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STATIN DRUG-DRUG INTERACTIONS IN A ROMANIAN COMMUNITY PHARMACY

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Abstract

Background and aim. *Statins are frequently prescribed for patients with dyslipidemia and have a well-established safety profile. However, when associated with interacting dugs, the risk of adverse effects, especially muscular toxicity, is increased.*

The objective of this study was to identify, characterize and quantify the prevalence of the potential drug-drug interactions (pDDIs) of statins in reimbursed prescriptions from a community pharmacy in Bucharest.

Methods. *We analyzed the reimbursed prescriptions including statins collected during one month in a community pharmacy. The online program Medscape Drug Interaction Checker was used for checking the drug interactions and their classification based on severity: Serious – Use alternative, Significant – Monitor closely and Minor.*

Results. *132 prescriptions pertaining to 125 patients were included in the analysis. Our study showed that 25% of the patients who were prescribed statins were exposed to pDDIs: 37 Serious and Significant interactions in 31 of the statins prescriptions. The statins involved were atorvastatin, simvastatin and rosuvastatin.*

Conclusions. *Statin pDDIs have a high prevalence and patients should be monitored closely in order to prevent the development of adverse effects that result from statin interactions.*

Keywords*:* drug interactions, statins, drug prescriptions

Introduction

Drug-drug interactions (DDIs) are an important source of preventable and sometimes severe adverse effects (AEs). The percentage of hospital admissions caused by DDIs which results in AEs varies between 0.6 and 1.2, and up to 4.8 among the elderly [1].

Given that for most patients optimal therapeutic effect can only be obtained by polypharmacy, awareness of the mechanisms and manifestations of DDIs, their incidence and clinical relevance is the first step towards reducing and preventing AEs.

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The 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors, also known as statins, are frequently used for lowering serum low-density lipoprotein cholesterol concentrations and for the prevention of cardiovascular events [2-6]. The safety profile of statins is well established. The main safety concerns related to the use of statins are the muscle-related AEs of variable intensity, the risk of which can be augmented by DDIs [7,8].

Most statins undergo a cytochrome P450 metabolism (CYP3A4, CYP3A5, CYP2C9 and CYP2C19 are the major microsomal enzymes that metabolize statins) [9] and consequently have a wide range of possible interactions with other cytochrome P450 inhibitors or substrates. In

addition, other hypolipidemic drugs such as fibrates may also interact with statins due to additive pharmacodynamic effect. Furthermore, statins may increase the plasmatic concentration and potential toxicity of other drugs (e.g. digoxin, acenocoumarol), which may also enhance the risk of AEs [10-12].

Objectives

The objective of this study was to identify the potential DDIs of statins in reimbursed prescriptions from a community pharmacy in Bucharest, during the month of May 2014. Also, we aimed at quantifying the prevalence and to characterize the pDDIs in terms of severity and mechanism.

Materials and methods

A retrospective study was conducted following a method described by *Bucşa C et al.* [13], on reimbursed prescriptions pertaining to one month (May 2014) from a community pharmacy in Bucharest, Romania.

The drugs were encoded with Anatomical Therapeutic Chemical (ATC) classification system [14]. The prescriptions that contained statins were selected and analyzed using the online program Medscape Drug Interaction Checker [15]. For patients with more than one prescription, all prescribed drugs were screened for pDDIs if they were to be used at the same time.

A pDDI was defined as the possible interaction between a statin and another drug, which might cause an alteration of the therapeutic effect and/or the toxicity of one/both of the drugs involved. The pDDIs were classified according to Medscape Drug Interaction Checker, based on severity, as follows: *Serious – Use alternative, Significant – Monitor closely* and *Minor*. For the prescriptions containing drugs which were not included within the Medscape Interaction Checker program's database (i.e. acenocoumarol, nicergoline and diosmin), the summary of product characteristics was employed as a reference.

The data were analyzed using descriptive statistics.

Results

Patients and drug therapy

132 reimbursed statin prescriptions were analyzed, pertaining to 125 patients, age range 39 to 93 years. The patients' characteristics and prescribed drugs are shown in Table I.

Drug-drug interactions with statins

We identified 37 pDDIs in 31 of the statins prescriptions; 25 prescriptions contained one pDDI and 6 prescriptions contained 2 pDDIs each. The number of drugs prescribed on a single prescription varied between 2 and 7. From the age and gender perspective, there were no major differences between all patients under statin treatment and the patients exposed to pDDIs.

