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THE ISSUES OF DRUG INTERACTION IN COMBINATION PHARMACOTHERAPY IN CARDIOLOGICAL PRACTICE

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Abstract

Background. The objective of this study was to analyze the frequency and structure of appointment of undesirable combinations of statins with other drugs. We have taken into account their interactions at the level of metabolism CYP3A isoenzymes of cytochrome P450 and transportation of proteins-transporters P-glycoprotein and OATP1B to identify significant and potentially dangerous drug combinations.

Materials and methods. The study included medical records of people with diagnosis: Coronary heart disease with concomitant hypercholesterolemia, confirmed by laboratory methods. In total, we analyzed 2790 outpatients. The prevalence and structure of drug interactions at 14 medical institutions of Semey city (Kazakhstan) were studied (pharmacoepidemiological, cross-sectional study).

Results. Our study revealed the presence of significant and potentially dangerous interactions of statins with other drugs from the cardiovascular group in the majority of patients (62%). In cases where it is recommended to prescribe combinations of drugs for clinical indications with caution and under the control of biochemical and other indicators, we found no evidence of this control in 72.5% of cases.

Conclusion. We have determined a fairly high frequency of the prescription of undesirable combinations of statins with other drugs from the cardiovascular group, having a competitive metabolism at the level of CYP3A, OATP1B1 and P-glycoprotein in absolute terms and compared with the data of studies conducted in developed countries.

Keywords. *Pharmacoepidemiology, undesirable drug interactions, CYP3A isoenzymes, P-glycoprotein, OATP1B.*

Резюме

ВОПРОСЫ ЛЕКАРСТВЕННОГО ВЗАИМОДЕЙСТВИЯ КОМБИНИРОВАННОЙ ФАРМАКОТЕРАПИИ В КАРДИОЛОГИЧЕСКОЙ ПРАКТИКЕ

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Целью данного исследования был анализ частоты и структуры назначения нежелательных комбинаций статинов с другими лекарственными средствами. Учитывали особенности их взаимодействия на уровне метаболизма изоферментов CYP3 цитохрома P450 и транспортных систем белков транспортеров P-гликопротеина и OATP1B и для выявления потенциально опасных и значимых лекарственных сочетаний.

Материалы и методы. В исследование включены медицинские карты людей с диагнозом: ишемическая болезнь сердца с сопутствующей гиперхолестеринемией, подтвержденной лабораторными методами. В общей сложности мы проанализировали 2790 амбулаторных пациентов. Были изучены распространенность и структура лекарственных взаимодействий в 14 медицинских учреждениях города Семей (Казахстан) (фармакоэпидемиологическое, поперечное исследование).

Результаты. Было выявлено наличие нежелательных и опасных сочетаний у большинства больных, получавших терапию статинами (62%). В 72,5% случаев мы не обнаружили проведения контроля за безопасностью в

случаях, когда рекомендуется принимать статины с осторожностью и под контролем биохимических и других показателей

Выводы. Нами была определена довольно высокая частота назначения нежелательных сочетаний статинов с другими препаратами, обладающими конкурентным метаболизмом на уровне CYP3A, OATP1B1 и P-гликопротеина в абсолютном выражении и сравнении с данными исследований, проведенных в развитых странах.

Ключевые слова. *Фармакоэпидмиология, нежелательные взаимодействия, изофермент CYP3A, P-гликопротеин, OATP1B.*

Түйіндеме

КАРДИОЛОГИЯЛЫҚ ПРАКТИКАДАҒЫ АРАЛАС ФАРМАКОТЕРАПИЯНЫҢ ДӘРІЛІК ӨЗАРА ӘРЕКЕТТЕСУ МӘСЕЛЕЛЕРІ

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Бұл **зерттеудің мақсаты** статиндердің басқа дәрілік заттармен жағымсыз комбинацияларының жиілігі мен тағайындау құрылымын талдау болды. P450 цитохромы CYP3A изоферменттерінің және P-гликопротеин мен OATP 1в тасымалдаушы ақуыздардың тасымалдау жүйелерінің метаболизм деңгейінде және ықтимал қауіпті және маңызды дәрілік комбинацияларды анықтау үшін олардың өзара әрекеттесу ерекшеліктерін ескердік

