Journal of Thrombosis and Thrombolysis (2019) 47:369–374
https://doi.org/10.1007/s11239-018-1771-6

Adjusted versus actual body weight dosing of 4-factor prothrombin complex concentrate in obese patients with warfarin-associated major bleeding

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Published online: 20 November 2018

Abstract

The package insert of 4-factor prothrombin complex concentrate (4F-PCC) contains specific dosing recommendations stating to determine the patients dose based on their INR and weight, capping the weight at 100 kg. However, the mean body mass index (BMI) in the 4F-PCC U.S. approval study was 27 kg/m^2, and there is a lack of literature identifying the ideal dosing strategy in obesity. We conducted a retrospective analysis of obese patients (BMI ≥ 30 kg/m^2) who received 4F-PCC for warfarin associated emergent bleeding reversal. Treatment groups were those that received 4F-PCC on adjusted body weight (AdjBW) and those on actual body weight (ActBW). The primary outcome was the percent of patients achieving coagulopathy reversal, defined as a post-treatment INR < 1.4 for neurologic indications and < 1.5 for all others. A total of 78 obese patients were included (28 AdjBW and 50 ActBW). Baseline INR (3.1 vs. 2.8; p = 0.052) and BMI (33.6 vs. 33.6 kg/m^2) were similar between groups. Achievement of goal INR was significantly lower in the AdjBW group (36% vs. 68%; p = 0.006). A majority of patients had intracranial hemorrhage (32% vs. 54%; p = 0.06), and the median dose of 4F-PCC was lower in the AdjBW group (2120 vs. 2500 units; p = 0.02). Dosing 4F-PCC using adjusted body weight in obese patients resulted in a significantly lower rate of coagulopathy reversal. ActBW should be used to dose 4F-PCC in obese patients when the 100 kg dose cap is utilized per the package insert recommendations.

Keywords Anticoagulation therapy · Hematology · Hemorrhagic disorders · Prothrombin · Obesity

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11239-018-1771-6) contains supplementary material, which is available to authorized users.

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Highlights

- The appropriate dosing strategy for 4-factor prothrombin complex concentrate (4F-PCC) in obesity is unknown
- We compared the reversal of warfarin utilizing adjusted vs. actual body weight to dose 4F-PCC in obese patients
- Attainment of goal INR was significantly less likely in the adjusted body weight dosing group
- Dose 4F-PCC based on the package insert and use actual body weight (max 100 kg) in the obese patient population

Introduction

One in three adults in the United States are classified as being obese, which is defined as a body mass index (BMI) ≥ 30 kg/m^2 [1]. Despite the high prevalence of obesity, optimum medication dosing strategies for this

population are limited. Package inserts provide minimal guidance on alterations in pharmacokinetic parameters in those with high body weights, as most pre-clinical studies that define recommended doses do not include a significant amount of obese patients. Data are further limited when evaluating the impact obesity has on medications used to reverse bleeding [2]. The dosing recommendations in the package insert of 4-factor prothrombin complex concentrate (4F-PCC) (Kcentra, CSL Behring GmbH, Marburg, Germany) for warfarin associated bleeds are specified as: the patient's weight (capped at 100 kg) multiplied by a standardized 4F-PCC dose based on unactivated Factor IX units stratified by baseline INR (Fig. 1) [3].