The statins involved in pDDIs were: atorvastatin (15 cases), simvastatin (13 cases) and rosuvastatin (9 cases).

The pDDIs identified were classified as *Serious (*51.35%) and *Significant (*48.65%). No *Minor* pDDIs were identified (Figure 1).

According to the ATC classification system, the drugs involved in pDDIs were classified under three groups: C (Cardiovascular System) – 7 drugs, B (Blood and Blood Forming Organs) – one drug, and one drug under R (Respiratory System). The pDDIs identified, their severity and potential clinical outcome are listed in Table II.

Table I. Characteristics of the patients and prescribed drugs.

Characteristics		All patients under statin treatment	Patients exposed to pDDIs
Total no.		125	31
Age-years	Mean [CI 95%]	65.85 [63.76-67.95]	64.8 [60.95-68.66]
Elderly patients (>65 years)	No. (%)	59 (47.20)	13 (41.94)
Gender-no. (%)	Male	56 (44.80)	15 (48.39)
	Female	69 (55.20)	16 (51.61)
No. of drugs/ patient	Mean [CI 95%]	4.70 [4.42-4.98]	5.09 [4.58-5.59]
Prescribed drugs/ ATC* group-no. (%)	Cardiovascular system **(C)**	441 (75.13)	139 (80.35)
	Alimentary tract and metabolism **(A)**	41 (6.98)	8 (4.62)
	Musculoskeletal system **(M)**	24 (4.09)	6 (3.47)
	Other groups	80 (13.63)	19 (10.98)

*Anatomical Therapeutic Chemical (ATC) group [14], CI-confidence interval.

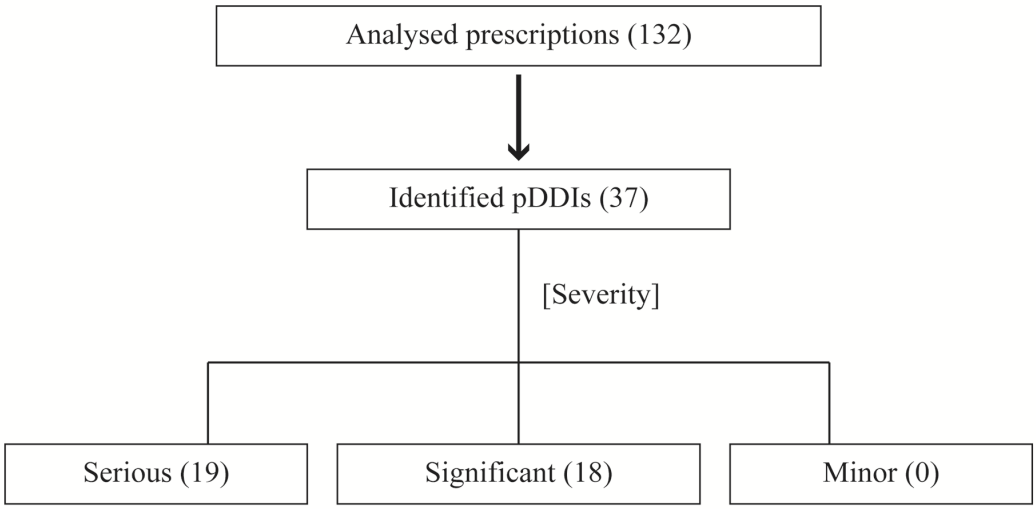

Figure 1. pDDIs severity.

Table II. Drugs involved in SDDIs.

Statin (no. of pDDIs)	Co-administrated drug	Pharmacological class	Severity	Potential outcome of the pDDI
Simvastatin (1)	Amiodarone	Class III antiarrhythmics	Serious	Decreased metabolism of the statin, increased risk of muscular toxicity
Atorvastatin (1) Rosuvastatin (3) Simvastatin (3)	Acenocoumarol	Anticoagulants, Vitamin K antagonists	Significant	Increased anticoagulant effect, increased risk of bleeding
Simvastatin (3)	Amlodipine	Calcium channel blockers (dihydropyridine-type)	Serious	Increased plasmatic level of statin, increased risk of muscular toxicity
Atorvastatin (2)	Diltiazem	Calcium channel blockers (benzothiazepine-type)	Significant	Increased level or effect of statin, increased risk of muscular toxicity
Atorvastatin (1) Simvastatin (2)	Valsartan	Angiotensin II receptor antagonists	Significant	Increased level or effect of valsartan, with risk of hypotension
Atorvastatin (3)	Spironolactone	Aldosterone receptor antagonists	Significant	Increased level or effect of statin, increased risk of muscular toxicity
Atorvastatin (7) Rosuvastatin (6) Simvastatin (2)	Fenofibrate	Fibrates	Serious	Pharmacodynamic synergism, risk of muscular toxicity
Simvastatin (2)	Digoxin	Cardiac glycosides	Significant	Increased level of digoxin with digitalis-induced toxicity
Atorvastatin (1)	Budesonide	Glucocorticoids (GC) (inhalation use)	Significant	Increase in the GC plasma level with risk of GC AEs

