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Pharmacokinetic Considerations for Combining Antiretroviral Therapy, Direct-Acting Antiviral Agents for Hepatitis C Virus, and Addiction Treatment Medications

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Abstract

There are many factors that can affect the pharmacokinetics (PK) of drugs. Pathophysiological changes from disease states can alter the mechanisms that control the PK of antiretrovirals (ARVs), direct-acting antivirals (DAAs) and addiction treatment medications. Drug-drug interaction pathways of certain ARVs and DAAs can be very complex, with agents being substrates, inhibitors or inducers of multiple metabolic and transporter pathways. Buprenorphine and methadone may be used in HIV and hepatitis C virus (HCV) - infected patients, and may also be affected by drug interactions. Current research is focused on novel PK analyses, which aim to describe the PK of agents within the organs that host the infection of interest, such as within hepatocytes during treatment for HCV. Modeling techniques allow for the prediction of drug PK in specific organs and the plasma compartment. This review will provide a summary of these areas while exploring PK considerations for ARVs, DAAs, and addiction treatment medications.

Introduction

Multiple factors can contribute to pharmacokinetic (PK) drug interactions. If drugs are administered orally, several possible mechanisms can modulate PK from within the gut, such as gastrointestinal absorption (*e.g.*, chelation, changes in pH, motility alterations), membrane transporters, and metabolism in the gut wall. When drug is transferred via the portal vein to the liver, hepatic processes that affect PK can occur, consisting of additional uptake and efflux membrane transporters, metabolism, elimination in the bile, and enterohepatic cycling.

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Pathophysiological changes from disease states can alter the mechanisms that control the PK of antiretrovirals (ARVs), direct-acting antivirals (DAAs) and addiction treatment medications. When drug-drug interaction studies are conducted in healthy volunteers this assumes that the PK profiles seen in these healthy adults will be comparable to patients with the disease state of interest. [1] However, this assumption has certain limitations. HIV and hepatitis C virus (HCV) infections affect the small intestine and liver, [2,3] which are major sites involved in drug absorption, transport, metabolism and elimination. [4] Possible pathophysiological changes in transporter and metabolic function from HIV and HCV are summarized in Table 1.

The possibility that individuals with disease may exhibit altered PK parameters has been discussed. [9] For example, HIV-infected patients demonstrate decreased relative bioavailability of efavirenz as compared to healthy subjects. [10] It has also been reported that subjects co-infected with HIV/HCV with or without cirrhosis had significantly lower oral nelfinavir clearance than HIV monoinfected subjects. [11] In a study of HIV+ adult males, and controls with comparable weight, BMI, and estimated creatinine clearance, significantly lower mean plasma fluconazole clearance was found in the HIV+ subjects with the lowest CD4+T cell count, versus HIV+ subjects with higher CD4+T cell counts and controls. [12]

Drug interactions in HAART era and today

Highly active antiretroviral therapy (HAART) was first introduced in the 1990s and has revolutionized the treatment of HIV, greatly improving the morbidity and mortality associated with HIV infection. However, combining these medications with other agents also came with an increased risk for drug interactions, based on the different PK effects each drug had on the others. In addition, HAART required a large pill burden, and certain drugs have specific administration requirements, such as food or pH dependencies. These concerns have been somewhat reduced as single daily medications have become available in co-formulated combinations.

Currently with the advancement in HCV therapies and increased rate of HIV/HCV co-infection being simultaneously treated, new drug-drug interactions have become a concern. [13] The effects may manifest in changes in systemic or tissue exposure of the direct-acting antiviral (DAA) or ARV. Potentially this could cause increases in exposure, resulting in adverse or toxic effects, or decreases in efficacy. In addition, these interactions could extend to concomitant medications commonly used in this patient population, such as antihypertensives, statins and opioid maintenance therapy. [1,14]

Factors Influencing Intrahepatic Drug Concentrations

Currently research interest has been extended beyond measuring only plasma concentrations, since it has been realized that this may not be representative of the drug that is present at the site of action, or tissue of interest. [15,16] Membrane transporters are important for hepatic uptake and efflux, potentially affecting plasma or hepatic drug concentration. [15] The question arises about whether to target plasma or liver concentrations

for deciding DAA dosing, and the importance of understanding information gained from hepatic drug sampling in addition to plasma pharmacokinetics. [17]

Clinical Pharmacology of New HCV DAAs

The interaction pathways of some current DAAs can be rather complex, with agents being substrates, inhibitors or inducers of multiple metabolic and transporter pathways. [13] In addition, DAAs with different mechanisms of action are given in combination to increased efficacy and decrease the chance of resistant virus emerging. Importantly, these combination of DAAs has allowed for the removal of interferon from HCV regimens,[18] thus limiting the toxicity and burden of injections associated with this agent. When ARVs and DAAs are combined to treat HIV/HCV co-infected populations, these patients could take at least 5 different medications to treat these two infections. Notably, these patients may also have multiple co-morbidities that require additional pharmacotherapy. Therefore, the net effect from these individual drug interaction pathways result in the pharmacologic/toxic effect that is observed within an individual.