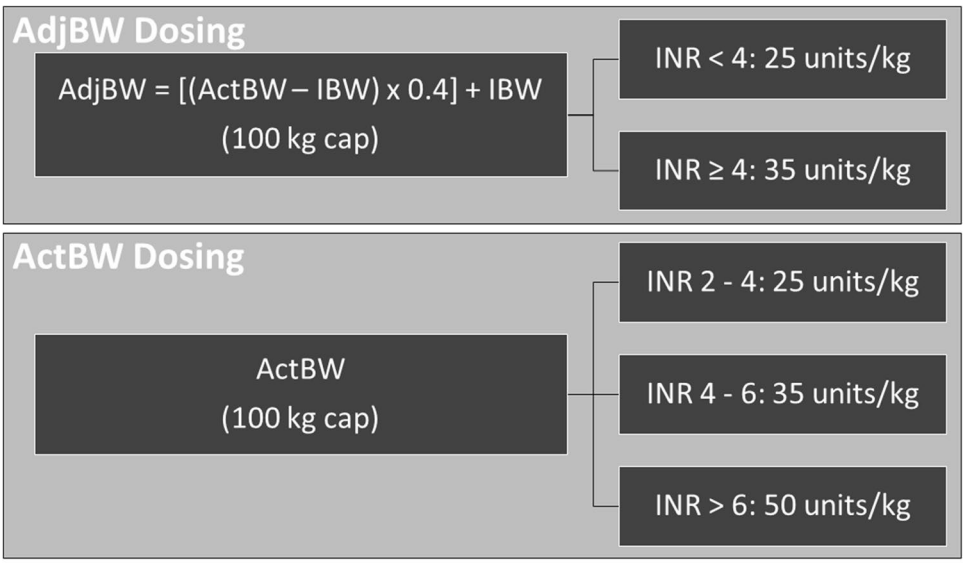
The dosing cap of 100 kg recommended in the package insert of the 4F-PCC product in the United States may oversimplify the complexity of providing an appropriate dose in the obese population which has been observed with other factor products. A cross-over study with six adult obese (BMI 30–45.8 kg/m^2) hemophilia A patients requiring Factor VIII found comparable clinical and pharmacokinetic data with ideal body weight dosing compared to using actual body weight (ActBW). This resulted in nearly a 50% reduction in factor use with an annualized mean savings of $133,000 per patient (2013 US Dollars) [4]. A case report describing the use of adjusted body weight (AdjBW) for activated factor VII in a morbidly obese patient (BMI 61 kg/m^2) with acquired hemophilia A requiring emergent surgery objectively assessed hemostasis utilizing ROTEM and prothrombin time (PT). While neither directly measures the amount of activated factor VII, they revealed successful hemostasis utilizing AdjBW without thrombosis-related complications. In this single patient, 132 mg of rFVIIa were saved throughout an 8-day treatment period which resulted in a cost avoidance of $200,000 (2016 USD) [2].

Upon adding 4F-PCC to formulary in December of 2015 one center included in this study implemented a 4F-PCC dosing protocol as a cost savings initiative based on adjusted body weight; understanding 4F-PCC is a hydrophilic medication and that this dose adjustment may provide sufficient blood concentrations of factor products and decrease the incidence of unwanted thrombotic events [5]. Our study directly compared the rates of successful INR reversal in utilizing AdjBW versus (vs.) ActBW in dosing 4F-PCC in obese patients (BMI ≥ 30 kg/m^2) experiencing a life-threatening hemorrhage while on warfarin.

Methods

This retrospective study was conducted at four academic medical centers in the United States and included a secondary analysis of a previously published, IRB-approved study that included patients discharged between January 1, 2012 to April 5, 2015 in addition to patients treated between December 1, 2015 to March 1, 2018 at one institution utilizing AdjBW for dosing 4F-PCC (Kcentra, CSL Behring GmbH, Marburg, Germany) in obesity [6].

We included patients ≥ 18 years of age who were treated with 4F-PCC for reversal of warfarin due to intracranial hemorrhage (ICH), gastrointestinal (GI) hemorrhage, other bleeding, or who required emergent reversal for acute surgical intervention. Exclusion criteria included those without a documented baseline INR or a baseline INR < 2.0, and patients who received 4F-PCC for indications other than reversal of warfarin associated major bleeding. Patients



AdjBW = adjusted body weight; ActBW = actual body weight; IBW = ideal body weight (Males: IBW = 50kg + 2.3kg for each inch over 5 feet / Females: IBW = 45.5kg + 2.3kg for each inch over 5 feet); INR = international normalized ratio; kg = kilogram

Fig. 1 4-Factor prothrombin complex concentrate dosing algorithms

were divided into two groups, those that received 4F-PCC dosed based on AdjBW and those who were dosed based on ActBW (Fig. 1) [3].

