Chapter

Pharmacokinetic Aspects of Statins

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Abstract

Statins are the most used therapeutic group in the treatment of hypercholesterolemia and reduce the risk of cardiovascular events and mortality. Long prescription periods and their pharmacokinetic characteristics increase the possibility of interactions, especially at the metabolism level. Simvastatin, lovastatin, and atorvastatin are metabolized by CYP3A4 isoenzymes, so they will have more significant interactions than fluvastatin, pitavastatin, and rosuvastatin that require CYP2C9. The main interactions are with macrolides, azole antifungals, antiretrovirals, platelet antiaggregants, anticoagulants, oral antidiabetics, calcium channel blockers, immunosuppressants, and other hypolipidemic agents, among others. A review of all medications that are taken by patients treated with statins should be performed at each medical consultation and during all healthcare transitions.

Keywords: drug interactions, metabolism, isoenzymes CYP3A4, rhabdomyolysis, hypolipidemic drugs

1. Introduction

As a consequence of the variability in their origin, statins have notable differences; however, their pharmacodynamic similarities allow them to be grouped together for study. As for the mechanism of action, its effects and the clinical consequences of its use, there is an important group congruence already well known.

Nowadays, seven statins are commonly used: lovastatin (first licensed in 1987), simvastatin (1988), pravastatin (1991), fluvastatin (1994), atorvastatin (1997), rosuvastatin, and pitavastatin (2003). Cerivastatin, approved in 1998, was subsequently withdrawn from the world market due to a high risk of rhabdomyolysis.

They are the most therapeutic group used in the treatment of hypercholesterolemia and most have been shown to reduce the risk of events and cardiovascular mortality; however, the long prescription periods of these drugs and their pharmacokinetic characteristics increase the possibility of drug interactions [1].

2. Statins pharmacokinetics

2.1 Absorption

The interaction of statins at the level of absorption can translate into a decrease in the absorption of the drug by a change in pH, a variation in the speed of intestinal motility or the formation of complexes and/or chelates.

All currently marketed statins are absorbed orally in a variable range (between 30% for lovastatin and 35% for pravastatin), so the influence of intake at the time of administration is very important to achieve an effect adequate therapeutic [2].

The absorption of a drug can be reduced, delayed, or increased by food consumption, as they share many physiological mechanisms and coincide with numerous organs. This is why the medication schedule is so important in these drugs. In general, all statins reduce their absorption in the presence of food so that their administration is usually at night, before bedtime, and without food, although there are some exceptions. When pravastatin is administered with food, its bioavailability is reduced by approximately 35% compared to that obtained in its administration before meals. This bioavailability reduction is also observed for fluvastatin, both water soluble, so it is recommended to space its administration with respect to meals at least 4 hours. As for atorvastatin, it seems that a meal with a medium fat content may slightly reduce its absorption, while with simvastatin, it does not seem that this fact is relevant. Unlike the previous ones, the administration of lovastatin after a meal increases its plasma concentration by 50% compared to the fasting state. Therefore, it is recommended that lovastatin be taken with food. As for the most recent statins, rosuvastatin and pitavastatin, rosuvastatin has an absorption in which plasma concentrations are reached at approximately 5 hours after oral administration. The total bioavailability is approximately 20%. Rosuvastatin, unlike its group mates, can be taken at any time of the day, its absorption being the same with both food and without food.

Likewise, pitavastatin is widely absorbed by 80%, without interacting with food. There is no accumulation due to repeat multiple doses; therefore, the single dose is accepted.

2.2 Distribution

Plasma protein binding is variable, but in general, it is very high. Except for 50% of pravastatin, all are above 95%. The tissue distribution is wide, crossing the blood-brain and placental barriers, even passing into breast milk. No clinically important interactions have been described by displacement of statins from their binding to plasma proteins. However, the fact that statins could be displaced by another drug is a fact that must always be taken into consideration and studied to discover a possible case.

The hepatic specificity of these drugs is determined by their degree of lipophilicity and by the presence of organic anion transport proteins (OATPs) that allow more hydrophilic statins such as pitavastatin, pravastatin, and rosuvastatin to enter the hepatocyte. The lipophilic statins (atorvastatin, fluvastatin, lovastatin, and simvastatin) can enter directly in cells. On the other hand, some statins can inhibit P-glycoprotein (multidrug resistance protein), a drug-carrying protein in the cell, so they could lead to drug interactions. Lovastatin and simvastatin are ingested as lipophilic lactone prodrugs, whereas other statins are administered as active acid forms.

2.3 Metabolism

Statins are metabolized by CYP450 isoenzymes, with the exception of pravastatin, which is metabolized in the cellular cytosol by sulfation. In addition, they present gastrointestinal and hepatic first-pass metabolism. There are differences in metabolism with respect to gender and age, but not enough to modify the doses in the absence of other pathologies (**Table 1**).

