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Statins - Macrolides Interaction

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Abstract

The aim of this study is to explore the mechanism and clinical significance of the specific interaction between statins and macrolides and how to prevent such interaction

The mechanism of the interaction is due to macrolides' inhibition of CYP3A4 isoenzyme and OAT1B transporter causing increased exposure to statins. The aim of this study was to explore the clinical significance of the specific interaction between statins and macrolides and provide recommendations on how to deal with such interaction.

Introduction

The most common cholesterol-lowering drugs are called statins.

Statins disrupt production of cholesterol by blocking an enzyme inside the liver cells. This results in less cholesterol being released into the bloodstream.1

On the other hand macrolide are a class of antibiotics which are widely used in treating different infections in community and hospital settings.

Pharmacokinetics

Chemically, simvastatin, atorvastatin, fluvastatin, and lovastatin are considered lipophilic compared to rosuvastatin, pitavastatin, and pravastatin.3

All statins are administered in the active form except simvastatin and lovastatin which are administered as lactone pro-drugs. Despite the rapid absorption of statins, their systemic bioavailability is low due to significant first-pass effect. However, since the liver is their main site of action, efficient first-pass uptake by hepatocytes has greater importance than systemic bioavailability. The major mechanism of hepatocyte uptake of lipophilic statins is passive diffusion, while the more hydrophilic statins will be subjected to an extensive transporter-mediated process.2 All statins are

significantly metabolized by hepatic CYP450 enzymes except pravastatin and rosuvastatin, both drugs are cleared from the body mainly unchanged in urine and feces. Rosuvastatin and pravastatin renal clearances occur mainly through active renal tubular secretion and accounts for 10% and 20% of the drug total clearance, respectively. Therefore, CYP3A4 inhibition has no significant impact on the pharmacokinetics of pravastatin and rosuvastatin.4,5

Pitavastatin is minimally metabolized by CYP2C9 and most of the dose is excreted unchanged in the feces.6

CYP3A4 isoenzyme; the most available CYP450 isoenzyme; is the major metabolizing enzyme in relation to simvastatin, lovastatin, and atorvastatin.7,8

Fluvastatin is extensively metabolized by CYP2C9; and to a lesser extent by CYP3A4 and CYP2C8; to three major metabolites, and only 5% of the administered dose is renally cleared.9

Table 1

Summary of selected pharmacokinetic data of statins 1,7,9,14,36,38

	Simvastatin	Lovastatin	Atorvastatin	Pravastatin	Rosuvastatin	Fluvastatin	Pitavastatin
Pro-drug	Yes	Yes	No	No	No	No	No
Bioavailibility (%)	<5	<5	12-14	17-18	20	24	51
Half-life(hours)	2-5	1.3-5	13-16	1-3	20	0.5-3	11
Protein binding (%)	>95	>95	80-99	43-55	88	>90	96
Hepatic extraction (%)	83	More than or equal to 70	70	45	63	>68	>60
Renal excretion (%)	13	10	<5	20	10	5	15
CYP450 metabolism and is enzyme	CYP3A4	CYP3A4	CYP3A4	Clinically not relevant	CYP2C9 minimally	CYP2C9	CYP2C9 minimally

Macrolides is a group of antimicrobial drugs characterized by the presence of a macrocyclic lactone ring in their structures. Erythromycin is rapidly degraded in the stomach's acidic environment to different compounds that are responsible for the gastrointestinal side effects of erythromycin. Clarithromycin, roxithromycin, and azithromycin are newer agents in this class and have been created semi-synthetically by modifications to erythromycin. The aim of these modifications is to create more acid-stable alternatives with longer half-life and extended spectrum of activity. The newer macrolides have an extended spectrum of activity toward certain species compared to erythromycin.10

Telithromycin is structurally related to macrolides (ketolides) designed to have dual binding to bacterial ribosomes in order to overcome the resistance of certain bacteria. The long half-life of telithromycin, azithromycin, and roxithromycin allows their use as a single daily dose. Erythromycin, clarithromycin, and telithromycin are extensively metabolized by CYP3A4 isoenzyme, roxithromycin undergoes limited metabolism, while azithromycin is not metabolized and mainly excreted as unchanged drug.10,11,12

Mechanism of interaction

Inhibition of CYP3A4

The most important site of interaction between statins and macrolides is CYP3A4 isoenzyme. The mechanism involves inhibiting CYP3A4 by certain macrolides, which will result in increased exposure to statins metabolized by the same isoenzyme. CYP3A4 is considered the most abundant CYP450 isoenzyme in the liver and intestine. It is involved in the metabolism of more than 50% of drugs currently available on the market. In the intestine, CYP3A4 is responsible for first-pass drug metabolism and contribute to drug clearance through the gut wall. Despite the fact that more than 20 allelic variants of CYP3A4 have been identified, the clinical significance of this variation has not been demonstrated in clinical practice.13