Complexities with Substance Abuse

In a study examining the influence of active substance related disorder (SRD) in HIV subjects receiving combination antiretroviral therapy, [19] subjects were divided into those with SRD and those without.[19] Pharmacokinetic evaluation was performed by sampling ARV trough concentrations and additional samples after an observed dose. It was noted that those subjects with SRD were more likely to have efavirenz or protease inhibitor trough concentrations below the desired range ($p=0.048$).[19] At the time of therapeutic drug monitoring, patients with active SRD had a significantly lower percentage of those with HIV-1 RNA < 75 copies/mL compared to those without active SRD ($p=0.044$), however, in a multivariate linear regression model known substance use was not significantly associated with CD4+ cell count and HIV RNA <75 copies/mL at study entry.[19]

Drug Interactions with Addiction Treatment Medications

Buprenorphine and methadone are addiction treatment medications recommended to treat opioid addiction in HIV and HCV infected patients. In-vitro, buprenorphine and methadone are both substrates of cytochrome P450 3A4, with methadone also primarily being metabolized by CYP2B6. [20,21] Thus, these agents may be subject to potential drug interactions with ARV or DAA regimens that modulate these metabolic enzymes. Caution is warranted and understanding possible interactions is necessary when these drugs are co-administered. The investigation of buprenorphine and methadone drug interactions with ARVs have been extensively performed and reported in the literature. [22–25]

Pharmacokinetic Analysis Approaches

Traditional PK analysis consists of the estimation of PK parameters from intensive drug concentration sampling over time. Population pharmacokinetic modeling is a method that can utilize not only intensive data, but also data from sparse sampling strategies [26] that cannot be used for traditional PK analysis. [26] Population pharmacokinetics is used to

evaluate the pharmacokinetic variability seen in individuals within a population.[27] However, a limitation to population pharmacokinetic modeling is that this method of analysis cannot be used to anticipate new drug-drug interactions in conditions where multiple medications are given.

Another modeling approach called physiologically-based pharmacokinetic (PBPK) modeling estimates parameters based on physiology, with models containing multiple compartments that correspond to organs within the body that are connected using physiologic blood flow rates. [28] PBPK models can estimate traditional PK parameters, [28] while also accounting for pathophysiological changes that occur during a disease state of interest to predict the pharmacokinetic effect. [28] Also, in-vitro data can be extrapolated to in-vivo and used to inform these models. [29] These PBPK models can incorporate information from various sources, and predict the PK of drug(s) in various situations, populations or disease states. [28]

Pharmacogenomics

Utilizing pharmacogenomics to tailor patients pharmacotherapy is a growing field, but is still in its infancy. [30] Looking at differences in gene expression can be examined as a covariate to explain differences in treatment response or adverse outcomes. In a study examining the effect of single nucleotide polymorphisms (SNPs) for the gene encoding the delta-opioid receptor, the association of the genetic effect with buprenorphine treatment outcome in men and women was examined separately. An association between certain SNPs and buprenorphine treatment outcome was found for women, depending on the genotype there was a significantly worse outcome, however, validation is required in an independent study. [31] In a study of 366 Asian subjects who were on maintenance methadone treatment, researchers examined a matrix of genetic variants from *CYP2C19*, *CYP2B6*, and *CYP3A4* polymorphisms. It was found that the methadone dose was significantly influenced by allelic variants associated with the *CYP2C19* gene. [32]

Conclusion

The pharmacokinetic interactions of ARV, DAAs and addiction therapy are complex, potentially leading to alterations in drug concentrations and treatment outcomes with certain agents. Due to the high potential of drug interactions, patient's medications should be closely examined prior to HCV treatment, including attention to addiction treatment medications. Re-evaluation of the patient's medication list should be performed after the completion of DAA therapy.

Liver sampling strategies may advance virologic and pharmacologic studies as well as identify drug interactions. It is important to be cognizant of possible tissue uptake/efflux and where the site of action of the drug is, and to remember that plasma pharmacokinetics may not be representative of drug concentration at the tissue of interest.

Lastly, a variety of modeling and analysis tools are available to help answer the question of interest. The choice of which tool to use should be based on the study design, type of data that will be collected, and the question that is to be answered.

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Table 1

Possible changes in transporter/metabolic function from HIV- or HCV-infection[5–8]

	P-gp	CYP3A4	MRP2	OATP2B1	BCRP	CYP2D6	OATP1B1/3
HIV		↓***	↓		↓		
HCV		↓**	↓ *	↑	↓ *	↓	↓ *

* HCV-infected, liver cirrhosis compared to non-infected, non-cirrhosis group.

** Patients with cirrhosis, compared to those with hepatic angioma.

*** Trend toward downregulation. Increase ↑; decrease ↓

P-gp; P-glycoprotein. CYP3A4; Cytochrome P450 3A4. MRP2; Multidrug resistance-associated protein 2. OATP2B1; Organic Anion Transporting Polypeptide 2B1. BCRP; Breast Cancer Resistance Protein. CYP2D6; Cytochrome P450 2D6. OATP1B1/3; Organic Anion Transporting Polypeptide 1B1 and 1B3.