Enzyme	Statin Substrates	Inhibitors	Inducers
CYP2C9	Fluvastin, rosuvastatin (also CYP2C19)	Amiodarone, capecitabine, etravirine, fluconazole, fluvoxamine, fluvastatin, ketoconazole, metronidazole, miconazole, oxandrolone, sulfamethoxazole/ trimethoprim, voriconazole, zafirlukast	Carbamazepine, phenobarbital, phenytoin rifampin
CYP3A4	Atorvastatin, lovastatin, simvastatin	Amiodarone,amlodipine, aprepitant, atorvastatin, bicalutamide, cilostazol, cimetidine, ciprofloxacin, clarithromycin, conivaptan, cyclosporine, diltiazem, erythromycin, fluconazole, fluoxetine, fluvoxamine, grapefruit juice, imatinib, isoniazid, itraconazole, ketoconazole, mibefradil, midazolam, nefazodone, nilotinib, posaconazole, protease inhibitors, ranolazine, sertraline, tacrolimus, telithromycin, ticagrelor, tricyclic antidepressants, verapamil, voriconazole	Aprepitant, bosentan, carbamazepine, cyclophosphamide, corticosteroids, efavirenz, modafnil, nafcillin, nevirapine, phenytoin, pioglitazone, phenobarbital, rifampin, St. John's wort
P-gp	Atorvastatin, lovastatin, pitavastatin, simvastatin	Amiodarone, atorvastatin, azithromycin, captopril, carvedilol, cimetidine, clarithromycin, colchicine, conivaptan, cyclosporine, diltiazem, dipyridamole, dronedarone, erythromycin, felodipine, grapefruit juice, itraconazole, ketoconazole, lovastatin, mefloquine, nicardipine, omeprazole, protease inhibitors, quinidine, ranolazine, reserpine, sertraline, simvastatin, tacrolimus, verapamil	Carbamazepine, phenytoin rifampin, St. John's wort
OATP1B1	Atorvastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin	Carbamazepine, clarithromycin, cyclosporine, erythromycin, gemfibrozil, protease inhibitors, roxithromycin, rifampin, sildenafil, sacubitril, telithromycin	Unknown
OATP1B3	Fluvastatin, pravastatin, rosuvastatin	Clarithromycin, cyclosporine, erythromycin, rifampin, roxithromycin, rifampin, sacubitril, telithromycin	Unknown

CYP: cytochrome P; OATP: Organic Anion-Transporting Polypeptide; P-gp: permeability glycoprotein

Table 1.
Common P-gp substrates, inhibitors, and inducers associated with the CYP450 enzymes affecting statin metabolism [42].

CYP450 metabolizes a high percentage of drugs, especially the CYP3A4 isoenzyme (about 36%). The main factors that affect the metabolism by this route are enzyme induction, enzyme inhibition, and genetic polymorphisms.

Enzymatic inducer is that medication that stimulates the synthesis and/or activity of a CYP450 isoenzyme, usually CYP3A4. This produces a stimulation of the metabolism of both the inducing drug itself (self-induction) and the drug administered concomitantly, in this case the statin, so it would reduce more rapidly its plasma concentrations. A reduction in plasma concentrations results in a lower effect of the hypolipemiant drug. In the case of having to administer the two medications, it would be necessary to perform blood concentration tests and, if necessary, increase the dose of statin. The most frequent enzyme inducers are rifampicin, rifabutin, phenobarbital, carbamazepine, phenytoin, nevirapine, efavirenz, troglitiazone, polyglitazone, or St. John's wort (Hipérico).

Enzymatic inhibitor is that medication that, administered together with the statin, inhibits a CYP450 isoenzyme. This produces a decrease in statin metabolism, increasing its plasma concentrations, and can cause adverse effects. The most potent and frequent enzyme inhibitors are protease inhibitors such as ritonavir (potent antiretroviral used precisely because of its inhibitory role in potentiation pharmacokinetics) and some macrolides such as erythromycin, proton pump inhibitors such as omeprazole, azole antifungals such as ketoconazole or itraconazole, or the juice of Grapefruit, among many others.

The metabolites can be hydroxylated, omega or beta-oxidized, methylated, or glucuronized derivatives, whose pharmacological activity is highly variable.

Therefore, the spectrum of clinical effectiveness is wide, from lovastatin or simvastatin, which are really pharmacologically inactive lactones and that carry out their pharmacological activity through their metabolites, to fluvastatin, which has practically inactive metabolites.

Simvastatin and lovastatin undergo significant CYP3A4 metabolism and atorvastatin undergoes a lesser amount as one of its minor metabolic pathways.

This is in contrast to fluvastatin, pitavastatin, and rosuvastatin, which require CYP2C9. Because CYP3A4 is the most common enzyme involved in drug metabolism, simvastatin and lovastatin will have more interactions that will likely require intervention [2].

Thus, state-of-the-art statins, rosuvastatin and pitavastatin, are minimally metabolized by CYP450 isoenzymes and by P-glycoprotein. This causes them to have a lower probability of interactions. Pitavastatin, on the other hand, has minimal hepatic metabolism due to the first step (enterohepatic circulation). It is practically not metabolized; it is mainly eliminated by bile route; and its renal excretion as an active drug is minimal (less than 2%). The main metabolic pathway of pitavastatin is lactonization/glucuronidation. Rosuvastatin is also not metabolized by cytochrome CYP3A4; it uses CYP2C9 and CYP2C19 but it does so in a very low percentage [3].

P-glycoprotein (P-gp) is responsible for the intestinal and biliary elimination of some of the statins such as pravastatin or atorvastatin.

2.4 Excretion

The amount of statin that is excreted in its unchanged form through renal elimination is small. The overall dependence of statin metabolites on renal elimination is modest, with pravastatin being the highest at 20% and atorvastatin being the lowest at <2%.

Fluvastatin, lovastatin, pravastatin, and simvastatin have a relatively short half-life (less than 5 hours). These medications are optimally dosed at night or given as an extended-release formulation to maximize the effect (fluvastatin or lovastatin). By contrast, pitavastatin (12 hours), atorvastatin (14 hours), and rosuvastatin (between 15 and 30 hours) have longer half-lives and can be dosed at any time of the day.

Statins are also excreted into bile and feces as a means of drug elimination. This excretion is facilitated by OATPs. Similar to CYP450, there are several subtypes of OATP that can affect the elimination of rosuvastatin and pitavastatin [2].

The drug interactions with statins may sometimes be attributable to decreased drug excretion, especially in patients with impaired glomerular filtration rate, and are related to the extent the statin is renally excreted. This potential issue is limited with atorvastatin, which has the least amount of renal excretion (<2%), but may be a consideration for other statins that have a higher degree of renal excretion (pitavastatin, pravastatin, rosuvastatin, simvastatin) (**Table 2**).

