Effects of Organic Anion Transporting Polypeptide (OATP1B1/SLCO1B1) Genetic Polymorphism on Statin Therapy

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ABSTRACT

The 3-HMG-CoA reductase inhibitors (statins) which are substrates of OATP1B1 transporter protein, is reputed to be effective in reducing morbidity and mortality associated with cardiovascular disease. The OATP1B1 transporter protein is encoded by the SLCO1 genes and almost exclusively expressed in human liver cells. It plays a crucial role in the hepatic uptake and clearance of many drugs including statins. There is a high probability of drug-drug interactions since statins are co-administered with other drugs which may inhibit the OATP1B1 transporter leading to elevated serum levels and statin-induced adverse effects. The OATP1B1 (SLCO1B1) genetic polymorphism is quite invaluable in influencing clinical decisions on the use of statins. Consequently, genotyping for selected SLCO1B1 variants is recommended to identify individuals at increased risk of developing adverse drug effects following statin therapy.

Key words: Clinical significance, Genetic polymorphism, OATP1B1, SLCO1B1, Statins.

INTRODUCTION

The organic anion transporter protein 1B1 (OATP1B1) is the major transporter responsible for hepatic uptake of drugs and endogenous compounds. The 3-HMG-CoA reductase inhibitors, commonly referred to as statins, are known to be effective in lowering cholesterol thereby drastically reducing mortality and morbidity associated with cardiovascular events. Statins which are generally acclaimed to have low therapeutic index are substrates of OATP1B1 transporter. There is the probability of these cholesterol lowering drugs being co-administered alongside other drugs which are inhibitors of the OATP1B1 transporter, resulting in higher serum drug concentration and leading to increased incidence of adverse drug effects; especially myopathy, rhabdomyolysis with associated risk of renal failure and hepatotoxicity due to elevated liver enzymes. A wide inter-individual variability exists in drug disposition and clinical response to 3-HMG-CoA reductase inhibitors. Attempts at explaining these differences has focused on genetic variations in hepatic influx and efflux transporters. A crucial step in the elimination of statins is access into the hepatocytes. OATP1B1 expressed on the basolaleral membrane of liver cells is one of the major influx transporters1-4. The translocation of drugs via active and passive mechanisms in and out of cells is mediated by these transporters which are integral membrane proteins1. The role of transporters in influencing drug response and pharmacokinetics has been well documented2. The 3-HMG-CoA reductase inhibitor pravastatin was one of the first recognized substrates for OATP1B1 transporter5. Currently, all statins in clinical use are known substrates of OATP1B16-10. This review paper examines the role of genetic variations in the OATP1B1 (SLCO1B1) transporter in the disposition and pharmacodynamic response of statins.
Characteristics of OATP1B1 (SLCO1B1) Genetic Polymorphism

The OATP1B1 comprises 12 putative membrane spanning domains and a large fifth extracellular loop\textsuperscript{11-13}. The molecular mass is reduced following deglycosylation to 58KDa though the apparent molecular mass is given as 84KDa\textsuperscript{11}. The solute carrier organic anion transporter 1 (SLCO1) consists of genes encoding OATP1B1 as well as other transporters including OATP1A2 (first cloned human OATP), OATP1B3 and OATP1C1\textsuperscript{14,15}. The OATP1B1 transporter protein is almost exclusively expressed in human liver cells, hence playing a significant role in hepatic uptake and clearance of albumin-bound amphipathic drugs. A number of transient and stable heterologous expression systems affect in vitro assessment of OATP1B1 function\textsuperscript{2}. The study of influx and efflux transporters interplay in the transcellular transport of drugs is facilitated by employing stable expression of OATP1B1 in combination with efflux transporters\textsuperscript{7,16}. A study that investigated the pharmacokinetic effects of SLCO1B1 variants revealed that subjects with the SLCO1B1*1B/*15 genotype had significantly reduced non-renal clearance compared with those persons with the *1B/*B genotype\textsuperscript{17}. The effects of SLCO1B1c.521T>C SNP, in a series of genotype-panel studies, on the pharmacokinetics of various statins were investigated and the largest observed effect attributed to simvastatin\textsuperscript{18,19}. It could be predicted, based on the concentration-dependent skeletal muscle toxicity of statins, that the low activity SLCO1B1 variants may be associated with an increased risk of statin-induced myopathy\textsuperscript{18}. A study reported AUC of pravastatin 35% lower in healthy individuals with SLCO1B1*1B/*1B genotype as compared to persons with the *1A/*1A genotype, consistent with an enhanced hepatic uptake in association with the *1B haplotype\textsuperscript{20}. The pharmacokinetics of another 3-HMG-CoA reductase inhibitor rosuvastatin, however, seem not to be affected by the SLCO1B1/*1B haplotype\textsuperscript{21}. OATP1B1 transporter is inhibited in vitro by a number of substrates, some of which are non-specific for OATP1B1 but may competitively inhibit other substrates that bind at the same site of OATP1B1. The wide variations in IC\textsubscript{50} values of individual inhibitors on different substrates lend credence to the idea that OATP1B1 may possess multiple substrate binding sites.