Investigators at each site extracted all data from their institution's electronic medical record. The primary outcome was the percent of patients achieving goal INR (< 1.4 for any intracerebral hemorrhage and < 1.5 for all other indications) at initial follow-up INR after 4F-PCC administration [7, 8]. Other data collected included age, height, body weight, ethnicity, gender, indication for 4F-PCC use, administration of vitamin K and/or fresh frozen plasma (FFP), baseline and subsequent INR results, and PCC dosing information. Secondary outcomes included discharge status and incidence of any major thrombotic events (myocardial infarction, acute ischemic stroke, pulmonary embolism, and deep vein thrombosis) within 7 days of PCC administration. A post-hoc analysis was performed in the ActBW and AdjBW group to assess the efficacy of the 100 kg max recommended in the package insert.

Statistics

Continuous data were analyzed using the Student *t* test for parametric data and Mann–Whitney *U* test for nonparametric data. Categorical data were analyzed using either the χ^2 test or Fisher exact test. Normally distributed data are presented as mean (standard deviation) and non-normally distributed data are presented as median (25–75% interquartile range (IQR)). All tests were 2-tailed, and $p < 0.05$ was used to represent statistical significance. Baseline parameters with p values ≤ 0.2 were evaluated for effect on the primary outcome utilizing mixed stepwise multivariable binomial logistic regression analysis. These data are presented as odds ratios (OR) and 95% confidence intervals. All analysis was performed using JMP®, Version *14*. SAS Institute Inc., Cary, NC.

Results

A total of 78 patients were included (AdjBW, n = 28 and ActBW, n = 50). Median baseline BMI [33.6 (32.3–39.4) vs. 33.6 (31.8–37.5) kg/m^2; p = 0.553], ActBW [105.1 (96–119.1) vs. 99.3 (87.5–113.1) kg; p = 0.286] and baseline INR [3.1 (2.7–5.1) vs. 2.8 (2.2–3.5); p = 0.052] were similar between groups. No differences were noted in other baseline characteristics (Tables 1, 2). The most common overall indication of PCC use amongst the entire cohort was ICH (46%). A breakdown of indication use between treatment groups is provided in Table 1. Nearly all patients in both groups (92.9 vs. 90%; p = 0.672) received vitamin K. The median units of FFP received were higher in the AdjBW group [3 (2–4) vs. 2 (1–2); p = 0.022]. All detailed information regarding 4F-PCC and supplemental reversal agents can be found in Table 2.

Overall, achievement of the primary outcome of INR < 1.4 for any intracerebral hemorrhage and < 1.5 for all other indications was significantly lower in the AdjBW

Table 1 Patient demographic and clinical baseline characteristics

Characteristics	Adjusted body weight (n = 28)	Actual body weight (n = 50)	p-value
Age (years)[a]	65.4 [14.2]	71 [12]	0.066
Male, n (%)	18 (64.3)	29 (58)	0.586
African American, n (%)	5 (17.9)	10 (20)	0.818
Height (cm)[a]	171.1 [10.2]	169.3 [11.5]	0.487
Actual body weight (kg)	105.1 [96.0–119.1]	99.3 [87.5–113.1]	0.286
Adjusted body weight (kg)[a]	82.6 [12]	80 [12.7]	0.394
Body mass index (kg/m^2)	33.6 [32.3–39.4]	33.6 [31.8–37.5]	0.553
Reversal indication			
Emergent surgery, n (%)	3 (10.7)	6 (12)	0.999
Gastrointestinal hemorrhage, n (%)	8 (28.6)	10 (20)	0.389
Intracranial hemorrhage, n (%)	9 (32.1)	27 (54)	0.063
Other, n (%)	8 (28.6)	7 (14)	0.117
Coagulation markers			
Baseline international normalization ratio	3.1 [2.7–5.1]	2.8 [2.2–3.5]	0.052
Baseline 2–3.9, n (%)	18 (64.3)	39 (78)	0.190
Baseline 4–5.9, n (%)	6 (21.4)	9 (18)	0.712
Baseline ≥ 6, n (%)	4 (14.3)	2 (4)	0.180

All data are presented as median [25–75% interquartile range] unless otherwise noted

[a]Data presented as mean (standard deviation)

Table 2 Comparison of reversal agents received between adjusted and actual body weight groups