	Absorption		**Distribution**		**Metabolism**			**Excretion**	
	Bioavailability %	T_{max} h	Protein binding %	Lipophilicity	Major P450 Hepatic Enzyme	Prodrug	Active metabolites	Excretion Biliary Renal %	$T_{1/2}$ h
Atorvastatin	12	1-2	>98	Yes	CYP3A4	No	Yes	<1% <2%	14
Fluvastatin	24	<1	>98	Yes	CYP2C9	No	No	>90% 6%	3
Lovastatin	<5	2-4	>95	Yes	CYP3A4	Yes	Yes	83% 10%	2-3
Pitavastatin	>60	1	>99	Yes	CYP2C9	No	No	79% 15%	12
Pravastatin	18	1-1,5	50	No	Non-CYP	No	No	71% 20%	1-3
Rosuvastatin	20	3-5	90	No	CYP2C9	No	Minimal	90% 10%	19
Simvastatin	<	4	>95	Yes	CYP3A4	Yes	Yes	58% 13%	2

CYP: cytochrome P; t1/2: drug half-life; Tmax: time that a drug is present at the maximum concentration in serum.

Table 2.
Pharmacokinetic properties of statins [2].

3. Interactions

The long prescription periods of these drugs and their pharmacokinetic characteristics already exposed, increase the possibility of drug interactions. The most frequent adverse effects are headache, gastrointestinal discomfort, cramps, and asymptomatic elevation of transaminases, among others. The most important safety problem is myopathy, which can progress to rhabdomyolysis and death of the patient (**Table 3**).

3.1 Drug-drug interactions

HMG-CoA reductase inhibitors have different pharmacokinetic profiles, which may affect potential drug interactions.

3.1.1 Antiplatelet agents

There is controversy between the interaction of clopidogrel with statins motivated mainly by differences in the design and method of the studies.

So, no effect of atorvastatin or any statin on antiplatelet activity of single dose of clopidogrel found in prospective study of 25 patients taking atorvastatin, 25 patients taking other statin, and 25 patients taking no statin [4].

This administration of CYP3A4-metabolized statins in clopidogrel treated patients does not induce any changes in the conversion of clopidogrel into its active thiol form and therefore neither has a quantitatively nor clinically relevant influence on clopidogrel efficacy [5].

Several randomized clinical trials (RCTs) compare the results of patients in whom clopidogrel was associated and a statin metabolized by CYP3A4 (atorvastatin, lovastatin, simvastatin); with those treated with statins not metabolized by CYP3A4 (fluvastatin and pravastatin). Patients treated with atorvastatin had similar rates of bleeding and complications, without any interaction being checked [6]. In other trials, the inhibition of platelet aggregation was similar when fluvastatin, pravastatin, or atorvastatin was associated with clopidogrel [7].

In a cohort study conducted in 10,491 patients who were prescribed clopidogrel, when comparing 43.5% of the patients who were associated with atorvastatin, with whom a non-CYP3A4 statin was associated, or with the group that did not receive statin, there was no increase in possible side effects [8].

A clinical trial of 50 patients comparing the association of clopidogrel-acetylsalicylic acid with that of atorvastatin-clopidogrel, after a "bypass" of the coronary artery, shows that the combination with atorvastatin further increased platelet inhibition and, consequently, the antiaggregant effect would be greater than the association with acetylsalicylic acid [9].

Clinical trials have evaluated pharmacokinetic interactions of ticagrelor coadministered with atorvastatin, simvastatin, or lovastatin. They have shown an increase in Cmax (maximum concentration) and AUC (area under the curve) of atorvastatin, simvastatin, or lovastatin as a result of CYP3A4 inhibition by ticagrelor. However, these changes were not statistically significant [10]. The dose of simvastatin and lovastatin should not exceed 40 mg daily when prescribed with ticagrelor. There were no clinically significant interactions when ticagrelor is used in combination with pravastatin, fluvastatin, pitavastatin, or rosuvastatin, and no dosing restrictions were needed. No clinically significant drug interactions have been reported with prasugrel in combination with statins.

Interacting Agent		Statin	Effect	Magnitude	Recommendation
Antiarrhythmic agent	Amiodarone	Simvastatin Lovastatin	Increased statin exposure/increased risk for muscle-related toxicity	Minor	Combination therapy may be considered
	Dronedarone	Lovastatin Simvastatin	Decreased metabolis of statin leading to increased concentrations increased statin exposure/increased risk for muscle-related toxicity	Moderate	Combination may be considered
	Digoxin	Atorvastatin	Increased levels of digoxin	Minor	Combination is reasonable
Azole antifungals (fluconazole, itraconazole)		Simvastatin Lovastatin Atorvastatin Fluvastatin	Increased statin exposure/increased risk for muscle-related toxicity	Severe	Combination is potentially harmful
Anticoagulants (warfarin)		Simvastatin Lovastatin Fluvastatin Rosuvastatin	Increase INR/ potential for increased bleeding	Variable	Combination therapy is useful
Antiretroviral	All protease inhibitors	Simvastatin Lovastatin	Increased statin exposure/increased risk for muscle-related toxicity	Severe	Combination is potentially harmfull
	Saquinavir/ritonavir Nelfinavir	Atorvastatin	Increased statin exposure/increased risk for muscle-related toxicity	Moderate	Administer lower dose of atorvastatin
	Nelfinavir	Pravastatin	Decreased metabolism of statin	Moderate	Combination is reasonable, adjust dose pravastatin
	Lopinavir/ritonavir Atazanavir/ritonavir	Rosuvastatin	Increased statin exposure	Moderate	Combination is reasonable, adjust dose rosuvastatin
	Efavirenz	Simvastatin Lovastatin Atorvastatin Pravastatin	Decreased metabolis of statin	Moderate	Combination is reasonable, adjust dose statin
Calcium channel blockers	Dihydropyridine calcium antagonist (amlodipine)	Lovastatin Simvastatin	Increased statin exposure/increased risk for muscle-related toxicity	Minor	Combination therapy may be considered
	Non-dihydropyridine calcium antagonists (verapamil)	Lovastatin Simvastatin Atorvastatin	Decreased metabolis of statin leading to increased concentrations increased risk of muscle-related toxicity	Moderate	Combination may be considered
Colchicine		Atorvastatin Fluvastatin Lovastatin Pitavastatin Pravastatin Rosuvastatin Simvastatin	Increased statin or colchicine exposure/increased risk for muscle-related toxicity	Variable	Combination may be considered
Fibrates (fenofibrate)		Atorvastatin Fluvastatin Lovastatin Pitavastatin Rosuvastatin Simvastatin	Potential increase in muscle-related toxicity	Insignificant	Combination is reasonable
Gemfibrozil		Atorvastatin Pitavastatin Rosuvastatin	Decreased metabolis of statin leading to increased concentrations /increased risk for muscle-related toxicity	Minor/ moderate	Combination may be considered
		Lovastatin Pravastatin			Combination should be avoided
		Simvastatin			Avoid combination
Inmunosuppressants (cyclosporine/tacrolimus/ everolimus/sirolimus)		Atorvastatin Fluvastatin Pravastatin Rosuvastatin	Increased statin exposure through multiple mechanisms Increased risk for	Severe	Combination therapy may be considered
		Simvastatin Lovastatin Pitavastatin	muscle-related toxicity		Combination is potentially harmfull
Macrolides (clarithromycin, erythromycin, telithromycin)		Simvastatin Lovastatin Atorvastatin	Increased statin exposure/increased risk for muscle-related toxicity	Severe	Combination is potentially harmful
Ranolazine		Lovastatin Simvastatin	Increased statin exposure/increased risk for muscle-related toxicity	Minor	Combination therapy may be considered
Ticagrelor		Atorvastatin	Increased statin exposure/increased risk for muscle-related toxicity	Minor	Combination is reasonable
		Lovastatin Simvastatin	Decreased metabolis of statin leading to increased concentrations /increased risk for muscle-related toxicity	Moderate	Combination may be considered

