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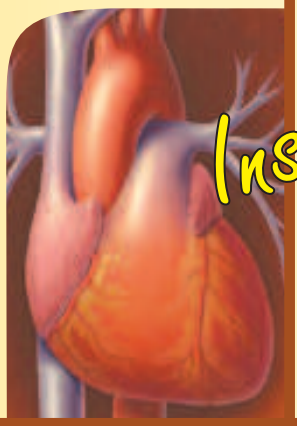

Insight HEART

Vol: 9 No: 1; 2013

SQUARE
PHARMACEUTICALS LTD.
BANGLADESH

Drug–drug interactions with statins: will pitavastatin overcome the statins' Achilles' heel?

Introduction

The use of statin treatment for the prevention of cardiovascular disease (CVD) is supported by a greater body of clinical evidence than is available for any other drug class. Since the launch of lovastatin in the USA in 1987, an unprecedented series of clinical outcome trials has demonstrated the benefits of lipid-lowering treatment with statins in reducing the incidence of CVD events and mortality. The most recent statin to become available is pitavastatin, which was launched in Japan in 2003 and in the USA in 2010; pitavastatin was approved by the EU in 2010.

Despite the clear benefits of statins, the most recent results from the EUROASPIRE survey showed that up to 46% of patients who should be treated remain at risk because they are either not being treated or have not reached their treatment target. The primary reasons for this are non-compliance by patients because of intolerance and the reluctance of prescribers to use adequate doses for fear of adverse drug reactions (ADRs), both of which may be related to the risk of drug–drug interactions (DDIs). Although statin treatment is generally well-tolerated, the most common adverse effect is myopathy, which is characterised by muscle pain or weakness and, in rare cases, may include muscle necrosis that may lead to muscle breakdown and associated renal impairment (rhabdomyolysis). The rate of myopathy with statin monotherapy is low, but factors that raise the circulating concentrations of statins, such as DDIs, can increase the risk. DDIs thus represent the 'Achilles' heel' of statins, because most patients receiving statin treatment are elderly and/or have comorbid metabolic conditions, such as coronary heart disease, hypertension or diabetes mellitus, and so will generally be prescribed multiple medications. Although necessary to provide optimal care, 'polypharmacy' increases the risk of DDIs and consequent ADRs.

In this review, polypharmacy and the potential for DDIs with statins will be discussed with regard to the pharmacokinetic profiles of each member of the statin class. We focus on the disposition and propensity for DDIs with pitavastatin, which is not only the newest arrival to the class in the EU and USA, but also has a distinctive metabolic profile that may lead to a lower risk of DDIs and consequent ADRs compared with established statins.

Statin DDIs and muscle-related ADRs

Why do DDIs with statins matter? Although statins are generally well-tolerated and serious adverse events are rare, the risk increases among patients receiving multiple concomitant medications. In particular, DDIs with a drug that increases statin exposure may lead to an increased risk of muscle-related adverse events, such as myalgia, myopathy and (more rarely and more seriously) rhabdomyolysis. Indeed, cerivastatin was withdrawn from the market in 2001 because of a relatively high incidence of cases of rhabdomyolysis, most of which involved DDIs.

Broadly, the most common causes of DDIs that increase the plasma concentrations of statins involve coprescribed agents that inhibit the metabolism of the statin by CYP enzymes (particularly CYP3A4), or that inhibit the activity of transporter proteins involved in statin cell influx and efflux. Drugs that can increase the plasma concentrations of statins and thereby increase the risk of myopathy include cyclosporine, macrolides, fibrates, protease inhibitors, azole antifungals, calcium channel blockers, amiodarone and fusidic acid. A retrospective analysis of statin associated muscle adverse events conducted by the US Food and Drug Administration from January 1990 to March 2002 identified 3339 reports of rhabdomyolysis, of which about half were associated with a statin DDI. A systematic review of statin safety, including data from randomised controlled trials, showed that 60% of cases of

rhabdomyolysis among patients receiving simvastatin, lovastatin or atorvastatin involved the co-administration of CYP3A4 inhibitors, and 19% involved the co-administration of fibrates.

Adverse drug reactions, polypharmacy and statin DDIs

In a study of 18,820 hospital admissions in the UK, the prevalence of ADRs was 6.7%; 80% of these led to hospitalisation. Although some ADRs may be the result of the effects of ageing and illness, which can alter the disposition of some drugs, important 'preventable' factors include inappropriate prescribing, polypharmacy involving unsuitable combinations of therapies, poor adherence and errors in monitoring. Indeed, it is estimated that preventable DDIs may account for up to one-quarter of hospitalisations for ADRs.