Discussion

The data analysis showed that 25% of the patients were at risk of experiencing an AE following a pDDI between a statin and one or two drugs. When compared with a study conducted in Bulgaria (2014), the number of cases found was largely similar, with 26.1% pDDIs identified at admission and 24.4% at discharge [16]. In Canada, a transversal study (2002) showed that 20.8% of the patients under statin therapy had a risk of experiencing an AE caused by polypharmacy [17]. A retrospective cohort study from the United States of America (2007) concluded that the patients at risk of experiencing an AE as a result of pDDIs totaled 19% of all statin users included in the study [18]. In Switzerland, however, (2005) the percentage of statin users at risk of SDDIs was lower: 6.9% [19]. A similar percentage (6.9), was obtained in an observational cohort study in Finland (2008), which analyzed the possible DDIs of patients under treatment with lovastatin and simvastatin [20].

Our results showed that there were no major differences between the average age of the patients exposed to pDDIs compared to all statin users, whereas in a study from Switzerland which assessed the age-related differences in the prevalence of DDIs in patients treated with statins (2007), elderly patients (>75 years) were prescribed more drugs with a potential for DDIs compared to younger patients (<54 years): 18.4% as opposed to 7.9%. These differences were justified by the high level of comorbidities and polypharmacy associated with elderly population [21]. Unlike the patients analyzed in the Swiss study, the prevalence of pDDIs for the Romanian patients included in this study did not increase with age: the number of patients <65 years exposed to a pDDI was higher than the number of patients >65 years.

Most cases of pDDIs were associated with the concurrent use of fenofibrate (15 cases). According to Medscape Drug Interaction Checker, the association between a statin and fenofibrate has a major risk of interaction by pharmacodynamic synergism [15], which may lead to serious muscular toxicity, especially in patients with history of muscular disorder. Thus, the association of fenofibrate with a statin is reserved for patients with severe mixed dyslipidemia and an increased risk for cardiovascular events, with no history of muscular disorder. The decision to initiate this combination should be made with caution and the patients should be monitored closely for an early detection of myopathy [22].

Amiodarone is another drug with a major interaction potential when associated with statins: one case was identified. Amiodarone is a CYP3A4 and CYP2C9 inhibitor, which can decrease the metabolism of atorvastatin, lovastatin, simvastatin and fluvastatin and increase the risk of AEs such as myopathy and rhabdomyolysis [23]. A minimization of this risk may be achieved by associating amiodarone with a statin that is not metabolized through CYP3A4 (i.e. pravastatin, rosuvastatin), or by adjusting the dose of the statin (the recommended maximum dose/24 h is 40 mg for lovastatin and 20 mg for simvastatin) [24,25].

We identified 7 cases of statin-acenocoumarol possible DDIs. Information available in literature concerning the DDIs of this coumarin anticoagulant is limited compared to warfarin (e.g. the Medscape Drug Interaction Checker program contains no information regarding acenocoumarol). Acenocoumarol is a racemic mixture of an S-enantiomer (substrate of CYP2C9) and an R-enantiomer (substrate of CYP3A4), which makes acenocoumarol's competitive inhibition of CYP clinically relevant not only with fluvastatin and rosuvastatin, but also with simvastatin, atorvastatin and lovastatin. The only statin exempt from this possible interaction is pravastatin, which has a unique metabolic pathway in comparison to the other members of its class, as it is chemically degraded in the stomach [11,26]. The co-administration of acenocoumarol with statins may lead to an enhancement of the anticoagulant effect, with an increased risk of bleeding. In the case of a statin-acenocoumarol association, blood clotting tests should be performed regularly (twice per week) and the patient should be closely monitored [12].