Table 3.
Statin interactions [7, 8, 13, 23, 25, 37, 39].

3.1.2 Anticoagulants

The warfarin and statin interaction information is limited; however, the case reports show a possible effect on coagulation, especially with fluvastatin or rosuvastatin [11] (for its potent inhibitory effect on CYP2C9) and lovastatin (possibly due to the displacement of protein binding). Other statins, except pravastatin, could have interactions, by inhibition of warfarin or acenocoumarol metabolism, or by displacement of protein binding.

Several studies neither have demonstrated significant interaction between warfarin-pitavastatin [12] and warfarin-atorvastatin [13], nor have shown clinically significant drug interactions with statins and new anticoagulants such as dabigatran, apixaban, rivaroxaban, and edoxaban.

The use of statins with warfarin as combination therapy is useful when clinically indicated. It is advisable to monitor the international normalized ratio (INR) more closely when a statin is started or changed in dose. The impact on the INR appears lowest for pitavastatin and atorvastatin [14].

3.1.3 Oral antidiabetics

It has been shown that statins and metformin reduce inflammation and oxidative stress. These results show an additional cardioprotective effect, as a direct action mechanism or through its pleiotropic effects. That is why patients with type II diabetes mellitus often take metformin and statins together to control the risk of cardiovascular disease and glucose metabolism. Metformin shows beneficial effects on both dyslipidemia and glycemic control and it has been shown to reduce the risk of cardiovascular disease. While statins can have an additional beneficial effect on the risk of cardiovascular disease, the combined treatment with both medications seems be a good therapeutic option [15].

The prescription of statins and dipeptidyl peptidase 4 (DPP-4) inhibitors is becoming common in patients with type 2 diabetes mellitus and hyperlipidemia. Several mechanisms have been proposed to describe the interaction between the two, ranging from the effects of sitagliptin on renal excretion of statins to interaction at the level of liver metabolism [16]. A case report of simvastatin-induced rhabdomyolysis in the presence of sitagliptin proposed that the nephrotoxicity of sitagliptin led to reduced renal excretion of simvastatin [17].

However, a clinical trial that studied the effects of sitagliptin on the pharmacokinetics of simvastatin in 12 healthy human subjects aged 18–45 years, both male and female, showed no effect on simvastatin metabolism [18]. The authors did not recommend dose adjustment, when simvastatin was coadministered with sitagliptin. Similarly, another study in 10 patients found no effects of the use of simvastatin on the pharmacokinetics of sitagliptin, and no dose adjustment was recommended for any of the drugs [19].

In a case report of rhabdomyolysis induced by lovastatin and sitagliptin, the authors suggested an interaction between statin and sitagliptin at the CYP3A4 level as the cause. They claimed that because both are metabolized by CYP3A4, when coadministered, they can compete for the same enzyme, resulting in a higher serum statin concentration, which leads to statin-induced rhabdomyolysis [20]. Two other case reports of rhabdomyolysis with atorvastatin and sitagliptin had similar suggestions, indicating that sitagliptin leads to an increase in serum concentration of atorvastatin through its effects on liver metabolism by CYP3A4 rather than on renal excretion. A thorough review of the literature suggests that atorvastatin and sitagliptin are not prone to drug pharmacokinetic interactions, either separately or in a fixed combination of drugs.

Statins that can cause rhabdomyolysis by interaction with sitagliptin are lovastatin, atorvastatin, and simvastatin as they are all metabolized by CYP3A4. This interaction is not described with statins that are not metabolized by CYP3A4 such as pravastatin, rosuvastatin, pitavastatin, and fluvastatin.

When exenatide (10 mcg twice daily) was administered concomitantly with a single dose of lovastatin (40 mg), the values of AUC and Cmax of lovastatin decreased approximately 40 and 28%, respectively, and the Tmax (maximum concentration time required) was delayed about 4 hours. In the 30-week placebo-controlled clinical trials, the concomitant use of exenatide and hydroxymethylglutaryl coenzyme A (HMG CoA) inhibitors was not associated with consistent changes in lipid profiles. Although no dose adjustment is required, possible changes in LDL-C or total cholesterol should be taken into account. The lipid profile should be evaluated regularly. Liraglutide did not modify the general exposure of atorvastatin to a clinically significant degree following the administration of a single dose of 40 mg of atorvastatin; therefore, no dose adjustment of atorvastatin is necessary when administered with liraglutide. There was a 38% decrease in atorvastatin Cmax, and the average Tmax was delayed 1–3 hours with liraglutide [3].

