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Impact of Drug Transporters on Hepatic Drug Disposition: Insights into Drug-Drug Interactions and Hepatotoxicity

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Abstract

Through drug metabolizing enzymes and transporters, the liver plays a crucial role in the pharmacokinetics of drugs. Non-alcoholic steatohepatitis (NASH) makes illness explicit changes the retention, conveyance, digestion, and discharge (ADME) processes, remembering a decline for protein articulation of basolateral take-up carriers, an expansion in efflux carriers, and alterations to compound action. As a result, adverse drug reactions (ADRs) and drug exposure may rise. Predicting drugs that are more likely to cause ADRs in NASH patients was our objective. Bibliographic examination distinguished 71 medications with detailed ADRs in patients with liver illness, essentially non-alcoholic greasy liver sickness (NAFLD), 54 of which are known substrates of carriers as well as processing chemicals. Based on NASH-specific alterations to ADME processes, we identified additional drugs at risk because NASH, the progressive form of NAFLD, is frequently undiagnosed. Based on their transport and/or metabolism processes, we present another list of 71 drugs at risk for pharmacokinetic disruption in NASH here. It includes medications from various pharmacological classes that, when administered to NASH patients, may cause adverse drug reactions (ADRs), particularly if they are eliminated through multiple disease-altering pathways. As a result, clinicians may benefit from these findings when selecting medications for NASH patients.

Keywords: Drug transporters; Hepatic drug disposition; Drug-drug interactions; Hepatotoxicity; Organic anion transporting polypeptides (OATPs)

Introduction

The chronic liver disease known as non-alcoholic fatty liver disease (NAFLD) is characterized by steatosis and the accumulation of fat in the liver that is unrelated to alcohol consumption1. Non-alcoholic steatohepatitis (NASH) is a progressive and irreversible form of NAFLD1. Inflammation, hepatocyte ballooning, and fibrosis are all risk factors for NASH, which raises the patient's risk of comorbidities and other complications [1]. In addition to the risk of cirrhosis and hepatocellular carcinoma, cardiac and metabolic disorders are the most common complications, making NASH one of the most important candidates for liver transplants. The worldwide prevalence of NASH is estimated to be between 1.5% and 6.45 percent, or several hundreds of millions of patients. Nonetheless, this rate is reasonable misjudged, since NASH must be analyzed utilizing a liver biopsy, which is exceptionally obtrusive and presents many dangers to the patient8. According to a recent review of the available literature, the general population of NAFLD patients accounts for approximately 11.2%–37.2% of the prevalence of biopsy-confirmed NASH9. As a result, NASH is a major public health issue with serious health effects [2].

Drug Metabolism and Pharmacokinetics (DMPK) is an important area of research in the field of pharmaceutical sciences. There are several interesting and relevant topics you can consider for your research in DMPK. Here are a few suggestions:

Drug-Drug Interactions: Investigate the impact of drug-drug interactions on the pharmacokinetics and metabolism of commonly used drugs. Focus on specific drug combinations and explore how the interactions affect drug absorption, distribution, metabolism, and excretion. Proteins that are membrane-bound and pump their substrates out of cells or compartments of cells are known as efflux transporters. The majority of efflux transporters are members of the ABC superfamily, which uses active transport (ATP hydrolysis) to propel substrate movement across biological membranes [3]. MATEs, a subfamily of SLC transporters that uses proton gradients rather than active transport to efflux their substrates, are the one exception to this rule. Although many efflux transporters transport clinically relevant drugs and their metabolites, they also have endogenous substrates. The intestine, liver, kidneys, and blood-tissue barriers are just a few of the numerous organs and tissues that contain these transporters. Drug movement into and out of these organs and tissues is controlled by efflux transporters, which are found either on the apical or basolateral membranes of epithelial cells. Drug pharmacokinetics are significantly influenced by efflux transporters, which can either restrict or facilitate drug movement between tissues and systemic circulation [4].

