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Incidence of statin-drug interactions in Croatian community pharmacy

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Statins are among the most frequently issued drugs that patients usually need to take for a lifetime. They are often an integral part of a polytherapeutic approach in preventing and treating cardiovascular diseases. As such, they might often interact with drugs prescribed for treating acute and chronic conditions. A pharmacist is the final professional control before a drug reaches the patient and his role in preventing drug-drug interactions is crucial. The objective of this research was to analyse the incidence and relevance of potential drug interactions with statins in community pharmacy. We retrospectively analysed the prescribed pharmacotherapy of 153 patients who were taking statins. Lexicomp® Lexi-Interact™ Online (Lexi-Comp, Inc., Hudson, USA) was used to identify interactions. The mean age of study patients was 65.5 (52.3% women). The most frequently used statin was atorvastatin and the least used was fluvastatin. The average number of coprescribed drugs was 4. The highest number of interactions which required enhanced patient surveillance were registered with atorvastatin, while interactions which might need specific therapy modification were mostly seen with simvastatin. Systematic and regular control of potential clinically significant drug-drug interactions in the prescribed pharmacotherapy is important for therapy outcomes and appropriate pharmaceutical surveillance in issuing pharmacotherapy.

1. Introduction

Statins are the most frequently used hypolipidemics and one of the most frequently used drugs in general. Inhibiting the enzyme HMG-CoA reductase, they inhibit cholesterol synthesis and cause the lowering of low denssity lipoproteins (LDL) and total cholesterol. Moreover, they have pleiotropic effects which regulate endothelial function, inflammatory processes and thrombogenesis. Statins have an important role in treating cardiovascular diseases (CVD) which are the number one cause of death globally. In 2012, 17.5 million people died from CVD. It is estimated that, by 2030, the number of CVD deaths will grow to more than 23.6 million (WHO). Therefore, it is expected that the consumption of statins will continue to grow in the future. Prevention and treatment of CVD usually requires a polytherapeutic approach. Polytherapy increases the possibility of drug-drug interactions (DDI) and statins need to be carefully observed as potential drug interactants. It is important to determine incidence and relevance of potential DDIs, in order to reduce drug related problems. Potential DDIs are a common drug related problem (Paulino et al. 2004; Schorr et al. 2014). DDIs can significantly compromise the therapy outcome and cause hospitalizations and deaths (Juurlink et al. 2003). Becker et al. (2007) estimated that 4.8% of hospital admissions in the elderly were caused by DDIs. DDIs are also a very important economic problem for healthcare systems (Moura et al. 2009). Individualization and rationalization of pharmacotherapy is incomplete without the prevention of DDIs. Potential damage to patients can be prevented or decreased if DDIs are perceived on time. A critical viewpoint is necessary when evaluating the data on DDIs (Bacic-Vrca et al. 2005). Pharmacists in the community pharmacy are the last in the professional chain to identify and resolve drug related problems (Hämmerlein et al. 2007; Paulino et al. 2004). DDI prevention is an important and mandatory aspect of pharmaceutical activity. Recognizing the relevance of potential DDIs is necessary for therapy outcomes and planning appropriate pharmaceutical surveillance in issuing pharmacotherapy.

2. Investigations, results and discussion

This research retrospectively analysed the prescribed pharmacotherapy of patients treated with a statin and at least one more drug. Pharmacotherapies were analyzed consecutively in the period of 40 days. Therapies were taken from the official register of issued pharmacotherapies which is being held in the electronic database. The objective was to analyse the incidence and relevance of potential drug interactions with statins. Only a prescribed therapy was included in the analysis as an official register of over-the-counter drugs is not obligatory and is mostly not kept in community pharmacies in Croatia. Interactions were identified using Lexicomp® Lexi-InteractTM Online (Lexi-Comp, Inc., Hudson, USA) program which categorizes interactions according to the level of clinical relevance in five risk rating categories (A, B, C, D and X). Only categories C, D and X are considered to be clinically significant interactions.

