ORIGINAL ARTICLE

UDC: 616.12-085-06:615.065
DOI: 10.2298/VSP140710104M

Adverse drug reactions in hospitalized cardiac patients: characteristics and risk factors

Neželjena dejstva lekova kod hospitalizovanih kardioloških bolesnika – karakteristike i faktori rizika

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Abstract

Background/Aim: Adverse drug reactions (ADRs) appear more frequently than actually reported and registered. The main goal of our work was to analyze risk factors, incidence and characteristics of ADRs in hospitalized cardiac patients. **Methods.** This prospective study included 200 patients, hospitalized at Cardiology Center of the Clinical Centre of Montenegro. ADRs were collected using specially designed questionnaire, based on the list of symptoms and signs that could point out to potential ADRs. Data from medical charts of patients, lab tests and other available parameters were observed and combined with the data from questionnaire. Severity of ADRs were assessed as serious or non-serious according to the World Health Organization criteria. Causality was assessed using the Naranjo probability scale. **Results.** A total of 34% of all the patients experienced at least one ADR. The most common ADRs occurred as nervous system disorders, less frequent were cardiovascular disorders, while the immune system disorders were the rarest. Sixteen percent of all ADRs were characterized as serious, most often caused by carvedilol and amiodarone. The majority of patients (97.3%) recovered without consequences. The multivariate analysis showed independent significant associations between ADRs and age, gender, comorbidities and polypragmasia. **Conclusion.** ADRs represent a significant issue in hospitalized cardiac patients population. The most significant predictors for ADRs in observed population were age, comorbidity, number of medications used during hospitalization and patients' gender. Preventive measures such as pharmacotherapy rationalization and continual education of health care professionals could reduce the frequency of ADRs appearance in patients with detected risk factors.

Key words:
drug toxicity; heart diseases; hospitalisation; risk factors.

Apstrakt

Uvod/Cilj. Neželjene reakcije na lekove (NRL) javljaju se mnogo češće nego što se registruju i prijavljuju. Glavni cilj rada bio je analiza rizičnih faktora, učestalosti pojavljivanja i karakteristika NRL kod hospitalizovanih kardioloških bolesnika. **Metode.** Sprovedena je prospektivna studija, u koju je bilo uključeno 200 hospitalizovanih bolesnika u Centru za kardiologiju Kliničkog centra Crne Gore. NRL su prikupljane korišćenjem specijalno urađenog upitnika, baziranog na listi simptoma i znakova koji bi mogli ukazati na eventalne NRL. Iz istorija bolesti prikupljani su podaci o laboratorijskim nalazima i drugim relevantnim parametrima, koji su kombinovani sa podacima iz upitnika. Klasifikacija NRL je izvršena po kriterijumima Svetske zdravstvene organizacije, a uzročno-posledična povezanost korišćenjem Naranjo skale. **Rezultati.** Ukupno 34% bolesnika ispoljilo je bar jednu NRL. Najčešće NRL su se ispoljile kao poremećaj u centralnom nervnom sistemu, zatim kao kardiovaskularni poremećaji, dok su najređe bili zastupljeni poremećaji imunog sistema. Ozbiljne NRL su činile 16% od svih otkrivenih NRL, najčešće prouzrokovane korišćenjem lekova karvedilol i amjodaron. Većina bolesnika (97,3%) oporavila se bez posledica. Multivarijantna analiza je ukazala na postojanje nezavisne povezanosti između pojavljivanja NRL i starosti bolesnika, pola, pridruženih bolesti kao i pol-

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ipragmazije. **Zaključak.** Pojava NRL predstavlja veliki problem u populaciji hospitalizovanih kardioloških bolesnika. Najznačajniji prediktori za njihov nastanak su starost bolesnika, pridružene bolesti, polipragmazija i pol bolesnika. Uvođenjem preventivnih mera, kao što su racionalizacija farmakoterapije i dodatne mere obuke zdravstvenih radnika, mogla bi se sniziti učestalost pojavljivanja NRL kod bolesnika sa faktorima rizika.

Ključne reči:
lekovi, toksičnost; srce, bolesti; hospitalizacija; faktori rizika.