3.1.4 Azole antifungals

Azole antifungals are inhibitors of the CYP3A4 isoenzyme although itraconazole is more potent than fluconazole. When administered concomitantly with statins, a metabolic block can occur with an increase in plasma concentrations of the latter and the possibility of unwanted effects [21].

There are case reports of myopathy and rhabdomyolysis due to the simultaneous use of simvastatin or atorvastatin with itraconazole and fluconazole. A study that evaluated the effect of itraconazole on the pharmacokinetics of lovastatin in 12 healthy volunteers showed an increase in Cmax of 13 times (range 10–23 times) and 20 times in the AUC of the active metabolite of lovastatin [22].

On the other hand, two randomized double-blind, two-phase, cross-sectional studies conducted to evaluate the effect of fluconazole on plasma concentrations of fluvastatin and pravastatin showed an increase in the AUC and Cmax of fluvastatin by 84 and 44%, respectively; while no significant changes in pravastatin levels were documented.

Itraconazole increased by 15 times the AUC and the Cmax of lovastatin; likewise, simvastatin showed a significant increase in the Cmax and AUC of the acid form (β-hydroxy acid) by 17 and 19 times, respectively. Therefore, the concomitant use of lovastatin and simvastatin with itraconazole should be avoided by the potential increase in toxicity on skeletal muscle. On the other hand, the use of itraconazole with fluvastatin or pravastatin did not generate significant changes in the levels of these statins. Similarly, the combination of fluconazole with rosuvastatin generated an increase in the AUC and Cmax of rosuvastatin without clinical relevance [23].

3.1.5 Antiretroviral agents (ARV)

The use of lipid-lowering drugs in patients with HIV/AIDS is increasingly frequent, due to the increase in life expectancy of this group of patients, a situation that is associated with the presentation of other health problems, such as increased cardiovascular risk, accelerated biological aging, chronic inflammatory process, and prolonged exposure to medications ARV [24].

Metabolism of protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) is mainly due to CYP3A4 inhibition. Pravastatin, due to its metabolic mechanism of sulfation, is of choice in patients treated with PI (except darunavir), although in some cases, it may be necessary to increase the dose of

pravastatin, for example, with nelfinavir or ritonavir. The use of simvastatin, lovastatin, and atorvastatin (except pravastatin, fluvastatin, and rosuvastatin) should be avoided in patients with PI treatment, especially with ritonavir, atazanavir, saquinavir, or nelfinavir [25]. However, it is necessary to keep in mind that the combination of rosuvastatin with lopinavir/ritonavir caused an increase in the AUC and Cmax of rosuvastatin of 2.1 and 4.7 times, respectively. AUC and Cmax of rosuvastatin were increased by 213 and 600% when atazanavir/ritonavir was administered.

Efavirenz decreased the AUC of atorvastatin, simvastatin, and pravastatin by 43, 58, and 40%, respectively. It is recommended to carry out a closer follow-up and if necessary, adjust the dose of statins [26].

3.1.6 Calcium channel blockers

Non-dihydropyridine calcium antagonists (verapamil and diltiazem) have a significant increase in AUC and Cmax when coadministered with simvastatin, lovastatin, and atorvastatin, due to inhibition of P-gp activity (decreased efflux) or enzymatic inhibition of CYP3A4. Lovastatin increased the AUC and Cmax of verapamil by 62.8 and 32.1%; while verapamil AUC was increased by 42.8% in the presence of atorvastatin. On the other hand, simvastatin increased its AUC and Cmax 2.6 and 4.6 times, respectively, due to the use of verapamil. Additionally, there are reports of cases of rhabdomyolysis due to the combination verapamil, cyclosporine, and simvastatin. Diltiazem can cause an increase in Cmax by 3.6 times and the AUC by 5 times of simvastatin and 3.5 times of lovastatin; effect that is not evident in the case of pravastatin [27]. It should be noted that although the inhibitory effect of diltiazem on simvastatin increases the pharmacological effect of statins, an increased risk of myopathy is also observed. According to the above, there is a report of cases of myopathy and/or rhabdomyolysis with doses equal to and greater than 20 mg of simvastatin or atorvastatin. A dose adjustment is recommended in patients treated with verapamil and simvastatin (maximum 20 mg) or lovastatin (maximum 40 mg). Pravastatin, for which no relevant interactions have been described at the CYP450 level, could be an alternative for patients who need treatment with calcium channel blockers that interfere with CYP3A4.

Dihydropyridine calcium antagonist (amlodipine) produces an increase in the Cmax and AUC of simvastatin and atorvastatin, without significant effects on lipid or blood pressure and combination therapy may be considered [28]. The separate administration of at least 4 hours of simvastatin and amlodipine minimizes the occurrence of this interaction [29, 30].

3.1.7 Antiarrhythmic agents

Amiodarone is an inhibitor of CYP3A4 (irreversibly) and P-gp (reversible), causing interactions when used concomitantly with statins metabolized by CYP450 or substrates of the P-gp. There have been reports of toxicity between amiodarone and statins that are CYP3A4 substrates, particularly simvastatin. Thus, a 75% increase in AUC and Cmax of simvastatin has been demonstrated when co-administered with amiodarone. However, there are no significant pharmacokinetic interactions between amiodarone and pravastatin [31].

Muscle-related toxicity was the most commonly reported adverse event with combination therapy (77%). The percentages of simvastatin and atorvastatin adverse events reported in which amiodarone was concomitantly used were 1.0 and 0.7%, respectively. By contrast, the percentage of pravastatin adverse events in which amiodarone was used was only 0.4%. Patients on simvastatin-amiodarone combination therapy were more likely to be hospitalized and were on a higher statin

dose compared with atorvastatin-amiodarone-treated patients. No dose adjustment for rosuvastatin, pravastatin, fluvastatin, and pitavastatin is necessary when coadministered concomitantly with amiodarone.