Demographic data of patients are presented in Table 1. We enrolled 153 patients (52.3% female). The average age was 65.5 (range 41-84) years and the average number of other concomitant drugs was 4. Four statins have been identified in analyzed pharmacotherapies: atorvastatin, simvastatin, rosuvastatin and fluvastatin. Most commonly prescribed co-medications were beta blockers, ACE inhibitors and oral antidiabetics. All co-administered drugs and their prevalence are listed in Table 2.

We determined at least one potential clinically significant DDI in 56 (36.6%) subjects. Overall, 62 potential clinically significant interactions were identified: 46 C (74.2%) and 16 D (25.8%) interactions, while there were no X level interactions. Atorvastatin was the most prescribed statin with 35 interactions (56.5%), while 18 (29%) and 9 (14.5%) interactions were identified with simvastatin and rosuvastatin, respectively (Table 3).

Previous studies have shown that the prevalence of potential drug-statin interactions range from 6.9 to 32.1% (Badiu et al. 2016; Busca et al. 2015; Zhelyazkova-Savova et al. 2014; Tirkkonen et al. 2008; Stang et al. 2007; Rätz Bravo et al. 2005; Einarson et al. 2002).

Table 1: Demographic data

	All patients (n=153)	
Age (y), mean	65.5	
Gender, n (%)		
Men	73 (47.7)	
Women	80 (52.3)	
Other prescribed drugs (non-statin) (mean, range)	4 (1-11)	
Interactions, n	62	Patients, n (%)
[a]C, n (%)	46 (74.2)	41 (26.8)
[b]D, n (%)	16 (25.8)	15 (9.8)
[c]X, n (%)	0 (0)	0

Abbreviations: [a]C - monitor therapy; [b]D - consider therapy modification, [c]X - avoid combination.

Table 2: Concurrently issued drugs with statins

Concurrently used drugs	Number of patients (%)
Beta blockers	64 (41.8)
[a]ACE inhibitors	63 (41.2)
Oral antidiabetic drugs	52 (33.9)
Calcium channel blockers	47 (30.7)
Thiazides	34 (22.2)
Angiotensin II receptor antagonists	21 (13.7)
Low threshold diuretics	20 (13.1)
Proton pump inhibitors	17 (11.1)
[b]NSAID	16 (10.5)
Other hypolipidemics	13 (8.5)
Insulins	13 (8.5)
H2-receptor antagonists	12 (7.8)
Loop diuretics	12 (7.8)
Other antihypertensives	10 (6.5)
Clopidogrel	9 (5.9)
Antibiotics	8 (5.2)
Warfarin	8 (5.2)
Allopurinol	6 (3.9)
Levothyroxine	6 (3.9)

Abbreviations: [a]ACE – angiotensin converting enzyme; [b]NSAID – non steroid antiinflammatory drug

Table 3: Proportion of prescribed statins and clinically significant statin-drug interactions

Statin	Patients n (%)	C	D	X
Atorvastatin	92 (60.1)	30	5	0
Simvastatin	35 (22.9)	7	11	0
Rosuvastatin	24 (15.7)	9	0	0
Fluvastatin	2 (1.3)	0	0	0

In Croatia, statin drugs are issued exclusively on prescription. Statins identified in our study (atorvastatin, simvastatin, rosuvastatin, fluvastatin) are the only currently registered statins in Croatia. Atorvastatin is the most frequently prescribed statin in the Republic of Croatia since 2008 (HALMED). Atorvastatin and simvastatin have been comprehensively studied in the primary and secondary prevention of cardiovascular events (Arca and Gaspardone 2007; Kapur and Musunuru 2008). Rosuvastatin is a relatively new drug, first registered in 2003. It is the first statin approved by the regulatory authorities since the withdrawal of cerivastatin (Davidson 2004). As a result of the JUPITER clinical trial, in 2010 rosuvastatin was registered for primary prevention of cardiovascular events as well (Ridker et al. 2008; Carter 2010;). Fluvastatin has the weakest impact in lowering lipids (Kapur and Musunuru 2008).