Introduction

Adverse drug reactions (ADRs) appear more frequently than actually reported and registered. Adverse drug reactions are common causes of morbidity and mortality within the hospital setting. The hospital environment, with its clearly defined patient population, is an ideal setting to identify potential adverse drug reaction signals [1].

According to the literature information, it has been estimated that 10–30% of hospitalized patients experience ADRs [2–5] and 0.3–10% of all hospital admissions are actually the results of ADRs [6–8]. In hospital environment, 3% of all fatal outcomes are caused by ADRs [9]. ADRs also cause prolongation of the hospitalization period and increase of hospital costs [5].

It is estimated that ADRs could have been prevented in about 50% of cases [8–11].

Varieties in frequency of occurrence of ADRs during hospitalization among different studies could be explained by different methods of investigation. While in some studies only spontaneously reported ADRs were recorded, in others, ADRs were recorded by using intensive monitoring systems [6, 12]. Furthermore, there are significant differences between stimulated *versus* non-stimulated reporting systems, as well as between manual and electronic active monitoring systems [12]. Prospective collection of ADRs, in contrast to retrospective data collection (which rely on chart review), has many advantages, mostly due to, most often, daily visits by a trained health care professionals on selected departments, over a restricted time period, in order to obtain records of all patients and suspected events [13–15].

Furthermore, earlier studies have emphasized that adverse drug events (ADEs) could often be prevented if physicians had had possible risk factors in mind [16–19]. Risk factors for ADEs include patient characteristics, drug-drug interactions, inappropriate number or dose of drugs and poor compliance [20].

Cardiovascular diseases are still the leading cause of morbidity and mortality worldwide. It is estimated that cardiovascular medications are one of the most common class of drugs associated with medication errors and ADRs [21]. The ADE prevention study group showed that odds ratio (OR) of severe ADEs with cardiovascular medication was 2.4 times greater than with other medications [22].

National ADR reporting system in Montenegro is organized by the Pharmacovigilance Department of the Agency for Medicines and Medical Devices of Montenegro. However, data show that the number of reports coming from health care professionals is quite low [23].

The main goal of this study was to analyze ADRs, as well as the potential risk factors for their appearance in patients hospitalized in the Cardiology Center of the Clinical Center of Montenegro. In order to prevent the occurrence of ADRs, it is necessary to provide proposals and measures for establishing ADR monitoring system in hospital environment.

Methods

Study design and patients selection

This prospective study included 200 patients hospitalized in the Cardiology Center of the Clinical Center of Montenegro in a 6-month period (April 1–October 1 2013).

Before the interview, the patients received an information sheet and gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of the Clinical Center of Montenegro.

Inclusion criteria were: adult patients, older than 18 years, of both gender admitted to Cardiology Center, hospitalized for three or more days, conscious, oriented and capable to understand questions and provide clear and comprehensible answers.

Exclusion criteria were: patients younger than 18 years, those with dementia or other causes of disorientation, with severe illness (e.g. cardiogenic shock, pulmonary oedema, etc.), short period of hospitalization (less than 3 days) and patient's refusal to participate in the trial.

Definition and classification of adverse drug reactions (ADRs)

Definition of ADRs according to the World Health Organization (WHO) was used in this research [24].

ADRs were characterized by using Rawlins and Thompson classification [25]. Each ADR severity was assessed in accordance with the WHO criteria [24]. The causality relationship between the drug and the effect was established by using Naranjo's ADR probability scale [26]. ADRs were classified by criteria suggested by Meyboom et al. [27] as type A ("drug actions"), type B ("patients reactions") and type C ("statistical ").

In addition, the level of intervention was attributed, using a 4-level scale (level 1 – no change in the treatment; level 2 – dose adjustment or drug stop, no additional treatment required; level 3 – dose adjustment or drug stop, additional treatment required, and level 4 – transfer to intensive care unit). Each ADR was also classified according to the system-organ class.

Patient interview

A special questionnaire was designed to register patient data, disease state(s), reason(s) for hospitalization and use of medi-

cation in the hospital. The interviewers completed this part of the questionnaire before interviewing the patient, in order to have the drug use in mind when interviewing the patients.

