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The potential for drug interactions with statin therapy in Ireland.

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- **Abstract:**

The clinical relevance of drug interactions is evident as it is estimated that 7% of acute admissions to hospital result from adverse drug reactions and that 25% of these are due to drug interactions. Statin medications, widely used in the primary and secondary prevention of coronary heart disease are generally well tolerated with severe adverse effects occurring predominantly in the presence of other lipid lowering drugs or with medications that alter statin metabolism. In this study, we found that co-prescribing of simvastatin, atorvastatin and fluvastatin with recognised competing substrates and inhibitors of their metabolism was evident in 32%, 26% and 13.4% of prescriptions issues. When statins are co-prescribed with recognised inhibitors of drug metabolism, pravastatin which does not undergo significant hepatic metabolism would be the statin of choice in an attempt to reduce pharmacokinetic drug interactions which may result in increased toxicity.

- **Introduction:**

The efficacy of the HMG Co-Enzyme A Reductase Inhibitors (Statins) in the primary and secondary prevention of coronary heart disease is well established.[1-5] Over 175,000 prescriptions for statin medications were issued under the General Medical Services Scheme in 1998 when statins accounted for over 96% of all lipid lowering agents prescribed.[6] These drugs are generally well tolerated with adverse effects being noted in approximately 3% of patients.[1, 2, 5] The less frequent but more important serious adverse events associated with the use of statins include hepatotoxicity and myopathy which may progress to rhabdomyolysis resulting in renal failure. These severe adverse effects occur predominantly in the setting of co-prescribing with other lipid lowering agents (such as fibrates and nicotinic acid) or medications that alter the metabolism of the statin drugs.[7] Interaction with other lipid lowering agents is a pharmacodynamic effect whereas interaction with drugs altering statin drug metabolism may be explained on a pharmacokinetic basis. The pharmacokinetic parameters of the statins are shown in table 1. It is seen that lovastatin, simvastatin, atorvastatin and cerivastatin undergo hepatic metabolism predominantly by the hepatic isoenzyme cytochrome P450 3A4. Fluvastatin is metabolised predominantly by cytochrome P450 2C9, whereas pravastatin does not undergo any significant hepatic drug metabolism. In this study, utilising data available under the general

medical services scheme in 1998, we investigated the co-prescribing of simvastatin and atorvastatin with recognised inhibitors of cytochrome P450 3A4 and fluvastatin with recognised inhibitors of cytochrome P450 2C9. The co-prescribing of enzyme inhibitors may increase toxicity whereas administration of enzyme inducing drugs e.g. anticonvulsants and rifampicin may reduce efficacy as these drugs enhance the metabolism of lipid lowering drugs which undergo hepatic biotransformation. Data from the large lipid lowering trials of statin medications indicate that as many as one third of all patients may receive concomitant medication with the potential to interact with the statin drug.[2, 8] In this study we investigated co-prescribing of the frequently used statin medications, pravastatin, simvastatin, atorvastatin and fluvastatin with interacting drugs in the Irish setting.

Method:

We utilised Eastern Health Board data from the General Medical Services (GMS) scheme from January to December 1998. The number of statin medications prescribed during that time period was identified using the recognised ATC classification coding index for the statins [ATC Index with DDDs 1999, WHO Collaborating Centre for Drug Statistics Methodology]. Concomitant medications were also identified under their ATC classification, eg Diltiazem (C08DB01), Verapamil (C08CA01) and Phenytoin (N03AB02). We identified co-prescribing when statins and concomitant medications were administered under the same GMS claim number. For pravastatin, simvastatin and atorvastatin, co-prescribing with recognised cytochrome P450 3A4 substrates/inhibitors eg. calcium antagonists, macrolide antibiotics, azole antifungals and ethinylestradiol was documented. For fluvastatin, which is metabolised by cytochrome P450 2C9, co-prescribing with other 2C9 substrates i.e. non steroidal anti inflammatory drugs and warfarin was documented [Figure 1]. The co-prescribing of all four lipid lowering agents with recognised enzyme inducers was also investigated. Statistical analysis, investigating the co-prescribing of enzyme inducers and inhibitors with pravastatin as compared to the other statin medications was carried out using the Pearson Chi squared test.

