Oral

[O25-2] O25-2: CNS and miscellaneous

Chairs: Koichiro Tsuchiya, Japan / Yasuo Takeda, Japan
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[O25-2-3] Quantification and explanation of the pharmacokinetic variability in factor VIII-response in non-severe hemophilia A patients treated with desmopressin

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Keywords: desmopressin, factor VIII, population pharmacokinetics, variability

Background

Non-severe hemophilia A (HA) can be treated with desmopressin as it leads to an increase of endogenous factor (FVIII) plasma levels. However, there is a large interindividual variation (IIV) in FVIII-response after desmopressin, making it difficult to predict the hemostatic effect. Aim was to quantify FVIII-response after desmopressin and to explain its variability by population pharmacokinetic (PK) modeling.

Methods

Non-severe HA patients (age 7-75 years) receiving a weight-based intravenous dose of desmopressin (0.3 g/kg) were included. Patient characteristics and FVIII-activity (FVIII:C) in 1 to 7 blood samples within 24 hours after administration, were collected. PK modeling was performed by NONMEM. FVIII-response was defined as the difference between FVIII:C baseline level and peak FVIII:C level and as duration of FVIII:C levels >0.30 IU/mL.

Results

131 HA patients underwent 153 desmopressin administrations, leading to 657 FVIII:C measurements. The FVIII:C-time profile was best described by a two-compartment model with 1st-order absorption and a baseline FVIII:C parameter. The most recently measured FVIII:C (measured >24 hours before desmopressin administration, *FVIII-recent*) was positively associated with the baseline FVIII:C parameter ($p<0.001$). *FVIII-recent* levels were negatively associated with FVIII clearance (CL) and central volume of distribution (V_c) ($p<0.001$). These relationships demonstrate that in this setting a higher *FVIII-recent* correlates with a higher absolute increase of FVIII:C after desmopressin. It also shows that higher *FVIII-recent* correlates with a longer duration of the FVIII:C levels >0.30 IU/mL. Furthermore, presence of C1-domain mutations of the *F8*-gene were shown to be associated with the baseline FVIII:C parameter ($p<0.001$): patients with this mutation had a 37% lower FVIII:C baseline compared with patients without this mutation. Consequently, this mutation is associated with a shorter duration of FVIII:C response >0.30 IU/ml. These correlations could explain 41% of IIV in the baseline FVIII:C parameter, 18% IIV in V_c and 31% IIV in CL, still leaving 44%, 60% respectively 59% IIV unexplained.

Conclusions

Variability in FVIII-response to desmopressin in non-severe HA patients can partially be explained by *FVIII-recent* and C1-domain mutations of the *F8*-gene. Yet, much variability remains unexplained. This PK model

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will be used for TDM to guide FVIII concentrate dosing on top of desmopressin administration.

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