

Development and evaluation of the population pharmacokinetic models for FVIII and FIX concentrates of the WAPPS-Hemo project

Dagmar M Hajducek¹, Pierre Chelle¹, Cedric Hermans², Alfonso Iorio³, Alanna McEneny-King¹, Jacky Yu¹, Andrea Edginton¹

Affiliations + expand

PMID: 32281726 DOI: 10.1111/hae.13977

Abstract

Background: The Web-Accessible Population Pharmacokinetic Service (WAPPS) project generates individually predicted pharmacokinetic (PK) profiles and tailored prophylactic treatment regimens for haemophilic patients, which rely on a set of population PK (PopPK) models providing concentrate-specific priors for the Bayesian forecasting methodology.

Aim: To describe the predictive performance of the WAPPS PopPK models in use on the WAPPS-Hemo platform.

Methods: Data for modelling include dense PK data obtained from industry sponsored and independent PK studies, and dense and sparse data accumulated through WAPPS-Hemo. WAPPS PopPK models were developed via non-linear mixed-effect modelling taking into account the effects of covariates and between-individual-and sometimes between-occasion-variability. Model evaluation consisted of (a) prediction-corrected Visual Predictive Check (pcVPC), (b) Limited Sampling Analysis (LSA) and (c) repeated hold-out cross-validation.

Results: Thirty-three WAPPS PopPK models built on data from 3188 patients (ages 1–78 years) under treatment by factor VIII or IX products (FVIII, FIX) were evaluated. Overall, models exhibit excellent performance characteristics. The pcVPC shows that the observed PK data fall within acceptable 90% interpercentile predictive bands. A slight overprediction beyond the expected half-life, an anticipated result of using sparse data, occurs for some models. The LSA results in lower than 3% of relative error for FVIII and FIX products and 16% for engineered FIX products. Cross-Validation analysis yields relative errors lower than 1.5% and 1.4% in estimates of half-life and time to 0.02 IU/mL, respectively.

Conclusion: The WAPPS-Hemo models consistently showed excellent performance characteristics for the intended use for Bayesian forecasting of individual PK profiles.

Keywords: factor IX; factor VIII; population pharmacokinetics.