Use of ACE-Inhibitors in Serbia in 2009 and 2010

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SUMMARY

Introduction Cardiovascular diseases (CVD) are the most frequent cause of morbidity and mortality in many countries as well as in our country. That explains why medications for the treatment of CVD are the most used group of drugs. The aim of this study was to analyze the consumption of ACE-inhibitors in Serbia and Norway during 2009 and 2010.

Material and methods The data about the use of ACE-inhibitors in Serbia and Norway in 2009 and 2010 were taken from the Agency for Drugs and Medical Devices of the Republic of Serbia and from the site of Norwegian Institute of Public Health.

Results Use of drugs of first choice in the treatment of hypertension in Serbia was very uneven, where the consumption of ACE-inhibitors was dominant. Opposed to this condition, the consumption of the first choice antihypertensive drugs was very balanced in Norway. During both analyzed years large part of consumption of ACE-inhibitors was taken by more expensive drugs in Serbia, as fosinopril, cilazapril and quinapril. In Norway in the observed period, dominated the consumption of cheaper drugs such as enalapril and ramipril. The situation is similar when it comes to fixed combination of diuretics and ACE-inhibitors. In Norway dominated the fixed combination of diuretics and cheaper ACE-inhibitors like enalapril and lisinopril. However, in Serbia, we have large consumption fixed combinations of diuretics with expensive ACE-inhibitors, such as cilazapril and fosinopril.

Conclusions In both countries, ACE-inhibitors and their fixed combination with diuretics are most frequently used drugs within the group of drugs which is used for treatment of CVD in Serbia in 2009 and 2010. The amount and structure of the utilized ACE-inhibitors in Serbia is different from the amount and structure of the utilized ACE inhibitors in Norway. From pharmacoeconomic point of view, high consumption of expensive ACE-inhibitors (plain and fixed combination with diuretics) in 2009 and 2010 in Serbia resulted in the higher spending of funds.

Keywords: pharmacoepidemiology, ACE-inhibitors, cardiovascular system, hypertension

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INTRODUCTION

Cardiovascular disease (CVD) and kidney disease are the most common cause of morbidity and mortality in industrialized countries [1]. In 2008, the rate of mortality from CVD in Serbia stood at 55.8% which ranks Serbia among the countries with the highest cardiovascular mortality [2]. It is therefore understandable why drugs which are in use for the treatment of cardiovascular disease (group C according to ATC classification) are the most frequently used group of drugs. Besides, consumption of drugs from the C group has steadily increased in Serbia. In 2004, the total consumption of drugs amounted to 30.54%, while in 2008 it amounted to 38.89% [2, 3]. In relation to all drugs of C group, in the world, and in our country angiotensin converting enzyme inhibitors (ACE-inhibitors), drugs used in treatment of hypertension and cardiac insufficiency, occupy an important place [4, 5, 6].

Hypertension is a major risk factor for the development of other cardiovascular diseases including coronary artery disease, stroke, heart failure and end stage of renal disease [4, 7]. According to the World Health Organization (WHO) and International Society of Hypertension (ISH) in 2003 was estimated that hypertension occurs in 4-5% of cases compared to the more global disease, and it is widespread in both developing and developed countries. Globally, complications associated with hypertension are the third in a row in terms of mortality. WHO estimates that the number of people diagnosed with hypertension will be increased by 60% over the next few years [5]. Modern approach in treatment of hypertension is based on application of five groups of drugs: diuretics, β-blockers, ACE-inhibitors, calcium channel blockers and angiotensin II receptor antagonists (ARBs). Also, in the treatment of hypertension is recommend use of fixed combinations of ACE-inhibitors and angiotensin receptor blockers with diuretics and calcium channel blockers [4, 5, 8].

The mechanism of action of ACE-inhibitors takes place through the renin-angiotensin-aldosterone system (RAAS). Hemodynamic effects of ACE-inhibitors are caused by reduction levels of angiotensin II and aldosterone, and by increasing levels of bradykinin. Bradykinin have vasodilator and hypotensive actions. These drugs reduce tension at the level of the arteries and veins and relieve the heart by reducing afterload and preload. As a result there is a decrease in systolic and diastolic blood pressure [9]. Adverse effects of ACE-inhibitors include: hypotension, dry cough, hyperkalemia, renal failure, fetal anomalies [9]. Indications for the benefit of ACE-inhibitors include: hypertension, congestive heart failure, myocardial infarction, ischemic heart disease, stroke [4].