There were three approaches of gathering information from patients, regarding ADRs. At the beginning, patients were asked a standard open question, i.e. whether they experienced an ADR. In case of a positive answer, such ADRs were noted. Afterwards, patients were asked questions regarding complaints concerning the different organ systems, which helped them to recall experienced ADRs. Finally, the patients were asked about specific ADRs, mentioned in summary of product characteristics, in relation to drugs administered during hospitalization.

For reports based on the patient interview, interviewer and the treating physician discussed the causality of ADRs.

Data from patients' history, referring possible ADRs, complemented by data from the questionnaire, were imported together in the electronic database.

Statistical analysis

Statistical data analysis was performed using IBM SPSS Statistics 22 (SPSS Inc., Chicago, IL, USA). Results were presented as frequency, percent and mean ± standard deviation (SD). For parametric data, independent samples, *t*-test was used to test differences between the groups. Mann-Whitney U test was used for obtaining a significance between ordinal data. χ^2 test or Fisher's exact test was used to test the differences between nominal data (frequencies). The association between potential risk factors and ADRs was evaluated using binary logistic regression, expressing the strength of association by crude and adjusted odds ratio (OR) with 95% confidence intervals (CI). A p value of < 0.05 was considered significant.

Results

Inclusion criteria were met by 200 patients, whose general characteristics are presented in Table 1.

The average age of all the patients was 60.5 ± 10.0 years. Significantly more ADRs occurred in the elderly.

A significance was also obtained in the frequency of ADRs between the male and the female patients (significantly higher in females), also in the patients with comorbidities. No significant differences in ADRs occurence were observed among different patients occupations, as well as concerning education level. The presence of risk factors for cardiovascular diseases has not affected significantly ADRs manifestation.

The most commonly used medicines among our patients were acetylsalicylic acid, clopidogrel, pantoprazole, simvastatin and ramipril (Table 2).

Table 1

Demographic data of the tested cardiac patients

Characteristic	Patients without ADRs (n = 132)	Patients with ADRs (n = 68)	*p*
Age (years), n (%)			
≤ 65	95 (70.9)	39 (29.1)	0.037*
> 65	37 (56.1)	27 (43.9)	
Sex, n (%)			
male	100 (72.5)	38 (27.5)	0.004*
female	32 (51.6)	30 (48.4)	
Occupation, n (%)			
employed	24 (70.6)	10 (29.4)	0.643
unemployed	46 (62.2)	28 (37.8)	
retiree	62 (67.4)	30 (32.6)	
Education level, n (%)			
elementary	7 (63.6)	4 (36.4)	
college	87 (66.9)	43 (33.1)	0.871
undergraduate	19 (59.4)	13 (40.6)	
graduate	18 (69.2)	8 (30.8)	
Comorbid condition, n (%)	32 (24.2)	36 (52.9)	< 0.001*
Risk factors for CVD*, n (%)	124 (93.9)	63 (92.6)	0.766
Number of drugs, $\bar{x}$ ± SD	7.1 ± 2.6	8.9 ± 2.6	< 0.001*
Duration of hospitalization (days), $\bar{x}$ ± SD	6.4 ± 3.9	8.6 ± 6.6	0.016*

CVD – cardiovascular disease; ADRs – adverse drug reactions; *statistically significant difference.

Table 2

The most commonly used medicines and therapeutic drug groups

10 most commonly used medicines		10 most commonly used therapeutic drug groups	
Name of the medicine	n (%)	Name of the therapeutic drug group	n (%)
Acetylsalicylic acid	168 (11.2)	Antiplatelet drugs	281 (18.7)
Clopidogrel	112 (7.4)	ACE inhibitors	179 (11.9)
Pantoprazole	108 (7.2)	Beta blockers	143 (9.5)
Simvastatin	87 (5.8)	Diuretics	140 (9.3)
Ramipril	69 (4.6)	Statins	138 (9.2)
Metoprolol	66 (4.4)	Proton-pump inhibitors	110 (7.3)
Enoxaparin	54 (3.6)	Nitrates	86 (5.7)
Furosemide	47 (3.1)	Anticoagulants	69 (4.6)
Hydroclorothiazide	46 (3.1)	Antidiabetics	56 (3.7)
Atorvastatin	43 (2.9)	Calcium channel blockers	43 (2.9)
Total	1.505 (100.0)	Total	1.505 (100.0)

A total of 34% of all the patients experienced one of the ADRs, but 7 of them experienced two ADRs at once.

