Title

Population Pharmacokinetic Analysis of Bilastine in subjects with various degrees of renal insufficiency: prediction in elderly populations

Authors and affiliation

Lo Re V[1,2], Rodríguez M[2], Lukas JC[2], Encinas E[2], Campo C[3], Garcia A[3] ,Suarez E[1]

[1] Department of Pharmacology, UPV/EHU. 48940 Leioa, Vizcaya, Spain.

[2] Dynakin, SL. PTB, Ed. 801-B, 48160 Derio, Vizcaya, Spain.

[3] FAES FARMA, SA. 48940 Leioa, Vizcaya, Spain.

Objective

The aim of this work was to evaluate, using a population modeling approach, the relationship between renal function and the pharmacokinetics (PK) of Bilastine also assessing whether posology adjustment is warranted in elderly patients with impaired renal function and the consequent dosing recommendations.

Materials and Methods

A population PK model was developed for oral Bilastine in NONMEM (FOCE method) using observations (drug plasma levels and urinary excretion data) from an open-label, single-dose, parallel-group study comprising a total of four groups (n=6) of subjects with a mean age across the groups between 65 and 72 years either healthy or with various degrees of renal insufficiency (RI) according to their glomerular filtration rate (GFR) values. The analysis included covariate modelling of GFR as a continuous indicator of renal insufficiency within the population runs.

Results and discussion

A two-compartment PK model including interindividual variability (modelled as exponential) in all parameters (except TLag) best described the observations from the study. A base model for the full patient (all GFR levels) population was first developed. Then, the four RI patient subgroups were modelled as a categorical covariate. Consistently, the inclusion of GFR as a covariate into CL/F, V2/F led to a significant decrease in the objective function OBJ. Graphical exploration revealed a trend of increasing AUC and C_{max} across the 4 RI groups. Data from literature suggest that all physiological renal changes age-related (decreased kidney size, decreased renal blood flow, decreased number of

functional nephrons) lead to a decrease glomerular filtration rate and thus, to a reduced renal clearance, directly impacting the total clearance for a drug with exclusive renal clearance such as Bilastine.

In fact, a reduction of both plasma and renal clearance linked to the decrease in GFR across the 4 sub-groups lead to an increase in exposure to the drug. However, this increase was deemed clinically irrelevant in terms of efficacy and safety of the drug even in elderly patients.

Conclusions

Population PK analysis revealed that although the effect of aging in addition to RI condition cause increased exposure to Bilastine, the drug can be safely administered, at the therapeutic dose.