

THE USE OF CARDIOVASCULAR DRUGS IN NIŠ REGION OF SERBIA

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Summary. Cardiovascular disease mortality is high in Serbia. Analysis of cardiovascular drugs utilization in the population is the basis for the assessment of cardiovascular pharmacotherapy appropriateness. The aim of this study was to analyze the out-of-hospital cardiovascular drug utilization in the Niš region of Serbia & Montenegro. Using the ATC/DDD methodology, we analyzed the utilization of cardiovascular drugs dispensed on prescription in the Niš region in years 2003 and 2004. The study was retrospective, based on data obtained from Central City Pharmacy Niš, and results were expressed in DDDs/1000 inhabitants/day. The most frequently prescribed drug in 2003 and 2004 was enalapril (31.16 and 41.71 DDDs/1000 inhabitants/day, respectively). The consumption of other ACE inhibitors was much less (7.36 and 10.83 DDDs/1000 inhabitants/day, respectively). The next most commonly used drugs were a selective beta blocker and a ACE inhibitor (atenolol-8.49 DDDs/1000 inhabitants/day; cilazapril 6.48 DDDs/1000 inhabitants/day in 2003). The use of amlodipine significantly increased in 2004 (from 6.41 in 2003 to 10.21 DDDs/1000 inhabitants/day in 2004), while that of nifedipine decreased (from 4.45 in 2003 to 3.82 DDDs/1000 inhabitants/day in 2004). Marginal use of diuretics was noted (4.4 DDDs/1000 inhabitants/day in 2003, and 5.5 DDDs/1000 inhabitants/day in 2004). This analysis pointed to significant therapeutical irrationalities in the Niš region, which could be overcome by targeted education of the prescription-givers.

Key words: Utilization of drugs, cardiovascular system, defined daily dose

Introduction

Within Europe, large differences exist in mortality due to cardiovascular diseases. These diseases show the highest rates in Eastern Europe, with the Russian Federation far ahead (1). Serbia & Montenegro is not an exception, with age-standardized mortality due to coronary heart disease between 110 and 172 cases per 100.000 inhabitants, and with similar mortality due to stroke (between 140 and 215 cases per 100.000 inhabitants) (1).

Being the poorest country in Europe, with extremely limited annual health budget, not exceeding 90 \$ per capita (2), Serbia & Montenegro strives to provide necessary cardiovascular drugs for a growing population of the patients. A trend towards predominant treatment of acute medical problems, with neglect of secondary prevention, was noted in the previous study on inpatients from a tertiary care university hospital in Kragujevac, Serbia & Montenegro (3,4). A rather narrow choice of cardiovascular drugs was also noted, but data about the outpatients was lacking.

The aim of our study was to analyze the out-of-hospital cardiovascular drugs utilization at the Niš region of Serbia & Montenegro (South-East Serbia) during the years 2003 and 2004, and to identify the practice of drug overuse, under-use or misuse.

Materials and Methods

The data were obtained from City Pharmacy Department which supplies approximately 350.000 inhabitants, through the network of 25 state-owned pharmacies. All data for period 2003-2004 were centrally collected, and analyzed. The City Pharmacy Department automatic report on drugs prescribed by physicians for certain diagnoses was used as data source. The analysis included also the cost of dispensed drugs from the City Pharmacy Department.

The data were obtained by retrospective study and expressed as a number of defined daily doses per 1000 inhabitants/day (DDDs/1000 inhabitants/day).

All pharmaceuticals were classified by groups of Anatomic Therapeutic Chemical classification.

Results

The data obtained by retrospective study are expressed as a number of defined daily doses per 1000 inhabitants/day (DDDs/1000 inhabitants/day) and number of drug prescriptions for 2003-2004 period. The total of 6.750.342 prescriptions was analyzed, with 3.574.709 (53%) being the prescriptions of cardiovascular drugs.

The most utilized drugs were ACE inhibitors (39.52 and 52.53 DDDs/1000 inh/day, respectively), especially

enalapril (35%). The next most used drugs were beta blockers (15.06 and 17.13 DDDs/1000 inh/day, respectively) and calcium channel blockers (14.03 and 17.27 DDDs/1000 inh/day, respectively) (Table 1). The use of amlodipine significantly increased in 2004 (from 6.41 DDDs/1000 inh/day in 2003 to 10.21 DDDs/1000 inh/day in 2004). Besides, utilization of nifedipine was low (4.45 in 2003 and 3.82 DDDs/1000 inh/day in 2004).

Table 1. shows utilization of cardiovascular drugs by pharmacological groups (in DDDs/ 1000 inhabitants/day) and cost, on a yearly basis. There was a positive correlation between the number of prescriptions, DDDs/1000 inhabitants/day and the cost for all drugs, except amlodipine and cilazapril.

In 2004, the most widely prescribed class of drugs was that for cardiovascular system (1.2 million prescriptions).

Out-of-hospital use of cardiovascular drugs in period of 2003-2004 in Niš region is shown in Table 2. The proportion of drugs prescribed for the cardiovascular system disorders increased from 23%, in 2003 to 25.3% in 2004.

