

Comparison of Ideal vs. Actual Weight Base Factor Dosing

Background

Hemophilia is an x-linked (mainly affecting males) genetic disorder characterized by a mutation in the clotting factor VIII gene (hemophilia A) or the clotting factor IX gene (hemophilia B) resulting in spontaneous and trauma-induced bleeding. This bleeding can be treated and prevented with clotting factor concentrate which has been available since the 1960s. A randomized clinical trial published in 2007 [Manco-Johnson, NJEM 2007] established that prophylactic treatment with factor several times a week prevents bleeding and adverse clinical outcomes due to bleeding such as joint arthropathy. Thus, prophylactic treatment with clotting factor became standard of care.

Clotting factor replacement is given intravenously and is based on a patient's weight. The clotting factor circulates in the plasma with a half-life of hours to days (depending on the product). It does not get distributed in the adipose (fat) tissue. Although total plasma volume might increase with body mass index, it does not increase proportionally. The current standard of calculating a patient's dose on actual body weight may overestimate the appropriate dose, and calculations based on ideal body weight may be more accurate. Inappropriate dosing may not only be harmful for the patient but also leads to unnecessary health care cost.

Hypothesis: Factor dosing based on ideal body weight will result in hemostatic factor levels (recovery of at least 66% of predicted).

Null Hypothesis: Factor dosing based on ideal body weight will not result in hemostatic factor levels (recovery of at least 66% of predicted).

Trial Design

This is a randomized, prospective, multicenter, open-label, cross-over study comparing the pharmacokinetics (PK) of ideal vs. actual body weight dosing of factor concentrate in overweight and obese participants with hemophilia A.

The study will be conducted at the Washington Center for Bleeding Disorders (WCBD), Oregon Health & Science University (OHSU), Seattle Children's Hospital (SCH) and Providence Sacred Heart Children's Hospital (SH). Ethics approval will be obtained at each individual location before trial enrollment begins for that location.

Primary outcomes:

1. To compare the recovery to a 50 units/kg ($\pm 20\%$) dose of factor VIII (FVIII) concentrate in participants age 12 and above with hemophilia A when calculated on *actual body weight (ABW)* versus *ideal body weight (IBW)*.
2. To determine the likelihood of under dosing when using IBW or over-dosing with ABW

Secondary outcomes:

- To determine the effect on half-life of these dosing strategies
- To determine the effect on PK differences of hemophilia severity
- To determine differences in participants receiving half-life (HL) vs. extended half-life (EHL) products
- To determine the differences, if any, between overweight and obese participants

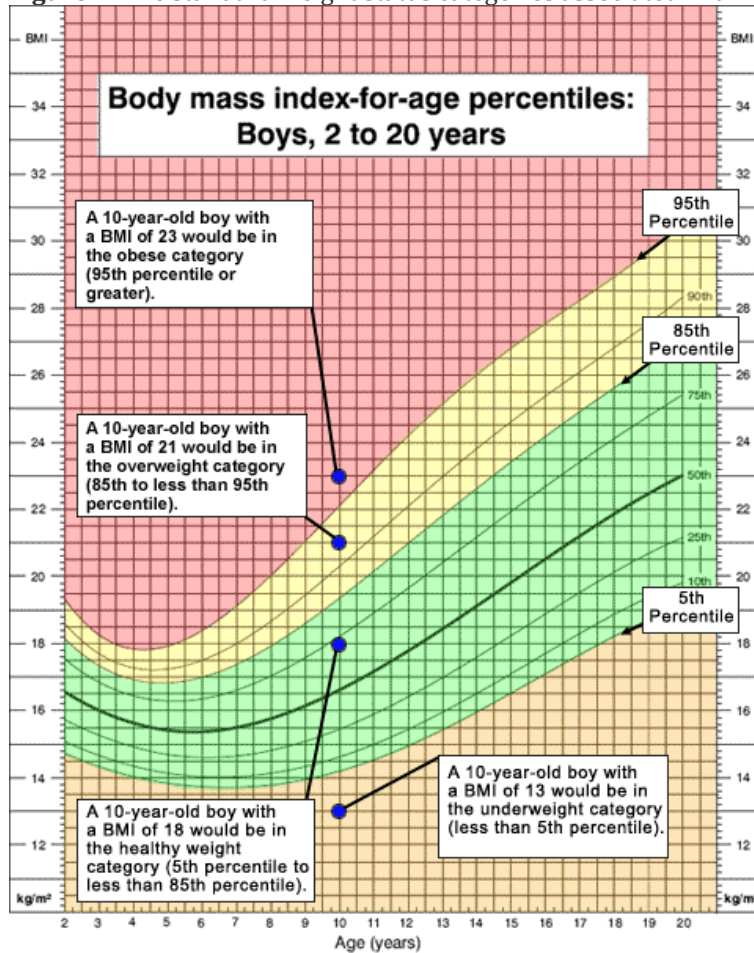
Inclusion Criteria

- At least 12 years of age
- Hemophilia A
- Male gender
- Able and willing to comply with PK testing schedule
- Either overweight or obese BMI (using CDC definitions by age)