Материалдар мен әдістер. Зерттеуге зертханалық әдістермен расталған гиперхолестеринемиямен бірге жүретін жүректің ишемиялық ауруы диагнозы қойылған адамдардың медициналық жазбалары енгізілген. Барлығы біз 2790 амбулаториялық пациентті талдадық. Семей қаласының (Қазақстан) 14 медициналық мекемесінде дәрілік өзара әрекеттесулердің таралуы мен құрылымы зерттелді (фармакоэпидемиологиялық, көлденең зерттеу).

Нәтижелер. Статинмен емделген науқастардың көпшілігінде (62%) жағымсыз және қауіпті комбинациялардың болуы анықталды. Статиндерді аса сақтықпен және биохимиялық және т.б.көрсеткіштерді бақылауға алу ұсынылған кезде ,қауіпсіздікті бақылау жүргізуде 72.5% жағдайда табылмады.

Қорытынды. Біз статиндердің CYP3A, OATP1B1 және P-гликопротеин деңгейінде бәсекелестік метаболизмі бар басқа препараттармен жағымсыз комбинацияларын абсолютті түрде және дамыған елдерде жүргізілген зерттеу деректерімен салыстыра отырып тағайындаудың өте жоғары жиілігін анықтадық.

Негізгі сөздер. *Фармакоэпидемиология, жағымсыз өзара әрекеттесу, CYP3A изоферменті, P-гликопротеин, OATP1B1*

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Introduction

Anticholesterol drugs (lipid lowering drugs) from the group of statins are one of the most common drug classes for the treatment of hypercholesterolemia. The need for statins is indicated in various recommendations, including the 2016 ESC/EAS recommendations [5]. An important feature of the use of statins is the need for long-term treatment, in most cases for patients at the elderly and senile age, with a high prevalence of co-existing diseases (comorbidities). Comorbid conditions in cardiology suggest the inevitability of polypragmasia, which leads to the risk of drug interactions [15].

Nowadays in Kazakhstan, statins are part of the guaranteed volume of free medical care. At the same time, in cardiological practice there are very high percentage of the appointment of undesirable combinations of drugs [24].

For that reason giving attention to pharmacokinetic and pharmacodynamic features of statins and drug interaction with medications of certain groups is an important aspect of their safe use [34].

The presence of certain drugs in the blood plasma causes a change in the pharmacological response to statin therapy, and also affects the safety profile of these medicine remedies. There are following key points of statins' pharmacokinetics: enzymes, carrying out reactions I (CYP3A4/5, CYP2C9, CYP2C8, CYP2C19, CYP2D6) and II phase of metabolism of medicine remedies (isoenzymes of UDP (uridine diphosphate)- glucuronosyltransferase 1A1 and 1A3); P-glycoprotein (P-gp); organic anion transporters, carrying out the excretion of drugs into the bile [1].

The development of statin-induced adverse reactions is mostly associated with the peculiarities of organic anion vectors encoded by the SLCO1B1 gene [36, 29].

Drugs administered simultaneously with statins may be inducers or inhibitors (substrates) of isoenzymes CYP3A4/A5 of liver cytochrome P450, which should be considered in daily clinical practice in the management of this category of patients [37, 22].

It is known that strong inhibitors of CYP3A lead to a 5-fold increase (decrease in clearance by >80 %), moderate – to 2-5-fold (decrease in clearance by 50-80%), weak – to 1.25-2-fold (decrease in clearance by 20-50%), respectively, increase the area under the pharmacokinetic curve "concentration – time" (AUC), characterizing the total concentration of drugs in blood plasma throughout the duration of action. Strong inductors, on the contrary, cause a decrease in AUC by 80%, moderate – by 50-80%, weak – by 20-50%, respectively [34].

The simultaneous use of moderate and/or weak CYP3A inducers/inhibitors does not always require dose adjustment.

The inclusion of pharmacogenetic testing for the safety of statins in clinical guidelines and in the future in care standards is relevant.