Polypharmacy is increasingly prevalent in older people. A US study of 126,682 pharmacy fill records from TRICARE beneficiaries aged 65 years or older showed that half of the patients were receiving more than five medications, on average from three therapeutic categories – most commonly, cardiovascular drugs, central nervous system agents and hormones/synthetic substitutes. A recent study in Austria of 543 hospitalised patients aged more than 75 years showed that patients were receiving, on average, a total of 7.4 medications; the authors concluded that 'polypharmacy in old age is the rule rather than the exception'. Moreover, among patients receiving more than six medications, the number of drugs prescribed was almost directly proportional to the incidence of potential DDIs, which may be related to the fact that the majority of physiological processes decreases gradually with ageing, including renal and liver function. Indeed, all the pharmacokinetic phases from absorption to excretion are affected by ageing. Delayed gastric emptying, increased gastric pH, delayed intestinal transit rate, reduced gastrointestinal (GI) blood flow, and intestinal surface area and modified GI barriers can affect bioavailability. In addition, differences in body composition, and reduced serum albumin binding may lead to changes in volume of distribution. Regarding metabolism, the liver undergoes physiological and anatomical changes with age, such as a reduced liver flow and mass, potentially leading to reduced hepatic clearance and an increased half-life. Phase I metabolism (i.e., via CYP expression and activity) either decreases or remains unchanged, while phase II metabolism is less affected by ageing. Finally, changes in renal function with age, including reduced renal blood flow and mass, reduced creatinine clearance and decreased tubular function are well documented.

Statins and polypharmacy

The treatment of patients at high risk of CVD almost inevitably involves multiple medications; hence, patients receiving statin therapy are likely to be receiving concomitant therapies that may increase the risk of DDIs.

Various studies have characterised the risk factors for polypharmacy and statin DDIs in ambulatory and hospitalised patients. A cross-sectional study of 2742 ambulatory patients with dyslipidaemia, showed that patients aged ≤54 years and ≥75 years received a mean of 3.8 and 5.8 concomitant medications, respectively, and that the most frequent comorbidities were hypertension (52.1%), coronary heart disease (42.5%) and diabetes (19.0%). There were 198 potential statin DDIs identified, nearly all of which were pharmacokinetic interactions; statin DDIs represented 41.3% and 30.6% of all potential DDIs in patients aged ≤54 years and ≥75 years, respectively. In another study of the same sample of 2742 ambulatory statin-treated patients, the proportion who experienced potentially harmful statin DDIs ranged from 0.3% for pravastatin to 12.1% for simvastatin. The study also showed that statin DDIs occurred in 9.5% of patients coprescribed fibrates or nicotinic acid, and in 70.5% of patients coprescribed a CYP3A4 inhibitor.

Although numerous statin DDIs involving CYP enzymes have been well-characterised, potentially interacting combinations are still frequently prescribed. In a study of 951,166 records from 2005 to 2006, of 792,081 patients who were prescribed a CYP3A4-metabolised statin, 30% were coprescribed a CYP3A4-inhibiting drug. This is despite the fact that nearly one-third of these drugs were described as an inhibitor of the statin in respective statin Summary of Product Characteristics. These studies suggest that even well-characterised statin DDIs continue not to be considered adequately by physicians in their prescribing decisions.

Pharmacokinetic differences among the statins

Pharmacokinetic interactions underpin the majority of statin DDIs, and so it is important to take into account the different pharmacokinetic profiles of each statin; these have been reviewed elsewhere and so will be summarised only briefly in this paper (Table 1). All statins are rapidly absorbed, reaching a peak concentration in up to 4 hours, and most exhibit low systemic bioavailability (ranging from about 5% for simvastatin, lovastatin and fluvastatin, to up to about 20% for pravastatin and rosuvastatin, and 51% for pitavastatin). The terminal elimination half-lives of the statins range from less than 5 hours for fluvastatin, lovastatin, pravastatin and simvastatin, to about 13 hours for pitavastatin, and between 15 and 30 hours for atorvastatin and rosuvastatin. Rosuvastatin and pravastatin are eliminated in bile and renally through tubular secretion, but the major route of elimination for all statins is via the bile into the faeces.