Table 1: The standard weight status categories associated with BMI ranges for adults (≥ 20 year old)

BMI	Weight Status
Below 18.5	Underweight
18.5 – 24.9	Normal or Healthy Weight
25.0 – 29.9	Overweight
30.0 and Above	Obese

Figure 1: The standard weight status categories associated with BMI ranges for boys (2 to 19 years)



Exclusion Criteria

- Inhibitor of > 0.6 BU twice in the past, or documented abnormal recovery of less than 66% (of expected) in the past.
- Known other bleeding disorder
- Known other prolongation in aPTT (lupus anticoagulant, FXII deficiency)
- Female gender

Recruitment

Participants will be recruited through the participating centers. Washington Center for Bleeding Disorders (WCBD), Oregon Health & Science University (OHSU), Seattle Children's Hospital (SCH) and Providence Sacred Heart Children's Hospital (SH).

Randomization

Randomization will be performed centrally at the Washington Center for Bleeding Disorders. When a participant has completed the consent and eligibility forms and is able to be enrolled, the participating center will contact WCBD to receive the subject ID and treatment arm assignment. Randomization will be determined by blocked randomization.

Study design - Primary outcome:

Participants age 12 and up and considered to be overweight or obese by either calculated BMI (ages 20 and over) or the McLaren method (ages 12 to 19) and diagnosed with hemophilia A of any severity will be enrolled.

There must be a period of at least 48 hours for standard half-life products or at least 72 hours for extended half-life products since the last dose of factor. Participants will be randomized to receive 50 U/kg ($\pm 20\%$) of the factor product they routinely use either based on IBW or ABW and will have pharmacokinetic (PK) labs drawn as described in the PK protocol section. After a period of at least 48 hours for standard half-life products or at least 72 hours for extended half-life products but no more than 60 days, participant will receive a second dose of factor at 50 U/kg ($\pm 20\%$) based on the alternate dosing strategy and will have a second set of PK labs drawn.

PK studies will be delayed until the resolution of any acute bleeding episodes [after a period of at least 48 hours for standard half-life products or at least 72 hours for extended half-life products]. If the participant has an acute bleed after the recovery draw, then that episode will not be used in the analysis. The episode will be attempted again at a later date within the 2-month window.

Intention to treat:

If a participant experiences a 10% or greater change in BMI between the first and second dose, the participant will be included in the analysis.

Minimum of 8 participants ages 12 and over



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Ideal body weight and BMI calculations:

BMI Calculations:

Sites shall use CDC website to calculate BMI for all participants and to determine if participants are overweight or obese.

Ages 12 to <20: <https://nccd.cdc.gov/dnpabmi/Calculator.aspx>

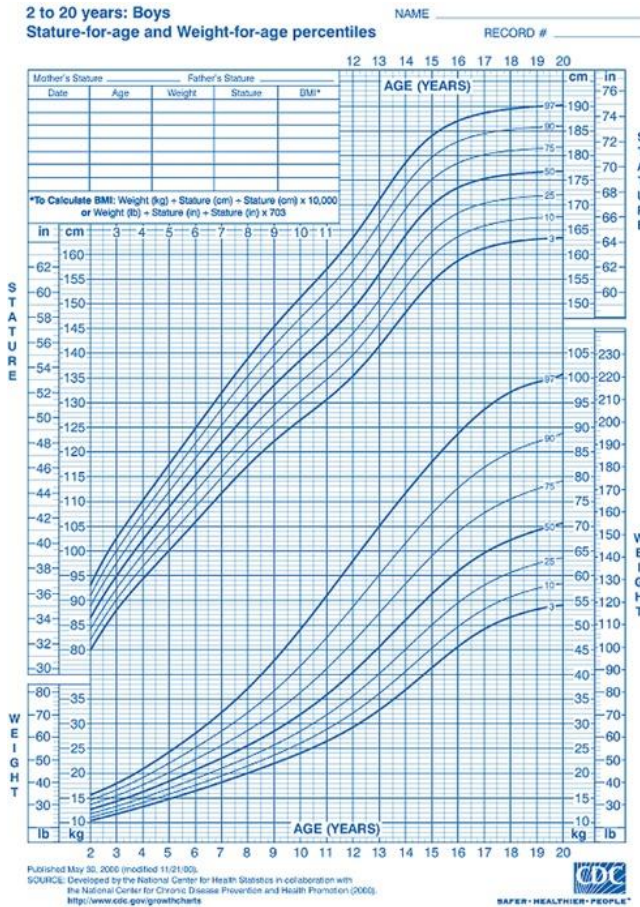
Ages 20 and older:

http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/metric_bmi_calculator/bmi_calculator.html