Inhibition of CYP3A4 isoenzyme is expected to have a significant impact on the blood level concentration of simvastatin, lovastatin, and atorvastatin. However, the magnitude of this inhibition will vary depending on the potency of the inhibition and the relative contribution of intestinal and hepatic CYP3A4 to the total bioavailability of the drug. Simvastatin and lovastatin's bioavailability is more dependent on CYP3A4 isoenzyme than atorvastatin, therefore the inhibition of CYP3A4 isoenzyme has a larger effect on their exposure compared to atorvastatin.7,14

The affinity or the potency of inhibition of CYP3A4 isoenzyme by different macrolides has been explored in many in vitro studies. These studies concluded that erythromycin, clarithromycin, and telithromycin are the most potent inhibitors of CYP3A4 isoenzyme, followed by the weak inhibitor, roxithromycin, and finally azithromycin, which in some studies showed results comparable to placebo.15-18

The dual inhibition of intestinal and hepatic CYP3A4 does not occur at the same speed, intestinal CYP3A4 has a fast onset which peaks in about 2 days, while hepatic CYP3A4 may take a few days to reach maximum inhibition.19

The inhibition of CYP3A4 by macrolides is believed to be due to mechanism-based inhibition which results in the formation of a tight and irreversible metabolic intermediate (MI) complex which inactivates the isoenzyme. The N-demethylation of erythromycin, clarithromycin, troleandomycin, and oleandomycin forms reactive nitrosoalkanes which inactivate CYP3A4 by forming MI complex.20

Mechanism-based inhibition of CYP3A4 is more likely to cause significant drug-drug interaction than reversible inhibition, as the body will not overcome this inhibition until new CYP3A4 proteins are synthesized. Macrolides' inhibition of CYP3A4 through the formation of MI complex is expected to be time-dependent in its onset and more evident after multiple doses compared to a single dose.21

Membrane transporters can either facilitate the uptake of their substrates into cells (influx) or facilitate the excretion of their substrates out of cells (efflux). Human OATPs are a membrane influx transporter family which consists of eleven proteins; OATP1B1, OATP1A2, OATP1B3, and OATP2B1 are the most characterized ones in relation to their influence on drug disposition.22

OATP1B1, 1B3, and 2B1 are expressed mainly in the sinusoidal membranes of hepatocytes and facilitate the entry of many endogenous and exogenous substances into liver cells. *SLCO1B1* gene is responsible for the formation of OATP1B1 transporter and it has been found to be polymorphic with many single nucleotide polymorphisms (SNPs), and sequence variations have

been identified. Two important SNPs that can form four distinct haplotypes are c.521T > C (p.Val174Ala) and c.388A > G (p.Asn130Asp). Haplotypes *SLCO1B1*5* (c.388A-c.521C) and *SLCO1B1*15* (c.388G-c.521C) have been associated with reduced transport activity.23

Simvastatin acid, the active form of simvastatin, is a substrate of OATP1B1. The contribution of this transporter to the hepatic uptake of simvastatin acid is estimated to be 75% of the hepatic extraction ratio.7

In a single dose study in healthy volunteers who carry *SLCO1B1* c.521T > C variant, simvastatin acid exposure was increased by 40%.24

For atorvastatin, no human data available for the contribution of OATP1B1 in its hepatic uptake, but data from studies conducted on rats indicate more than 90% of the total hepatic uptake is mediated by OTAP1B1 transporter.25

In a single dose study in healthy volunteers (atorvastatin 40 mg), the administration of rifampin infusion, an OATP1B1 inhibitor, increased atorvastatin acid exposure by 6.8 fold.26

Pravastatin is mainly renally excreted and the rest will undergo hepatic metabolism. Since pravastatin is a hydrophilic compound, OATP1B1 transporter is needed for hepatic cellular uptake.7

In one study, a participant with *SLCO1B1* c.521CC genotype showed 91% and 74% more pravastatin exposure compared to participants with c.521TT or c.521TC genotypes respectively, while fluvastatin exposure did not show any significant difference. In a rat model, when rifampicin (OATP1B1/1B3 inhibitor) was coadministered with fluvastatin, area under the serum concentration-time curve (AUC) increased by 2.5 fold. This supports the assumption that fluvastatin's hepatic uptake is more dependent on OATP1B3 transporter.27,28

Metabolism of rosuvastatin is a minor route with most of the drug excreted unchanged in feces and urine. It is estimated that OATP1B1/B3 is responsible for 70% of rosuvastatin's total hepatic uptake, the rest (about 30%) is transported via bile acid uptake transporter.7

