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Statins and Drug Interactions: Do they have an impact on health care resources?

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Drug-drug interactions in patients taking multiple medications are responsible for considerable morbidity and may be responsible for as many as 7% of all hospital admissions.[1] Whilst many drug-drug interactions are well known (eg, between warfarin and amiodarone or digoxin and quinidine) with readily identified adverse outcomes; other interactions are either less frequent, more subtle, or just not recognized as such. Hence, it is important to identify possible drug-drug interactions, quantify the incidence of adverse outcomes, and then make recommendations about how to avoid such interactions. The HMG-CoA reductase inhibitors (statins) are widely used in the management of hyperlipidemia. Although it is recognized that drug interactions with statins may rarely cause serious and life-threatening adverse outcomes, the frequency of less severe adverse interactions that might have an important impact on patient morbidity and health care resources, is unknown. This review will examine the mechanisms of drug interactions with the statins, review the clinical relevance, and then present new epidemiological data presented at a Satellite Symposium to the ACC that suggest that interactions with certain statins can make an important impact on health care resources.

Drug interactions and the statins

Drug interactions can be due to alterations in pharmacokinetics such as changed concentration of free drug available to interact with the tissues due to altered uptake, metabolism, distribution, or elimination, (eg, simvastatin with erythromycin); or to changes in pharmacodynamics such as changes in tissue sensitivity or response to similar concentrations of the drug (eg, lovastatin with gemfibrozil).

Changes in pharmacokinetics, especially those of drug metabolism, are responsible for many of the recognized interactions between the statins and other drugs. Such interactions can result from:

- another drug interfering with the metabolism and elimination of the statin, hence increasing statin levels, or
- the statin inhibiting the metabolism of the other drug and increasing its free level.

Whether these interactions result in an adverse clinical outcome depends on both patient and drug factors (Figure 1). Certain patients may be especially sensitive to drug

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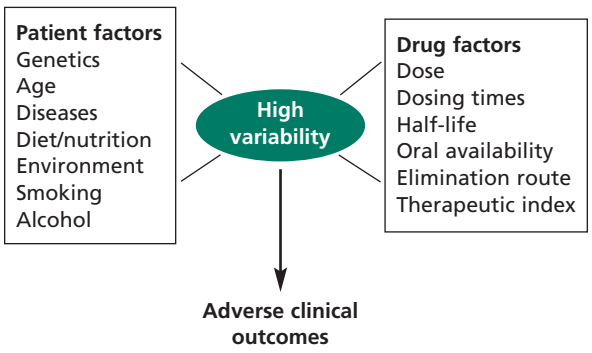
Figure 1: Factors influencing outcome of drug interactions



interactions if they are genetically deficient in an enzyme important in its metabolism, or because they lack adequate renal or hepatic function to eliminate enhanced drug levels due to disease or age. On the drug side, doses and drug half-lives become important if free levels are increased by a drug interaction. Whether there is an adverse reaction when there are increased free levels of drug available to the tissues may depend on the steepness of the dose response curve, or if the drug shows toxicity within or near the therapeutic range.

Metabolism of most drugs occurs in the liver where the addition of hydroxyl, amino or carboxylic acid, glucuronide, and sulphate moieties change a predominantly lipid-soluble drug to a polar metabolite that is not easily taken up by the tissues and more readily eliminated. As most of the statins are largely metabolized during their first pass through the liver, any inhibition of the metabolic process could result in a profound (10- to 20-fold) increase of unmetabolized lipid-soluble statin reaching the systemic circulation, and a high risk of drug toxicity.

