

Publication

ADME pharmacogenetics: investigation of the pharmacokinetics of the antiretroviral agent lopinavir coformulated with ritonavir

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 3704459

Author(s) Lubomirov, Rubin; di Iulio, Julia; Fayet, Aurélie; Colombo, Sara; Martinez, Raquel; Marzolini, Catia; Furrer, Hansjakob; Vernazza, Pietro; Calmy, Alexandra; Cavassini, Matthias; Ledergerber, Bruno; Rentsch, Katharina; Descombes, Patrick; Buclin, Thierry; Decosterd, Laurent A.; Csajka, Chantal; Tenti, Amalio; Swiss HIV Cohort Study,

Author(s) at UniBasel [Marzolini, Catia](#) ;

Year 2010

Title ADME pharmacogenetics: investigation of the pharmacokinetics of the antiretroviral agent lopinavir coformulated with ritonavir

Journal Pharmacogenetics and Genomics

Volume 20

Number 4

Pages / Article-Number 217-30

Mesh terms Adult; Aged; Aged, 80 and over; Alleles; Anti-HIV Agents, pharmacokinetics; Biological Availability; Cohort Studies; Cytochrome P-450 CYP3A; Cytochrome P-450 Enzyme System, genetics; Female; Genetic Association Studies; Genetic Variation; Humans; Liver-Specific Organic Anion Transporter 1; Lopinavir; Male; Middle Aged; Models, Genetic; Multidrug Resistance-Associated Proteins, genetics; Organic Anion Transporters, genetics; Pharmacogenetics; Polymorphism, Single Nucleotide; Pyrimidinones, pharmacokinetics; Ritonavir, pharmacokinetics; Young Adult

An ADME (absorption, distribution, metabolism and excretion)-pharmacogenetics association study may identify functional variants relevant to the pharmacokinetics of lopinavir co-formulated with ritonavir (LPV/r), a first-line anti-HIV agent.; An extensive search of literature and web resources helped select ADME genes and single nucleotide polymorphisms (SNPs, functional and HapMap tagging SNPs) with a proven or potentially relevant role in LPV/r pharmacokinetics. The study followed a two-stage design. Stage 1 (discovery) considered a Caucasian population (n=638) receiving LPV/r, where we selected 117 individuals with low LPV clearance (cases) and 90 individuals with high clearance (controls). Genotyping was performed by a 1536-SNP customized GoldenGate Illumina BeadArray. Stage 2 (confirmation) represented a replication study of candidate SNPs from the stage 1 in 148 individuals receiving LPV/r. The analysis led to formal population pharmacokinetic-pharmacogenetic modeling of demographic, environmental and candidate SNP effects.; One thousand three hundred and eighty SNPs were successfully genotyped. Nine SNPs prioritized by the stage 1 analysis were brought to replication. Stage 2 confirmed the contribution of two functional SNPs in SLCO1B1, one functional SNP in ABCC2 and a tag SNP of the CYP3A locus in addition to body weight effect and ritonavir coadministration. According to the population pharmacokinetic-pharmacogenetic model, genetic variants explained 5% of LPV variability. Individuals homozygous rs11045819 (SLCO1B1*4) had a clearance of 12.6 l/h, compared with 5.4 l/h in the reference group, and 3.9 l/h in individuals with two or more variant alleles of rs4149056 (SLCO1B1*5), rs717620 (ABCC2) or rs6945984 (CYP3A). A subanalysis confirmed that although a significant part of the variance in LPV clearance was attributed to fluctuation in ritonavir levels, genetic variants had an additional effect on LPV clearance.; The two-stage strategy successfully identified genetic variants affecting LPV/r pharmacokinetics. Such a general approach of ADME pharmacogenetics should be generalized to other drugs.

Publisher Lippincott Williams & Wilkins

ISSN/ISBN 1744-6872 ; 1744-6880

edoc-URL <https://edoc.unibas.ch/69528/>

Full Text on edoc No;

Digital Object Identifier DOI 10.1097/FPC.0b013e328336eee4

PubMed ID <http://www.ncbi.nlm.nih.gov/pubmed/20139798>

ISI-Number WOS:000276373800001

Document type (ISI) Journal Article