Calcium channel blockers have a high potential risk of interaction with statins: according to Medscape Drug Interaction Checker, the association of simvastatin with amlodipine poses a serious risk, whilst associating simvastatin or atorvastatin with diltiazem has a significant risk of DDI. A review performed in China (2014) observed that concomitant administration of multiple doses of amlodipine (10 mg/24h) could increase the plasma concentration-time curve (AUC) and maximum concentration (Cmax) of simvastatin (40 mg/24h) by 1.8- and 1.9-fold, respectively, and that amlodipine had no effect on the Cmax of atorvastatin, but increased the AUC of atorvastatin by 18% [27]. For patients under concomitant treatment with amlodipine, the simvastatin dose should be limited to 20 mg/24h [28]. Diltiazem may increase the plasma concentration of simvastatin, atorvastatin and lovastatin through CYP3A4 and P-glycoprotein inhibition [29,30]. Statin therapy in patients taking diltiazem should be started with the minimum effective dose and increased gradually. Also, an adjustment in the dose of statin is recommended for patients initiating diltiazem therapy [29,30].

According to Medscape Interaction Checker, concomitant administration of a statin with spironolactone has a significant risk of DDI: 3 cases were identified. The mechanism suggested is the inhibition of the P-glycoprotein by the diuretic, which may lead to an increase in the statin plasma level (e.g. lovastatin, simvastatin, atorvastatin). However, other authors consider this DDI to be of limited clinical relevance [25]. Caution is advised, as well as careful monitoring of the patient [15,31].

The P-glycoprotein is responsible for the interaction

between statins and digoxin: 2 cases were identified [32]. The patients under treatment with a statin and digoxin may experience a rise in the plasma level of digoxin with subsequent digitalis-induced toxicity (e.g. nausea, vomiting, cardiac glycoside toxicity). Digoxin has a narrow therapeutic index and this association has been classified by Medscape Interaction Checker as posing a significant risk of AEs. Careful monitoring of the digoxin plasma level is recommended for the patients undergoing treatment with this cardiac glycoside and who are initiating statin therapy (especially atorvastatin and simvastatin); adjusting the digoxin dose may be necessary [10,15,33].

Valsartan is another drug with a potential pharmacokinetic competition with statins for a hepatocyte membrane transporter: 3 cases were identified. Valsartan and statins share an affinity for OATP1B1 and their co-administration might lead to an increase in the valsartan plasma level and subsequent hypotension. Monitoring the blood pressure of the patients undergoing this treatment is recommended [15,25].

One case of a possible DDI with budesonide was identified. The probable mechanism of this interaction is the statin inhibition of the P-glycoprotein, which might lead to an increase in the glucocorticoid plasma level and in the subsequent risk of AEs [15,32]. Although it is not known whether this DDI is of clinical relevance in the case of inhalation administration of budesonide, a cautious approach is recommended: avoiding the association or maximizing the time frame between the administrations of the two drugs [34].

Despite its high potential of producing AEs when associated with enzymatic inhibitors or inductors, some authors state that the incidence or myopathy and rhabdomyolysis caused by statins is relatively low: a study conducted in Ireland discovered that a third of the patients undergoing statin therapy were at risk of developing DDIs, of which only 3% experienced AEs [35]. An observational study from Finland (2008) showed that the clinical relevance of pDDIs is limited, as long as the statin doses are low [36].

Although it is possible that for certain associations with a potential for DDI the benefit outweighs the risk, close monitoring of patients is recommended in order to prevent AEs caused by DDIs.

Study limitations: It is not known to what extent these DDIs translated into AEs and if so, what the consequences for the patients and their health state, their quality of life and the costs entailed. Another limitation and possible source of bias of this study is the single-center source of the data. Furthermore, it is imperative to acknowledge that patients involved within the study may have been undergoing treatment with medicines/health supplements from other unknown sources, the details of which were not included in the study.

Conclusions

A quarter of the patients included in the study were at risk of developing an AE as a result of pDDIs with one or two drugs. The prevalence of pDDIs found in our study is higher than the ones found in Canada, the United States of America, Switzerland or Finland, but yielded similar results to one study conducted in Bulgaria.

A positive benefit-risk balance for the co-administration of a statin with a potentially interacting drug could be the explanation for this high percentage. However, it is recommended to closely monitor the patients in order to to avoid any AEs consecutive to DDIs.

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