The most important hepatic enzyme system for drug metabolism is the cytochrome P450 family of oxygenases. These enzymes are classified into families and sub-families according to their amino-acid homology. Cytochrome P450 enzyme families CYP2C, CYP2D, CYP3A are responsible for the metabolism of the majority of drugs. Whereas lovastatin, simvastatin, and atorvastatin are metabolized by CYP3A4, fluvastatin is metabolized by CYP2C9, and pravastatin elimination is independent of the P450 family. Agents that inhibit CYP3A4 (eg, ketoconazole, erythromycin, clarithromycin, tricyclic antidepressants, sertraline, cyclosporine, calcium channel blockers [especially diltiazem], midazolam, corticosteroids, grapefruit juice, and tamoxifen) will increase the availability of lovastatin and simvastatin (Table 1 Class B). Atorvastatin is metabolized by the CYP3A4 oxidase, however, the metabolites are pharmacologically active and any large increase in free drug may be offset by reciprocal changes of the active metabolites:[2] thus, adverse interactions with atorvastatin are less likely to occur than with lovastatin and simvastatin. Fluvastatin is metabolized by CYP2C9 which is inhibited by amiodarone and tolbutamide; however, alternative metabolic pathways usually minimize the effect of this interaction. In contrast, as the elimination of pravastatin is not dependent upon any of the P450 family of enzymes, drug interactions interfering with its elimination are much less likely to occur.[3]

Statins which are metabolized by the CYP2C9 and CYP2D6 oxygenases compete with other substrates, and

Table 1: Statin Interactions

Class A Drugs whose levels are increased by statins		**Class B** Drugs whose inhibition of a CYP3A enzyme increases statin blood levels	
Warfarin Amitriptyline Imipramine Diclofenac	Ibuprofen Phenytoin Tolbutamide	Cimetidine Danazol Erythromycin Itraconazole Fluoxetine	Clarithromycin Omeprazole Fluconazole Ketoconazole Quinidine

could theoretically increase the levels of drugs metabolized by these enzymes. (Table 1 Class A). Perhaps the only clinically important competitive metabolism is between statins and warfarin.

Consequences of drug interactions with HMG-CoA reductase inhibitors

Adverse reactions from the statins are uncommon and are associated with asymptomatic increases in liver enzymes and muscle abnormalities. Skeletal muscle disorders range from asymptomatic minor elevations of creatine kinase, benign myalgias, myopathy with large increases in creatine kinase and muscular weakness, to potentially fatal rhabdomyolysis. Although myopathy occurs in 0.1-0.2% of patients receiving statins,[4] and rhabdomyolysis is exceedingly rare, both are more likely to occur when statins are administered with agents which themselves are myotoxic, increase the levels of the statins into a toxic range, or have a pharmacodynamic effect (eg, fibrate/statin interaction). Type B drug interactions (Table 1) result in an almost 10-fold increase in the frequency of skeletal muscle disorders.[1]

The true incidence of symptomatic adverse reactions to the statins in clinical practice is not clear. Therapy with all available agents has an excellent safety record in large clinical trials.[4-6] Whether one agent is associated with a higher frequency of adverse reactions is unproven. There tends to be an increased number of reports of muscle disorders with both lovastatin and simvastatin; however, these reports probably do not reflect the true incidence of such events across the spectrum of drugs. A recent review of the literature[1] from the past 15 years found:

- one case of rhabdomyolysis associated with pravastatin (the patient was also receiving fenofibrate)
- 27 cases of rhabdomyolysis associated with simvastatin (combined with either gemfibrozil, cyclosporine, itraconazole, or mibefradil),
- 37 cases of rhabdomyolysis with lovastatin (combined with gemfibrozil, niacin, cyclosporine, itraconazole or erythromycin).