The benefits of ACE-inhibitors over the other antihypertensives are reflected in their increasing protective effect on the renal blood vessels in patients with diabetes mellitus. They have multiple effects on kidneys, including reducing of renovascular resistance, and also slowdown deterioration of renal function that occurs in diabetic nephropathy and thus prevents the progression of microalbuminuria in proteinuria [10]. ACE-inhibitors can be used in combination with a diuretic and with calcium channel blockers. These drugs can be applied in fixed combination with diuretics because, thiazide diuretics cause decrease of potassium and ACE-inhibitors potassium-sparing. In this way, it avoids the appearance of hypo or hyperkalaemia in the application of each of these drugs individually [4]. On the other hand, in primary hypertension, ACE-inhibitors do not show a significant advantage because they both reduce blood pressure, like other antihypertensive drugs of first choice. The advantage of ACE-inhibitors could be seen in terms of their kinetics, because most of these drugs are applied once a day [8]. Seen from pharmacoeconomic aspect, the structure of ACE-inhibitors which are consumed in Serbia in recent years is not rational because the drugs of this group were much more in use than other drugs of first choice in the treatment of arterial hypertension. We can also notice that the newer and more expensive preparations have priority, regardless they do not show significant efficacy compared to older and cheaper ACE-inhibitors [3, 11, 12, 13].

THE AIM

The aim of this study was to analyze the consumption of ACE-inhibitors in Serbia during 2009 and 2010 from pharmacotherapeutic and pharmacoeconomic point of view, as well as comparing that with consumption in Norway, which has developed pharmacotherapeutic
MATERIAL AND METHODS

The data about the use of ACE-inhibitors in Serbia in 2009 and 2010 were taken from the Agency for Drugs ans Medical Devices of the Republic of Serbia [14, 15]. The data of drug consumption in Norway were taken from the official site of the Norwegian Institute of Public Health [16]. Analysis of the consumption of drugs was done from the point of social perspective and there were no influence of any factors or any interest group. The amount of used drugs are expressed in the number of defined daily doses (DDD) per 1000 inhabitants per day (DDD/1000 inh/day).

Internationally recognized and widely accepted methodology in the study of drug use is based on the concept of anatomical-therapeutical-chemical classification of drugs (ATC) and defined daily doses. According to the ATC classification the drugs that we use in treatment of cardiovascular diseases belong to the C group, whereas drugs that act on the renin angiotensin system are belonging to a group of C09. Further analyzed in C09A group, we have monocomponent products, and the combination of ACE-inhibitors with diuretics which belong to the C09B group. In order to facilitate comparison of the intensity of use of certain drugs in time and in different geographical areas scientists created a separate statistical unit of measurement of use of drugs, labeled as defined daily doses (DDD). This unit is independent of price, size, packaging, protected names of individual manufacturers and even from the pharmaceutical dosage form. The concept of DDD offered as a statistical unit of use the agreed amount of drug that is commonly used for the most common indication. DDD is defined, whenever its possible, in weight units (or units of activity, for example, insulin). When it is impractical or even impossible to express the weight of the DDD, like in case with combined preparations, for the monitoring unit is taken dosage form (tablets, capsules, ampoules) and then it is referred to as effective dose (ED) [17].

RESULTS

Consumption of drugs for the treatment of cardiovascular diseases in Serbia in 2009 and 2010 year was sizeable. Drugs of the C group in 2009 year accounted for 35.21% of total drugs consumed in Serbia, and 2010, share of these drugs in the total consumption was even higher and amounted to 39.82%. In Norway, consumption of drugs for the treatment of cardiovascular disease observed in this two years was lower than in Serbia, amounting to about 31%, without trend of increasing consumption.

Comparative review of drug of first choice in the treatment of hypertension in Serbia and Norway in 2009 and 2010 are presented in Graphs 1 and 2.

Graph 1. Comparative review of drug of first choice in the treatment of hypertension in Serbia and Norway in 2009

- C03 - diuretics;
- C07 - beta blocking agents;
- C08 - calcium channel blockers;
- C09A+B - ACE inhibitors, plain and ACE inhibitors, combinations;
- C09C+D - angiotensin II receptor antagonists, plain and angiotensin II receptor antagonists, combinations

In the detailed analysis of the consumption of drugs from group C in the considered period in Serbia, it was found that the highest consumption in 2009 and 2010 was achieved in the group of drugs that act on the renin angiotensin aldosterone system (C09 group) and it was nearly half of all drugs that are used in the treatment of cardiovascular...
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The situation in Norway is different and consumption of drugs group C09 during these two years was about 32% which is less than one third of the total consumed drugs in the group C.

Comparative review of drug which is acting on the renin angiotensin aldosterone system (group C09) in Serbia and Norway in 2009 and 2010 is presented in Table 1.