Atorvastatin, lovastatin and simvastatin are lipophilic and undergo extensive first-pass metabolism via CYP3A4; fluvastatin, which is also lipophilic, is metabolised via CYP2C9 (Table 2). Pravastatin and rosuvastatin are hydrophilic and do not undergo substantial metabolism via

CYP pathways, although rosuvastatin interacts with CYP2C9. Unlike the other lipophilic statins, which undergo extensive microsomal metabolism via CYP enzymes, pitavastatin is mostly excreted in unchanged form and is only marginally metabolised by CYP2C9 and CYP2C8. The cyclopropyl moiety on the base structure of pitavastatin is thought to protect it from metabolism by CYP3A4. A minor proportion of a pitavastatin dose, however, undergoes glucuronidation by uridine diphosphate-glucuronyltransferase (UGT) 1A1, UGT1A3 and UGT2B7, and is then converted to an inactive lactone form before elimination in bile.

In addition to metabolism of statins by CYP enzymes, drug transporters in the liver, gut and kidney influence the disposition of statins, and thus also represent potential mechanisms for DDIs (Table 2). Organic anion-transporting polypeptide (OATP) mediates the hepatic uptake of all statins; in particular, OATP1B1 mediates hepatic uptake of all statins to some extent. OATP1B3, OATP2B1 and sodium-dependent taurocholate cotransporting polypeptide (NTCP) also mediate uptake of some statins, while P-glycoprotein, multidrug resistance associated proteins (MDR1 and MRP2) and breast cancer resistance protein (BCRP) may be involved in statin efflux to varying extents.

Clinically significant statin DDIs: differences among the statins

Statin DDIs with other cardiovascular agents

The broad range of drugs that have the potential for pharmacokinetic interaction with statins (Table 3) shows the importance of considering the DDI profile when selecting a statin for an individual patient. With regard to comorbid cardiovascular conditions, a patient with angina may be prescribed a calcium-channel blocker, such as verapamil or diltiazem, both of which are CYP3A4 inhibitors and may therefore interact with statins, such as atorvastatin, simvastatin and lovastatin. Patients with mixed dyslipidaemia may be prescribed a fibrate; this class of drug used alone brings an increased risk of myopathy that is multiplied in combination with a statin; gemfibrozil is particularly problematic as it is a potent inhibitor of CYP2C9, CYP2C8 and OATP1B1, and has been shown to interact with atorvastatin, simvastatin, lovastatin, pravastatin and rosuvastatin.

Statin DDIs may also be important in terms of their effects on other cardiovascular drugs. The heart failure treatment, digoxin, which is a substrate for P-glycoprotein, has a narrow therapeutic index and so careful monitoring is needed when it is co-administered with statins that interact with P-glycoprotein: a clinically relevant DDI has been demonstrated for digoxin and atorvastatin. Similarly, statin DDIs with warfarin are of concern because of the potential for excessive anticoagulant effects. The more potent S-enantiomer of warfarin is metabolised via CYP2C9, hence caution must be exercised with statins, such as fluvastatin and rosuvastatin, that interact with CYP2C9.

Statin DDIs with other agents

An important issue for physicians in considering the risk of statin DDIs in an individual patient is that many potential interactions involve medications prescribed for entirely unrelated conditions. These may include short-term treatment (e.g., antibiotics and antifungals) but also longterm or potentially lifelong treatments (e.g., antidepressants [serotonin-specific reuptake inhibitors] and immunosuppressants). In an observational study of 28,705 statin users in Canada between 1995 and 1998, macrolide antibiotics were identified as one of the most commonly prescribed potentially interacting classes of drug, with 8.2% of statin-treated patients being coprescribed erythromycin

Table 1. Pharmacokinetics of currently available statins.

	Atorvastatin	FluvastatinXL	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
Fraction absorbed (%)	30	98	30	75	34	50	60–80
t_{max} (h)	2–3	4	2–4	1.2	0.9–1.6	3	1.3–2.4
C_{max} (ng/mL)	27–66	55	10–20	18.2	45–55	37	10–34
Bioavailability (%)	12	6	5	51	18	20	5
Effect of food on bioavailability (%)	↓13	0	↑50	0	↓30	↑20	0
Lipophilicity	Yes	Yes	Yes	Yes	No	No	Yes
Transporter substrate	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Protein binding (%)	>98	>99	>95	>99	43–55	88	94–98
Hepatic extraction (%)	>70	>68	>70	Estimated>70	46–66	63	78–87
Systemic metabolites	Active	Inactive	Active	Inactive	Inactive	Active (minor)	Active
Systemic clearance (mL/min)	291.6	4433	303–1166	410	945	805	525
Renal clearance (mL/min)	No	No	No	No	>400	226	No
$t_{½}$ (h)	15–30	4.7	2.9	13	1.3–2.8	20.8	2–3
Faecal excretion (%)	70	90	83	78	71	90	58
Urinary excretion (%)	2	6	10	< 4	20	10	13