Results:

The data demonstrates that 7606 patients were prescribed either pravastatin, simvastatin, atorvastatin or fluvastatin during the course of 1998 [Table 2]. Consistent with evidence based medicine, pravastatin and simvastatin were the most widely prescribed drugs. For those patients treated with simvastatin, co-prescribing with the calcium antagonists, diltiazem, amlodipine and verapamil occurred in 13.7%, 10.9% and 1.2% of patients respectively. Similar values were obtained for atorvastatin. The rate of co-prescribing of the macrolide antibiotics erythromycin and clarithromycin was lower at 1.3% and 0.7% respectively with simvastatin and 1.5% and 1% with atorvastatin. For the azole antifungal drugs ketoconazole and itraconazole, the co-prescribing with simvastatin was 0.6% and 0% and with atorvastatin was 0.8% and 0.09% respectively. The co-prescribing of fluvastatin with non steroidal anti inflammatory drugs indomethacin, diclofenac, ibuprofen and mefenamic acid was recorded at 0.3%, 1%, 2.9% and 4.2% respectively. Approximately 5% of patients on fluvastatin also received warfarin. A small number of patients on statin medications (0.2% - 1.6%) also received an enzyme inducing agent. There was no significant difference in the extent of co-prescribing enzyme inducers or inhibitors with simvastatin and fluvastatin when compared with pravastatin. In contrast, patients receiving CYP 3A4 inhibiting drugs were less likely to be treated with atorvastatin as compared with pravastatin ($P < 0.002$). It is seen that 34% of patients on simvastatin, 28% of those on atorvastatin and 16% of patients on fluvastatin were receiving other medications with the potential for drug interaction.

Discussion:

Lovastatin, simvastatin and pravastatin are derived from the fungus asperigillus terreus. Lovastatin is a natural product whereas simvastatin and pravastatin are produced by semi synthetic processes. Both simvastatin and lovastatin are pro drugs. Fluvastatin, atorvastatin and cerivastatin are synthetic molecules and their structures are distinct from the other statin medications. The physical and chemical properties of the agents differ in that pravastatin is more hydrophilic than fluvastatin which in turn is more hydrophilic than the other agents[9]. Such physical and chemical properties may have a significant effect on the disposition of these drugs as pravastatin is excreted predominantly unchanged by the kidneys whereas the other agents are metabolised predominantly by the liver[10]. There are at least 15 human liver cytochrome P450s involved in drug metabolism but the isoenzymes CYP1A2, CYP3A, CYP2D6, CYP2C9 and CYP2C19 are responsible for the metabolism of the majority of drugs[11].

The single most important drug metabolising isoenzyme is cytochrome P450 3A4 which is responsible for the metabolism of lovastatin, simvastatin, atorvastatin and cerivastatin. Fluvastatin is metabolised by the isoenzyme cytochrome P450 2C9. As serious adverse events such as muscle and skeletal toxicity is dose and plasma concentration related, it is appreciated that the plasma levels of the statins such as simvastatin, lovastatin, atorvastatin and cerivastatin, may increase when these drugs are taken in combination with drugs competing as substrates, or inhibiting the isoenzyme CYP3A4.[10] Examples of such drugs include calcium antagonists (diltiazem, verapamil), macrolide antibiotics (erythromycin, clarithromycin), azole antifungals (ketoconazole, itraconazole) and ethinylestradiol.

The potential consequences of such interactions are highlighted by the 50 fold increase in lovastatin induced myopathy (0.1% to 5%) when combined with erythromycin.[12] When gemfibrozil and cyclosporin (3A4 inhibitor) are co-prescribed with lovastatin the relative risk of severe myopathy was 28%. [13] In the Irish setting, the statin drugs most frequently prescribed include pravastatin, simvastatin and atorvastatin. Drug interactions involving these drugs, particularly simvastatin and atorvastatin will be of relevance to prescribers.