Medication	Adjusted body weight (n = 28)	Actual body weight (n = 50)	p-value
4-Factor prothrombin complex concentrate			
Initial dose (units)	2119.5 [1689.8–2730.3]	2500 [2162.5–3000]	0.020
Initial dose per kilogram of ActBW (units/kg)	20.7 [17.2–27.4]	25.1 [22.9–28.5]	0.002
Initial dose per kilogram of AdjBW (units/kg)	27.2 [22.7–34.4]	31.2 [28.5–38.3]	0.001
Supplemental reversal agents			
Vitamin K, n (%)	26 (92.9)	45 (90)	0.672
FFP, n (%)	6 (21.4)	21 (42)	0.067
FFP, units	3 [2–4.5]	2 [1–2]	0.065

All data are presented as median [25–75% interquartile range] unless otherwise noted

PCC prothrombin complex concentrate; *FFP* fresh frozen plasma; *ActBW* actual body weight; *AdjBW* adjusted body weight

group (35.7 vs. 68%; p = 0.006) without any significant differences in the time between 4F-PCC dose and follow-up INR (49 vs. 47 min; p = 0.525) (Table 2). This was also observed in the INR achieved immediately after PCC administration (1.5 vs. 1.3; p = 0.005). The median change in INR from baseline to immediately after PCC was not different between groups (1.7 vs. 1.6, p = 0.273). Initial median 4F-PCC dose was significantly lower in the AdjBW group (2119.5 vs. 2500 units; p = 0.02), and remained when the dose was calculated using actual weight (20.7 vs. 25.1 units/kg; p = 0.002). The post-hoc analysis of the ActBW cohort (< 100 kg, n = 27 and ≥ 100 kg, n = 23) found no differences in attaining goal INR (66.7 vs. 69.6%; p = 0.827). Similarly, the post-hoc analysis of the AdjBW cohort (< 100 kg, n = 11 and ≥ 100 kg, n = 17) found no differences in attaining goal INR (27.3 vs. 41.2%; p = 0.689).

Two parameters remained in the stepwise multivariable binomial logistic regression analysis to identify predictors of achieving target INR. The use of actual body weight for dosing 4F-PCC was associated with target INR achievement (OR = 3.06; 95% CI 1.09–8.58), and baseline INR was associated with lower rate of target INR achievement (for every 1.0 increase in INR; OR = 0.62; 95% CI 0.42–0.92; R^2: 0.1726).

One thrombotic event was documented (1 myocardial infarction) which occurred in the ActBW group. There was no difference in median duration of hospitalization (7.5 vs. 9.5 days; p = 0.361) or mortality (14.3 vs. 28%; p = 0.263) between the two groups.

Discussion

Dosing 4F-PCC on AdjBW in the obese population would seem to be a reasonable cost savings initiative that would result in sufficient INR reversal and reduction in the incidence of unwanted thrombotic events given the pharmacokinetics of clotting factors. For example endogenous Factor IX is produced by the liver with a normal plasma concentration of 3–5 mcg/mL with minimal distribution into adipose tissue [5]. The dose needed to attain a desired concentration is dependent upon blood volume which is often described as 70 mL/kg in normal-sized adults. This estimation may grossly over-estimate the blood volume in obesity due to the non-linear association between BMI and blood volume, which decreases to roughly 60 ml/kg at a BMI of 30 kg/m^2 [9]. Given this finding, one method to indirectly account for this disparity in dosing weight-based, hydrophilic medications is to use an AdjBW calculation rather than ActBW [10, 11]. However, we observed a statistically significant difference in the rate of target INR reversal achieved immediately after 4F-PCC administration favoring the use of ActBW with a 100 kg dose cap as suggested in the package insert [3]. Further corroborated by the findings of the multivariable logistic regression which identified dosing on AdjBW and baseline INR as independent predictors of anticoagulation reversal failure. Similar rates of attaining the goal INR using ActBW were found as described in the study performed by Sarode et al. (68 vs. 62.2%) despite differences in BMI (33.6 vs. 27 kg/m^2) [12]. It is possible that the dosing cap recommended in the package insert accounts for the pharmacokinetic variability in the obese population resulting in the large disparity in attaining the goal INR we observed utilizing an AdjBW. This coincides with our post-hoc analysis of the ActBW group in that there was no difference in obtaining goal INR when stratified by a body weight below or above 100 kg. Although the difference in INR goal attainment was not apparent at 24 h between the groups it is likely due to co-administration of vitamin K. Lastly, the number of adverse thrombotic events was low with only one event occurring in the entire cohort of 78 patients.