IBW Calculations:

Ages 12 to <20: Sites shall use the McLaren method to calculate ideal body weight in participants under 20 years old. [Phillips et al 2007]

<http://www.cdc.gov/growthcharts/data/set1clinical/cj41c021.pdf>



Ages 20 and older: Sites shall use the following equation to calculate IBW in participants 20 years and older: $IBW = 50\text{ kg} + (2.3\text{ kg} * \text{every inch over 5 feet})$

PK Protocol:

PK studies will be measured in response to one 50 U/kg ($\pm 20\%$) dose of the participant's current product. Every effort shall be made to ensure the same size vials and same lot numbers are used with the second dose to ensure the second dose is as similar to the first dose as possible. All participants will undergo PK testing twice: One test will be with 50 U/kg ($\pm 20\%$) for hemophilia A based on ideal body weight and the other test will be with 50 U/kg ($\pm 20\%$) for hemophilia A based on actual body weight.

Post dose blood draws cannot be pulled from the port/IV that was used to administer factor. Sites may infuse factor through a peripheral line and obtain post blood draws through a port.

Blood Draw Policy and Schedules: The baseline and the recovery draws for the first and second doses must be completed by the same lab. Blood draws to measure half-life may be drawn in other local labs. If the 30-minute recovery draw is missed participant can still be included with another attempt of the dose/PK draw if the second dose/draw falls within the 2 month window.

Hemophilia A – regular half-life product

Baseline – 30 ± 10 minutes – 5 to 7 hours – 20 to 26 hours – 44 to 50 hours

Hemophilia A – extended half-life factor

Baseline – 30 ± 10 minutes – 5 to 7 hours – 20 to 26 hours – 44 to 50 hours – 69 to 75 hours – 93 to 99 hours

Statistics:

The first primary endpoint will be assessed by evaluation of the mean paired difference in recovery between the two methods (IBW vs. ABW dosing) by paired t-test or by Wilcoxon signed-rank test if recoveries are skewed.

The second primary endpoint will be evaluated by extension of estimated recovery distribution to estimate the likelihood of failure (under-dosing or over-dosing) of each dosing strategy.

For the first of the above evaluation measures, assuming approximate normality of recoveries, we estimate having 80% power to detect a mean reduction of 1 standard deviation in a study of 16 subjects assuming an intra-class correlation of at least 0.2. Greater (lesser) intra-class correlation would increase (decrease) statistical power for this evaluation.

In the event that the study is underpowered (due to a lower than anticipated intra-class correlation), distributional summaries for each approach and for paired differences (including histograms) as well as for the intra-class correlation would be useful for design of future studies if the ideal weight base factor dosing is not deemed unacceptable

Collecting and Reporting Adverse Events:

Serious adverse events are defined as when the patient outcome is either death, life-threatening, hospitalization (initial or prolonged), disability or permanent damage, congenital anomaly/birth defect, required intervention to prevent permanent impairment or damage, or other serious, important medical events. Serious adverse events should be tracked per patient and reported centrally to the Washington

Center for Bleeding Disorders. Adverse events that do not meet the criteria for serious adverse events but qualify as Grade 3 or 4 adverse events will be recorded and reported.

Information to collect and report on adverse events includes patient details, suspected medicinal product, other treatments, details of suspected adverse reactions, details on the reporter of the event.

References

1. Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R, Ingram JD, Manco-Johnson ML, Funk S, Jacobson L, Valentino LA, Hoots WK, Buchanan GR, DiMichele D, Recht M, Brown D, Leissing C, Bleak S, Cohen A, Mathew P, Matsunaga A, Medeiros D, Nugent D, Thomas GA, Thompson AA, McRedmond K, Soucie JM, Austin H, Evatt BL. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med.* 2007 Aug 9;357(6):535-44.
2. Phillips S, Edlbeck A, Kirby M, Goday P. Ideal body weight in children. *Nutr Clin Pract.* 2007 Apr;22(2):240-5.