Aim. The aim of this research was to study the frequency and structure of appointment of undesirable combinations of statins with other drugs

Materials and methods.

The study design was cross-sectional study. The study was carried out on the material of archival documents (outpatient cards) of 14 medical institutions, selected randomly from the list.

The study was carried out on the material of archival documents (outpatient cards) 14 medical institutions selected randomly from the list. The study included medical records of people with diagnosis: Coronary heart disease with concomitant hypercholesterolemia, confirmed by laboratory methods. In total, we analyzed 2790 outpatients. The depth of the retrospective analysis was not less than 1 year; the maximum period was determined by the period of outpatient observation of certain patients

The patients were aged from 34 to 85, the average age was 61.2±3.5. In the analysis of the gender composition there were 1665 men (59.7%) and 1125 women (40.3%).

At the same time, according to the recommendations of ESH/ESC 2016, the indications for the prescription of lipid-lowering therapy were differentiated depending on the degree of cardiovascular risk. In all cases, the need to reduce the content of low-density lipoprotein cholesterol less than 2.6 mm/l was postulated, in the presence of a very high risk – less than 1.8 mm/l [41]. The presence of evidence was the main criterion for inclusion in the study.

The frequency of simultaneous administration of statins with other drugs from the cardiovascular group was analyzed.

We have taken into account their interactions at the level of metabolism CYP3A isoenzymes of cytochrome P450 and transportation of proteins-transporters P-glycoprotein and OATP1B to identify significant and potentially dangerous drug combinations. Potentially dangerous interactions include those combinations of drugs, which appointment has a high risk of adverse reactions (AR), including serious. Significant drug interactions can also lead to adverse reactions and require careful administration and mandatory monitoring [1]. The scientific evidence of drug interactions has been documented in various large controlled clinical trials and analyzed by Drug Interaction Checker www.drugs.com), which is supported by the FDA (Food and Drug Administration, USA).

The terms of retrospective analysis of the data on the prescriptions of drugs in the examined group were within 12-54 months from the date of inclusion into the study (the average period of 23.2±2.8 months).

Statistical analysis

Methods of descriptive statistics (processed by EXCEL programme) were used. Numerical analysis of statistical significance was not carried out due to absence of necessity.

Ethical approval

The research work was approved by the bioethical committee of the Semey State Medical University (MoM No. 4 dated 28.02.2017). Informed consent was not required because the review of retrospective Drug-Drug Interactions alert logs and prescriptions did not involve individually identifiable data of any sort.

Results of a research

The structure of lipid-lowering therapy in the study is presented in the Table 1.

Table 1.

The Number of patients who were prescribed hypolipidemic therapy according to archival analysis.

	atorvastatin	simvastatin	rosuvastatin	fenofibrate	total
Absolute number	2503	49	237	39	2828
%	88,6	1,7	8,2	1,5	100

It must be kept in mind that we have analyzed all the drugs prescribed to patients during the treatment period, as a result, the total number of prescribed drugs exceeded the number of the studied patients.

Absolute dominance of atorvastatin was observed in the structure of prescriptions. The frequency of its use was 88.6%. In some cases, there was a transition to atorvastatin after the use of other antihypercholesterolemic drugs.

On the second place on frequency of prescriptions was rosuvastatin (8.2 %), followed by simvastatin (1.7 percent). The only drug registered in the period of analysis from the group of fibrates was phenofibrate, which was prescribed quite rarely (1.5%).

Transitions from the earlier prescribed atorvastatin to other medicines from the group of statins was noticed, but the frequency was minimal (0.5 percent).

All the patients were prescribed multicomponent therapy of cardiovascular disease, including antihypertensive agents, antiplatelets, anticoagulants, nitrates, cardiac glycosides.

The number of drugs prescribed at the same time ranged from 3 to 7.

Tables 2-4 present the results of the hazard identification and unwanted combinations of statin therapy with drugs from the cardiovascular group due to their interaction at the level of basic ways of the metabolism of statins (according to the Medscape Drug Interaction Checker: https://reference.medscape.com/drug-interactionchecker).

Table 2.

