ANALYSIS OF DRUG PRESCRIBING IN PATIENTS ON HEMODIALYSIS TREATMENT

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Potentially inappropriate prescribing (PIP) of drugs is defined as the use of drugs whose potential damage can overcome benefits. Elderly patients (65 years and older) with renal insufficiency are at particular risk, because they take a lot of drugs, and for the usage of the same, the patients need to have great knowledge and skills.

To identify the risk factors contributing to potentially inappropriate prescribing of drugs in elderly patients with renal insufficiency.

The study was designed as an observational case-control study. The research was carried out at the Clinic of Nephrology, Clinical Center Nis, Serbia. The data were collected from the medical files of elderly patients undergoing chronic hemodialysis treatment, as well as by interviewing. The cases were patients in whom the potentially inappropriate prescribing of drugs was determined by Beers criteria, and the controls were patients who used properly prescribed medications. The risk factors for PIP were established by univariate and subsequently by multivariate logistic regression.

The study included 68 patients older than 65 years who were on chronic hemodialysis treatment, 41 (60.3%) of them were men and 27 (39.7%) women. The average age of the studied population was 72.71 ± 5.92 years, among which the youngest patient was 65 and the oldest 85 years old. According to Beers criteria, PIP was found in 14 (21%) patients. A significantly higher number of drugs was given to the patients in whom the potentially inadequate prescription of medication was established (Z = 2.650; p = 0.008).

The patients to whom the drugs were potentially inappropriately prescribed had a significantly higher number of comorbidities compared to other patients (χ2 = 2.636; p = 0.008).

This study showed that patients who have multiple comorbidities and take multiple drugs are at a substantially greater risk of having at least one drug potentially inadequately prescribed. PIP often results in the occurrence of toxic or side effects, and ultimately damage to the body.


Key words: potentially inappropriate prescribing of drugs, Beers criteria, polypharmacy, elderly patients

Introduction

Choosing the right drug in order to produce the desired therapeutic effect is an everyday challenge for health workers (1). Although in practice there is a tendency for rational prescribing, errors and omissions are relatively common (2).

Potentially inappropriate prescribing (PIP) of drugs is defined as the use of medicines which potential damage can overcome the profit (3), or when the pharmacotherapy does not meet the medical standards. PIP results in more frequent adverse drug effects (ADE), hospitalization and a higher degree of health care usage, and higher cost of treatment (4).

Elderly patients (65 years and over) are at greater risk of potentially inappropriate prescribing of drugs because the physiology of their organism cha-
riages as they grow older (3), which results in frequent illness, and therefore the more frequent use of drugs and very often, the use of several medications at the same time, whose dose must be adjusted to the weakened functions of excretory organs (5). Elderly patients with renal insufficiency are at additional risk, because they receive more drugs than others and their doses must be precisely adjusted, and some drugs, even more, should be completely avoided (6,7).

PIP is a global problem, due to higher prevalence. Numerous studies have considered precisely the PIP among elderly people and found that the prevalence goes up to 79% depending on the criteria used and depending on the country where the study was conducted (5).

There is the question: how can we figure out which drug is inappropriate? There are two types of methods for identification of PIP- implicit and explicit. Implicit methods rely on clinical experience, they are more reliable because they can be used for each patient individually, while explicit methods are based on several criteria through which a potentially inappropriate medication prescribing in elderly patients is confirmed, therefore they are faster and easier, requiring less clinical assessment, but on the other hand less reliable. Due to easier usage, explicit methods widely applied (6), and commonly used are:

1. Beers criteria - a list of drugs which have much higher potential risks than benefits for people over 65 years (8)
2. STOPP criteria ("Screening Tool of Older Persons Potentially Inappropriate Prescriptions") - medicines to be avoided in elderly patients
3. START criteria ("Screening Tool to Alert doctors to the right Treatment") - medicines to be used in elderly patients on the basis of the evidence (9).

In essence, the PIP includes two aspects: 1. PIM (potentially inappropriate medication) when the drug is prescribed without adequate indications or when it is about the use of an indicated drug that in some situations can be more harmful than beneficial to the patient, and 2. PPO (potentially prescribing omissions) not prescribing the drug even though there is a clear indication (10).

**Aim**

The aim of this study was to reveal the factors that lead to PIP in elderly patients with renal insufficiency.