**Fig. 1:** Effects of Genetic Variation in OATP1B1/SLCO1B1 Transporter (SLCO1B1c.521T>C Variant) on Pharmacokinetic Disposition of Various Statins
Clinical Significance

The clinical implication of OATP1B1 (SLCO1B1) genetic polymorphism can be well illustrated by adverse drug effects associated with statin therapy. Statin-induced myopathy is a rare plasma concentration dependent adverse reaction. This usually manifests as weakness or muscle pain associated with increased creatine kinase levels and may result to rhabdomyolysis (muscle breakdown and myoglobin release) with increased risk of renal failure and mortality. A genome wide association study involving 85 patients who developed myopathy on a high dose 80mg daily simvastatin treatment and 90 matched control subjects as part of SEARCH (Study the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) trial provided a crucial evidence that the risk of simvastatin-induced myopathy is altered by at least one common variation in the SLCO1B1 gene.

The SLCO1B1c.521T>C SNP (short nucleotide polymorphism) increases risk of adverse effect during statin treatment, since statin-induced myopathy is concentration-dependent. The above study also revealed that simvastatin induced myopathy was associated with a non-coding SNP in the SLCO1B1 gene, which is in strong linkage disequilibrium with the c.521T>C SNP. Relatively milder forms of statin-induced myopathy had been associated with the SLCO1B1c.521T>C SNP despite the low dose statins.

Certain in vivo drug-drug interactions may be partly attributed to inhibitors of OATP1B1. The plasma concentration of statins can be markedly elevated by cyclosporine. Notwithstanding, that inhibition of CYP3A4 may partly account for the effects of cyclosporine on simvastatin, lovastatin, cerivastatin, atorvastatin; but is not so for other statins such as pitavastatin, pravastatin and rosuvastatin.

The inhibition of OATP1B1 mediated uptake of cerivastatin by the liver, resulted to a 3 to 8 fold increase in the AUC of cerivastatin in kidney transplant recipients on cyclosporine immunosuppressive therapy. However, another calcineurium inhibitor, tacrolimus does not affect plasma concentration of simvastatin or atorvastatin which suggests that it does not inhibit OATP1B1. The rate delivery elimination process should be given consideration in understanding the role of OATP1B1 transporter in hepatic drug clearance. The most important determinant of hepatic clearance is the hepatic uptake rather than the metabolic intrinsic clearance and this is influenced by genetic polymorphism of the OATP1B1 transporter. The pharmacokinetics of statins is influenced by genetic polymorphism of the OATP1B1 transporter, as crucial molecular determinant. Genetic variations in OATP1B1 drug transporter influence drug response and efficacy.

CONCLUSION

In conclusion, the OATP1B1 (SLCO1B1) genetic polymorphism has significant implication in influencing clinical decision pertaining to statin therapy. It is not only invaluable in understanding drug-drug interactions; but also influences dose adjustment with a view to minimizing adverse drug effects and enhancing clinical efficacy with statin use. Hence, gene testing (genotype) particularly for selected variants of SLCO1B1c.521T>C is recommended to determine individuals a risk of developing adverse drug effects.

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