The influence of *SLCO1B1* c.521cc genotype was larger on atorvastatin exposure compared to rosuvastatin in healthy volunteers, which indicates that atorvastatin uptake is more dependent on OATP1B1 transporter.29

For pitavastatin, hepatic elimination as unchanged drug in bile is the major metabolic pathway. In vitro studies showed that pitavastatin is an OATP1B1/B3 substrate with 1B1 as the major contributor to its hepatic uptake. Increased exposure to pitavastatin has been reported in individuals with *SLCO1B1* c.521CC genotype or when coadministered with rifampicin.30,31

Lovastatin is also a substrate of OATP1B1, but has not shown any affinity toward OATP1B3.32

The magnitude of macrolides' inhibition of different transporters as well as the level of contribution of each transporter to total drug clearance is essential information to determine the significance of drug-drug interactions. The inhibitory effect of different macrolides on OATP1B1/1B3 transporters was evaluated in an in vitro model, the IC50 for each macrolide against OATP1B1 was 96 µM (clarithromycin), 121 µM (telithromycin), 153 µM (roxithromycin), and 217 µM (erythromycin). In relation to macrolides' affinity for OATP1B3 using the same model, telithromycin showed the strongest inhibition in vitro with IC50 of 11 µM, while clarithromycin, erythromycin, and roxithromycin showed slightly similar affinities with IC50 of 32 µM,

34 µM, and 37 µM respectively. Azithromycin did not show any inhibition of both transporters.33

Hirano et al calculated the inhibition constant for clarithromycin and erythromycin against OATP1B1 and found that clarithromycin has a stronger affinity for OATP1B1 than erythromycin (8.25 µM and 11.4 µM respectively) and may cause a significant clinical interaction with OATP1B1 substrates.34

Consequences of the Interaction-

Assuming that macrolides inhibit the metabolism/clearance of statins, this may lead to increased patient exposure to statins. This in turn can lead to one of four possibilities: first: no symptoms at all or no changes in markers of muscle toxicity (creatine kinase (CK)), the second possibility is development of mild muscle pain or myalgia without any increase in blood markers of muscle toxicity, the third possibility is development of myalgia with increase in CK (<10 times upper limit of normal), the final possibility is development of rhabdomyolysis, which usually starts with progressive muscle pain and weakness that is followed by severe increase in CK (10× > upper limit of normal) and/or increase in myoglobin level which can be detected in urine and which contributes to acute kidney injury.35

Rhabdomyolysis is a potentially life-threatening syndrome resulting from the breakdown of skeletal muscle fibers with leakage of muscle contents into the circulation.

Implications of practice

- Muscle injuries are uncommon with statin therapy alone, with a frequency of myalgia (2 to 11%), myositis (0.5%) and rhabdomyolysis (0.1 %).
- Although the risk of rhabdomyolysis is uncommon with statin therapy alone, it substantially increases with concurrent therapy with strong inhibitors of CYP3A4 such as macrolides.
- The characteristic triad of warning signs in rhabdomyolysis are muscle pain, weakness and dark urine.
- Macrolides and statins are two groups of commonly used drugs. Physicians should be aware of the potential drug interactions and avoid concomitant prescription of these drugs. If treatment requires the use of macrolides then consider either stopping statins for a period of time or switch to an alternative statin which is not eliminated by CYP3A4 enzyme.

Discussion

There are many reports present in the literature showing result of statin-macrolide interaction which varies significantly between the different types of drugs. Most of this interaction was associated with simvastatin and lovastatin in case reports, while in healthy volunteers, simvastatin showed the highest level of increased exposure followed by atorvastatin 80 mg and pitavastatin 4 mg. In relation to macrolides, the risk of interaction is higher with telithromycin, erythromycin, and clarithromycin, while roxithromycin has less potential for the interaction and azithromycin appears to be safe to use.

However, from the 53 cases of rhabdomyolysis suspected to be due to azithromycin and statins combination mentioned by Strandell et al, in only three cases the reporters explicitly indicated that azithromycin was most likely to be the offending agent.37

Opinion

Drug interactions like these should never go unnoticed especially in countries where there are irrational use antibiotics. This does not only lead to antibiotic

resistance but can also cause adverse effects which a common person is not aware of. For instance, we all know statins are most commonly prescribed drugs for dyslipidemia and people usually self medicate themselves for mild sore throat infections by taking antibiotics which also includes macrolides like azithromycin. Hence, it should be kept under check if we have to avoid dangerous drug interactions like these which can lead to rhabdomylosis. This can be mostly achieved by bringing awareness in such groups so that incidents such like that couldn't happen in the future.

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