Among the top 10 prescribed drugs by DDDs, 7 were cardiovascular drugs (enalapril, atenolole, cilazapril, amlodipine, metoprolol, isosorbide mononitrate and digoxin) which made 74% of the top 10 drugs (Table 3).

Marginal use of diuretics was noted (4.4 DDDs/1000 inhabitants/day in 2003 and 5.5 DDDs/1000 inhabitants/day in 2004).

Also, inappropriately low utilization of hypolipemics was registered, especially statins, which could be explained by the cost of the drug.

Table 1. DDDs and cost according to use of group of cardiovascular drugs

Group of drugs	2003		2004	
	DDD/1000 inhabitants/day	Cost (€)	DDD/1000 inhabitants/day	Cost (€)
ACE inhibitors	39.52	748384.7	52.53	906354.5
Beta blockers	15.06	217412.9	17.13	271989.8
Ca antagonists	14.03	319539.8	17.27	463160.7
Nitrates	7.77	84578.5	8.96	90995.3
Digoxin	5.45	24781.3	5.74	24465.6
diuretics	4.42	84578.0	5.50	60.31
Antiarrhythmic drugs	2.81	74342.5	2.82	79311.3
Hypolipemics	0.06	60166.1	0.30	117567.3
Other drugs	1.68	3333.6	2.82	6957.1
Total	87.8	1583445.1	113.42	2021111.9

Table 2. Utilization of some cardiovascular drugs in Niš region, 2003/2004

2003			2004		
Drug	DDD/1000inh/day	Number of prescriptions	Drug	DDD/1000inh/day	Number of patients
Enalapril	32.16	266290	Enalapril	41.71	373313
Atenolol	8.49	125451	Amlodipine	10.21	91893
Cilazapril	6.48	43157	Atenolol	8.64	127680
Amlodipine	6.41	52040	Cilazapril	8.47	48448
Metoprolol	5.85	75247	Metoprolol	7.87	108568
Nifedipine	4.45	64757	Diuretics	5.50	93301
Diuretics	4.40	52020	Nifedipine	3.82	57401
Other	4.05	71230	Other	3.83	94442
Total	72.29	775661	Total	90.05	993046

Table 3. Top 10 prescription drugs in Niš region, during 2003-2004.

2003			2004		
Drug	DDD/1000 inh/day	Number of prescriptions	Drug	DDD/1000 inh/day	Number of prescriptions
Enalapril	32.16	266290	Enalapril	41.70	337313
Diclofenac	17.27	270935	Diclofenac	18.00	258009
Diazepam	11.76	195062	Diazepam	11.60	192246
Atenolol	8.49	125451	Amlodipine	10.21	91893
Cilazapril	6.48	43157	Atenolol	8.64	127680
Amlodipine	6.41	52040	Cilazapril	8.47	48448
Metoprolol	5.85	75247	Metoprolol	7.87	108568
Ibuprofen	5.66	174890	Isosorb.m.n	6.54	78918
Isosorb m.n*	5.61	67682	Digoxin	5.75	79244
Digoxin	5.46	75267	Ibuprofen	5.63	173597

* Isosorbide mononitrate

Discussion

In modern clinical practice, analyzing drug utilization is an important tool for achieving rational drug therapy in any clinical setting (5,6,7). It is necessary for identification of a problem, and then for following effectiveness of corrective interventions, undertaken by management of health facility.

Total cardiovascular drugs utilization in Niš region increased in 2004 compared with 2003 (113.42 vs. 87.8 DDDs/1000 inhabitants/day, respectively; $p < 0.05$). The predominance of cardiovascular drugs (53%) in total drug utilization volume is a consequence of high cardiovascular morbidity and mortality. Out of the total volume of cardiovascular drugs, the outpatients used ACE inhibitors the most, especially enalapril. This could be explained by widening of the indications for their use in hypertension, diabetic nephropathy, heart failure, etc. In the last decade ACE inhibitors became almost the most important drugs in cardiology, taking into consideration their cardioprotective and renoprotective effects (7). Many clinical studies confirmed reduction in morbidity and mortality in patients with acute myocardial infarction and congestive heart failure with use of ACE inhibitors (5,7,8). Some clinical studies on the use of antihypertensives, conducted in Estonia (9), also found ACE inhibitors to be the most prescribed class of drugs (35% patients with hypertension used ACE inhibitors, 32% Ca antagonists and 29% beta blockers).

Beta adrenergic receptor blockers are a class of cardiovascular drugs which was underused in our setting (15.06 in 2003 and 17.13 DDDs/1000 inhabitants/day in 2004). Cardioprotective and antihypertensive effects of this class of drugs justify much larger use in our patients. Beta blockers reduce mortality rate when used for primary and secondary prevention of myocardial infarction and chronic heart insufficiency (9,10). Cardioselective beta blockers, atenolol and metoprolol were the most prescribed drugs in the population in our study, which was a rational approach to the therapy (Tables 2 and 3). The use of carvedilol was found to be low, probably because it was not funded by the state health insurance.