The most frequent ADRs were caused by isosorbide mononitrate in 10.7%, by carvedilol in 8.0%, by metoprolol in 8.0% and by simvastatin and enoxaparin in 6.7% of patients. The characteristics of detected ADRs are presented in Table 3.

Table 3

Characteristics of the detected adverse drug reactions (ADRs)

Characteristics of ADRs	n (%)
Type	
A	64 (85.3)
B	4 (5.3)
C	7 (9.3)
Causality	
certain	8 (10.7)
probable	36 (48.0)
possible	31 (41.3)
Level of intervention	
1 (no change in dose)	29 (38.7)
2 (dose changed or drug stopped)	35 (46.7)
3 (drug stopped + additional therapy)	6 (8.0)
4 (transfer to intensive care unit)	5 (6.7)
Severity	
serious ADR	12 (16.0)
non serious ADR	63 (84.0)
Outcome	
recovery without consequences	73 (97.3)
recovery with consequences	2 (2.7)
ADR reported by	
a patient	30 (40.0)
the treating physician	29 (38.7)
the interviewer	16 (21.3)

According to Naranjo algorithm, causality was most commonly determined as probable. Certain ADRs were most commonly presented in patients who had taken isosorbid-mononitrate (flushing, headache), probable ADRs appeared with taking enoxaparin (injection site reactions) and possible ADRs were caused by metoprolol (bradycardia), carvedilol (bradycardia) and simvastatin (abdominal pain, constipation).

In almost 50% of all the patients with detected ADRs, dose change or discontinuation of the therapy had to be carried out.

A total of ADRs (16% of all of them) were classified as serious.

Serious ADRs were mostly caused by carvedilol (bradycardia that required additional therapy) and amiodarone (thyroid gland disorders, impaired vision). The majority of serious ADRs (9 of them) were recognized by treating physicians.

A great proportion of the patients recovered with no further consequences, but two patients had further complications.

ADRs most frequently affected the central nervous system (27%), than cardiovascular system (18%), gastrointestinal system (13%) and skin and subcutaneous tissue (12%).

Most common manifestations of ADRs were headache (16%), administration site reactions (10%), bradycardia (9%), dizziness (6%) and stomach ache (5%). The logistic regression analysis in which ADR was dependant variable was performed (Table 4).

Multivariate analysis, using binary logistic regression analysis with adjustment for the risk factors, is summarized in Table 4. There were several independent significant associations between ADR and age, gender and comorbidities (Adjusted OR > 2). We observed no significant co-linearity among potential risk factors. Interactions of all predictors in the model were examined, but we did not find any statistical significance among them.

Discussion

In the present study, ADRs occurred in 34% of the interviewed patients, and 16% of them were classified as serious ADRs.

The reported incidence of ADRs was higher than those reported in other studies, estimating that ADRs were present in 10–30% of hospitalized patients [27–38]. In the meta-analysis of Lazarou et al. [37], an incidence of 10.9% was found for patients experiencing an ADR during their hospitalization, among them serious ADRs amounted to 6.7%.

There could be several explanations for higher frequency of ADRs found in our study. Lazarou et al. [37] included only "definite" and "probable" ADRs, while in our analysis, we comprehended occurrence of "possible" ADRs [39, 40]. Furthermore, in our study, the patient interview was intensive, since the patients were also asked about ADRs related to their medication therapy.

In addition, hospitalized cardiology patients are often elderly with underlying comorbidities that impair the pharmacokinetics of drugs. These elderly patients are more likely to experience ADRs. Clearly, hospitalized patients are exposed to multiple risk factors predisposing them to ADRs [40, 41]. Predisposing factors like age, gender, comorbidity, number of drugs taken, and duration of hospitalization, have been reported as significant risk factors for the development of ADRs [42, 43].