Consumption of ACE-inhibitors (plain) in the Republic of Serbia and Norway in the years 2009 and 2010 is presented in Table 2.

DISCUSSION

The contemporary approach to pharmacotherapeutic treatment of high blood pressure is based on five groups of drugs. These includes: diuretics, β-blockers, ACE-inhibitors, calcium channel blockers and angiotensin receptor antagonists, and they are used like drugs of first choice in the treatment of arterial hypertension. There is no advantage in use from none of this five groups. In some cases, comorbidity, lack of the effect of the products and prices can affect in choice of drug, but it certainly should not substantially affect the dominance of the...
Consumption of some of these five groups of antihypertensive drugs [8].

But, the situation in Serbia is different. Consumption of these five groups of drugs is uneven and consumption of ACE-inhibitors convincingly is on the first place. In 2009 and 2010 in Serbia the most applied were ACE-inhibitors. Consumption of ACE-inhibitors in 2009 was 195.23 and in 2010 it was 190.39 DDD/1000 inh/day. On the second place were calcium channel blockers, whose consumption was three times lower in comparison to ACE-inhibitors. At the third position were beta blockers with four times lower consumption, while the fourth position occupy diuretics with nine times less applied consumption in relation to ACE-inhibitors. Used of ACE-inhibitors in Serbia in 2010 was neglected. Using these five groups of drugs in the observed period in Norway was balanced. In these two years the lower consumption had beta blockers and it ranged from approximately 40 DDD/1000 inh/day. Angiotensin receptor blockers were most applied and their consumption ranged about 78 DDD/1000 inh/day for (Graphs 1 and 2).

In Serbia, the consumption of ACE-inhibitors in 2010 was four times higher than in Norway (Graph 2). Opposed to this condition, the consumption of angiotensin receptor blockers in Norway was very large and the participation of drugs from this group was about 60%, while in Serbia it was only about 3% of total drugs consumed in Group C09. A similar

<table>
<thead>
<tr>
<th>ATC group</th>
<th>Pharmacotherapeutic group</th>
<th>Serbia</th>
<th>Norway</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2009</td>
<td>2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DDD %</td>
<td>DDD %</td>
</tr>
<tr>
<td>C09A</td>
<td>ACE inhibitors - plain</td>
<td>164.46</td>
<td>100.00</td>
</tr>
<tr>
<td>C09AA01</td>
<td>captopril</td>
<td>6.40</td>
<td>3.89</td>
</tr>
<tr>
<td>C09AA02</td>
<td>enalapril</td>
<td>88.40</td>
<td>53.75</td>
</tr>
<tr>
<td>C09AA03</td>
<td>lisinopril</td>
<td>2.31</td>
<td>1.40</td>
</tr>
<tr>
<td>C09AA04</td>
<td>perindopril</td>
<td>0.84</td>
<td>0.51</td>
</tr>
<tr>
<td>C09AA05</td>
<td>ramipril</td>
<td>22.51</td>
<td>13.69</td>
</tr>
<tr>
<td>C09AA06</td>
<td>quinapril</td>
<td>2.62</td>
<td>1.59</td>
</tr>
<tr>
<td>C09AA08</td>
<td>cilazapril</td>
<td>18.01</td>
<td>10.95</td>
</tr>
<tr>
<td>C09AA09</td>
<td>fosinopril</td>
<td>23.36</td>
<td>14.20</td>
</tr>
<tr>
<td>C09AA10</td>
<td>trandolapril</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C09AA15</td>
<td>zofenopril</td>
<td>0.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table 2. Comparative overview consumption of ACE inhibitors - plain (group C09A) in Serbia and Norway in 2009 and 2010

<table>
<thead>
<tr>
<th>ATC group</th>
<th>Pharmacotherapeutic group</th>
<th>Serbia</th>
<th>Norway</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2009</td>
<td>2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DDD %</td>
<td>DDD %</td>
</tr>
<tr>
<td>C09B</td>
<td>ACE inhibitors - combinations*</td>
<td>30.77</td>
<td>100.00</td>
</tr>
<tr>
<td>C09B02</td>
<td>enalapril, hydrochlortisid</td>
<td>12.00</td>
<td>39.00</td>
</tr>
<tr>
<td>C09B03</td>
<td>lisinopril, hydrochlortisid</td>
<td>0.08</td>
<td>0.26</td>
</tr>
<tr>
<td>C09B04</td>
<td>perindopril, indapamid</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C09B05</td>
<td>ramipril, hydrochlortisid</td>
<td>4.10</td>
<td>13.32</td>
</tr>
<tr>
<td>C09B06</td>
<td>quinapril, hydrochlortisid</td>
<td>1.31</td>
<td>4.26</td>
</tr>
<tr>
<td>C09B08</td>
<td>cilazapril, hydrochlortisid</td>
<td>6.88</td>
<td>22.36</td>
</tr>
<tr>
<td>C09B09</td>
<td>fosinopril, hydrochlortisid</td>
<td>6.40</td>
<td>20.80</td>
</tr>
</tbody>
</table>

