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A REVIEW ON PHARMACO KINETIC DRUG INTERACTIONS OF STATINS

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ABSTRACT

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are generally well tolerated as monotherapy. Statins are associated with two important adverse effects, asymptomatic elevation in liver enzymes and myopathy. Myopathy is most likely to occur when statins are administered with other drugs. Statins are substrates of multiple drug transporters (including OAT- -P1B1, BCRP and MDR1) and several cytochrome P450 (CYP) enzymes (including CYP3A4, CYP2C8, CYP2C19, and CYP2C9). Possible adverse effects of statins can occur due to interactions in concomitant use of drugs that substantially inhibit or induce their methabolic pathway. This review aim is to summarize the most important interactions of statins.

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INTRODUCTION

Statins (or HMG-CoA reductase inhibitors) represent a class of drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver. As of 2010, a number of statins have been on the market: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin Statins are associated with two uncommon, but important, adverse effects, asymptomatic elevation in liver enzyme activity and myopathy. (1, 2).

At the pharmacodynamic level (i.e., at their site of action), statins are not prone to interfere with other drugs. However, at the pharmacokinetic level (i.e., absorption, distribution, metabolism and excretion of a given drug), the available statins show notable differences, including half-life, systemic exposure, maximum plasma concentration (Cmax), bioavailability, protein binding, lipophilicity, metabolism, presence of active metabolites, and excretion routes that is explained below with examples for mechanism of drug inter actions.

Mechanisms

There are several mechanisms by which drugs may interact (3-5), and most of these mechanisms can be categorized as pharmacokinetic (involving intestinal absorption, distribution, metabolism, and elimination) or as pharmacodynamic, or as additive toxicity, respectively. Pharmacokinetic interactions: the interaction in intestinal absorption is best illustrated by an example: tetracylines and other broad-spectrum antibiotics may impair the absorption of oral contraceptives (in particular those with low-dose progestogens and/or estrogens) and hence render contraception unsafe. Several drugs are subject to inactivation via metabolic degradation it the liver, catalysed by various liver enzymes.

The formation of these enzymes can be induced or enhanced by drugs such as rifampicine, griseofulvine, and several anti-epileptics (carbamazepin, phenytoine, phenobarbital), but also by regular alcohol consumption.

This process, which requires several weeks of treatment and which is indicated as enzyme induction, enhances the metabolic degradation of several drugs.

In practice, enzyme induction may play a relevant role for oral anticoagulants (coumarin type), corticosteroids (glucocorticoids), oral contraceptives, or quinidine. Accordingly, these categories of drugs are metabolized/inactivated more rapidly and their doses should therefore be increased.

A comparable but opposite problem is the inhibition of liver enzymes involved in the biotransformation by a variety of drugs, such as cimetidine, erythromycin, metronidazole, tricyclic antidepressants, phenothiazine-neuroleptics, and sulphonamides (also in co-trimoxazole). Enzyme inhibitors of this type impair the biodegradation of certain drugs and hence increase their effects.

A wellknown problem is the enhanced effect of anticoagulants (as reflected by bleeding) induced by additional treatment with co-trimoxazole. Certain drugs may impair the renal excretion (3-5) of other agents, usually at the renal tubular level.

A well-known relevant example is the rise in the plasma level and toxicity of digoxin, provoked by verapamil, amiodarone, or quinidine. Similarly, thiazide diuretics may decelerate the renal elimination of lithium salts and hence reinforce their toxicity. A beneficial effect of such an interaction is the impaired excretion of penicillin antibiotics induced by simultaneously administered probenecide.

Pharmacodynamic interactions and additive toxicity (3-5: Pharmacodynamic interactions between similarly acting drugs may lead to additive or even over-additive effects (potentiation). A well-known example is the combination of i.v. verapamil and a ß-blocker, which may cause additive impairment of cardiac A-V conduction and the risk of A-V block.

Another possibility is the inhibition of the therapeutic effect of a drug by an additional agent. Over-additive adverse reactions are illustrated by the following example: a most important interaction, probably caused by non-specific mechanisms, is the mutual enhancement of the central nervous depressant effects of all drugs that are known to dampen the activity of the central nervous system.

This interaction holds for hypnotics, anxiolytics (minor tranquillizers), antipsychotics (neuroleptics, major tranquillizers), anti-epileptics, and opioids, but also for drugs with central nervous depressant adverse reactions, such as antihistamines, centrally acting antitussives (codeine, etc.), and scopolamine (3-5, 6).

Furthermore, alcohol enhances the central nervous depressant effects of all of the aforementioned therapeutics. Accordingly, enhanced sedation, impaired psychomotor skills (driving), but also respiratory depression may occur. The major drug interactions of statins tabulated below table.