All based on a 40 mg oral dose, except fluvastatin XL (extended release, 80 mg) and pitavastatin 2 mg; Cmax, maximum concentration; t_{max}, time to reach maximum concentration; $t_{½}$, terminal elimination half-life.

and 3.5% receiving clarithromycin. Macrolide antibiotics, such as erythromycin and clarithromycin, are CYP3A4 inhibitors and have been reported to increase the area under the concentration–time curve (AUC) of simvastatin and lovastatin; erythromycin is also an inhibitor of OATP1B1 and 1B3, and the labels of most statins recommend that statin treatment is used with caution or interrupted during erythromycin therapy. The antibacterial, rifampicin, acutely inhibits OATP1B1 but is a potent inducer of CYP3A4 and CYP2C9 enzymes, and has been demonstrated to decrease the AUC of statins that are metabolised via CYP3A4, including simvastatin, fluvastatin, pravastatin and atorvastatin. Rifampicin also induces MDR1 and MRP2, effects that could increase the metabolic clearance of a number of statins, including rosuvastatin and pravastatin.

Azole antifungal drugs, such as itraconazole and ketoconazole, are potent inhibitors of CYP3A4, and have been shown to increase the systematic availability of atorvastatin, simvastatin, lovastatin and rosuvastatin.

Patients infected with human immunodeficiency virus (HIV) have a high risk of statin DDIs because they require multiple medications, often including triple-drug antiretroviral therapy, and prophylactic antibacterials and antifungals in addition to statin therapy. The protease inhibitors, amprenavir, darunavir, fosamprenavir, indinavir, nelfinavir, ritonavir and saquinavir, are all potent inhibitors of CYP3A4, and ritonavir, indinavir and saquinavir are also inhibitors of MDR1 and/or OATP1B1. In a study of healthy volunteers, co-administration of ritonavir plus saquinavir increased the systemic exposure to simvastatin and atorvastatin, whereas pravastatin exposure was reduced. Statins that are given as lactone prodrugs (simvastatin and lovastatin) should not be used with protease inhibitors, and careful monitoring is needed for all HIV patients receiving statin therapy.

Another highly problematic agent with regard to statin DDIs is the immunosuppressant, cyclosporine, which has the potential to interact with all statins because of its ability to inhibit CYP3A4 and various drug transporters, including OATP1B1, OATP2B1, OATP1B3, MRP2, MDR1 and NTCP. Depending on the individual statin, concomitant treatment with cyclosporine is either contra-indicated or extreme caution is recommended; this is because cyclosporine may inhibit multiple modes of elimination for a given statin, resulting in large increases in statin exposure (up to 10–20-fold).

A final, but important, consideration is that polypharmacy includes not only prescribed medications, but also other over-the-counter medications, including vitamins, minerals and herbal remedies, and foodstuffs (grapefruit juice being the most well-known example). Elderly patients are the heaviest users of 'self-medication', but often do not report it unless specifically asked. These factors make it difficult for the busy physician to make a thorough assessment of the risk of statin DDIs for an individual patient.

Pharmacogenetic considerations for statin DDIs

A growing body of evidence suggests that single nucleotide polymorphisms (SNPs) in genes encoding drug transporter proteins may lead to differences between individual patients in the disposition of statins, although the clinical relevance of these remains to be established. Of particular interest have been SNPs in SLCO1B1, the gene that encodes OATP1B1; the results of in vitro pharmacokinetic studies suggest that c521T>C and c388A>G may account for part of the inter-individual variation in plasma concentrations of statins, while in vivo studies have shown that patients with certain genotypes may have higher (or lower) plasma concentrations than those with the wild-type genotype. Some evidence for the potential clinical relevance of these findings was provided by the genome-wide Study of the Effectiveness of Additional Reductions in Cholesterol and

Table 2. Enzymatic and drug transporter pathways involved in the pharmacokinetics of currently available statins

	Atorvastatin	Fluvastatin XL	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
CYP-mediated metabolism	CYP3A4	CYP2C9	CYP3A4	Biliary, CYP2C9/2C8 (minor)	Sulphonation	Biliary, CYP2C9, a2C19 (minor)	CYP3A4
UGT1A1/1A3-mediated metabolism	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Transporter proteins	Yes	Yes	Yes	Yes	Yes	Yes	Yes
OATP1B1	Yes	Yes	Yes	Yes	Yes	Yes	Yes
OATP1B3	NA	Yes	NA	Yes	Yes	Yes	Yes
OATP1A2	NA	NA	Yes	NA	NA	Yes	NA
OATP2B1	Yes	Yes	NA	Yes	Yes	Yes	NA
OAT3	NA	Yes	Yes	NA	Yes	NA	Yes
BCRP	Yes	Yes	NA	Yes	Yes	Yes	NA
MDR1/P-gp	Yes	No	Yes	Yes	Yes	No	Yes
MRP2	Yes	NA	NA	Yes	Yes	NA	NA
BESP	?	Yes	?	NA	Yes	?	?