Simvastatin undergoes extensive metabolism by the cytochrome P450 enzyme system resulting in the production of over ten metabolites. Two of these metabolites 6-β-carboxy simvastatin and 6-hydroxy simvastatin retain HMG-CoA reductase activity.[14] Clinical drug interaction studies strongly suggest a significant role for cytochrome P450 3A4 in simvastatin metabolism. Administration of the azole antifungal drug, itraconazole has been shown to result in a 19 fold increase in the area under the concentration time curve (AUC) for simvastatin. [15] Atorvastatin has two main active metabolites, ortho-hydroxy atorvastatin and para-hydroxy atorvastatin. Atorvastatin is a CYP3A4 substrate and the AUC is increased by 33% in the presence of erythromycin, a recognised inhibitor of CYP 3A4.[16] Similarly, itraconazole results in a three fold increase in atorvastatin AUC, thereby increasing the potential for adverse effects.[17]

The metabolism of fluvastatin is mediated by CYP2C9 and it's major metabolite N-des-isopropyl propionic acid is inactive.[18] As a CYP 2C9 substrate, potential drug interactions could be predicted when co-administered with the other

substrate/inhibitors including non steroidal anti-inflammatory drugs e.g. diclofenac and warfarin.[19] In contrast to the other statin drugs, pravastatin is excreted by the renal mechanism and does not undergo significant metabolism via the cytochrome P450 system. Its major metabolite 3-α-iso pravastatin is formed by non enzymatic acid degradation in the stomach.[20] Consequently, co-administration of pravastatin with diltiazem and itraconazole (CYP 3A4 inhibitors) does not result in any significant interactions,as may be predicted.

Therefore the potential for pharmacokinetic drug interactions and potential adverse effects can be minimised if recognised CYP3A4 inhibitors (diltiazem, erythromycin, itraconazole) are prescribed with pravastatin, in this clinical setting. From the Irish prescribing data presented here, it is seen that pravastatin is the most frequently prescribed statin and it appears that prescribers favour pravastatin to atorvastatin in the presence of a CYP3A4 inhibitor. There was no difference in the prescribing rate of simvastatin or pravastatin in the presence of CYP 3A4 inhibitors despite the fact that adverse effects are more likely with simvastatin in combination with such drugs. It is also seen that fluvastatin is prescribed in the presence of recognised inhibitors e.g. non steroidal anti-inflammatory drugs and warfarin.

The implications of co-prescribing with recognised inducers cannot be easily predicted. Whilst phenytoin, carbamazepine, phenobarbitone and rifampicin may enhance the metabolising capacity of the cytochrome P450 enzyme system and possibly reducing the plasma concentrations of substrates including simvastatin, atorvastatin and fluvastatin, whether this is offset by the increase in active metabolite concentration in the case of atorvastatin and simvastatin has not been demonstrated. It is seen that few patients are co-prescribed an enzyme inducing agent and a statin.

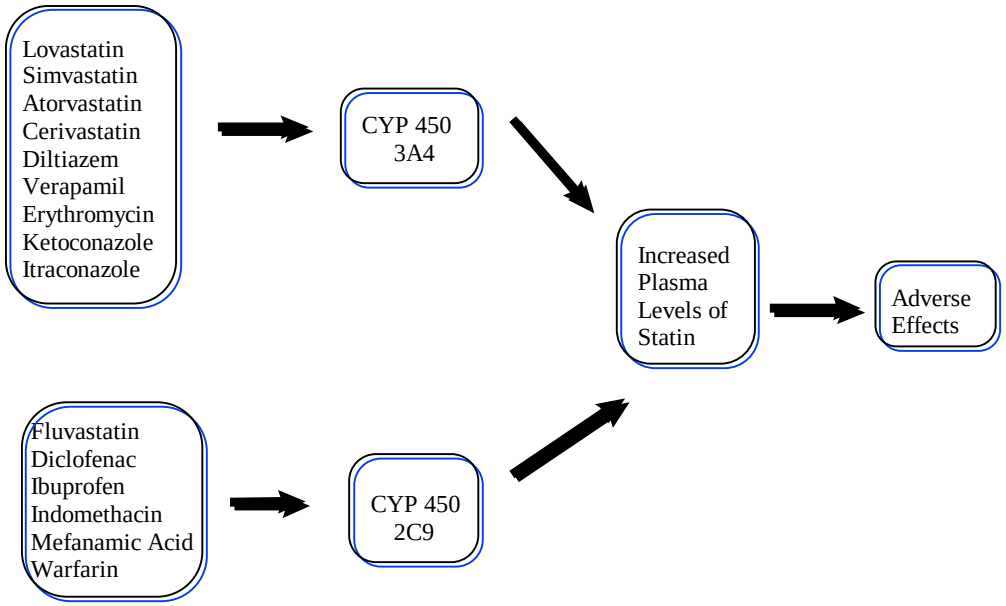
Conclusion:

The clinical relevance of this area is evident as it is estimated that 7% of acute admissions to hospital result from adverse drug reactions and that 25% of these are due to drug interactions. Our prescribing data form the Eastern Health Board area (1998) demonstrates that co-prescribing of the statin drugs simvastatin, atorvastatin and fluvastatin with recognised competing substrates and inhibitors of their metabolism was evident in 32%, 26% and 13.4% of prescriptions issued. The

available evidence suggests that in the presence of recognised inhibitors of drug metabolism, pravastatin would be the drug of choice in an attempt to reduce pharmacokinetic drug interactions which may result in increased toxicity.

Figure 1:

Proposed mechanism of pharmacokinetic interactions involving statin medications.



Atorvastatin, lovastatin, cerivastatin and simvastatin plasma levels may increase when taken with drugs competing for or inhibiting cytochrome P450 3A4, similarly for fluvastatin and cytochrome 2C9 substrates or inhibitors.

Table 1: Pharmacokinetic parameters of statin medications

Parameter	Lovastatin	Simvastatin	Pravastatin	Fluvastatin	Cerivastatin	Atorvastatin
Cytochrome (CYP) P450 substrate	CYP3A	CYP3A	No	CYP2C9	CYP3A	CYP3A
Oral Kinetics:						
Dose (mg/day)	20 - 80	10 - 40	20 - 40	20 - 80	0.1 - 0.3	2.5 - 80
Bioavailability (%)	<5	<5	18	10 - 35	60	12
Half life ($t_{½}$ hrs)	1.5 - 15	1.9 - 15.6	1.3 - 2.6	0.5 - 3.1	1.7 - 2.7	14
Renal Elimination (%)	30	13	20 - 60	6	30	< 2
Active Metabolites	Yes	Yes	No	No	Yes	Yes

Table 2:

Eastern Health Board GMS Data - 1998

	Pravastatin	**Simvastatin**	**Atorvastatin**	**Fluvastatin**
Number of patients prescribed a statin	4,845	1,347	1,101	313
Number of patients co-prescribed the following drugs:				
Inducers				
Phenytoin	40 (0.8%)	13 (1%)	5 (0.5%)	1 (0.3%)
Carbamazepine	50 (1%)	13 (1%)	12 (1.1%)	5 (1.6%)
Phenobarbital	11 (0.2%)	4 (0.3%)	1 (0.1%)	1 (0.3%)
Rifampicin	0	0	0	0
Total	*101 (2.1%)*	*30 (2.2%)*	*18 (1.6%)*	*7 (2.2%)*
CYP 3A4 Inhibitors				
Diltiazem	535 (11%)	184 (13.7%)	105 (9.5%)	/
Amlodipine	570 (11.8%)	147 (10.9%)	111 (10.1%)	/
Verapamil	100 (2.1%)	16 (1.2%)	12 (1.1%)	/
Oestradiol	119 (2.5%)	47 (3.5%)	24 (2.2%)	/
Erythromycin	85 (1.9%)	18 (1.3%)	16 (1.5%)	/
Clarithromycin	49 (1%)	10 (0.7%)	11 (1%)	/
Ketoconazole	46 (1%)	8 (0.6%)	9 (0.8%)	/
Itraconazole	3 (0.06%)	0	1 (0.09%)	/
Total	*1507 (31%)*	*430 (32%)*	*289 (26%)*	
CYP 2C9 Inhibitors				
Indomethacin	38 (0.8%)	/	/	1 (0.3%)
Diclofenac	196 (4%)	/	/	3 (1%)
Ibuprofen	82 (1.7%)	/	/	9 (2.9%)
Mefenamic acid	191 (3.9%)	/	/	13 (4.2%)
Warfarin	351 (7.2%)	/	/	16 (5%)
Total	*858 (17.7%)*			*42 (13.4%)*
Total Interacting Drugs		460 (34%)	307 (28%)	42 (16%)
		Prava vs Simva	**Prava vs Atorva**	**Prava vs Fluva**
CYP 450 Inducers		0.186 (p<0.66) *NS*	0.989 (p<0.32) *NS*	0.035 (p<0.85) *NS*
CYP 3A4 Substrate/Inhibitors		0.436 (p<0.59) *NS*	9.367 (p<0.002) ***S***	/
CYP 2C9 Substrate/Inhibitors		/	/	3.576 (p<0.06) *NS*

