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Issues complicating precision dosing for factor VIII prophylaxis

Leonard A. Valentino[a], Peter L. Turecek[b,c,*], Herbert Gritsch[b], Saulius Butenas[d], Kenneth G. Mann[d,e]

[a] Rush University, Chicago, IL, USA
[b] Shire, Vienna, Austria
[c] University of Vienna, Vienna, Austria
[d] University of Vermont, Burlington, VT, USA
[e] Haematologic Technologies, Essex Junction, VT, USA

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ABSTRACT

We previously showed that personalizing prophylaxis on the basis of an individual's pharmacokinetic (PK) response to factor VIII (FVIII) infusion reduces joint and other bleeding events in patients with hemophilia A. We theorized that the FVIII assay used, FVIII product selected, and interpatient differences impact PK assessment and the ability to precisely dose prophylaxis.

A comprehensive search of the literature for articles published from January 2004 to September 2017 was performed to identify the variables associated with these three domains.

Collectively, product- and patient-related assay discrepancies, variability among plasma-derived and unmodified and modified recombinant FVIII products, and interpatient differences in the response to FVIII infusions are obstacles to precision prophylactic dosing.

Stringent laboratory quality assurance programs and proficiency testing to improve the accuracy of FVIII measurement, the widespread use of PK assessment to fine-tune FVIII dosing, and new research to identify patient characteristics and other contributors to bleeding risk and complication development are essential to optimizing outcomes for patients with hemophilia A receiving FVIII prophylaxis.

1. Introduction

Prophylaxis is recommended as optimal care for children and adults with severe hemophilia A [1,2], yet a generic approach is not ideal, possibly leading to inefficient or unnecessarily costly dosing. Using an individual's pharmacokinetic (PK) response to factor VIII (FVIII) infusions to calculate the dose and dosing frequency is one strategy for personalizing the prophylactic regimen [3–5]. We previously showed that PK-guided prophylaxis is as effective as standard thrice-weekly prophylaxis in preventing joint and other bleeding events and may allow the dosing interval to be extended [6]. Yet PK is not immutable, and the FVIII assay used, FVIII product selected, and interpatient differences all have the potential to impact the PK assessment and, thus, the ability to precisely dose prophylaxis.

Here, we consider the influence of these three domains on FVIII PK and examine how they may complicate efforts at precision prophylactic dosing for patients with hemophilia A. In addition, we speculate on opportunities to reduce the influence of these factors with the intent of determining a more precise dosing strategy.

2. Methods

We conducted a search of the Medline database from January 2004 to September 2017 for English-language articles pertaining to variability in FVIII assays, FVIII products, and patients with hemophilia A. To remedy the lack of systematic studies investigating the influence of von Willebrand factor (VWF) on assays of FVIII-deficient plasma, we performed a one-stage clotting assay according to a pharmacopoeia method [7]. The assay was run on a coagulation analyzer and was based on the activated partial thromboplastin time (aPTT) clotting assay. Equal volumes of activator reagent, FVIII-deficient plasma, and diluted test sample were incubated at 37 °C for 4 min until a complex was formed, after which calcium chloride was added. Time to clot formation was recorded, and a reference curve constructed from different dilutions of the World Health Organization (WHO) 8th International Standard FVIII Concentrate was used to assign FVIII activity from

* Corresponding author at: Department of Pharmacology and Toxicology, University of Vienna and Senior Director, Global Medical Affairs, Shire, DC-Tower, Donau-City-Straße 7, 1220 Vienna, Austria.
E-mail address: peter.turecek@shire.com (P.L. Turecek).

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unknown samples. A commercially available FVIII-deficient plasma devoid of VWF was supplemented with increasing amounts of a highly pure recombinant VWF (rVWF) preparation. This plasma was used for preparation of the predilution to 1 international unit (IU) FVIII/mL for both the standard and test sample. A commercial FVIII-deficient plasma with a high VWF concentration was used as the control.

3. Results

3.1. Selection of an FVIII assay

FVIII primarily functions as a cofactor for activated factor IX (FIXa) in the activation of factor X (FXa). This activity can be measured downstream of the coagulation cascade by monitoring clot generation, or upstream by directly measuring FXa enzymatic activity following activation by the FVIIIa-FIXa (tenase) complex [8]. The accurate assessment of FVIII coagulant activity (FVIII:C) is essential for: 1) establishing the diagnosis of hemophilia A; 2) determining the severity of the bleeding phenotype; 3) identifying the post-infusion bioavailability and PK of FVIII concentrates; 4) monitoring FVIII replacement therapy (including perioperative) and prophylaxis; and 5) assigning potency to FVIII concentrates, which defines the quantity of active ingredient in a vial of drug product, guides dosing, determines pricing, and is required by regulatory authorities for product release [9,10].

3.1.1. Types of assays

Three assays are currently available for measuring FVIII in biologic samples: the one-stage (OSA) and two-stage (TSA) clotting assays and the chromogenic substrate assay (CSA) (Fig. 1A-C). All measure FVIII:C in generating FXa in the presence of calcium ions and phospholipids [11,12]. Because the TSA is more difficult to automate than the OSA, and since the principle and results for the TSA are similar to the CSA, the OSA and CSA are preferentially used [10,13].