Interacting Drug	Findings and Mechanism of Interaction	Recommendations/Comments
Amiodarone (e.g., Cordarone, generics)	• Increased risk for myopathy/rhabdomyolysis due to decreased metabolism of atorvastatin, lovastatin, and simvastatin. • Amiodarone is a CYP3A4 and CYP2C9 (moderate) inhibitor(.2)	1. Do not exceed 40 mg lovastatin or 20 mg simvastatin.[7,9,11] 2. Consider limiting atorvastatin dose.[11] 3. Fluvastatin is primarily metabolized bycyp3a4
Azole Antifungals Fluconazole (Diflucan, generics) Itraconazole (Sporanox) Ketoconazole (Nizoral, generics) Posaconazole (Noxafil [U.S.], Posanol [Canada]) Voriconazole (Vfend)	• Increased risk for myopathy/rhabdomyolysis due to decreased metabolism of atorvastatin, fluvastatin, lovastatin, and simvastatin. • Itraconazole, ketoconazole, posaconazole, and voriconazole are strong CYP3A4 inhibitors.64 • Fluconazole is a moderate CYP3A4 and CYP2C9 inhibitor.64	1. Hold lovastatin and simvastatin during the course of itraconazole, ketoconazole, or posaconazole treatment.[7,9] 2. Consider reduced lovastatin or simvastatin dose when used with voriconazole.[7,9,16] 3. Hold atorvastatin during the course of itraconazole treatment.[25] 4. Consider reduced atorvastatin dose if used with ketoconazole, posaconazole, or voriconazole.[26] 5. Use caution when coadministering fluconazole with atorvastatin, lovastatin, simvastatin, or fluvastatin.[18,19] 6. Fifty percent statin dose reduction suggested.18 Limit fluvastatin dose to 20 mg twice daily.[21] 7. Consider fluvastatin, rosuvastatin, or pravastatin rather than lovastatin, simvastatin, or atorvastatin with itraconazole or ketoconazole.[30,31]
Bile Acid Sequestrants Cholestyramine (e.g., Prevalite [U.S.]. Olestyr [Canada], generics) Colestipol (Colestid, generics [U.S.])	Decreased bioavailability of statins due to the drugs binding in the intestine.	1. Administer statins 1 hr before or at least 4 hrs after cholestyramine or colestipol.[25-27] 2. Some Canadian statin monographs (atorvastatin, lovastatin, and simvastatin) recommend at least 2 hours elapse between statin administration and administration of bile acid sequestrants.[12,14,24]
Calcium Channel Blockers (Amlodipine, Diltiazem, Verapamil)	Amlodipine: Increased risk for myopathy/rhabdomyolysis due to decreased metabolism of simvastatin	1. Do not exceed lovastatin 20 mg or 2. simvastatin 10 mg with verapamil ordiltiazem.[11,13]
Grapefruit/Grapefruit Juice	Increased risk formyopathy/rhabdomyolysis due todecreased metabolism of atorvastatin,lovastatin, and simvastatin. Grapefruit juice inhibits CYP3A4 and Pglycoprotein.	1. Experts suggest avoiding grapefruit withatorvastatin, simvastatin, and lovastatin.[33] 2. Consider using pravastatin, rosuvastatin, orfluvastatin.
Macrolide Antibiotics Clarithromycin (e.g., *Biaxin*, generics) Erythromycin	Increased risk for myopathy/rhabdomyolysis due to decreased metabolism of atorvastatin, lovastatin, and simvastatin. These macrolides are CYP3A4 inhibitors.64	1. Lovastatin and simvastatin should be heldduringtreatmentwiththesemacrolides.[11,13] 2. Do not exceed atorvastatin 20 mgwith clarithromycin. Also consider cautiousdosing with erythromycin.[24] 3. Use azithromycin if treatment

		withamacrolideantibioticisunavoidable. 4. Do not exceed pravastatin 40 mg withclarithromycin.[29] 5. Use rosuvastatin or fluvastatin inpatientswho require frequent orprolonged treatmentwith clarithromycin or erythromycin. 6. • Limit pitavastatin to 1 mg witherythromycin.
Warfarin	Potential increase in INR due to decreased warfarin metabolism and displacement of warfarin from protein binding sites.	1. Monitor INR closely when initiating,stopping, or changing the statin dos 2. Atorvastatin may be less likely to interact.[24,29]

CONCLUSION

Statins have proven to be safe in numerous clinical trials. However, studies have shown that they can interact with other co-administered medicines. The different pharmacokinetic profiles of different statins should be carefully examined in order to understand the different spectra of drug interactions. These interactions are important determinants of safety in patients with hypercholesterolemia, especially those requiring long-term therapy with drugs that are well-known CYP3A4 inhibitors/inducers

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