Table 3. Comparative overview consumption of ACE inhibitors - a combination (group C09B) in Serbia and Norway in 2009 and 2010

DDD - DDD/1000 inh/day

* - ACE inhibitors and diuretics
situation was in 2009 year.

During 2009 and 2010 in Serbia in the C09 group, the consumption of plain ACE-inhibitors was dominant, and it was about 164 DDD/1000 inh/day or 82.50% of total drugs consumed in group C09. On the other hand, in Norway, in 2009 and 2010 year the consumption of plain ACE-inhibitors was approximately 45 DDD/1000 inh/day or 34% of total drugs consumed in C09 group.

In Serbia, in the group of plain ACE-inhibitors during 2009, the most used preparation was enalapril, fosinopril then, and on the third place was ramipril. In 2010, the situation has not changed much. Enalapril was left in the first place, and fosinopril and ramipril have replaced their position.

Although the fosinopril, plain ACE-inhibitor, has a high price, the consumption of this drug in Serbia is large. In 2009 this drug was on the second, in 2010 on the third place in overall consumption of plain ACE-inhibitors. In the same period, the consumption of fosinopril in Norway, as ACE-inhibitor with high price, was not detected, and the cheaper drugs such as enalapril and ramipril were dominant. The situation was similar when we looked at the consumption of fixed combination of ACE-inhibitors with diuretics. During the observed period in Norway were dominant the fixed combination of diuretics and cheaper ACE-inhibitors like enalapril and lisinopril. Other combinations in Norway haven not been present. In Serbia, the most frequently used fixed combination was enalapril with diuretics. However, in Serbia, we have large consumption fixed combinations of diuretics with expensive ACE-inhibitors, such as cilazapril and fosinopril.

From pharmacoeconomic point of view on high consumption of expensive ACE-inhibitors (plain and fixed combination with diuretics) in 2009 and 2010 in Serbia have been allocated great financial resources.

The savings would be large if the structure of consumed drugs from the group of ACE-inhibitors were as in Norway. We must stress that the saving funds would not be on the account of the quality of pharmacotherapy because it is well known that Norway is the country with a developed pharmacotherapeutical practice.

As we can see from the results of this study, the consumption of ACE-inhibitor in Serbia is very large. The question is whether such a high consumption of these drugs is justified and do these drugs have an advantages in the treatment of hypertension when we compare them with other antihypertensives. Numerous comparative randomized studies have shown that a similar reduction in blood pressure can be achieved equally effectively in any of these five groups of drugs: diuretics, β-blockers, ACE-inhibitors, calcium channel blockers or angiotensin receptor antagonists [8]. According to the recommendations of the European Society of Hypertension, the treatment of isolated systolic hypertension should in most cases start with a diuretic, which is not very oftenly used in Serbia [8]. Analysis of drug consumption in Serbia comparing with Norway, as the country with a developed pharmacotherapeutical practice, indicate that the structure of consumption of drugs from the pharmacotherapeutic point of view is not adequate and that ACE-inhibitors in the relation to the other four group of drugs have great advantage unjustifiably.

CONCLUSIONS

In Serbia, ACE-inhibitors are the most used group of drugs from all drugs which are used in the treatment of cardiovascular diseases and their share in total consumption of drugs is higher than in Norway.

The structure of most frequently used drugs in the group of ACE-inhibitors and their fixed combination with diuretics in Serbia is different from the same drugs in Norway, the country with a developed pharmacotherapeutical practice.

From the pharmacoeconomic point of view on high consumption of expensive ACE-inhibitors (plain and fixed combination with diuretics) in 2009 and 2010 in Serbia have been allocated great financial resources.

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Upotreba ACE-inhibitora u Srbiji u 2009. i 2010. godini

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KRATAK SADRŽAJ


Materijal i metode Podaci o upotrebi ACE-inhibitora u Srbiji i Norveškoj za 2009. i 2010. godinu dobijeni su od Agencije za lekove i medicinska sredstva Srbije i sa sajta Norveškog instituta za narodno zdravlje.


Ključne reči: farmakoepidemiologija, ACE-inhibitori, kardiovaskularni sistem, hipertenzija

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