BCRP, breast cancer resistance protein; CYP, cytochrome P450; MDR, multidrug resistance; MRP, multidrug resistance protein; NA, not applicable; OATP, organic anion-transporting polypeptide; P-gp, P-glycoprotein; UGT, uridine glucuronyltransferase; Yes, interaction demonstrated; No, no interaction demonstrated; ?, unknown.

Homocysteine (SEARCH), which identified a defective SLCO1B1 allele associated with a fourfold increase in myopathy compared with wild-type in patients receiving simvastatin 80 mg; however, this may not be relevant at more commonly used lower doses. Reduced BCRP activity associated with polymorphisms in ABCG2, the gene encoding BCRP, has also been shown to increase the response to rosuvastatin, but not to simvastatin or pitavastatin. Although a Japanese study showed that polymorphisms of SLCO1B1 contributed to differences in mean plasma concentrations of pitavastatin, the overall variation among groups was small (less than threefold). While pharmacogenetic variability could account for the majority of the observed variation in plasma concentrations between individuals, it is worth noting that the variants described above are not particularly rare and so are likely to be well-represented in clinical study populations. In the absence of simple practice-based screening methods, pharmacogenetics currently remains of largely theoretical relevance to clinicians.

Case study: polypharmacy in an elderly patient with hypercholesterolaemia

Statin treatment is now being prescribed earlier and earlier; in the UK, for example, statin treatment is recommended for the primary prevention of CVD in patients with a predicted 10-year risk of CVD of 20% or more. A statin is therefore likely to be one of the first drugs prescribed for a patient at risk of CVD. Taking into account the potential DDI profile of a statin is therefore more important now than ever before, because the development of CVD and other diseases will lead to the future prescription of additional concomitant medications that may potentially interact with the statin.

An illustrative polypharmacy case study provides an example of the issues that may arise (Table 4). The first drug prescribed to this patient was a statin for the treatment of primary hypercholesterolaemia and the prevention of CVD; if, as in this example, the choice of statin was one that is metabolised by CYP3A4 (e.g., simvastatin or atorvastatin), his subsequent treatment would have given rise to several potential DDIs: first, through the prescription of amlodipine for hypertension; second, through the use of citalopram (a selective serotonin reuptake inhibitor) for depression; and third, through the use of amiodarone for arrhythmia. Amiodarone is an inhibitor of CYP3A4, and amlodipine and citalopram are substrates of CYP3A4; this combination therefore represents a potential risk of DDIs with simvastatin/atorvastatin, and their cumulative effect could have been sufficient to trigger an ADR (e.g., myopathy) in this patient. Similarly, if the patient required antifungal or antibiotic treatment, care would need to be taken to avoid agents that interact with CYP3A4 (such as azole antifungals or macrolide antibiotics).

The initial selection of a statin with a low risk of interaction is therefore important in safeguarding against the future development of DDIs when additional medications are subsequently prescribed.

Pitavastatin pharmacokinetics and the potential for drug–drug interactions

The distinctive metabolic profile of pitavastatin means that DDIs at the level of CYP isoenzymes are unlikely. A programme of pharmacokinetic studies in healthy volunteers has confirmed a lack of DDIs between

Table 3. Inhibitors and inducers of enzymatic pathways involved in the metabolism of statins.

Enzyme or transporter system	Substrate	Inhibitors	Inducers
CYP3A4	Atorvastatin, lovastatin, simvastatin	Ketoconazole, itraconazole, fluconazole, erythromycin, clarithromycin, tricyclic antidepressants, nefazodone, venlafaxine, fluvoxamine, fluoxetine, sertraline, cyclosporine, tacrolimus, mibefradil, amiodarone, danazol, diltiazem, verapamil, protease inhibitors, midazolam, corticosteroids, grapefruit juice, tamoxifen	Phenytoin, phenobarbital, barbiturates, rifampicin, dexamethasone, cyclophosphamide, carbamazepine, troglitazone, omeprazole, St John's wort
CYP2C9	Fluvastatin, rosuvastatin, pitavastatin	Ketoconazole, fluconazole, amiodarone, sulfaphenazole, oxandrolone, amiodarone (genetic polymorphism)	Rifampicin, phenobarbital, phenytoin, troglitazone
MDRP or P-gp	Atorvastatin, lovastatin, pravastatin, simvastatin, pitavastatin	Ritonavir, cyclosporine, verapamil, erythromycin, ketoconazole, itraconazole, quinidine, elacridar	Rifampicin, St John's wort
OATP1B1	All statins	Cyclosporine, rifampicin, gemfibrozil, gemfibrozil-O-glucuronide, clarithromycin, erythromycin, roxithromycin, telithromycin, indinavir, ritonavir, saquinavir	
UGT	All statins	Gemfibrozil, cyclosporine	Rifampicin

CYP, cytochrome P450; MDRP, multidrug resistance associated protein; OATP, organic anion-transporting polypeptide; P-gp, P-glycoprotein; UGT, uridine glucuronyltransferase.