Table 3 Primary and secondary outcomes for adjusted compared to actual body weight groups

Characteristics	Adjusted body weight (N = 28)	Actual body weight (N = 50)	p-value
INR at goal (< 1.4 for intracranial bleed and < 1.5 for all other indications), n (%)	10 (35.7)	34 (68)	0.006
INR Immediately after PCC	1.5 [1.3–1.8]	1.3 [1.2–1.5]	0.005
Change in INR immediately after PCC from baseline	1.7 [1.2–3.3]	1.6 [1–1.9]	0.273
INR 24 h-post PCC	1.3 [1.2–1.5]	1.3 [1.1–1.4]	0.098
Time between PCC dose and follow up INR (min)	49 [32–84]	47 [17.8–82]	0.525
Duration of hospitalization (days)	7.5 [5–16]	9.5 [5–14]	0.361
7 day adverse events			
Myocardial infarction, n (%)	0 (0)	1 (2)	0.451
Acute ischemic stroke, n (%)	0	0	–
Pulmonary embolism, n (%)	0	0	–
Deep vein thrombosis, n (%)	0	0	–
Infusion reaction, n (%)	0	0	–
Discharge status			
Died, n (%)	4 (14.3)	14 (28)	0.263
Facility, n (%)	13 (46.4)	17 (34)	0.279
Home, n (%)	11 (39.3)	19 (38)	0.911

All data are presented as median [25–75% interquartile range] unless otherwise noted

INR international normalization ratio

In our study, we chose the INR goal of < 1.4 for any intracerebral hemorrhage and < 1.5 for all other indications for several reasons. Current guidelines for reversal of warfarin associated intracranial hemorrhage recommend to administer 4F-PCC in those with an INR ≥ 1.4 [7]. Guidelines for the management of patients with acute lower GI bleeding do not explicitly state an INR reversal goal apart from administering a reversal agent before endoscopic hemostasis in those with an INR > 2.5 [13]. However, a point prevalence study in the United Kingdom and a systematic review of patients with acute nonvariceal upper gastrointestinal bleeding found increased rates of mortality in those who presented with an INR ≥ 1.5 [14, 15]. For those requiring emergent surgery international consensus guidelines recommend administering a reversal agent in life-threatening bleeds with an INR ≥ 1.5 [16]. Based upon these recommendations we felt dichotomizing bleeds to different INR goals based on bleed location for the primary outcome captured current recommendations across a heterogeneous population [7, 8].

Limitations to our study include the small sample size, which was likely the main limiting factor to capturing infrequent adverse events or be able to evaluate clinical outcomes. In part this may be one of the contributing factors as to why we observed higher mortality rates in the ActBW group although they were more likely to meet the INR goals set a priori. The ActBW group also had a higher percentage of ICH patients with longer lengths of stay indicating a higher burden of illness. Very few patients included in our study had a BMI > 40 m/kg^2, and only one patient in the AdjBW group had an AdjBW > 100 kg which may decrease the applicability of our results to this population. The strengths of our study are the well-matched baseline characteristics that impacted the primary outcome (i.e. baseline INR, body weight, BMI) and the results of the multivariable analysis which confirms that the dosing weight is an independent predictor of reaching goal INR (Table 3).

Our findings suggest that, until we have further information, providers should dose 4F-PCC based on the package insert and use actual body weight in the obese patient population. Given the lack of data on the safety and efficacy of administering 4F-PCC in obese patients, further research is warranted to understand the impact obesity may have on clinical outcomes.

Author contributions Study conception and design: KSS, RZ, CCM, MJE, ETVM, GMJ. Acquisition of data: KSS, RZ, CCM, MJE, GMJ. Analysis and interpretation of data: KSS, RZ, CCM, MJE, ETVM, GMJ. Critical revision of manuscript: KSS, RZ, CCM, MJE, ETVM, GMJ.

Compliance with ethical standards

Conflict of interest All authors of this study have no direct or indirect conflicts of interest to disclose.

