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An updated review of interactions of statins with antibacterial and antifungal agents

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Abstract

Numerous antimicrobial agents interact with statins. It is important to prevent these drug interactions and resulting statin toxicity and/or reduced efficacy. We review and highlight major drug-drug interactions between statins and antibacterial and antifungal agents; interactions with antiviral agents were not considered. Daptomycin interacts with statins via additive skeletal muscle toxicity. One possibility is to discontinue statins during daptomycin therapy, though no retrospective studies to date have shown a statistically significant elevation of adverse outcome risk. Multiple doses of rifampin induce cytochrome P450 (CYP), particularly 3A4 and 2C9, resulting in reduced systemic exposures to all statins, except rosuvastatin, for which the response was variable. Macrolide antibiotics are inhibitors of CYP3A4 and organic anion-transporting polypeptide-1B1. Azithromycin has the fewest drug interactions, while clarithromycin and erythromycin increase systemic exposure to all statins except rosuvastatin and fluvastatin. Azole antifungals are CYP450 inhibitors. Itraconazole and posaconazole are strong CYP3A4 inhibitors and mainly affect simvastatin, lovastatin, and atorvastatin, while fluconazole is an inhibitor of CYP2C9 and potentially CYP2C19 and mainly affects fluvastatin; however, risk cannot be ruled out with rosuvastatin.

Introduction

Statins (hydroxymethylglutaryl-CoA reductase inhibitors) are commonly used lipid-lowering medications that once started are typically administered for the life of the patient. Given that most people receive antimicrobial agents during their lifetimes, the co-administration of statins and antimicrobial agents is common. Statins are considered relatively safe; however, they can cause life-threatening rhabdomyolysis with acute kidney insufficiency (AKI). These effects may be aggravated by high doses and interactions with other drugs that result in high systemic exposure, measured by the area under the plasma drug concentration-time curve (AUC) [1,2]. Therefore, it is important to be proactive and intervene when necessary by changing the interacting drugs, doses, and/or monitoring the patient more closely.

Metabolic drug-drug interactions are caused by inhibition or stimulation of cytochrome P450 (CYP450) hepatic metabolizing enzymes and/or drug transporters. Nonetheless, the AUC of most statins increases considerably despite not being metabolized by CYP450. Rhabdomyolysis incidence with the use of statins metabolized by CYP3A4 is approximately 5 times higher than with the use of the non-CYP3A4metabolized statins [1,2].Patients receiving statins should be closely monitored for symptoms of skeletal muscle toxicity and increases in serum creatinine kinase (CK) concentrations. In addition, statin package inserts occasionally give clear recommendations on how to respond to a statin-antimicrobial interaction; these recommendations are summarized in Table 1. It should be noted that there are limitations with the drug interaction studies and the results of one study might not necessary be generalizable. The pharmacokinetic (PK) studies typically include healthy volunteers, whereasgeneral population could have several comorbidities that might affect the PKs of statins or increase the risk of adverse events. The objective of this review is to highlight the clinically relevant drug-drug interactions between statins and antibacterial/antifungal agents. In this review, statins were the object drugs and antibacterial/antifungal agents were the precipitant drugs. Antiviral agents were excluded from this study.

Statin metabolism

There are various mechanisms by which statins can interact with other medications. Numerous statins are substrates of CYP450, organic anion-transporting polypeptide (OATP)-1B1/3, and other transporters and metabolizing enzymes [3-5].Both simvastatin and lovastatin are prodrugs that require activation to simvastatin acid and lovastatin acid, respectively. Simvastatin and lovastatin are the principal CYP3A4 substrates, followed by atorvastatin [5-8], while fluvastatin and rosuvastatin is a CYP2C9 substrate [9,10]. Pravastatin, and pitavastatin are not substrates of CYP450 [11,12].

Literature review

A systematic search of PubMed was conducted without date or language restrictions through 2/3/2017. The Medical Subject Headings (MeSH) terms used were "Anticholesteremic Agents" and "Anti-Infective Agents", excluding “Antiviral agents”. PK and observational studies on drug-drug interactions between statins and antibacterial/

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Table 1. Manufacturer recommendations and AUC changes for selected interactions of antibacterial and antifungal agents with statins