Additionally, no dose adjustments are recommended for atorvastatin because data suggest that severe interactions with amiodarone are less likely to occur than with other statins metabolized via CYP3A4 (simvastatin and lovastatin). Lovastatin should not exceed 40 mg daily when prescribed in combination with amiodarone and simvastatin, and should be limited to no more than 20 mg daily. On the basis of pharmacokinetic and observational data and adverse events reported in randomized, controlled trials, combination therapy with amiodarone and rosuvastatin, atorvastatin, pitavastatin, fluvastatin, or pravastatin is reasonable.

Coadministration of amiodarone and dronedarone with either lovastatin or simvastatin may be considered. When used in combination with amiodarone, the dose of lovastatin should not exceed 40 mg daily and the dose of simvastatin should not exceed 20 mg daily. There are no known clinically significant interactions between dronedarone and other statins.

Digoxin is not dependent on the CYP450 system because it is not known to induce or inhibit any of these enzymes. Metabolism of digoxin is primary by gut bacteria. In a study that included 24 healthy volunteers, the addition of atorvastatin 80 mg to digoxin resulted in an average increase of 20% in the Cmax of digoxin and an average 15% increase in the AUC of digoxin [32]. However, lower doses of atorvastatin (10 mg) combined with digoxin did not alter the pharmacokinetics of digoxin. Atorvastatin appears to be the only statin that is reported to have this interaction. The mechanism is not fully understood but may be mediated by an impact of atorvastatin on the intestinal secretion of digoxin medicated by the P-gp efflux transporter, resulting in an increased digoxin absorption. The existence of alternatives to atorvastatin, such as fluvastatin, pravastatin, and rosuvastatin, which do not affect P-gp, may be of choice in patients treated with digoxin.

3.1.8 Immunosuppressants

The combination of statins with calcineurin inhibitors (cyclosporine and tacrolimus), due to its inhibitory effect of CYP3A4, inhibitor of OATPB1 and be substrates of P-gp, could cause an increase in serum statin levels and the risk of myopathy and rhabdomyolysis, especially at high doses of statins.

There are reports of cases of rhabdomyolysis with different statins, except fluvastatin and, to a lesser extent, pravastatin. In the case of simvastatin, AUC increases up to 20 times and the effect is enhanced by the use of other CYP3A4 enzymatic inhibitors. On the other hand, in the case of atorvastatin, cases of rhabdomyolysis present without alterations the pharmacokinetics of cyclosporine. Cyclosporine is associated with an increase in AUC and Cmax of rosuvastatin by 7.1 and 10.6 times, respectively.

There is evidence of the safety and effectiveness of fluvastatin in transplant patients treated with cyclosporine. This effect could be due to the fact that fluvastatin, compared to other statins, has a shorter elimination half-life, a greater capacity for protein binding and less circulating active metabolites. In the case of pravastatin, this drug does not accumulate significantly in plasma in patients receiving immunosuppression with cyclosporine, and with rosuvastatin, cyclosporine increased the AUC of this statin by 7.1 times.

Limited data exist on tacrolimus and statin interactions. One open-label evaluation of 13 healthy volunteers suggested that after 4 days of therapy with atorvastatin 40 mg daily, 2 doses of tacrolimus had no impact on the atorvastatin pharmacokinetics [33].

In case reports, the use of sirolimus in combination with statins has been associated with muscle-related toxicity, including rhabdomyolysis. Only one randomized, open-label, three-way crossover, single-dose study in 24 healthy volunteers has suggested that everolimus had no effect on the AUC of atorvastatin 20 mg or pravastatin 20 mg [34].

The combination therapy of cyclosporine, tacrolimus, everolimus or sirolimus with lovastatin, simvastatin, and pitavastatin is potentially harmful and should be avoided. The combination of cyclosporine, tacrolimus, everolimus, or sirolimus with daily dose of fluvastatin, pravastatin and rosuvastatin may be considered and should be limited to 40, 20, and 5 mg daily, respectively. The dose of atorvastatin >10 mg daily when coadministered with cyclosporine, tacrolimus, everolimus, or sirolimus is not recommended without close monitoring of creatinine kinase and signs or symptoms of muscle-related toxicity. The combination of fluvastatin-rapamycin has been linked to the appearance of rhabdomyolysis.

3.1.9 Macrolides

Macrolides, especially clarithromycin, erythromycin, and telithromycin, are the most potent inhibitors of the CYP3A4 isoenzyme, followed by the weak inhibitor, roxithromycin, and finally, azithromycin. CYP3A4 is an isoenzyme that metabolizes simvastatin, lovastatin, and atorvastatin, which increases their plasma concentrations and the risk of myotoxicity. Rosuvastatin, fluvastatin, and pravastatin are not significantly affected by this interaction. Of all macrolides, azithromycin can be used with statins. Erythromycin increased the Cmax of simvastatin (in its lactone form) by 3.4 times, the AUC by 6.2 times and its acid-hydroxy acid form by 3.9 times. Erythromycin increased Cmax and AUC of atorvastatin by 37.7 and 32.5%, respectively. The effect is attributed to decreased metabolism of statins, inhibition of intestinal P-gp, and decreased bile secretion.

In general, case reports of rhabdomyolysis are available due to the interaction between simvastatin and clarithromycin, between lovastatin and erythromycin, and between clarithromycin and azithromycin [35]. A study that evaluated the effect of azithromycin and clarithromycin on the pharmacokinetics of atorvastatin showed that clarithromycin increases AUC and Cmax by 82 and 56%, respectively; meanwhile, there were no significant changes with azithromycin.

3.1.10 Interactions between lipid lowering agents

Some patients may require the combination of several lipid lowering agents, the statin-fibrate association being the most common. However, the greater hypolipidemic effect is accompanied by an increased risk of myopathy, especially with gemfibrozil, due to its inhibitory effect on glucuronidation of statins, increasing the concentrations of the latter.