Pharmacogenomics: Study the influence of genetic variations on drug metabolism and pharmacokinetics. Identify key genetic polymorphisms that affect drug response and evaluate their impact on drug efficacy and safety. This research could lead to personalized medicine approaches and improved treatment outcomes.

Transporter-Mediated Drug Disposition: Explore the role of drug transporters in drug absorption, distribution, and elimination. Investigate specific drug transporters such as P-glycoprotein (P-gp) and organic anion transporters (OATs) and their impact on drug pharmacokinetics. This research can provide insights into drug-drug interactions and optimize drug therapy. Develop and validate novel in vitro and in vivo models to predict drug metabolism and pharmacokinetics. Investigate the utility of organ-on-a-chip systems,

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3D cell culture models, or animal models for accurate prediction of drug disposition [5].

Drug Metabolism Pathways: Investigate the metabolic pathways of specific drugs to understand the enzymes involved in their biotransformation. Identify the major metabolites formed and assess their pharmacological activities. This research can aid in drug design and optimization.

DMPK in Pediatric and Geriatric Populations: Study the impact of age-related factors on drug metabolism and pharmacokinetics in pediatric and geriatric populations. Investigate the differences in drug disposition between different age groups and optimize drug dosing regimens for these populations [6].

Drug Delivery Systems and DMPK: Evaluate the influence of drug delivery systems on drug absorption, distribution, metabolism, and excretion. Investigate different formulation strategies such as nanoparticles, liposomes, and prodrugs, and assess their impact on drug pharmacokinetics.

Sandwich-cultured hepatocytes: One of the major organs that is in charge of the metabolism and elimination of both endogenous and exogenous molecules is the liver. Primary hepatocytes remain the gold standard for evaluating hepatic drug metabolism and transport among numerous in vitro and in vivo model systems. To address species differences in drug metabolism, hepatocytes from the species of interest, including humans, can be isolated. Assessment of overall hepatobiliary drug disposition is made possible by the expression of multiple metabolic enzymes and transporters by primary hepatocytes. However, sandwich-cultured hepatocytes (SCH) regain polarity, allowing proper localization of basolateral and canalicular transporters as well as the formation of functional bile networks. Additionally, sandwich-cultured hepatocytes (SCH) regain polarity, allowing proper localization of basolateral and canalicular transporters as well as the formation of functional bile networks. However, hepatocytes in suspension or under conventional culture conditions quickly lose cell polar [7].

Materials and Methods

Determinants of PK

Drug-metabolizing enzymes and transporters play a crucial role in controlling PK. Determinants of PK In addition, posttranscriptional and transcriptional factors like nuclear receptors and noncoding RNAs (ncRNAs) play a crucial role in modulating PK and offer a comprehensive understanding of regulatory mechanisms that can be used to resolve PK issues. These system driven PK studies can work on the outcome of medication advancement connected with its adequacy and security and work on the sane utilization of drug in clinical practice [8].

Drug-metabolizing enzymes Control of PK

Drug-metabolizing enzymes in charge of PK metabolism Exogenous and endogenous substances are both metabolized by enzymes. The majority of drugs undergo metabolic transformation, which results in metabolites that are easily excreted and have a high water solubility. As a result, metabolizing enzymes are very important for controlling drug PK. Phase I and Phase II reactions exist in the biotransformation of xenobiotics by xenobiotic-metabolizing enzymes (XMEs). In order to prevent severe adverse drug reactions, advanced characterizations of enzymes involved in human drug metabolism are urgently required. The individual isoforms of numerous drug-metabolizing enzymes, such as cytochrome P450s (CYPs) and UGTs, as well as the selective substrates, inducers, and inhibitors of these enzymes, are being studied for their role in controlling PK. Since an increasing number of drugs are metabolized through these enzymes3, this section also covers conjugative and other oxidative enzymes that are not P450 [9].