Prescribing statins for the first time to elderly people is less frequent then to younger patients. The majority of developed countries have accepted the concept that elderly people are considered to be those of 65 years of age and over (WHO). Elderly people belong to a high risk group of patients for developing DDIs because of decreased physiological functions, numerous comorbidities and polypharmacy (Mallet et al. 2007). As the possibility of interactions increases significantly due to the above mentioned factors, application of statins in this population should be limited to lower doses (Walker and Jacobson 2008). Accordingly, every increase in statin dose and every introduction of a new drug in combination with statin in elderly people requires additional supervision of a pharmacist in revising DDIs and pharmacotherapy monitoring. In elderly people, the application of statins is justified in secondary prevention, while the data about the application of statins in primary prevention is limited. The Croatian Health Insurance Fund (HZZO) does not cover the cost of statin initiation for primary prevention of cardiovascular disease in patients older than 70 (HZZO). With higher life expectancy in the future, additional research is necessary to evaluate the advantage, risks and cost of statin application for primary prevention in elderly people (Chokshi et al. 2012).

More than half of the drugs used concurrently with statins are drugs which affect the cardiovascular system (drugs of the C group of the Anatomical Therapeutic Chemical (ATC) Classification System). This is not surprising as hyperlipidaemia and heart diseases are closely related. Since patients suffering from diabetes are prone to hyperlipidaemia, statins are frequently used for treating patients with diabetes. Although some data suggest that new cases of diabetes appear in patients using statin therapy, patients suffering from type 2 diabetes can greatly benefit from statins and it is recommended to introduce statins into their therapies (Sattar et al. 2010; Park et al. 2014). In all patients with type 2 diabetes target LDL should be < 2.6 mmol/L and in those who have CVD or chronic kidney disease or those over the age of 40 and at least one CV risk factor, target LDL should be <1.8 mmol/L (Catapano et al. 2016).

More than half of C risk rating interactions (25 interactions) have been recorded with drugs used for acidity disorders (A02 group according to the ATC Classification System) (Table 4). Most common interactions of C significance level were recorded with the proton pump inhibitor pantoprazole (17 interactions). Proton pump inhibitors are believed to be able to increase the concentration of statins. Therefore, in case of co-administration, there is an increased possibility of occurrence of rhabdomyolysis (Sipe et al. 2003; Marusic et al 2012). Pantoprazole is also a frequently used drug and the most frequently used proton pump inhibitor in Croatia. Since 2012, it has been among the top ten prescribed drugs in Croatia. Beside pantoprazole, other proton pump inhibitors registered in Croatia are esomeprazole, rabeprazole and omeprazole, but these are much less used (HALMED). Proton pump inhibitors interfere with all statins in C risk rating interaction. The second most common interaction of C risk rating level was atorvastatin/ranitidine. Ranitidine might sometimes be used instead of pantoprazole (van Zyl et al. 2000; Kaspari et al. 2001). Several statins, particularly atorvastatin and lovastatin, have been shown to interact with P glycoprotein (P-gp) as both are substrates and inhibitors at the molecular level (Holtzman et al. 2006). Ranitidine and loperamide are P-gp substrates. P-gp inhibitors decrease P-gp activity, generally leading to increased absorption, decreased elimination and enhanced distribution of P-gp substrates. Therefore, these interactions can result in increased serum concentrations of ranitidine and loperamide and greater effects or toxicity. Hence, special caution is required if a P-gp inhibitor is introduced in therapy or if the dose of a concurrently used P-gp inhibitor is increased. Close monitoring is advised when the dose of a concurrently used P-gp inhibitor is decreased because the final effects of P-gp substrates can be more expressed. It must be pointed out that, in Croatia, pantoprazole, ranitidine and loperamide are also available over the counter, but our analysis included only pantoprazole, ranitidine