**Methods**

The study was designed as an observational case-control study. The data were collected from medical files and by interviewing patients at the Clinic of Nephrology, Clinical Center Niš, in the period from June 2015 to June 2016. Inclusion criteria were patients aged 65 or older and end stage renal insufficiency treated with hemodialysis (HD). Exclusion criteria were cognitive impairment, psychiatric disorders, and the participation of patients in other clinical studies.

Data collected through the questionnaire included the following variables: socio-demographic characteristics of the patients (age, gender, height and weight, place of residence, whether they live alone or with someone, education level), previous treatment in the last year (the number of hospitalizations, duration of hospitalization, potentially adverse effects), laboratory, habits (smoking, coffee, alcohol), if they read the drug instructions, if they ask the doctor about adverse drug reactions and interactions, whether the doctors give them the information about adverse drug reactions and interactions; comorbidities, all the drugs that a patient receives (total number and individual drugs), how long the patient is on hemodialysis, how many times a week he goes to dialysis and how long one dialysis treatment lasts. Potentially inappropriate prescribing of at least one drug (PIP) was determined according to the Beers criteria.

The approval for this study was obtained from the Ethics Committee of the Medical Faculty, the University of Niš.

Entering, tabular and graphical presentation of the data was performed by using MS Office Excel program. The results of the statistical analysis were presented in tables. Statistical calculations were performed by using the SPSS version 22.

The data were primarily described by absolute numbers, relative numbers (%), mean and standard deviation (SD). The normality of distribution was analyzed by Kolmogorov-Smirnov test. The Mann Whitney U test was used for comparison of continuous variables, and hi-square test for comparison of categorical variables. Univariate and subsequent multivariate logistic regression were used to determine the risk factors for potentially inappropriate prescribing of drugs by Beers criteria. The results were considered statistically significant if the probability of the null hypothesis was less than 0.05.

**Results**

The study included 68 patients older than 65 years which were on chronic hemodialysis (HD) treatment, of which 41 (60.3%) were men and 27 (39.7%) women. The average age of the studied population was 72.71 ± 5.92 years, including the youngest patient who was 65 and the oldest 85 years old. The age structure of men and women was not statistically significantly different (72.63 ± 6.29 vs. 72.81 ± 5.41, p = 0.903).

According to Beers criteria PIP was found in 14 (21%) patients.
Table 1. Distribution of variables in relation to Beers criteria

<table>
<thead>
<tr>
<th>Variables</th>
<th>Potentially inappropriate prescribing of drugs according to Beers criteria</th>
<th>Z/χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>Z/χ²</td>
</tr>
<tr>
<td>Total number of drugs</td>
<td>3,67 ± 2,16</td>
<td>6,14 ± 3,27</td>
<td>2,650</td>
</tr>
<tr>
<td>Length of therapy</td>
<td>1,61 ± 0,94</td>
<td>1,15 ± 0,36</td>
<td>1,594</td>
</tr>
<tr>
<td>Number of comorbidities</td>
<td>1,20 ± 0,73</td>
<td>1,78 ± 0,69</td>
<td>2,636</td>
</tr>
<tr>
<td>Other comorbidities</td>
<td>no</td>
<td>yes</td>
<td>2,636</td>
</tr>
<tr>
<td></td>
<td>43(79,6)</td>
<td>7(50,0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>yes</td>
<td></td>
<td>11(20,4)</td>
</tr>
<tr>
<td>HD internship</td>
<td>≤5 years</td>
<td>26(48,1)</td>
<td>12(95,7)</td>
</tr>
<tr>
<td></td>
<td>&gt;10</td>
<td>9(16,7)</td>
<td>0(0,0)</td>
</tr>
<tr>
<td>Reading of drug instructions</td>
<td>no</td>
<td>yes</td>
<td>2,636</td>
</tr>
<tr>
<td></td>
<td>20(77,3)</td>
<td>4(16,7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>yes</td>
<td></td>
<td>34(83,3)</td>
</tr>
<tr>
<td>Whether they ask the doctor about adverse drug reactions (ADR)</td>
<td>no</td>
<td>yes</td>
<td>2,636</td>
</tr>
<tr>
<td></td>
<td>36(66,7)</td>
<td>5(35,7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18(33,3)</td>
<td>9(64,3)</td>
<td>3,250</td>
</tr>
</tbody>
</table>