The use of calcium channel blockers increased in 2004, on account of amlodipine. This drug reached second place in the list of „top ten“ drugs used in 2004. The use of amlodipine is increasing worldwide too, due to its favourable pharmacokinetics (one time a day dosing) and efficiency in control of hypertension and prophylaxis of angina pectoris (8,9).

Our data showed very low use of diuretics (5.5 DDDs/1000 inhabitants/day), especially thiazides (2.3 DDDs/1000 inhabitants/day), which could be explained by inadequate prescribing policy of the physicians. Thiazide diuretics are fundamentals of antihypertensive therapy. Diuretics are recommended as

initial monotherapy in older patients with stage I or II of hypertension, or in combination with other antihypertensives in patients with severe hypertension. Similar results were reported by the authors from Estonia. Irs et al. reported that only 2% of patients with hypertension used diuretic as initial therapy (11). Pharmacoepidemiologic analysis of out-of-hospital use of cardiovascular drugs in Banja Luka region (Bosnia and Hercegovina) showed similar results (12). ALLHAT study (The Anti-hypertensive and Lipid Lowering treatment to prevent Heart Attack Trial) in over 40.000 patients older than 55, in the period of 4-8 years, showed better antihypertensive effect and higher reduction of cardiovascular events in patients taking thiazides, compared to calcium antagonists and ACE inhibitors (8). Considering that this and other trials confirmed thiazides as a drugs of the first choice for the therapy of hypertension, their underuse observed in our study calls for correction of the prescribing policy (13).

In Serbia & Montenegro pharmacoepidemiologic surveys are scarce. However, our study demonstrated increase in cardiovascular drugs use (7 out of 10 the most prescribed drugs are for cardiovascular diseases). Enalapril was the most prescribed drug (60 DDDs/1000 inhabitants/day). Australia, Norway and Sweden were selected for comparison, being the countries with high national standards and the most rational use of drugs. Statins are dominant cardiovascular drugs, which reflects adequate pharmacotherapy attitudes, health policy and economic power of these countries. Statin use is followed by calcium antagonists (diltiazem in Australia, amlodipine in Norway), ACE inhibitors (ramipril, and enalapril, respectively), and diuretics – especially furosemide (9).

However, our study showed underutilization of antihypertensives (113.42 DDDs/1000 inhabitants/day), when compared with developed western countries in Europe (Sweden -185 DDD/1000 inhabitants/day). It could be concluded that in Serbia & Montenegro fewer patients were treated. Our data also confirmed underuse of antihypertensives with the best cost/effectiveness ratio (diuretics and beta blockers).

Conclusion

Analysis of cardiovascular drugs use offers insight into the actual prescribing practice. Our study demonstrated certain irrationalities in the therapy of arterial hypertension. Underuse of diuretics and inadequate use of beta blockers remains to be changed by undertaking educative interventions to correct the prescribing practice. This study will also be the basis for further evaluation of cardiovascular drugs utilization in Serbia & Montenegro.

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UPOTREBA KARDIOVASKULARNIH LEKOVA U NIŠKOM REGIONU

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Kratak sadržaj: Analiza upotrebe kardiovaskularnih lekova u populaciji čini osnovu za procenu racionalnosti kardiovaskularne farmakoterapije. Radi upoređivanja sa drugim populacijama, upotreba lekova se izražava kao broj definisanih dnevnih doza (DDD) na 1000 bolesničkih dana, ako se radi o populaciji hospitalizovanih bolesnika ili na 1000 stanovnika na dan, ako se radi o opštoj populaciji. Cilj ove studije bio je da analizira vanbolničku upotrebu kardiovaskularnih lekova u regionu Niša. Koristeći ATC/DDD metodologiju, analizirali smo upotrebu kardiovaskularnih lekova na osnovu broja propisanih recepata u niškom regionu, u 2003 i 2004 godin. Retrospektivna analiza je bazirana na podacima dobijenim iz Centralne gradske apotekarske ustanove. Rezultati su prikazani brojem DDD/1000 stanovnika/dan. Najčešće propisivani lek u 2003. i 2004. bio je Enalapril (31,16 : 41,71 DDD/1000 stanovnika/dan). Najviše korišćeni beta blokator je bio Atenolol (8,49 DDD/1000 stanovnika/dan). ACE inhibitor Cilazapril se nalazi na trećem mestu po broju propisanih recepata u 2003g (6,48 DDD/1000 stanovnika/dan). Upotreba Amlodipina značajno je povećana u 2004. (6,41 : 10,21 DDD/1000 stanovnika /dan), a Nefedipina smanjena (4,4 : 3,82 DDD/1000 stanovnika/dan). Zabeleženo je marginalno korišćenje diuretika (4,4 : 5,5 DDD/1000 stanovnika/dan), statina i drugih ACE inhibitora, osim Enalapрила i Cilazaprila. Ova analiza je pokazala značajne terapijske iracionalnosti u farmakoterapiji kardiovaskularnih oboljenja, koje se mogu prevazići odgovarajućom edukacijom.

Ključne reči: Upotreba lekova, kardiovaskularna oboljenja, definisana dnevna doza