Impact of statin interactions in clinical practice

At the recent Satellite Symposium at the ACC in Lake Louise, Michael Iskedjian and Thomas Einarson presented preliminary findings of a population-based study to determine healthcare utilization in patients prescribed statins and a drug that could have potential adverse interactions.[7] From the Drug Programs Information Network (DPIN) of the Manitoba Health Database, patients were identified who were taking a statin (primarily lovastatin, pravastatin, and simvastatin) between January 1, 1995 to March 31, 1998. Patients were separated into two groups: those who were already taking a statin at the start of the study (prevalent group), and those who were started on a statin during the study (incident group). From the prevalent and incidents groups, statin interacters were identified who had been prescribed one of the drugs that may cause adverse drug interactions (Table 1). The utilization of medical resources was estimated from hospital admissions and physician visits to hospital outpatients, emergency rooms, and office visits. Costs were attributed to hospital admissions from the average cost/weighted case determined by the severity codes associated with the patient's illness.

The majority of the 28,705 patients were prescribed lovastatin (7159 or 24.9%), simvastatin (8303 or 28.9%), or pravastatin (5818 or 20.3%). During the period of the study, fluvastatin was prescribed for 7.4%, and atorvastatin in 3.8%. Statin interactions were more likely to occur in patients who were already on a statin when the study began (prevalent users 26%, incident users 16%). Hospital admissions were more frequent in the statin interacters whether they were in the prevalent (1.4 vs 0.7 admissions/statin user p=0.0001), or the incident groups (1.2 vs 0.6 admissions/statin user p=0.0001). Consequently, the cost of hospital admission/patient was more than two-fold for the statin interacters. Physician visits were also more frequent for statin interacters in both the prevalent group (26.5 vs 22.1), and the incident group (22.5 vs 12.3). Drug costs for prescribed medication were higher for the statin interacters (prevalent group $1822 vs $1055, incident group $1811 vs $963).

Table 2: Health care resource utilization in interacters by statin use

	Hospital admission (days / patient exposed over time of study)	MD visits (number/patient during study)
Incident use† (Started on statin during period of study)		
Pravastatin (723)	1.1	20.8
Lovastatin (598)	1.3	23.5*
Simvastatin (966)	1.1	22.3
Prevalent use (Started on statin before period of study)		
Pravastatin (1063)	1.3	24.2
Lovastatin (1678)	1.7*	28.0*
Simvastatin (1647)	1.2	25.6*

*Statistically significant difference to pravastatin rate by Wilcoxon non-parametric statistic

†At the time of the study, patient numbers with atorvastatin, fluvastatin and cerivastatin were too small for statistical analysis.

Drug interactions with lovastatin were more likely to result in a greater expenditure of health care resources than with either pravastatin or simvastatin, especially for patients already on a statin when the study began (Table 2). For patients started on a statin during the observation period (incident group), drug interactions with lovastatin resulted in greater health care costs compared to patients treated with pravastatin due to a greater number of physician visits in the lovastatin-treated patients.

The increased use of health care resources in the patients prescribed interacting medication could have resulted from greater co-morbidity in this group. However, the baseline characteristics as obtained from hospital discharge data did not appear to differ between the interacters and non-interacters. This preliminary study supports the hypothesis that health care resources may be increased when patients receiving a statin metabolized by the cytochrome P450 pathway are given an interacting drug. Yet the present analysis included both class A and class B (Table 1) interactions. As class A interactions are common to statins – whether metabolized by CYP 3A4 or not – the mechanistic argument would be more powerful if the analysis had been performed for both class A and class B interactions individually.

Conclusion

Medications are commonly prescribed for patients who are currently receiving statins that may interact and result in adverse reactions. The longer the patient has been taking a statin, the more likely an interacting drug will be prescribed. Whether adverse outcomes from interacting drugs are more likely the longer the patient has received a statin is unknown. Although the incidence of serious life-threatening interactions appears to be low, less severe interactions that may cause morbidity may be more common than is currently appreciated. Pravastatin may be associated with the use of less health care resources than lovastatin and simvastatin in patients prescribed potentially interacting medications.

The physician must be aware of potential interactions, as well as idiosyncratic sensitivity to the statins. For this reason, it is important to periodically monitor liver enzymes and markers of muscle injury such as creatine kinase. Such monitoring becomes particularly important when a medication with potential type B interaction is prescribed.

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