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REGULAR ARTICLE

Prothrombin complex concentrate versus recombinant factor VIIa for reversal of coumarin anticoagulation

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Abstract

Introduction: Prothrombin complex concentrate (PCC) is recommended for emergency reversal of oral coumarin anticoagulation. Recently, recombinant factor VIIa (rFVIIa) has also been investigated for this purpose, although no direct comparison of PCC and rFVIIa has been reported. This study was designed to compare the effectiveness of PCC and rFVIIa for reversal of both acute and sustained coumarin anticoagulation.
Materials and methods: In the acute model, rats received 2.5 $mg \cdot kg^{-1}$ phenprocoumon, and reversal of anticoagulation by 4.88 $mL \cdot kg^{-1}$ saline, 100 $\mu g \cdot kg^{-1}$ rFVIIa (NovoSeven) or 50 $U \cdot kg^{-1}$ PCC (Beriplex P/N) was assessed at 16 h. For the sustained model, a second phenprocoumon dose was administered at 24 h and anticoagulation reversal evaluated at 48 h. Study endpoints were activated partial thromboplastin time (aPTT), prothrombin time (PT) and tail tip bleeding.
Results: Acute anticoagulation raised median PT to 4.3 fold the normal level. This elevation was nearly completely reversed both by rFVIIa and PCC. aPTT increase was minor. Effects of sustained anticoagulation were more severe and pervasive, with aPTT, PT and blood loss increasing to 7.7, 51 and 30 fold the control levels, respectively. In the sustained model, rFVIIa substantially reduced and PCC fully normalized PT. In this model, PCC also diminished aPTT ($p<0.01$), fully normalized blood loss ($p<0.01$) and shortened bleeding time ($p=0.008$), while rFVIIa was without significant effect on these endpoints.

Abbreviations: aPTT, activated partial thromboplastin time; CI, 95% confidence interval; FFP, fresh frozen plasma; INR, international normalized ratio; IQR, interquartile range; PCC, prothrombin complex concentrate; PT, prothrombin time; rFVIIa, recombinant factor VIIa.

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Conclusions: In a sustained anticoagulation animal model designed to simulate standard long-term oral coumarin therapy in patients, PCC was more effective than rFVIIa in restoring hemostatic function.

Introduction

Coumarin oral anticoagulants, such as warfarin, phenprocoumon and acenocourmarol, are increasingly used long term to prevent thromboembolism in patients with stroke risk due to atrial fibrillation, mechanical heart valves, susceptibility to venous thrombosis and anti-phospholipid syndrome [1]. These agents display a narrow therapeutic index, with wide inter-individual and intra-individual variations in dosage requirements. The primary complication of coumarin oral anticoagulant therapy is bleeding, and intracranial hemorrhage is a particularly serious complication [1,2]. In cases of acute major bleeding, emergency surgery or highly elevated international normalized ratio (INR), rapid reversal of coumarin action becomes imperative [1,2].

Coumarin oral anticoagulants act by inhibiting the synthesis of functional vitamin K-dependent coagulation factors II, VII, IX and X, and thus create a functional deficiency of these proteins. These factors require γ-carboxylation by vitamin K for biological activity, and by inhibiting the vitamin K conversion cycle, coumarins induce hepatic production of partially decarboxylated proteins with reduced coagulant activity [2]. Coumarins also produce a functional deficit of anticoagulant proteins C and S.

For rapid reversal of warfarin effects, a number of recent clinical guidelines have recommended the use of either prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP), both of which contain the full complement of vitamin K-dependent coagulation factors [2—7]. Several studies have shown that PCCs can reverse warfarin-related coagulopathy more rapidly than FFP [8—12]. The vitamin K-dependent clotting factors are present in a concentrated form in PCCs, which can be administered within minutes without the need for checking the blood group or thawing the product, as is the case with FFP [13]. Moreover, unlike most FFP preparations, PCCs are prepared using viral inactivation methods [14].

Beriplex® P/N (ZLB Behring GmbH, Marburg, Germany), a biochemically well-characterized plasma-derived PCC prepared using pasteurization and nanofiltration, contains coagulation factors II, VII, IX and X, as well as anticoagulant proteases antithrombin III and proteins C and S [14,15]. This PCC reverses warfarin-induced overanticoagulation rapidly [16—19]. Recently, several case reports and case series suggested that Novo-Seven® (Novo Nordisk A/S, Bagsværd, Denmark), a recombinant factor VIIa (rFVIIa) preparation, can also be successfully used for emergency reversal of warfarin overanticoagulation [20—25].

No studies directly comparing rFVIIa and PCC for rapid reversal of coumarin overanticoagulation have been reported thus far. The present study compares the reversal by rFVIIa and PCC of coagulation and bleeding abnormalities in rats resulting from acute or sustained anticoagulation with phenprocoumon, a coumarin compound with a comparatively long half-life of 3—5 days that is very commonly used in Europe.

Materials and methods

This open-label study was designed to compare directly the effectiveness of saline, rFVIIa and PCC for the reversal of coumarin anticoagulation. These three test agents were compared in models of both acute and sustained anticoagulation. The study design is illustrated in Fig. 1.

Animals

Female rats 6—8 weeks old weighing 190—220 g (Charles-River Wiga, Sulzfeld, Germany) were housed at 21—22 °C and 40—50% relative humidity under a 12 h/12 h light—darkness cycle in macrolon cages with bedding of wood shavings. The animals were provided tap water ad libitum and fed standard rat chow (Ssniff-Versuchsdiäten, Soest, Germany). All animals received care in compliance with the European Convention on Animal Care, and the study was approved by the institutional Ethics Committee.

Anticoagulation

For both models of acute and sustained anticoagulation, a single 2.5 mg · kg^{-1} dose of phenprocoumon (Marcumar®, Hoffmann-La Roche AG, Grenzach-Wyhlen, Germany) was administered p.o. at baseline. In the sustained anticoagulation model, a second 2.5 mg · kg^{-1} dose was given p.o. after 24 h.