Table 4: Potential clinically significant drug-statin interactions of C level

Drug	Drug group	Interacting statin	Interactions	Total interactions	Interaction
Pantoprazole	Proton pump inhibitor	Atorvastatin Simvastatin Rosuvastatin	10 3 4	17	Increased risk of myopathy/rhabdomyolysis due to an increased serum concentration of statins
Ranitidine	H2 receptor antagonist	Atorvastatin	7	7	Increased effect of ranitidine
Sitagliptine	Inhibitor of dipeptidyl peptidase 4	Atorvastatin Simvastatin	3 2	5	Increased risk of myopathy/rhabdomyolysis in case of concurrent use with simvastatin. Possibility of occurrence of hypoglycaemia in case of concurrent use with atorvastatin.
Carvedilol	Alpha- and beta-receptor blocker	Atorvastatin	3	3	Possible increased effect of both atorvastatin and carvedilol (both substrates and inhibitors of P-gp)
Warfarin	Anticoagulant	Rosuvastatin Simvastatin	1 1	2	Potential increase of the INR
Linagliptin	Inhibitor of dipeptidyl peptidase 4	Atorvastatin	2	2	Possibility of occurrence of hypoglycaemia in case of concurrent use with atorvastatin
Calcium carbonate	Calcium	Simvastatin Rosuvastatin	1 1	2	Decreased effect of statin
Clopidogrel	Platelet aggregation inhibitor	Rosuvastatin	2	2	Increased risk of myopathy and rhabdomyolysis in concurrent use with rosuvastatin
Esomeprazole	Proton pump inhibitor	Rosuvastatin	1	1	Increased risk of myopathy/rhabdomyolysis due to an increased serum concentration of statins
Loperamide	Anti-diarrhoeal drug	Atorvastatin	1	1	Increased effect of loperamide
Metildigoxin	Cardiotonic	Atorvastatin	1	1	Increased effect of digoxin
Risperidon	Antipsychotic	Atorvastatin	1	1	Increased effect of both atorvastatin and risperidone
Spironolactone	Aldosterone antagonist	Atorvastatin	1	1	Atorvastatin can increase the toxic effects of spironolactone
Ciprofloxacin	Quinolone antimicrobic	Atorvastatin	1	1	Increased effect of ciprofloxacin

Table 5: Potential clinically significant drug-statin interactions of D level

Drug	Drug group	Interacting statin	Interactions	Total interactions	Interaction
Amlodipine	Calcium channel blocker	Simvastatin	9	9	Increased risk of myopathy/rhabdomyolysis due to a decreased simvastatin metabolism
Amiodarone	Antiarrhythmic	Atorvastatin Simvastatin	4 1	5	Increased risk of myopathy/rhabdomyolysis due to a decreased metabolism of atorvastatin and simvastatin
Verapamile	Calcium channel blocker	Atorvastatin Simvastatin	1 1	2	Increased risk of myopathy/rhabdomyolysis due to a decreased metabolism of atorvastatin and simvastatin. Atorvastatin can increase the serum concentration of verapamil.

and loperamide which are issued at the physician's recommendation (prescription). Since these drugs are widely used and issued over the counter, the real incidence of this potential interaction is most probably higher, and it might remain unrecognised in a large number of patients. For all patients taking statins, the pharmacist must carefully choose the adequate OTC drug and its dosage.

To avoid most clinically significant D interations identified in this study, limitation of statin dose would be the best intervention. Most common D risk rating interactions were detected between calcium channel blockers and statin (11 interactions) (Table 5). Some calcium channel blockers can interfere with statins and cause clinically significant interactions (Zhou et al. 2014). In this study, two calcium channel blockers (amlodipine, verapamil) have been identified in potential clinically significant interactions with statins. Using amlodipine in combination with simvastatin can result in an increased concentration of simvastatin. Therefore, the concurrent use of simvastatin and amlodipine increases the possibility of occurrence of myopathy and rhabdomyolysis (Zhou et al. 2014; Nishio et al. 2005). Some companies' prescribing information suggest that in case of unavoidable co-administration, the simvastatin dosage should be limited to 20 mg and the patient should be monitored (Zocor 2011; Norvasc 2015). Regarding other statins identified in this study, the guidelines for their prescription do not indicate that there is a clinically significant risk for an interaction with amlodipine. Verapamil was identified in interaction with atorvastatin and simvastatin. Verapamil can increase the concentration of both statins and increase the possibility of occurrence of adverse events. The interaction between these statins and diltiazem has the same clinical significance (Zhelyazkova-Savova et al. 2014). Prescribing information recommend limitation of simvastatin dose to 10 mg in combination with verapamil and diltiazem (Zocor 2011). If statins are used concomitantly with amiodarone, monitoring of statin toxicity is advaisable (e.g., myalgia, liver function test elevations, rhabdomyolysis, etc.). Amiodarone is a CYP3A4 inhibitor so dose reduction of the HMG-CoA reductase inhibitor may be necessary with concurrent amiodarone therapy. Statins primarily oxidized by CYP3A4 (simvastatin, lovastatin and atorvastatin) are mostly prone to interact through these mechanisms (Zhelyazkova-Savova et al. 2014). Prescribing information specifically recommends that the dosage of simvastatin with amiodarone should be limited to 20 mg