Z- Mann Whitney U test

Table 1. shows the results of comparison of the investigated variables between groups of patients with at least one drug potentially inadequately prescribed and the group of patients with no PIPs. In patients receiving significantly greater number of drugs, potentially inadequate prescription of drugs, according to Beers criteria, was confirmed (Z =2.650; p = 0.008). Patients who were confirmed potentially inadequate prescription of drugs had a significantly higher number of comorbidities compared to patients who were prescribed medications appropriately (χ² = 2.636; p = 0.008). Other comorbidities were more frequent in patients with potentially inadequately prescribed drugs (χ²=5.015; p=0.025).

HD internship significantly differed among the examined groups of patients (χ² = 6.713; p = 0.035). It was further observed that a significantly greater number of patients in whom PIP was registered were on dialysis for less than 5 years (χ² = 6.364; p = 0.011).

Reading of drug instructions was not significantly different among the examined groups (χ² = 0.077; p = 0.782), nor whether the patient asked the doctor about the side effects of drugs and their interactions (χ² = 3.250; p = 0.071). Further, it did not turn out statistically significant whether the patient was also suffering from some other disease (χ² = 3.608; p = 0.058), neither did the length of therapy (χ² = 1.594; p = 0.111).

Table 2. Univariate logistic regression in relation to the potentially inappropriate prescription of drugs according to the Beers criteria

<table>
<thead>
<tr>
<th>Variables</th>
<th>B</th>
<th>SE</th>
<th>OR</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of drugs</td>
<td>0,372</td>
<td>0,132</td>
<td>1,450</td>
<td>1,119 - 1,880</td>
<td>0,005</td>
</tr>
<tr>
<td>Length of therapy</td>
<td>-0,802</td>
<td>0,472</td>
<td>0,448</td>
<td>0,178 - 1,131</td>
<td>0,089</td>
</tr>
<tr>
<td>Number of comorbidities</td>
<td>1,034</td>
<td>0,425</td>
<td>2,812</td>
<td>1,222 - 6,472</td>
<td>0,015</td>
</tr>
<tr>
<td>Other comorbidities</td>
<td>1,363</td>
<td>0,632</td>
<td>3,909</td>
<td>1,132 - 13,500</td>
<td>0,031</td>
</tr>
<tr>
<td>HD internship</td>
<td>-1,671</td>
<td>0,745</td>
<td>0,188</td>
<td>0,044 - 0,811</td>
<td>0,025</td>
</tr>
<tr>
<td>Reading of the drug instructions</td>
<td>-0,386</td>
<td>0,655</td>
<td>0,680</td>
<td>0,188 - 2,456</td>
<td>0,556</td>
</tr>
<tr>
<td>Asking the doctor about adverse drug reactions (ADR)</td>
<td>-1,281</td>
<td>0,628</td>
<td>0,278</td>
<td>0,081 - 0,951</td>
<td>0,041</td>
</tr>
</tbody>
</table>
Univariate logistic regression analysis confirmed, as a significant independent factors associated with PIP by Beers criteria, the total number of drugs, number of comorbidities, other comorbidities, HD internship and asking the doctor about ADR. With each new drug the risk for PIP is increased by 45% (OR = 1.450, p = 0.005). Each new comorbidity increases the risk of potentially inappropriate drug prescription almost three times (OR = 2.812, p = 0.015), while the other comorbidities increased the risk almost 4 times (OR = 3.909, p = 0.031). Patients with less HD internship have a higher risk of the occurrence of PIP (OR = 0.188, p = 0.025), as well as the patients who do not ask doctors about ADR (OR = 0.278, p = 0.041).