Antimicrobial-Statin Interaction	Increase in Statin AUC (times its original value)	Package Insert Recommendation
Clarithromycin with atorvastatin	3.5	Atorvastatin maximum=20 mg/day
Clarithromycin with simvastatin	11	Contraindicated
Erythromycin with simvastatin	4	Contraindicated
Clarithromycin with pravastatin	2	Pravastatin maximum=40 mg/day
Erythromycin with pitavastatin	3	Pitavastatin maximum=1 mg/day
Itraconazole with simvastatin	19	Contraindicated
Itraconazole with lovastatin	15	Contraindicated
Itraconazole with atorvastatin	2.5-3.3	Atorvastatin maximum=20 mg/day
Fluconazole with fluvastatin	2	Fluvastatin maximum=20 mg/day
Posaconazole with simvastatin	7-8	Contraindicated

antifungal agents were included. In addition, the package inserts of statins and the precipitating antibacterial/antifungal agents were checked for manufacturer recommendations.

For macrolides, a systematic search identified two [13,14] observational studies and five [15-19] PK studies, and a manual search identified one additional PK study [20]. For daptomycin, systematic and manual searches identified four PK studies [21-24] and one [25] observational study, respectively. For rifampin, a systematic search identified three PK studies [26-28] assessing the impact of single dose and four PK studies [29-32] assessing the impact of multiple doses. Eight [33-40] PK studies were identified for azole antifungals.

Discussion

Statins interactions with macrolides

CYP3A4 is inhibited strongly by clarithromycin, moderately by erythromycin, and weakly by azithromycin [41-44].Unlike azithromycin, clarithromycin and erythromycin also inhibit OATP1B [45].In a population-based cohort of older adults, concomitant administration of clarithromycin and/or erythromycin with statins was associated with a higher risk of adverse events compared to concomitant administration of azithromycin with statins [13,14].

Clarithromycin increase the AUC of atorvastatin by up to 3.5 times its original value, while erythromycin increases it by 1.3 times its original value [15-17].In contrast, azithromycin has no impact on the AUC of atorvastatin.22 The manufacturer of atorvastatin recommends against a dosage exceeding 20 mg/day when co-administered with clarithromycin [16,17].Clarithromycin and erythromycin should be avoided with simvastatin because they increase the AUC of simvastatin acid by 11 times and 4 times their original values, respectively [7,16,18,42]. A similar effect is expected with lovastatin given that it is a major CYP3A4 substrate [46].

The manufacturer of pitavastatinrecommends against exceeding a dosage of 1 mg/day when co-administered with erythromycin because erythromycin increases the AUC of pitavastatin by 3 times its original value [47]. The manufacturer of pravasatin recommends against exceeding a dosage of 40 mg/day when co-administered with clarithromycin because clarithromycin results in a doubling of the pravastatin AUC [12,16,42]. Rosuvastatin and fluvastatin could be considered for use as safer alternative statins because the AUC of neither drug increases when co-administered with erythromycin [9,10,19,20,48]. Azithromycin could also be considered for use as a safer alternative macrolide when co-administered with statins.

Statins interactions with daptomycin

Both daptomycin and statins can cause skeletal muscle toxicity and require CK monitoring; concomitant administration may increase this risk [49]. A case of rhabdomyolysis and AKI has been reported with the co-administration of daptomycin with simvastatin; in this case, serum creatinine and CK normalized after stopping daptomycin [50]. The prescribing information for daptomycin recommends considering suspending statin during treatment with daptomycin [49]. To date, studies have not found a higher risk of adverse outcomes with concomitant administration; however, these studies are retrospective and could be underpowered [21-25].

McConnell et al.'s study compared 233 patients receiving daptomycin (53 with statins and 180 without statins) and did not find a statistically significant difference in frequency of CK elevation (5.7% vs 1.1%, respectively; $p = 0.08$) [25]. Bland et al's study compared 220 patients receiving daptomycin (49 with statins vs 171 without statins) and did not find statistically significant differences in frequencies of myalgia (6.1% vs 2.9%, respectively; $p = 0.38$), CK levels of >1,000 U/liter (10.2% vs 5.3%, respectively; $p = 0.32$), or therapy discontinuation due to CK elevations with concurrent myalgia (6.1% vs 3.5%, respectively; $p = 0.42$). [21]. Berg et al.'s study compared 498 patients receiving daptomycin (63 with statins and 384 without statins) and did not find a statistically significant difference in frequency of CK elevation (*Hazard Ratio*, 0.44; *95% Confidence Interval*, 0.14- 1.40; $p = 0.17$) [22]. Golightly et al.'s study compared 157 patients receiving statins (52 with daptomycin and 105 without daptomycin) and did not find a statistically significant difference in frequency of CK elevation (9% vs 21%, respectively; $p = 0.135$) [23].Parra-Ruiz et al.'s study compared 104 patients receiving daptomycin (52 with statins and 105 without statins) and did not find a statistically significant difference in frequency of CK levels>1000 U/L (8% vs 10%, respectively; $p = 0.746$) [24].

