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 the1960's. 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 arthopathy. Thus, prophylactic treatment with clotting factor became standard of care.

Clotting factor replacement is given intravenously is based on participant's weight. The factor circulates in the plasma with a half-life of hours to days (depending on the product). It does not get distributed the adipose (fat) tissue. Although total plasma volume might increase with body mass index, it does not do this proportionally. The currently standard of calculating a participants dose on actual body weight, may therefore overestimate the needed dose calculations based on ideal body weight may be more accurate. Inappropriate dosing may not only be harmful for the participant 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)..

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 participants with hemophilia.

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.

<u>Primary outcomes</u>

1. To compare the recovery to a 50 units/kg dose of factor VIII (FVIII) concentrate in participants above age 12 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 outcome

- to compare the recovery after 50 units/kg dose of factor VIII (FVIII) concentrate in participants **less than 12 years** old with **hemophilia A** when calculated on *actual body weight* versus *ideal body weight*.
- To determine the effect of these dosing strategies on half-life
- To determine the effect of hemophilia severity on PK differences
- To determine differences in participants taking half-life (HL) vs. extended half-life (EHL) products
- To determine the difference in overweight (BMI 25-30) vs. obese (BMI >30)

Inclusion Criteria

- At least 12 years of age.]
- Hemophilia A
- Male gender
- Able and willing to comply with PK testing schedule
- Either overweight body weight (BMI 25 - <30) or obese (BMI > or equal to 30)

Comment [LE1]: Evaluate budget to determine if we have enough funds to include less than 12 years old.

Exclusion Criteria

- Inhibitor of > 0.6 BU twice in the past, or documented abnormal recovery of less than 66% 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).

Study design - Primary outcome:

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

There must be a period of at least 48 hours for standard half-life products and at least 72 hours for extended half-life products since the last dose of factor.

Participants will be randomized to receive 50 U/kg of the factor product they routinely use either based on IBW or ABW and will have pharmacokinetic (PK) labs drawn as described below. After a period of at least 48 hours for standard half-life products and 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 based on the alternate dosing strategy and will have a second PK test. drawn

Comment [LE2]: Remove factor IX

Pk studies will be delayed until the resolution of any acute bleeding episodes. If the participant has an acute bleed after the recovery draw

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

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

Ages 12 to 19: 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

Sites shall use the McLaren method to calculate ideal body weight in participants under 20 years old. http://www.cdc.gov/growthcharts/clinical_charts.htm

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

PK protocol:

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

Post dose blood draws cannot be pulled from the same port/IV as the factor was delivered. Sites may infuse factor through a peripheral line and obtain post blood draws through a port.

Hemophilia A – regular half-life product

Baseline – Recovery drawn **30 min ± 10 minutes**, if the 30 minute 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. **5 to 7 hours, 20 to 26 hours, and 44 to 50 hours**

Hemophilia A – extended half-life factor

Baseline – 30 min to 60 min – 5 to 7 hours – 20 to 26 hours – 44 to 50 hours – 69 to 75 hours – 93 to 99 hours

[The pre-Pk 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.

Statistics

The primary endpoint 1. Will be assessed by evaluation of the mean paired difference in recovery between the two methods (IBW vs. ABW dosing)

The primary endpoint 2. Will be evaluated by extension of estimated recovery distribution to estimate the likelihood of failure (under-dosing or over-dosing) of each dosing strategy.

- The "heterogeneity" between subgroups (e.g., effects only in the obese group with BMI>30)
- Establishing a "non-inferiority" margin indicating excess risk of dosing failure or excess loss of recovery using ideal body weight dosing compared to actual weight dosing

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 according to thresholds for acceptability (to be determined prior to study initiation).

Power for paired comparisons of probabilities, and consideration of non-inferiority evaluation, require additional consideration and discussion.

Collecting and reporting out on adverse events and serious adverse event. Serious adverse events are defined 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.

Comment [LE3]: Get standard definitions of those two. FDA website for definitions. Donna and Ryan.

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.

Patient information to collect will be initials, other relevant identifier, gender, age, weight and height. Suspected medicinal product information and other treatments information to collect will be brand name, international non-proprietary name, batch number, indication, dosage form and strength, daily dose and regimen, route of administration, starting date and time of day, and stopping date and time (or duration of treatment). Details of suspected adverse drug reaction to collect will be full description of reactions, start date (and time), stop date (and time), dechallenge and rechallenge information, setting, and outcome. Details on the reporter of the event to collect are the name, address, telephone number, and profession.