Gemfibrozil increases the AUC of simvastatin by 35% and the AUC of simvastatin in its acid form by 135% and of lovastatin acid by 280%. Therefore, there is a report of cases of rhabdomyolysis and kidney disease, due to the combination of gemfibrozil with simvastatin, atorvastatin, and lovastatin.

In addition, gemfibrozil increases the AUC of rosuvastatin by 1.88 times and its Cmax by 2.21 times [36]. Gemfibrozil had only a modest effect when administered with pitavastatin in 24 subjects with an increase of 45% in the AUC [37]. Metabolism is only a minor pathway for pitavastatin via CYP2C9, which is unaffected by gemfibrozil. Fluvastatin transport in hepatocytes via the OATP transporters is potently inhibited by gemfibrozil [38]. However, in at least 1 study

of 17 subjects, no significant difference was observed in the AUC and Cmax in a comparison of the gemfibrozil-fluvastatin combination and gemfibrozil alone.

Related to this interaction, it is important to note that fenofibrate is considered more suitable than gemfibrozil, which is supported in studies showing the absence of interaction of fenofibrate with pravastatin, simvastatin, and atorvastatin.

However, fenofibrate may increase rosuvastatin plasma levels and there is a case report of renal failure in a patient taking this combination.

The combination of gemfibrozil with lovastatin, pravastatin, and simvastatin is potentially harmful and should be avoided. Although gemfibrozil interacts with atorvastatin, pitavastatin, and rosuvastatin, the result is only a minor increase in statin concentrations, and the combination may be considered if clinically indicated. Fluvastatin may be used in combination with gemfibrozil without any specific dose limitations, and this particular statin does not interact with gemfibrozil.

Combination therapy with fenofibrate/fenofibric acid and any statin is reasonable when clinically indicated.

Ezetimibe is well tolerated and does not interact with fluvastatin, lovastatin, rosuvastatin, or simvastatin. However, cases of myopathy have been reported in patients due to the combination ezetimibe and atorvastatin.

3.1.11 Antidepressants

Although coadministration of statins and antidepressants is likely, given the association between depression and many chronic diseases, the prevalence of clinically relevant interactions between them is not well-documented.

With the exception of atorvastatin and fluvastatin, which inhibit the activity of CYP3A4 and CYP2C9, respectively, most statins do not appear to be inhibitors or inducers of the main drug metabolizing enzymes. On the other hand, some antidepressants act as inhibitors of several CYPs and, therefore, may impair the elimination of statins metabolized through these isoforms. Based on this knowledge, it can be anticipated that concomitant use of nefazodone or fluvoxamine, potent or moderate CYP3A4 inhibitors, respectively, with atorvastatin, lovastatin, or simvastatin should increase the plasma concentrations of these statins.

Statin metabolism may be susceptible to OATP inhibition by imipramine, nortriptyline, and amitriptyline, with a possible increase in drug concentration. Atorvastatin, a CYP3A4 inhibitor, can act on the metabolism of tricyclic antidepressants (excluding nortriptyline). Also, an interaction between imipramine (a P-gp substrate) and statins (P-gp inhibitors) could be hypothesized.

Fluvoxamine is the only moderate CYP3A4 inhibitor, and may be associated with an increased risk of interactions if administered with atorvastatin, lovastatin, and simvastatin. While the potential interaction between fluoxetine and statins has not been investigated in humans, experimental evidence in animal models found that the combination of simvastatin with fluoxetine may enhance anxiolytic and antidepressant properties. Both fluvoxamine and fluoxetine act as moderate inhibitors of CYP2C9 activity and, in theory, can increase plasma concentrations of fluvastatin, which is metabolized primarily through this isoform. However, the magnitude of this interaction would probably be below the threshold of clinical importance. Due to the theoretical risk of a metabolic interaction, lower doses of atorvastatin, lovastatin, and simvastatin may be indicated in patients treated with fluvoxamine. On the other hand, it is unlikely that the pharmacokinetics of pitavastatin and rosuvastatin, minimally metabolized by CYP2C9, may be significantly affected by the coadministration of fluvoxamine and fluoxetine.

In the case of joint administration of selective inhibitors reuptake serotonins (SSRIs) with statins, escitalopram, citalopram, and sertraline appear to be safe with all statins.

Coadministration with statins metabolized through CYP3A4 (atorvastatin, simvastatin, and lovastatin) or, to a lesser extent, fluvastatin through CYP2D6, could lead to a potentially competitive inhibition. However, there are no clinical or in vitro studies available on possible interactions between serotonin and norepinephrine reuptake inhibitor (SNRI)/norepinephrine reuptake inhibitor (NRI)/vortioxetine and statins. Venlafaxine and duloxetine have two main metabolic pathways: CYP2D6 and CYP3A4 or CYP2D6 and CYP1A2, respectively.

There are no studies on the coadministration of specific noradrenergic and serotonergic antidepressants (NaSSA), mirtazapine coadministered with statins. According to in vitro studies, mirtazapine is metabolized by CYP1A2, CYP2D6 and, to a lesser extent by CYP3A4 and inhibits CYP2D6 and CYP1A2 with negligible potency. Therefore, there is a low probability of interactions.

With respect to the norepinephrine-dopamine reuptake inhibitor (NDRI), bupropion is a moderate CYP2D6 inhibitor and is metabolized by CYP2D6. Considering the lacking of in vitro and in vivo pharmacokinetics studies and the metabolic pathway of statins, with only fluvastatin metabolized to a lesser extent by CYP2D6 and the high rate of renal excretion (>85%), the intereactions pharmacokinetics are no probable [39].

3.1.12 Other drugs

The joint use of simvastatin with *erlotinib* or *imatinib* has been related to cases of rhabdomyolysis. In addition, imatinib (CYP3A4 inhibitor) increases the AUC of simvastatin 3.5 times [40].