References

1. Ogden CLCM, Fryar CD, Flegal KM (2015) Prevalence of obesity among adults and youth: United States, 2011–2014. National Center for Health Statistics Data Brief Centers for Disease Control and Prevention, Washington, DC
2. Lonardo NW, Lonardo LF, Mone MC, Simons HJ, Barton RG (2016) Should the dose of recombinant activated factor VII be adjusted for morbidly obese patients? Balancing risk of bleeding with thrombosis. J Hematol 5:60–66. https://doi.org/10.14740/jh256w
3. Kcentra® [package insert] (2013) CSL Behring, KoP, PA
4. Graham A, Jaworski K (2014) Pharmacokinetic analysis of anti-hemophilic factor in the obese patient. Haemophilia 20:226–229. https://doi.org/10.1111/hae.12300
5. Adcock D, Bethel MA, Macy PA (2006) Coagulation handbook. Esoterix, Inc. https://www.esoterix.com/sites/esoterix/files/imce/uploads/L3692.pdf. Accessed 21 Mar 2018
6. Jones GM, Erdman MJ, Smetana KS, Mohrien KM, Vandigo JE, Elijovich L (2016) 3-Factor versus 4-factor prothrombin complex concentrate for warfarin reversal in severe bleeding: a multicenter, retrospective, propensity-matched pilot study. J Thromb Thrombolysis 42:19–26. https://doi.org/10.1007/s11239-015-1330-3
7. Frontera JA, Lewin JJ 3rd, Rabinstein AA, Aisiku IP, Alexandrov AW, Cook AM, del Zoppo GJ, Kumar MA, Peerschke EI, Stiefel MF, Teitelbaum JS, Wartenberg KE, Zerfoss CL (2016) Guideline for reversal of antithrombotics in intracranial hemorrhage: a statement for healthcare professionals from the Neurocritical Care Society and Society of Critical Care Medicine. Neurocrit Care 24:6–46. https://doi.org/10.1007/s12028-015-0222-x
8. Radaelli F, Dentali F, Repici A, Amato A, Paggi S, Rondonotti E, Dumonceau JM (2015) Management of anticoagulation in patients with acute gastrointestinal bleeding. Dig Liver Dis 47:621–627. https://doi.org/10.1016/j.dld.2015.03.029
9. Lemmens HJ, Bernstein DP, Brodsky JB (2006) Estimating blood volume in obese and morbidly obese patients. Obes Surg 16:773–776. https://doi.org/10.1381/096089206777346673
10. Devine B (1974) Gentamicin therapy. DICP Ann Pharmacother 8:650–655
11. Cheymol G (1993) Clinical pharmacokinetics of drugs in obesity. An update. Clin Pharmacokinet 25:103–114. https://doi.org/10.2165/00003088-199325020-00003
12. Sarode R, Milling TJ Jr, Refaai MA, Mangione A, Schneider A, Durn BL, Goldstein JN (2013) Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation 128:1234–1243. https://doi.org/10.1161/CIRCULATIONAHA.113.002283
13. Strate LL, Gralnek IM (2016) ACG clinical guideline: management of patients with acute lower gastrointestinal bleeding. Am J Gastroenterol 111:755. https://doi.org/10.1038/ajg.2016.155
14. Shingina A, Barkun AN, Razzaghi A, Martel M, Bardou M, Gralnek I, Investigators R (2011) Systematic review: the presenting international normalised ratio (INR) as a predictor of outcome in patients with upper nonvariceal gastrointestinal bleeding. Aliment Pharmacol Ther 33:1010–1018. https://doi.org/10.1111/j.1365-2036.2011.04618.x
15. Jairath V, Kahan BC, Stanworth SJ, Logan RF, Hearnshaw SA, Travis SP, Palmer KR, Murphy MF (2013) Prevalence, management, and outcomes of patients with coagulopathy after acute nonvariceal upper gastrointestinal bleeding in the United Kingdom. Transfusion 53:1069–1076. https://doi.org/10.1111/j.1537-2995.2012.03849.x
16. Tran HA, Chunilal SD, Tran H (2014) An update of consensus guidelines for warfarin reversal. Med J Aust 200:82