Universität Basel

Research Project

Use of physiologically based pharmacokinetic modelling to simulate dosing requirements of long-acting intramuscular antiretroviral drugs in special populations and to manage drug-drug interactions

Third-party funded project

Project title Use of physiologically based pharmacokinetic modelling to simulate dosing requirements of long-acting intramuscular antiretroviral drugs in special populations and to manage drug-drug interactions
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Combined antiretroviral treatments have significantly improved the morbidity and mortality related to HIV infection thus transforming HIV infection into a chronic disease. However, the efficacy of antiretroviral treatments is highly dependent on the ability of infected individuals to adhere to life-long drug combination therapies. Incomplete treatment adherence can indeed promote the emergence of drug-resistant HIV viruses resulting in loss of virological control and leading consequently to the risk of HIV transmission. A major milestone will be achieved in 2019 with the marketing of the first long-acting intramuscular antiretroviral drugs, cabotegravir and rilpivirine, for the treatment and prevention of HIV infection. Intramuscular injections create a “depot” in the muscle from where the drug is released for an extended period thus allowing for infrequent drug administration (e.g. once a month or bimonthly) with the potential to improve adherence to therapy and treatment satisfaction. Although intramuscular formulations hold great promises for long-term treatment of HIV infection, a number of questions about their optimal use remain unresolved. The absorption and bioavailability of drugs administered intramuscularly is impacted by factors such as obesity, exercise and blood flow in the muscle, thus cabotegravir and rilpivirine pharmacokinetics in special HIV infected populations like obese, elderly or pregnant women is currently unknown. Furthermore, intramuscular release of drugs cannot be interrupted, therefore the management of drug-drug interactions (DDI) with any inducing/inhibiting comedications required to treat inaugural diseases (e.g. epilepsy, mycobacterial infection) while on long-acting intramuscular therapy is also unknown. The aims of this project are a) to characterize the pharmacokinetics of intramuscular cabotegravir and rilpivirine and dosing requirements in special populations and b) to simulate dosage adjustments to overcome DDIs using physiologically based pharmacokinetic (PBPK) modeling. This technique allows the prediction of drug pharmacokinetics in virtual individuals (generated considering anatomical and physiological changes related to a specific condition like obesity, aging or pregnancy) using in vitro data and a mathematical description of drug distribution after intramuscular administration thus offering the possibility to simulate clinical scenarios of interest. The performance of the PBK models will be verified by comparing simulated intramuscular profiles of cabotegravir and rilpivirine against available clinical data (obtained in a standard population). After successful prediction, simulations will be carried out in special populations. This research project is of particular clinical importance as it will provide guidance on dosing requirements in special populations, which have not been evaluated during drug development but which may also benefit from this novel treatment paradigm aiming to improve the

chances of life-long maintenance of HIV suppression. In addition, this project will provide guidance on the management of DDIs, which are not always preventable because intramuscular injections are not reversible. Addressing these questions will enable to broaden the use of injectable antiretroviral drugs thus offering an effective strategy for the treatment and prevention of HIV infection and the perspective to curb the HIV epidemic. Furthermore, this project will provide a comprehensive knowledge of factors influencing intramuscular drug disposition.

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