It is shown that age is an important risk factor for ADRs. The incidence of ADRs is significantly higher in elderly, which is understandable since pharmacodynamics

Table 4

Logistic regression analisys [advanse drug reactions (ADRs) as dependent variable]

Independent variables	Univariate logistic regression		Multivariate logistic regression	
	crude OR (95% CI)	*p*	adjusted OR (95% CI)	*p*
Age (≤ 65 years old)	1.91 (1.03–3.52)	0.039*	2.29 (1.14–4.63)	0.020*
Gender	2.47 (1.32–4.60)	0.004*	2.04 (1.01–4.11)	0.047*
Co-morbidity	3.52 (1.89–6.54)	< 0.001*	3.81 (1.89–7.64)	< 0.001*
No of medications used during hospitalization	1.29 (1.14–1.46)	< 0.001*	1.29 (1.12–1.47)	< 0.001*
Duration of hospitalization	1.09 (1.02–1.15)	0.008*	1.07 (0.99–1.14)	0.073

***Statistically significant potential risk factors; OR – odds ratio; CI – confidence interval.**

and pharmacokinetics change with age. In addition, homeostatic mechanisms become more and more impaired, which contributes to the increased occurrence of ADRs, along with the effect of coexisting disease. Increased consumption of medicines is another contributing factor for increased incidence of ADRs [44].

A study of Carbonin et al. [45] on 9,000 Italian patients, mainly older than 60 years, show that frequency of ADRs occurrence increases from 1.2% of patients medicated with one drug to 10% of patients comedicated with 9 drugs and 50% of patients with more than 10 drugs.

The presence and frequency of ADRs in Canadian patients, older than 50 years, were observed in a study of Grymonpre et al. [46] showing the increase of ADRs frequency from 5% of patients on therapy with 2 drugs, to more than 20% of patients co-medicated with 5 and more drugs.

Earlier studies have also reported a higher incidence of ADRs in females [34, 47].

This could be explained by the gender differences in the rate of drug metabolism, since they are significant even after correction made for lean body mass and body surface area [48]. In this context, higher occurrence of ADRs in women could be the consequence of lower body weight and glomerular filtration rate, as well as higher percentage of body fat in comparison with men [49].

In our study, causality was assessed as "certain" in 8% of cases, which does not differ from other available literature data [50–52], where the most "certain" ADRs were below 10% of cases. The majority of ADRs were assessed as probable and possible.

Frequency of serious ADRs in our study was lower (16%) comparing with some other research data. In a study performed by French Pharmacovigilance Center [53], serious ADRs occurred in 33% of cases, and Somers et al. [52] reached even 38%. Some other researchers [6, 34, 37] reported even lower frequency of serious ADRs, possibly as the consequence of differences in methodology and population of patients among performed studies.

Among ADRs registered using intensive monitoring system, the most frequent manifestations were observed as nervous system disorders, followed by cardiovascular and gastrointestinal disorders, which is consistent with literature data [54], especially when safety profile of cardiology patient therapy was considered.

Of all medicines, nitrates and beta-blockers caused the most ADRs. In similar research, performed by Sharminder et al. [55], nitrates and diuretics caused the majority of ADRs. In other study of Zaidenstein et al. [30], that included only cardiology patients, the main causes of ADRs were fibrinolytics, anticoagulation drugs and beta-blockers.

The occurence frequencies of ADRs type A, B and C in our study fully comply to data obtained from other authors [34, 52]. The higher incidence of type A ADRs compared to type B and type C suggests that numerous ADRs could be avoided.

Conclusion

Our results show that ADRs represent a significant issue in the population of hospitalized cardiac patients. The most significant predictors for ADRs occurred in the observed population are age, comorbidity, number of medications used during hospitalization and gender. It is necessary to implement preventive measures, recommended for all hospitalized cardiology patients in order to minimize the frequency of ADRs, as well as for better control of its detection. There is a necessity for urgent pharmacotherapy rationalization, in order to reduce the risk for ADRs. Therefore, additional educational efforts assigned for health care professionals should be made in order to raise consciousness regarding ADRs importance and risk factors contributing to their occurrence.

The importance of this research lies in the fact that this is the first ADRs monitoring in hospitalized cardiology patients in Montenegro, conducted in accordance with internationally accepted methodology, which may help increasing awareness to ADRs and conducting of further pharmacovigilance studies.

Acknowledgements

This study was part of a national project of Agency for Medicines and Medical Devices of Montenegro funded by the Ministry of Science and the Ministry of Health of Montenegro (01-907/2).

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Received on July 10, 2014.
Revised on August 3, 2014.
Accepted on August 6, 2014.
Online First September 2015.