The OSA (Fig. 1A) is based on correction of the prolonged aPTT by dilution of the patient's plasma into substrate plasma from a FVIII-deficient individual or normal plasma made FVIII deficient via immunochemical absorption, both of which are phenotypically variable [9]. This assay relies on the intrinsic coagulation pathway, in which the reaction is initiated by a contact activator (ie, ellagic acid, kaolin, silica, Celite®, polyphenols), is propagated by natural or synthetic phospholipids, and ends with fibrinogen clotting [9,10,14]. Owing to its simplicity, the availability of reagents, ease of automation, and lower cost relative to the CSA, the OSA is used by the vast majority of clinical laboratories worldwide [15–17] and is required by the US Food and Drug Administration for the assignment of FVIII concentrate potency [18]. Accurate potency assignment is necessary to: 1) define the quantity of active substance in a vial, thereby ensuring safety and efficacy and allowing comparison among products; 2) uphold the integrity of the IU; and 3) guide dosing [19].

The CSA (Fig. 1C) is based upon quantitation of FXa as a measure of FVIIIa cofactor activity on FIXa [15]. Two sequential reactions initially form FXa, after which a chromogenic substrate specific for FXa is enzymatically cleaved and photometrically quantified (Fig. 1B) [9,10,20]. The CSA is the reference method for FVIII potency designation required by the European Pharmacopoeia and used by the International Society on Thrombosis and Haemostasis for this purpose [15,18].

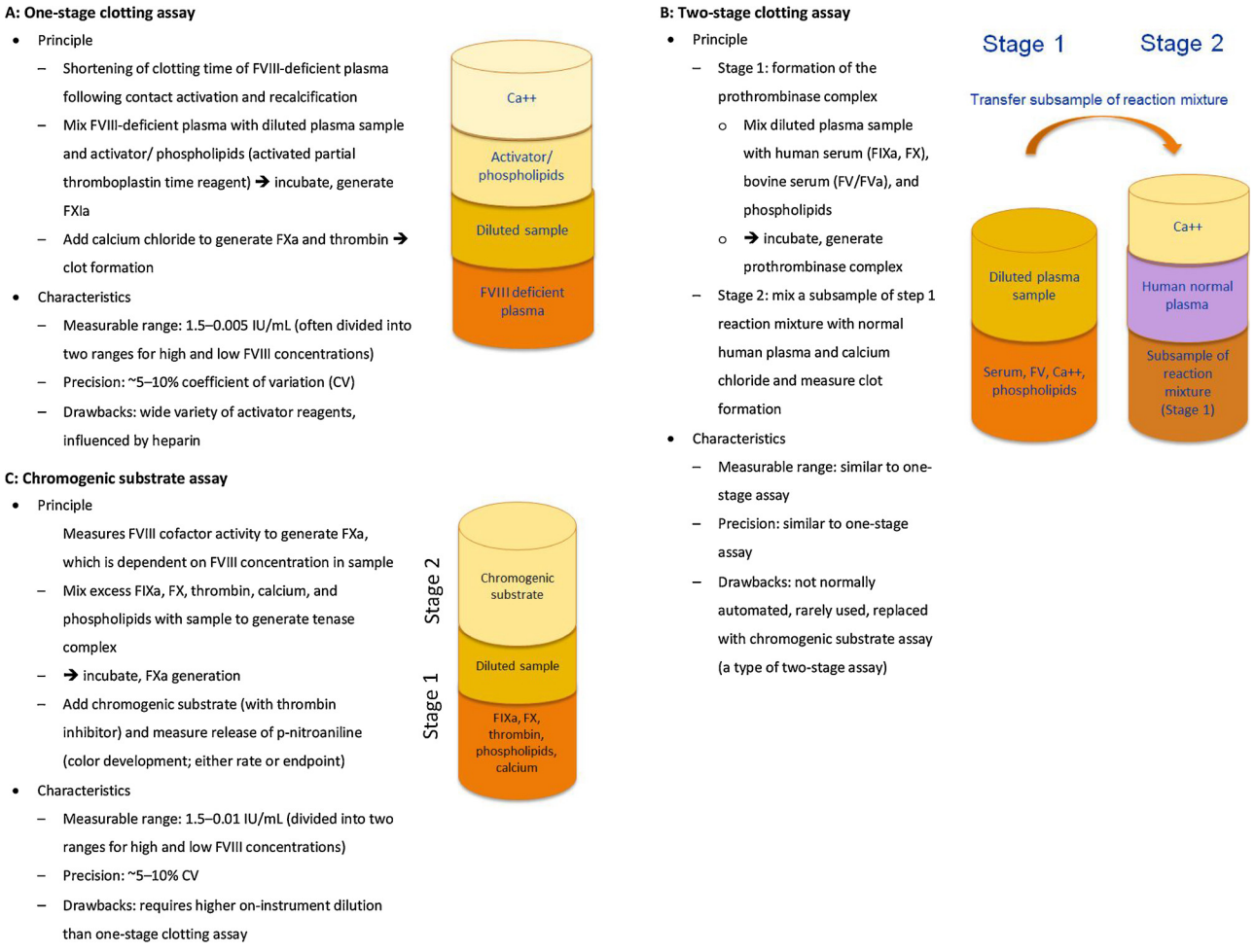

Fig. 1. Types of FVIII clotting assays.