### Table 3. Multivariate logistic regression of examined variables in relation to potentially inappropriate prescribing of drugs by Beers criteria

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>SE</th>
<th>OR</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of drugs</td>
<td>0.317</td>
<td>0.165</td>
<td>1.373</td>
<td>0.995 - 1.896</td>
<td>0.048</td>
</tr>
<tr>
<td>Number of comorbidities</td>
<td>0.077</td>
<td>0.596</td>
<td>1.080</td>
<td>0.336 - 3.475</td>
<td>0.897</td>
</tr>
<tr>
<td>Other comorbidities</td>
<td>0.514</td>
<td>0.827</td>
<td>1.673</td>
<td>0.331 - 8.463</td>
<td>0.534</td>
</tr>
<tr>
<td>HD internship</td>
<td>-1.389</td>
<td>0.852</td>
<td>0.249</td>
<td>0.047 - 1.325</td>
<td>0.103</td>
</tr>
<tr>
<td>Asking the doctor about ADR</td>
<td>-1.017</td>
<td>0.722</td>
<td>0.362</td>
<td>0.088 - 1.488</td>
<td>0.159</td>
</tr>
</tbody>
</table>

Multivariate logistic regression was conducted for assessing the connection between studied factors and the likelihood of the risk for potentially inappropriate prescribing of drugs determined by Beers criteria (Table 3). The multivariate included all the variables that were distinguished as individual statistically independent factors: the total number of drugs, number of comorbidities, other comorbidities, HD internship and questioning the doctor about ADR. The model with all predictors was statistically significant χ2 ((5, N= 68) = 18.680, p = 0.002), which indicates that the model makes distinction between the subjects who are at risk and those who are not. The model entirely explains between 24.0% (R squared Cox and Snel) and 37.6% (R squared Naagelkerkea) of risk for having PIP and correctly classifies 86.8% of cases. Only total number of drugs that a patient received has significant influence on risk from PIPs (OR = 1.373, p = 0.048).

### Discussion

To our best knowledge, this is the first study to analyze the factors that contribute to potentially inappropriate prescribing of drugs in elderly patients on hemodialysis. Out of the 68 patients who took part in our study, in 14 (21%) of them PIP was found, which is considerably less than in some other studies (11–13), although it is difficult to compare them because they included different population in the study, and used different criteria and guidelines for determination of the PIP.

Out of the 14 patients with potentially inappropriate prescribing of drugs, 10 patients (71%) have one PIP, two have 2 (14.3%) PIPs and two patients (14.3%) have 3 PIPs. From a total of 19 potentially inappropriately prescribed drugs, 52.3% were benzodiazepines, 31.6% methyldopa and one ticlopidine and zolpidem.

Our study showed that patients with a greater number of comorbidities, those who are on shorter program of hemodialysis and patients who do not ask their physicians about adverse drug reactions and interactions are more likely to have PIP.

The optimal outcome of medical treatment is certainly a priority for every doctor. Treatment of elderly patients (65 years and above) is particularly challenging because they are a special group of patients. Aging is associated with an increase in the number of chronic diseases, and therefore with a greater number of patients taking drugs (4, 14), which, according to our study represents one of the most important factors that contribute to potentially inappropriate prescribing. The results of our study indicate that with each newly prescribed drug the risk of PIP increases by 45% (OR = 1.450, p = 0.005). The results of many other studies are also in accordance with the results of our study (4, 10, 14–19).

In the study (16) the polypharmacy is present in 70% of patients. The main reason for this, as Wang and colleagues cite, is the increasing of morbidity with age. They also stated, as an important fact, that doctors follow the guidelines of clinical research which does not involve elderly patients.

Another study showed that a high prevalence of polypharmacy in the elderly people, leads to a higher rate of adverse drug reactions, a greater possibility that the patient has at least one PIP, and therefore a greater likelihood of treatment failure (20).

The results of our studies further show that
with the increase in the number of comorbidities increases the likelihood that the patient consumes potentially inappropriately prescribed medication. With every new disease, the risk of occurrence of PIP by Beers criteria, is almost three times higher than in patients with a small number of diseases (OR = 2.812, p = 0.015). This is also confirmed by the study (21), as well as numerous other studies that actually claim that, with the increasing number of comorbidities, the number of drugs that the patient takes also increases, and therefore, a chance that the patient gets potentially inappropriately prescribed drug is incomparably higher (4, 14–16).

According to our study, patients who had shortly been on dialysis (< 5 years) were more likely to have potentially inappropriately prescribed drug (OR = 0.188, p = 0.025). Since we did not find similar studies, this information did not have what to be compared with.