Table 4. Polypharmacy case study in an elderly patient.

David is a 74-year-old who lives on his own at home. Lately he has been having difficulty walking to the shops and has to stop frequently to catch his breath. He has suffered from angina for 5 years. Primary hypercholesterolaemia was diagnosed in 2004 for which he was prescribed simvastatin, and hypertension was diagnosed in 2005, when amlodipine was prescribed; enalapril and hydrochlorothiazide were added later to try to achieve blood pressure control. During a hospital admission in 2008, ventricular arrhythmias were noted on electrocardiogram, and amiodarone was added to the regimen. His other main complaint is osteoarthritis. He takes piroxicam for the pain in his knees and wrist, which was broken last year. He feels depressed, and has been receiving citalopram since 2006 His current medications are presented.

Medication	Start date
Piroxicam 20 mg once daily	2009
Amiodarone 100 mg once daily	2008
Citalopram 40 mg once daily	2006
Hydrochlorothiazide 12.5 mg once daily	2006
Enalapril 10 mg once daily	2005
Amlodipine 10 mg once daily	2005
Simvastatin 40 mg once daily	2004

pitavastatin and agents known to influence drugs that interact with CYP isoenzymes, such as grapefruit juice (CYP3A4 inhibitor) and itraconazole (CYP3A4 inhibitor), and with CYP substrates, such as warfarin (CYP2C9 substrate) and enalapril (non-specific CYP substrate). The lack of effect of pitavastatin on the pharmacokinetics of digoxin also demonstrates a low likelihood of DDIs at the level of P-glycoprotein.

In vitro studies, Hirano and co-workers evaluated the relative uptake of pitavastatin by a selection of active transporters, in order to assess the potential for in vivo DDIs with. The results indicated potential for in vivo interaction with the OATP1B1 inhibitors, gemfibrozil, atazanavir/indinavir, rifampicin, clarithromycin/erythromycin and cyclosporine; hence, pharmacokinetic studies in healthy volunteers were performed to test the potential for in vivo interaction.

Although exposure to pitavastatin was increased by co-administration with gemfibrozil, atazanavir and rifampicin, changes in pitavastatin maximum concentration (C_{max}) and AUC were not more than two fold and thus unlikely to be clinically relevant. However, concomitant administration of erythromycin increased pitavastatin C_{max} by 3.6-fold and AUC by 2.8-fold, whereas cyclosporine administration increased pitavastatin Cmax by 6.6-fold and AUC by 4.6-fold. These findings are consistent with these agents being potent inhibitors of multiple OATP transporters, including OATP1B1. It should be noted that the interaction of pitavastatin with cyclosporine is modest compared with most other statins; the observed less than five fold increase in pitavastatin AUC is smaller than that observed during co-administration with cyclosporine for all other statins except fluvastatin.

In a recent review, the pharmacokinetic profile of pitavastatin was shown to be superior to that of other statins in terms of DDIs with CYP and OATP inhibitors and the associated increase in plasma statin levels.

Pitavastatin clinical efficacy

A broad clinical development programme conducted in Japan and Europe has shown that pitavastatin 1–4 mg is highly effective for the treatment of primary hypercholesterolaemia and mixed dyslipidaemia, and has shown that the lipid-lowering efficacy of pitavastatin is non-inferior versus atorvastatin 20 mg, simvastatin 40 mg, and pravastatin. In addition to lowering LDL-cholesterol, pitavastatin has favourable effects on other clinically relevant lipids, such as HDL-cholesterol and triglycerides, and also provides anti-atherosclerotic benefits.

Post-marketing safety surveillance with pitavastatin

Post-marketing safety surveillance for pitavastatin has provi ded evidence that the distinctive metabolic profile of this

Table 5. LIVES 2-year post-marketing safety data: no increase in the risk of ADRs with concomitant administration of pitavastatin with antiplatelet, antidiabetic, antihypertensive or lipid-lowering drugs.

