Population pharmacokinetics of lisinopril in hypertensive children and adolescents with normal to mildly reduced kidney function

Eva Degraeuwe[1], Louis Sandra[2], Paulien De Bruyne[1], Siegrid De Baere[1], Siska Croubels[1], Jan Van Bocxlaer[1], Ann Raes[1], Johan Vande Walle[1], Elke GASTHUYS[1], and An Vermeulen[1]

[1]Ghent University
[2]Janssen Pharmaceutica NV

June 16, 2023

Abstract

Background: Lisinopril, an angiotensin-converting enzyme inhibitor (ACEi), is a frequently prescribed antihypertensive drug in the pediatric population, while being used off-label under the age of 6 years in the US and for all pediatric patients globally. The SAFEPEDRUG project (IWT-130033) investigated lisinopril pharmacokinetics in hypertensive pediatric patients corresponding with the day-to-day clinical population. Methods: The dose-escalation pilot study included 13 children with primary and secondary hypertension who received oral lisinopril once daily in the morning; doses ranged from 0.05mg.kg-1 to 0.2 mg.kg-1. Patients were aged between 1.9 and 17.9 years (median 13.5 years) and weight ranged between 9.62 and 97.2kg (median 53.2kg). All data were analyzed using Monolix version 2020R1 (Lixoft®, France) and R version 3.6.2. Results: A one-compartment model with 1st order absorption and 1st order elimination optimally describes the data. Parameter estimates of ka (0.077h-1 [9.6%], typical value [relative standard error]), V/F (32.9L 70.g-1 [37%]) and CL/F (23.1L h-1 .70kg-1[8.5%]) show good predictive ability. Significant covariate effects include total body weight on elimination clearance, and distribution volume and estimated glomerular filtration rate (eGFR) on elimination clearance. The effects of eGFR on the elimination clearance are optimally described by a power law parameterization centered around 105 mL.min.1.73m2. The effects of body weight were implemented using fixed allometric exponents centered around an adult weight of 70kg. Conclusion: Lisinopril dose and regimen adjustments for pediatric patients should include eGFR on top of weight adjustments. An expanded model characterizing the pharmacodynamic effect is required to identify the optimal dose and dosing regimen.

Hosted file

`Manuscript_lisinopril_popPKmodel_BJCP_FINAL.docx` available at https://authorea.com/users/629900/articles/649881-population-pharmacokinetics-of-lisinopril-in-hypertensive-children-and-adolescents-with-normal-to-mildly-reduced-kidney-function

Hosted file

`Tables_Manuscript_Lisinopril.docx` available at https://authorea.com/users/629900/articles/649881-population-pharmacokinetics-of-lisinopril-in-hypertensive-children-and-adolescents-with-normal-to-mildly-reduced-kidney-function

Hosted file

`Figures_Manuscript_Lisinopril.docx` available at https://authorea.com/users/629900/articles/649881-population-pharmacokinetics-of-lisinopril-in-hypertensive-children-and-adolescents-with-normal-to-mildly-reduced-kidney-function