Statins interactions with rifampin

Rifampin is an inducer of CYP450, particularly 3A4 and 2C9, and some drug transporters, while it is an inhibitor of other transporters such as OATP1B1/3 [51-53]. The interaction of atorvastatin with rifampin is interesting because it is time-dependent and caused by a dual interaction mechanism. One dose of concomitant rifampin resulted in an increase in the AUC of atorvastatin, pitavastatin, and pravastatin by 7 times, 5.8 times, and 2.3 times their original values, respectively [26-28]. This effect can be explained by rapid OATP1B1/3 inhibition by rifampin [26]. In contrast, 5 days of rifampin non-simultaneous administration resulted in an 80% decrease in the AUC of atorvastatin [29]. This is due to slower CYP450 induction by rifampin. However, there was no reduction in atorvastatin AUC with simultaneous administration of rifampin, which is why the manufacturer recommends simultaneous rather than delayed administration of atorvastatin after rifampin administration [6]. In other studies, concomitant administration of rifampin decreased the AUC ofsimvastatin acid, pravastatin, fluvastatin, and pitavastatin by 90%, 50%, 30%, and 30% respectively [9.11,30,31].A small study looked at the pharmacokinetics of rosuvastatin when co-administered with rifampin. However, the response was variable and the dose used was 450 mg/day rather than the common dose of 600 mg/day [32]. Further studies are needed to better understand the impact of rifampin on rosuvastatin.

Statins interactions with azole antifungals

Itraconazole is a strong CYP3A4 inhibitor and increases the AUC of lovastatin acid and simvastatin acid by 15-20 times and 19

times their original values, respectively [33,34,54]. Therefore, the co-administration of itraconazole with these statins is contraindicated [7,8]. Itraconazole also increases the AUC of atorvastatin by 2.5-3.3 times its original value; therefore, the manufacturer of atorvastatin recommends not exceeding a dosage of 20 mg/day when co-administered with itraconazole [6,35,36]. The AUCs of pitavastatin, fluvastatin, pravastatin, and rosuvastatin are not significantly affected by co-administration with itraconazole [11,30,33,36,37,54].

Fluconazole is a strong inhibitor of CYP2C9 and potentially CYP2C19 and therefore approximately doubles the AUC of fluvastatin. Given this effect, the manufacturer of fluvastatin recommends not exceeding a dosage of 20 mg/day when co-administered with fluconazole [9,38]. The AUCs of pravastatin and rosuvastatin are not significantly affected by co-administration with fluconazole; however, caution is advised with rosuvastatin,especially with polymorphism of CYP2C9 [38,39]. In addition, as fluconazole is a moderate CYP3A4 inhibitor, it may increase the AUC of lovastatin, simvastatin, and atorvastatin; thus, caution when co-administering fluconazole with these statins is advised [55-57].

Posaconazole is a strong CYP3A4 inhibitor and increases the AUC of simvastatin acid by approximately 7-8 times its original value [40]. Per prescribing information, its administration is contraindicated with simvastatin, lovastatin, and atorvastatin [58]. Ketoconazole is a strong CYP3A4 inhibitor and its concomitant administration with simvastatin and lovastatin is also contraindicated [59]. However, it does not affect fluvastatin and rosuvastatin significantly [48,60].

Statins interactions with fusidic acid

Statins should be avoided during and until 7 days post-therapy with systemic fusidic acid [61]. Although the exact mechanism is still unknown, it seems the interaction can be explained partially by inhibition of CYP3A and drug transporters BCRP and OATP1B1 [62].

Conclusion

This review discussed clinically relevant interactions of statins with antibacterial and antifungal agents based on the pharmacokinetic properties of object and precipitant drugs, pharmacokinetic studies, observational studies, and manufacturer recommendations. The pharmacokinetic differences among statins should be considered when evaluating drug interactions with antimicrobial agents. Some statins require dose adjustments, discontinuation during antimicrobial therapy, changing antimicrobial therapies, or simple monitoring. Clinicians should combine current knowledge and recommendations with their clinical judgment to determine the best intervention for each patient; however, we provided this summary to help guide decision-making when encountering statin-antimicrobial drug interactions.

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