Concomitant medication	Status	Total number of patients	Number of patients with an ADR*	Incidence rate (%)*	95% CI	p-value
Antiplatelet drugs	No	15,764	1639	10.4	9.9–10.9	0.913
	Yes	4159	430	10.3	9.4–11.3	
Antidiabetic drugs	No	15,957	1672	10.5	10.0–11.0	0.387
	Yes	3966	397	10.0	9.1–11.0	
Antihypertensive drugs	No	9375	962	10.3	9.7–10.9	0.591
	Yes	10,549	1107	10.5	9.9–11.1	
Lipid-lowering drugs	No	18,555	1954	10.5	10.1–11.0	0.013
	Yes	1368	115	8.4	7.0–10.0	

*All treatment-emergent ADRs including those not considered to be drug related. The cumulative ADR incidence during the 2 years of the study was 10.4%, which was lower than the incidence (20.6%) recorded in the pre-marketing long-term (52 weeks) clinical trial.
ADR, adverse drug reaction; CI, confidence interval; LIVES, Livalo Effectiveness and Safety study.

statin translates into a low incidence of DDIs and ADRs in real-life clinical practice. The Livalo® Effectiveness and Safety (LIVES) study evaluated pitavastatin treatment for up to 2 years of follow-up in a total of 20,279 patients with hypercholesterolaemia or familial hypercholesterolaemia enrolled from 2811 centres in Japan. The Treatment Outcome Study was an openlabel, non-comparative observational study of 3-month outcomes, which is a regulatory requirement in Japan. The similar design of the corresponding 3-month analyses conducted for atorvastatin and rosuvastatin allows for cross-study comparisons; although these should be interpreted with caution, the results were reassuring in that the incidence of ADRs with pitavastatin was 6.1% (1206/19,921 patients), approximately half of that observed with atorvastatin (12.0%; 576/4805 patients) and rosuvastatin (11.1%; 978/8795 patients).

An analysis of the occurrence of ADRs stratified by concomitantly administered drugs showed that co-administration of various antiplatelet, antihypertensive and/or antidiabetic drugs did not significantly increase the incidence of ADRs during pitavastatin treatment (Table 5). Moreover, the LIVES 2-year analysis showed no significant increase in the incidence of ADRs with pitavastatin, even with concomitant administration of azole antifungals, macrolide antibiotics, coumarin anticoagulants, nicotinic acid and cholestyramine, fibrates or cyclosporine – all agents that have been shown to increase the risk of DDI related ADRs with other statins. The LIVES study thus provides convincing evidence that pitavastatin is associated with a low risk of DDIs and related ADRs in real-life clinical practice, even when co-administered with agents that are known to interact with other statins. Post-marketing surveillance data from the USA and Europe are now needed to evaluate the long-term safety and tolerability of pitavastatin treatment in the broad range of patients who will receive the drug in routine clinical practice in these regions.

Discussion

Patients who are receiving statin therapy are often receiving multiple medications for comorbid conditions, and so are at increased risk of ADRs associated with pharmacokinetic interactions at the level of CYP enzymes and/or OATP transporter systems. DDIs with statins commonly manifest as muscular ADRs, such as myalgia and myopathy; these may adversely affect patient compliance with statin therapy but rarely lead to serious side-effects, such as rhabdomyolysis. All of the marketed statins carry labelled warnings and precautions depending upon their pharmacokinetic characteristics and potential for DDIs. Despite this, large, well-conducted, retrospective studies in various clinical settings have shown that an unacceptably large proportion of patients are coprescribed a statin and potentially interacting therapies, suggesting that the impact of polypharmacy on the safety profile of statins may be underappreciated.

Each statin has it own unique pharmacokinetic profile, which determines its propensity for DDIs. Simvastatin, atorvastatin and lovastatin are metabolised via CYP3A4, and must therefore be used with caution in combination with a wide range of commonly used drugs, such as macrolides, azoles, serotonin-specific reuptake inhibitors, corticosteroids and some calcium-channel blockers, all of which interact with CYP3A4. Rosuvastatin, pravastatin and fluvastatin are not extensively metabolised via CYP3A4, but may be prone to interaction with drugs that inhibit OATP transporter systems, such as macrolides, gemfibrozil, cyclosporine and protease inhibitors.