Also according to our survey, the patients who asked physicians about adverse drug reactions and interactions among the drugs had a smaller risk of being prescribed the potentially inappropriate drug (OR = 0.278, p = 0.041). Gordon and his associates, in their study (22), showed that patients are a part of the decision making process regarding their treatment, but they also stated that it is known that counseling by physicians is only one phase of the patients' participating in the conducting of their treatment according to their needs.

Finally, our study also had some limitations. Data on drugs that patients were taking were taken from their medical files, as well as directly from the patients during the survey. Considering that these are elderly patients, suffering from serious illnesses, and many of them with associated numerous comorbidities, it is possible that data on the number of drugs they took was not accurate because many of them could not remember the names of all the medicines they were taking, as well as those which they took in the last year.

Also, it should be borne in mind that the criteria that indicate potentially inappropriate prescribing of drugs, such as the Beers criteria that we used in our study, are general. They do not take into account each person, considering his nationality, weight, and body mass index (23). People, after all, differ among themselves, and each patient should be seen as a separate individual. What is, under valid criteria, potentially inadequately prescribed remedy, perhaps suits to some of the patients. If the guidelines require that the dosage of a certain drug should be reduced, perhaps this dosage is still insufficient to some patients.

**Conclusion**

We believe that the results of our study will raise the awareness about the high prevalence of PIP in elderly patients on chronic hemodialysis treatment and its harmful consequences. PIP needs to be paid special attention in patients with a greater number of comorbidities, those who are on shorter program of hemodialysis and patients who do not ask their physicians about adverse drug reactions and interactions. Early detection of PIP plays a key role in improving the quality of treatment, and reducing the costs of treatment.
References


ANALIZA PROPISIVANJA LEKOVA KOD BOLESNIKA KOJI SE NALAZE NA HRONIČNOM TRETMANU HEMODIJALIZE

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Potencijalno neadekvatno propisivanje (Potentially inappropriate prescribing, PIP) lekova se definiše kao upotreba lekova čija potencijalna šteta može nadvladati dobit. Stariji bolesnici (65 godina i više) sa bubrежном insuficijencijom su pod posebnim rizikom, jer uzimaju mnogo lekova za čije je doziranje potrebno mnogo znanja i veštine.

Cilj rada bio je da se utvrde faktori rizika koji doprinose potencijalno neadekvatnom propisivanju lekova kod starijih bolesnika sa bubrежном insuficijencijom. Studija je dizajnirana kao opservaciona studija slučaj/kontrola. Istraživanje je sprovedeno na Klinici za nefrologiju Kliničkog centra Niš. Prikupljanje podataka je vršeno iz istorija bolesti starijih bolesnika koji se nalaze na hroničnom tretmanu hemodijalize, kao i anketiranjem. Slučajevi su bili bolesnici kod kojih je utvrđeno potencijalno neadekvatno propisivanje lekova prema Beers kriterijumima, a kontrole bolesnika kod kojih su lekovi adekvatno propisani. Univarijantnom i naknadno multivarijantnom logističkom regresijom utvrđeni su faktori rizika za pojavu PIP-a kod ovih bolesnika.

U istraživanju je učestvovalo 68 bolesnika starijih od 65 godina koji su na hroničnom programu hemodijalize, od kojih je 41 (60,3%) muškarac i 27 (29,7%) žena. Prosečna starost ispitivane populacije iznosila je 72,71 ± 5,92 godina; najmlađi bolesnik imao je 65, a najstariji 85 godina. Prema Beers kriterijumu, PIP je utvrđen kod 14 (21%) bolesnika.

Značajno veći broj lekova primali su bolesnici kod kojih je utvrđeno potencijalno neadekvatno propisivanje lekova (Z = 2,650; p = 0,008). Bolesnici kojima su lekovi pote-najzadimalno neadekvatno propisani imali su značajno veći broj komorbiditeta u odnosu na ostale bolesnike (x² = 2,636; p = 0,008).

Ova studija je pokazala da su bolesnici koji imaju više komorbiditeta i primaju više lekova pod značajno većim rizikom da im bar jedan lek bude potencijalno neadekvatno propisan. Potencijalno neadekvatno propisivanje često ima za posledicu pojavu toksičnih ili neželjenih dejstava, i u krajnjem, oštećenje organizma.

**Ključne reči:** potencijalno neadekvatno propisivanje lekova, Beers kriterijum, polifarmacija, stariji bolesnici