(Zocor 2011). When possible, advantage should be given to statins which do not metabolise through the CYP3A4 enzyme: pravastatin, fluvastatin and rosuvastatin (Marot et al. 2011).

We found no potential X interactions in our study population. However, there are drugs which must not be used with statins. Gemfibrozil is contraindicated in patients taking statins as it increases the risk of rhabdomyolysis (Ho and Walker 2012). Cyclosporin is contraindicated with atorvastatin and simvastatin (Lipitor 2012; Zocor 2011). Cyclosporin can increase atorvastatin concentration up to ten times (Lipitor 2012). Concurrent use of erythromycin with simvastatin is contraindicated. Concurrent use of clarithromycin or erythromycin together with simvastatin, lovastatin or atorvastatin was associated with an increased risk of hospitalization for rhabdomyolysis, acute kidney injury, or all-cause mortality as compared to concurrent use of azithromycin with the statins (Patel et al. 2013). Strong CYP3A4 inhibitors (itraconazole, voriconazole, ritonavir) may increase the serum concentration of simvastatin so they are also considered contraindicated.

In this study potential drug-statin interactions primarily result in an increased risk of occurrence of myopathy/rhabdomyolysis as most of the interfering drugs increase statins' concentration. Some drugs can decrease statins' concentration (rifampicin, phenytoin) and cause statin failure (Frishman and Horn 2008). The most adequate, but not always possible choice would be to select a drug which does not interfere with statins or a statin which does not interact with the existing therapy. Decreasing the dose of the statin is an option that might contribute to decreasing the risk of occurrence of some interactions. In such interactions pharmacists should monitor the dose of statin and intervene when it is necessary. The cardiovascular risk of statin withdrawal must be carefully considered as option when managing DDIs. Withdrawal of statin for up to six weeks in a stable patient seems safe (McGowan 2004), but if statin therapy is discontinued after a myocardial infarction and/or ischemic stroke morbidity and mortality rates are much higher (Daskalopoulou et al. 2008; Spencer et al. 2004). Statin consumption is constantly increasing (Walley et. al. 2005). It is estimated that a large number of patients who could benefit from statins are not receiving statin therapy (Schwand and Brady 2004). Systematic and regular checking for potential clinically significant drug interactions in the prescribed pharmacotherapy is important for therapy optimization and planning appropriate pharmaceutical interventions. Accordingly, pharmacists should aim to develop models of pharmaceutical interventions. Based on our results we can conclude how the introduction of a OTC drug register in a pharmacy would be useful. More and more drugs are being granted the status of an OTC drug. The responsibility for selecting an OTC drug is transferred exclusively to the pharmacist. Introducing an OTC drug registry into pharmacies would also contribute to improved quality of pharmaceutical care by preventing DDIs and improving the quality of patient health protection.

3. Experimental

This study enrolled consecutive outpatients during a period of 40 days who visited a community pharmacy with prescriptions for a statin and at least one other drug. Identification of patients' demographic data and concomitant therapy was taken through pharmacy record data analysis. Potential DDIs were identified using Lexi-Interact software which categorizes potential interaction according to clinical significance in five groups: (A) no known interaction; (B) specified agents may interact, but there is little or no evidence for clinical concern; (C) the specified agents may interact in clinically significant manner and monitoring of therapy is suggested; (D) the two medications may interact in clinically significant manner and modification of therapy is suggested; (X) contraindicated combination. Descriptive statistical analysis was used to describe patients' demographic data, their therapies and potential DDIs. Proportions were calculated for categorical variables.

Conflicts of interest: None declared.

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