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Publication

Influence of Drug-Drug Interactions on the Pharmacokinetics of Atorvastatin and Its Major Active Metabolite ortho-OH-Atorvastatin in Aging People Living with HIV

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People living with HIV (PLWH) are aging and experience age-related physiological changes and comorbidities. Atorvastatin is a widely prescribed lipid-lowering agent metabolized by cytochrome P450 (CYP) 3A4, whose hepatocyte uptake is facilitated by organic anion transporting polypeptide (OATP) 1B1/1B3. Inhibition or induction of this enzyme and hepatic transporter can increase or decrease atorvastatin exposure, respectively.; This study aimed to describe the pharmacokinetic profile of atorvastatin and its major metabolite, and to evaluate drug-drug interactions (DDIs) with antiretrovirals (ARVs).; The atorvastatin pharmacokinetic profile was best described by a two-compartment model with first-order absorption and elimination. Metabolite concentrations were described by considering both linear metabolism from atorvastatin and presystemic metabolism. The influence of demographic and clinical covariates on drug and metabolite pharmacokinetics was assessed using NONMEM; ő; . Model-based simulations were performed to evaluate the magnitude of DDIs with ARVs.; Full pharmacokinetic profiles (98 atorvastatin + 62 o-OH-atorvastatin concentrations) and sparse concentrations (78 and 53 for atorvastatin and o-OH-atorvastatin, respectively) were collected in 59 PLWH. Interindividual variability was high. The coadministration of boosted ARVs decreased atorvastatin clearance by 58% and slowed down o-OH-atorvastatin formation by 88%. Atorvastatin clearance increased by 78% when coadministered with CYP3A4 inducers. Simulations revealed a 180% increase and 44% decrease in atorvastatin exposure (area under the curve) in the presence of ARVs with inhibiting and inducing properties, respectively.; This study showed an important interindividual variability in atorvastatin pharmacokinetics that remains largely unexplained after the inclusion of covariates. Since boosted ARVs double atorvastatin exposure, the initial dosage might be reduced by half, and titrated based on individual clinical targets.
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