With the concomitant use of simvastatin and *pazopanib*, an increase in the incidence of ALT elevations has been documented, so simvastatin treatment should be discontinued when these alterations are observed. In addition, it cannot be ruled out that pazopanib affects the pharmacokinetics of other statins (atorvastatin, fluvastatin, and rosuvastatin). This potential for interaction and morbidity in cancer patients can be minimized by the use of pravastatin, instead of simvastatin, since this drug is excreted by the kidneys and has no significant metabolism via CYP3A4.

The interaction of *Rifampicin* with pravastatin is contradictory, on the one hand in one study, rifampin increased the AUC of pravastatin by 2 times; while another, in healthy volunteers, showed that rifampicin decreases plasma statin levels by 40%. With atorvastatin, rifampin decreases the AUC of atorvastatin by 80%. In the case of simvastatin, the decrease reaches 87%. On the other hand, with rosuvastatin, the effect was minor and was not considered clinically relevant.

Cholestyramine: there is possible reduction of plasma levels of statins, by fixation to the resin in the intestinal lumen and lipid-lowering activity, although clinical practice seems to indicate otherwise. It is recommended to administer the statin 1 hour before or 4 hours after the resin.

Sildenafil: there is a report of myopathy with rosuvastatin and a case of rhabdomyolysis with simvastatin.

Ciprofloxacin (weak CYP3A4 inhibitor): there is a report of rhabdomyolysis with simvastatin.

Efalizumab: there is a case report of rhabdomyolysis with pravastatin.

Danazol: it is a moderate androgen receptor agonist and a partial progestogenic agonist. It is able to inhibit the metabolism of some statins by increasing their plasma concentrations. Cases of myopathy and rhabdomyolysis have been described. Likewise, a case of acute pancreatitis was published in an 80-year-old patient treated with this combination of drugs. Although documented cases affect simvastatin and

lovastatin, it is advisable to exercise caution with any statin administered in conjunction with danazol and control the occurrence of muscle symptoms.

Risperidone and simvastatin: risperidone inhibits the oxidative metabolism of statin and increases its toxicity with a risk of rhabdomyolysis. Muscle pain and weakness, with increased creatin kinase, have been reported in a patient with simvastatin 30 mg/day, 12 days after taking risperidone 1 mg/24 h.

In patients taking *ranolazine,* the use of statins, whose metabolism is highly dependent on CYP3A4 as simvastatin or lovastatin, should be limited due to the risk of rhabdomyolysis [3].

3.2 Drug-food interactions

There are phytotherapeutic agents that can interact with medications. St. John's wort is a CYP3A4 enzyme inducer, while grapefruit juice is an enzyme inhibitor.

Some studies show a decrease in statin concentrations and, therefore, their effectiveness when St. John's wort is administered with rosuvastatin, atorvastatin, or simvastatin. The effect is not observed for pravastatin. It is recommended to avoid grapefruit juice with lovastatin and simvastatin; avoid large quantities of grapefruit just if taking atorvastatin (increases in area-under-the-curve to 2.5-fold have been reported with consumption of ≥750 mL to 1.2 L per day). In the case of lovastatin, grapefruit juice causes a 12-fold increase in Cmax and 15-fold increase in AUC; on the other hand, for the acid form of lovastatin, the increase in Cmax was 4 times, and in AUC, it was 5 times. In the case of orange juice, its administration has been linked to a significant increase of pravastatin AUC in healthy volunteers [2].

Red yeast rice is a popular over-the-counter treatment for hyperlipidemia. Red yeast rice has varying amounts of monacolin K (similar to lovastatin). The products are not standardized and no red yeast rice product should be administered to a patient taking a prescribed statin.

Licorice (*Glycyrrhiza glabra* L., Licorice) in vitro has shown a slight inhibition of CYP3A4 and CYP2D6. Some cases of muscular alteration with increased creatin kinase and, in some cases, rhabdomyolysis have been reported in patients taking high amounts. The risk may increase when associated with drugs that cause muscle toxicity, such as statins, so their combination should be avoided [41].

3.3 Influence of genetic variations in the pharmacokinetic profile of the statins

The activity of the CYP3A4 and CYP2C9 isoenzymes has great interindividual variability as a result of their genetic polymorphism. SLCO1B1 polymorphisms (gene encoding the organic anion transport polypeptide, OATP1B1) can cause variability in statin plasma levels. OATP1B1 affects the hepatic uptake of statins, where statins are going to be metabolized and exert their action at the intracellular level. A reduced activity of OATP1B1 may decrease their efficacy and increase their plasma concentrations, with the consequent risk of muscle toxicity.

Thus, the Genome Wide Association Study (GWAS) studied 300,000 polymorphisms in patients treated with statins and who had presented myopathies in front of a control group with statins and who had not presented myopathies. The conclusions reached were: patients who presented the C521T > C polymorphism of the SLCO1B1 gene (also encoded as SLCO1B1* 5) should not receive treatment with statins, since they have a high risk of suffering from myalgias or myopathy after a few months of treatment; patients with polymorphisms of the CYP2C9 gene that conditions a poor metabolizer (PM) phenotype of the CYP2C9 enzyme (although they do not present mutations in the SLCO1B1 gene) will eliminate fluvastatin less efficiently and may have myopathies (administration of other types of statins is

recommended); simvastatin, atorvastatin, and lovastatin are eliminated by cytochrome CYP3A4 and CYP3A4 polymorphisms that induce poor metabolizers (PM) have not been found, but it must be taken into account that many drugs are potent CYP3A4 inhibitors and a comedication with these statins could induce myopathies due to drug interaction. The application of genetic information to individualize pharmacological treatments to maximize efficacy and avoid adverse events, or pharmacogenetics, is an important component of precision medicine [42].

4. Conclusions

A review of all medications that are treated by patients treated with statins should be performed at each medical consultation and during all healthcare transitions within a health system so that drug interactions can be identified early, evaluated, and properly managed, implementing adjustments of dose, changing to another safer statin or discontinuing when necessary. A thorough understanding of the pharmacokinetics of statins and other concomitantly administered medications is paramount to ensure patient safety.

Conflict of interest

The authors declare no conflict of interest.

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