The frequency of dangerous and undesirable combinations of rosuvastatin therapy.

Rosuvastatin, n=237					
	абс.	%	Interaction level	Probable complications	Researches
Warfarin	31*	13,1	Nonspecific mechanism of interaction	Increased risk of bleeding	Simonson S.G. et al., 2005 [31].
Digoxin	3*	1,3	OATP1B1	Increased toxicity of rosuvastatin, the risk of myopathy Must be carefully monitored!	Rätz Bravo A.E. et al., 2005 [27].
Total	34	14,3	Notes: * - significant interactions		

Table 3.

The frequency of dangerous and undesirable combinations of simvastatin therapy.

Simvastatin, n=49					
	абс.	%	Interaction level	Probable complications	Researches
Amiodarone	3#	6,1	CYP3A4	myopathy risk and rhabdomyolysis risk are increased	Prom R. et al., 2013 [25] Roten L. et al., 2004 [28]
Amlodipine	19#	38,8	CYP3A4	myopathy risk and rhabdomyolysis risk are increased	Son H. et al., 2014 [32].
Warfarin	8*	16,3	CYP3A4	rhabdomyolysis risk and bleeding are increased	Shaik A.N. et al., 2016 [30]
Verapamil	4#	8,1	CYP3A4	toxicity of simvastatin, myopathy risk is increased	Methaneethorn J. et al., 2014 [21].
Digoxin	1*	2,0	P-glycoprotein OATP1B1	1. the concentration and toxicity of digoxin are increased 2. Digoxin increases the toxicity of simvastatin, myopathy risk	Kasichayanula S. et al., 2012 [13].
Diltiazem	3#	6,1	CYP3A4	myopathy risk and rhabdomyolysis risk are increased	Kanathur N. et al., 2001 [12]
Nifedipine	1#	2,0	CYP3A4	toxicity of simvastatin, myopathy risk are increased	Martínez-Jiménez C. et al., 2018 [20].
Total	39	79,5	Notation: * - significant interactions; # - potentially dangerous interactions		

Table 4.

The frequency of dangerous and undesirable combinations of atorvastatin therapy.

Atorvastatin, n=2503					
	Abs.	%	Interaction level	Probable complications	Researches
Amiodarone	102*	4,1	P-glycoprotein	the level or effect of atorvastatin is increased	Franz C.C. et al., 2011 [8,].
Amlodipine**	1157*	46,2	CYP3A4	Increased myopathy risk	Khan S. et al., 2018 [14].
Verapamil	231*	9,2	CYP3A4 and P-glycoprotein	the level or effect of atorvastatin is increased	Srinivas N.R., 2008 [33].
Digoxin	23*	0,9	P-glycoprotein	the concentration and toxicity of digoxin are increased	Lennernäs H., 2003; Boyd R.A. et al., 2000 [16, 4].
Diltiazem	144*	5,8	CYP3A4	myopathy risk and rhabdomyolysis risk are increased	Lewin J.J. et al., 2002 [17].
Total	1657	66,2	*Notation: * - significant interactions; # - potentially dangerous interactions** - there are publications that allow to include the combination in this category, but it is not included in the database DrugInteractionCheckerMedscape*		

The most frequent combination of drugs included in the list of significant was the simultaneous administration of atorvastatin and amlodipine (46.2%). Amlodipine is one of the most common antihypertensive drugs and refers to drugs, which provision is carried out within the guaranteed volume of free medical care. As an extremely important circumstance, it should be emphasized that this combination has been classified as potentially dangerous on the basis of recent results [14]. The frequency of simultaneous administration of simvastatin and amlodipine from the list of potentially dangerous (38.8%) was similar (38.8%).

Among antihypertensive drugs the second place in the frequency of undesirable combinations with statins was taken by verapamil, the third place takes diltiazem.

According to the analyzed medical records, we were unable to identify the specific adverse effects. Moreover, the corresponding analysis in a retrospective study is always very difficult, since their targeted diagnosis is not carried out, and potential adverse effects can be interpreted as concomitant diseases or simply are not detected.

