]. The plasma concentration of this dose was studied in two pharmacokinetic studies showing peak ($C_{max}$) levels 254 ng/mL in one study and 184 ng/mL in the other [16,17], thus an average of 220 ng/mL was chosen as the standard peak concentration in this review. Melagatran is the active form of the oral thrombin inhibitor, ximelagatran. Due to hepatotoxicity, further clinical investigation has been halted since 2005 [18]. However, since melagatran may have a similar mechanism of action compared with dabigatran, we elected to include the data so that we could comprehensively compare the reversal of anti-FIIa and anti-FXa inhibitions. Before its removal from clinical use, ximelagatran at 36 mg BID was used in the treatment of VTE in a large randomized study [19]. At this dose, pharmacokinetic analysis showed that the peak plasma concentration of melagatran was 0.4-0.5 μmol/L [20]. Additionally, in a study administrating melagatran parentally to normal human volunteers, 12.5 mg melagtran administered at 0.29 mg/mL over 10 min, followed by an infusion of 0.033 mg/min