Pitavastatin was launched in Japan in 2003; it was launched in the USA in 2010 and approved in the EU in 2010. Pitavastatin has a distinctive metabolism that means it is minimally metabolised by CYP enzymes. Pharmacokinetic studies in healthy subjects have confirmed that pitavastatin does not interact with digoxin, warfarin, rifampicin, enalapril, atazanavir or itraconazole; the only notable potential interactions with pitavastatin involve potent inhibitors of multiple transporters including OATP1B1 (for which pitavastatin is a substrate), such as cyclosporine. The LIVES post-marketing study, which has collected safety data in more than 20,000 patients in Japan for up to 2 years of follow-up in real-life clinical practice, demonstrated that pitavastatin treatment is associated with a relatively low risk of DDIs, and that the risk of an ADR was not increased by concomitant administration of a range of drugs (such as calcium-channel blockers, azole antifungals, macrolide antibiotics, coumarin anticoagulants, fibrates and cyclosporine) that are known to interact with other statins.

As the clinical complexity of patients with multiple comorbid conditions increases, so does the potential for DDIs; this represents a potential 'minefield' for prescribing physicians. The growing trend towards earlier statin treatment for the prevention of CVD means that physicians must anticipate future polypharmacy when their patients require additional medications for comorbid conditions. Avoiding DDIs and consequent ADRs is essential in order to optimise compliance and thus improve the treatment of patients who remain at high and residual risk of heart attack and stroke.

Conclusions

The combination of established efficacy with a proven long-term safety profile provides a strong rationale for the use of pitavastatin. In particular, the addition of pitavastatin to the range of available statins provides prescribing physicians with a new treatment option that is expected to have a low risk of DDIs and related ADRs, and which should help them individualise lipid-lowering regimens based on the patient profile and concomitant medications.

Drug–drug interactions with statins: will pitavastatin overcome the statins' Achilles' heel? Alberto Corsini, Richard Ceska. Current Medical Research & Opinion Vol. 27, No. 8, 2011, 1551–1562.

Insight HEART
Vol: 9 No: 1 ; 2013

Cardiology News

Some Antidepressants May Boost Arrhythmia Risk

Patients who receive high doses of some, but not all, antidepressants may be at risk of developing prolongation of the QT interval, a marker for possible ventricular arrhythmia, new research suggests. Investigators examined more than 38,000 electronic medical records and found a "slight but significant" association between QT prolongation and prescriptions of citalopram or escitalopram. Similar to previous research, a significant association was also found for amitriptyline and methadone. Other antidepressants, including fluoxetine, paroxetine, and sertraline, showed no effect on QT interval, whereas bupropion was actually associated with shortening of the QT interval. Results showed that a significantly longer than normal QT interval was found for the patients receiving the selective serotonin reuptake inhibitors (SSRIs) citalopram ($P < .01$) and escitalopram ($P < .001$), the tricyclic antidepressant amitriptyline ($P < .001$), and methadone ($P < .001$).

J Am Coll Cardiol Intv 2012;5:57-63.

Selenium Supplements 'Not Justified' for CVD Prevention

Taking selenium in the form of supplements does not prevent cardiovascular disease, at least not in well-nourished individuals, and could even slightly increase the risk of type 2 diabetes. In this systematic review, they analyzed 12 randomized controlled trials on the effects of selenium-only supplementation on major CVD end points, mortality, changes in CVD risk factors, and type 2 diabetes in adults. A total of 19 715 participants were randomized in the 12 trials. There were no significant effects of selenium supplementation on all-cause mortality , nonfatal CVD events, or all CVD events. Selenium supplementation reduced total cholesterol, but not significantly, and did not significantly alter mean high-density lipoprotein (HDL) levels. The small increased risk of type 2 diabetes seen with selenium supplementation did not reach significance (RR 1.06), but other, more minor, adverse effects were seen more frequently in those taking selenium supplements, including alopecia and dermatitis grade 1 to 2.

Cochrane Database Syst Rev 2013; DOI:10.1002/14651858.CD009671.

SQUARE PHARMACEUTICALS LTD. has donated 02 Haemodialysis machines (complete set up) with 02 specialized hospital beds in fond memory of the ***founder Chairman Mr. Samson H Chowdhury*** to NHFH & RI, Mirpur, Dhaka. The inauguration program was held on 21st January 2013 at NHFH & RI auditorium. Around 300 participants were present in the program.

Managing Director of ***SQUARE PHARMACEUTICALS LTD.***, ***Mr. Tapan Chowdhury*** was present in the program. National Professor Brig. (Rtd.) ***Abdul Malik*** along with Vice Presidents of National Heart Foundation of Bangladesh ***Mr. S M Al-Hussaeni*** and ***Profesor R K Khandaker*** thanked ***SQUARE*** for this contribution.

Editorial Note

Dear Doctor,

We are happy to present the 28th issue of "Insight Heart".

This issue is focused on statin which is a common drug in clinical practice and it's side effects. We will appreciate your thoughtful comments.

Thanks and regards.