Co-presciption of statin medications with recognised inducers and competing substrates or inhibitors of drug metabolism.

NS = Not significant; S = significant using the Pearson Chi square test.

References:

1) The Scandinavian Simvastatin Survival Study Group.Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-1389.

2) Sacks FM, Pfeffer MA, Moye LA. et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335:1001 - 1009.

3) The Lipid Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339:1349 - 1357.

4) Shepherd J, Cobbe SM, Ford I et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301 - 1307.

5) Downs JR, Clearfield M, Weis S et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/TexCAPS. *JAMA* 1998;279:1615 - 1622.

6) Barry M, Heerey A, Sheehan O. et al. Pharmacoeconomics of lipid lowering therapy in Ireland. *IMJ* 1999;92:430 - 432.

7) Christians U, Jacobsen W, Floren LC. Metabolism and drug interactions of 3'-hydroxy-3'-methylglutaryl coenzyme A reductase inhibitors in transplant patients: Are the statins mechanistically similar? *Pharmacol Ther* 1998;80:1 - 34.

8) Pitt B, Waters D, Brown WV, et al. Agressive lipid - lowering therapy compared with angioplasty in stable coronary artery disease. *N Engl J Med*. 1999;341:70 - 76.

9) Lennernas H, Fager G. Pharmacodynamics and pharmacokinetics of the HMG-CoA reductase inhibitors: similarities and differences. *Clin Pharmacokinet* 1997;32:403 - 425.

10) Bottorff M. 'Fire and forget ?' - pharmacological considerations in coronary care. *Atherosclerosis* 1999;147:Suppl 1. 23 - 30.

11) Wrighton SA, Steven JC. The human hepatic cytochromes P450 involved in drug metabolism. *Crit. Rev. Toxicol* 1992;22:1 - 21.

12) Blum CB. Comparisons of properties of four inhibitors of 3-hydroxy-3 methylglutaryl-coenzyme A reductase. *Am J Cardiol* 1994;73:3 - 11.

13) Pierce LR, Wysowski DK, Gross TP. Myopathy and rhabdomyolysis associated with lovastatin - gemfibrozil combination therapy. *JAMA* 1990;264:71 - 75.

14) Cheng H, Schwartz MS, Vickers S. Metabolic disposition of simvastatin in patients with T - tube drainage. *Drug Metab Dispos* 1994;22:139 - 142.

15) Neuvonen PJ. Kantola T, Krivisto KT. Simvastatin but not pravastatin,is very susceptible to interact with the CYP 3A inhibitor itraconazole. *Clin Pharmacol Ther* 1998;63:332 - 341.

16) Yang BB, Smithers JA, Stern HR et al. Atorvastatin pharmacokinetic interactions with other CYP 3A4 substrates:erythromycin and ethinylestradiol. *Pharm Res1996*;13:Suppl 1 437.

17) Kantola T,Kivisto KT,Neuvonen PJ. Effect of itraconazole on the pharmacokinetics of atorvastatin. *Clin Pharmacol Ther* 1998;64:58 - 65.

18) Dain JG, Fu E, Gorski J et al. Biotransformation of fluvastatin sodium in humans. *Drug Metab Dispos* 1993;21:567 - 572

19) Transon C, Leeman T, Vogt N, Dayer P. In vivo inhibition profile of cytochrome P450 (CYP 2C9) by fluvastatin. *Clin Pharmacol Ther* 1995;58:412 - 417.

20) Triscari J, O'Donnell D, Zinny M, Pan HY. Gastrointestinal absorption of pravastatin in healthy subjects. *J Clin Pharmacol* 1995;35:142 - 144.