In cases where it is recommended to prescribe combinations of drugs for clinical indications with caution and under the control of biochemical and other indicators, we found no evidence of this control in 72.5% of cases

Discussion

The problem of interaction of drugs at different levels of pharmacokinetics and pharmacodynamics, nowadays it is becoming more and more relevant. Pharmacotherapy of the most common chronic diseases is lifelong or is carried out by long-term and repeated courses, which causes a high probability of simultaneous administration of other drugs interacting with long-term drugs [10]. Polypragmasy is significant for the modern level of the development of domestic medicine [35] which makes the presence of undesirable combinations of drugs almost inevitable.

Statins are among the most frequently and long-term drugs used in people with cardiovascular diseases and the risk of their development [11]. Their metabolism is carried out by several enzymes, which simultaneously provide chemical modifications of other drugs. The competitive metabolism of statins with preparations of other pharmacological groups is proved in a number of research [26]. In practice, this may mean a sharp increase in the concentration of statins in the blood with their simultaneous administration with other drugs, which is not safe [3, 6]. Complications of statin therapy are most often muscle tissue lesions and even rhabdomyolysis [7, 9].

On the other hand, competitive metabolism may cause the effects of statin therapy on the effects of other drugs. The most known increase in the concentration of cardiac glycosides in the blood with their simultaneous appointment with statins, which can serve as a risk factor for their adverse effects [16].

Our study revealed the presence of significant and potentially dangerous interactions of statins with other drugs from the cardiovascular group in the majority of patients (62%). The predominant role in their structure was played by combinations of the most frequently prescribed drugs such as amlodipine and atorvastatin. Their concomitant prescription can lead to the development of myopathies and rhabdomyolysis [14]. The risk has been identified relatively recently, which may be one of the reasons for the high frequency of the combination. At the same time, the final conclusion about the degree of risk of this combination at the level of the FDA has not been accepted yet, which does not allow it to be the most dangerous.

However, other undesirable combinations of statins with antihypertensive drugs from the group of calcium antagonists remain quite frequent. It must be noted that the combination of not all statins with calcium antagonists is dangerous, in particular it concerns to rosuvastatin, which metabolism differs from the metabolism of drugs of this group and is carried out to a greater extent CYP2C9 [19]. In the same way, the combination of statins with other groups of antihypertensive drugs, for example, beta-blockers and ACE inhibitors are absolutely safe, which is similarly explained by different metabolic pathways of these drugs [38, 39].

Therefore, in cases where the risk of adverse effects of statins is increased, their combination with other drugs must be reconsidered and, in cases of dangerous combinations, replaced with an alternative drug.

It is worth emphasizing that hypolipidemic and antihypertensive drugs are prescribed by the same specialist, if dangerous and undesirable combinations proceed, it indicates a lack of his knowledge of the interaction of the drugs. The lack of information in the existing guidelines for doctors and health system management requires close attention to this problem.

The studies conducted in different health care systems and at different times represent a wide range of frequencies of dangerous and undesirable combinations of statins. Very unfavorable indicators were found in the Russian Federation, where the frequency of combinations of this class reached 66.0%, including more than 20% of dangerous [34]. A similar situation was found in China, where the frequency of simultaneous administration of drugs competing at the level of CYP3A, including statins, reached 20% [41, 18].

On the other hand, peculiarities of training and organization of work of doctors in the conditions of developed health systems have significantly reduced the frequency of prescribing unreasonable combinations of drugs, including those from the group of statins. A recent study conducted in France provides data on no more than one percent frequency of dangerous combinations of pharmacotherapy with statins and other drugs [23]. Similar results were found in the frequency of undesirable combinations in other European countries and the United States [2, 40].

Conclusion.

We have determined a fairly high frequency of the prescription of undesirable combinations of statins with other drugs from the cardiovascular group, having a competitive metabolism at the level of CYP3A, OATP1B1 and P-glycoprotein in absolute terms and compared with the data of studies conducted in developed countries.

The obtained data indicates the need for measures to correct the approaches of doctors to prescribe lipid-lowering therapy, providing seminars on the rational and safe use of statins, as well as improving the system of training and education of medical personnel in the field of clinical pharmacology

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