Result and Discussion

Pharmacokinetics-based connections of remedial biologics

Direct contest between remedial biologics and little particles in PK isn't normal due to their unmistakable pharmacokinetic pathways 163. However, there may be some indirect pharmacokinetic DDI. Immunosuppressive medications might make the therapeutic protein less immunogenic, which would make it harder to get rid of 163. For instance, the clearance of mAbs such as golimumab164, adalimumab162, and infliximab165 can be lowered when methotrexate, an immunosuppressant, is administered concurrently. Cytokine–CYP modulation is yet another indirect pharmacokinetic DDI mechanism. By altering the PK of co-administered small molecules that are substrates of the affected CYPs159,163,166, several biologics with immunomodulatory effects may alter CYP activities. For instance, it was discovered that simvastatin systemic exposure was decreased by tocilizumab, which can decrease interleukin 6 levels and induce CYP3A4 activity167 [10].

In a similar vein, it has been reported that influenza vaccination reduces CYP activity and thus influences the systemic exposure of CYP substrates like clozapine168 by causing inflammation. PBPK modeling has been successfully used to quantitatively predict DDIs of CYP-modulating protein drugs (such as blinatumomab and sirukumab) and small molecule CYP substrates in patients169,170. PBPK modeling is a powerful tool for the investigation of pharmacokinetic-based interactions between therapeutic biologics and small molecules. However, there are few reports of pharmacokinetic interactions between therapeutic biologics. However, specific binding between two biologics may result in such pharmacokinetic DDIs. The heparin-binding domain-containing truncated form of the endogenous fibroblast growth factor, for instance, is called palifermin. The systemic exposure to palifermin was found to be up to 5-fold171 higher when palifermin was administered in conjunction with heparin [11].

Pharmacodynamics-based interactions of therapeutic biologics

Therapeutic biologics' pharmacodynamics-based interactions are more frequently reported in comparison to the pharmacokinetics-based DDIs of therapeutic biologics. Due to their intricate signaling networks, numerous cases have demonstrated pharmacodynamic interactions between hormones159. Insulin, for instance, can interact with a variety of medications, including hormones, diabetes medications, antibiotics, antipsychotics, and others172. Small-molecule hormones like glucocorticoids, estrogens, thyroxin, and others interact with recombinant growth hormone159. Co-administration of biologics for the same disease typically results in synergistic or additive efficacy, but it can also cause toxicity. Rheumatoid arthritis can be treated with either etanercept or anakinra. However, the use of the two biologics in combination resulted in severe side effects, such as an increased infection risk and neutropenia, but no significant improvement in therapeutic efficacy173 [12].

Risk assessment for DDIs of therapeutic biologics

Assessment of therapeutic biologics' risk of DDIs because of their distinct pharmacokinetic and pharmacodynamic properties, the

standard method for predicting DDIs for small molecules might not work with therapeutic biologics. It is essential to advocate for developing strategies and regulations regarding potential DDIs involving biologics in light of the rising number of therapeutic biologics on the market. Assessment of the modulation of CYP activities and immunogenicity is recommended on the basis of the most recent findings regarding the major mechanisms for the pharmacokinetic-based DDIs of therapeutic biologics. In terms of pharmacodynamics-based DDIs, it is highly recommended to identify and monitor clinical endpoints that are relevant to therapeutic biologics' efficacy as well as their adverse effects [13].

Conclusion

The complex models-based experimental scientific exploration of drug discovery and development continues. For predicting the behavior of a drug in patients, these models provide a variety of data from studies on healthy human subjects, in vivo animal species, and in vitro systems. These data either reveal the entire distributional and dispositional properties of a drug, as revealed by a human ADME study using 14C-labeled compounds, or they address a specific aspect of drug metabolism, such as permeability and transporter properties, as derived from Caco-2 models. It's very important to choose the right model, then use that model or models with the right strategy and right data interpretation. Some of the most common experimental models used in drug metabolism and disposition have been discussed in this review. The majority of modern drugs are discovered and developed by utilizing the appropriate experimental models at the appropriate times [14].

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