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Original article

A QUESTIONNAIRE STUDY ON THE KNOWLEDGE OF PHARMACOVIGILANCE AMONG HEALTHCARE PROFESSIONALS IN THE REPUBLIC OF NORTH MACEDONIA

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Abstract

Introduction: The higher incidence of adverse drug reactions (ADR) is a global health problem which requires the attention of all stakeholders. Spontaneous ADR reporting system is a global phenomenon, and the cornerstone of pharmacovigilance activities. Therefore, healthcare professionals play a crucial role in the pharmacovigilance system.

The **aim** of our study was to evaluate the health workers' knowledge about pharmacovigilance in the Republic of North Macedonia

Material and method: This study included 400 health workers (100 doctors of medicine, 100 doctors of dental medicine, 100 pharmacists and 100 medical nurses/technicians) employed in public and private healthcare institutions in the city of Skopje. The research was conducted using an anonymous survey questionnaire and the collected data were statistically analyzed by using SPSS Statistica v23 for Windows.

Results: Our results showed that pharmacists' knowledge was significantly better than that of other healthcare professionals regarding the definition of the term "pharmacovigilance", the main goal of the pharmacovigilance, the obligations for reporting adverse drug reactions and the function of the system of pharmacovigilance in our country. In our study, doctors of medicine, although with weaker knowledge than pharmacists, showed a good level of knowledge of the pharmacovigilance system, while doctors of dentistry and nurses/technicians had the least knowledge of this system.

Conclusion: We believe that by predicting the curricula on pharmacovigilance and the adverse drug reactions in the undergraduate studies, adequate knowledge of this system will be provided which will contribute to improving the quality of care for patients and reducing the under-reporting of ADRs.

Keywords: pharmacovigilance, knowledge, healthcare professionals

Introduction

Adverse drug reactions (ADR) are defined by the World Health Organization (WHO) as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in people for the prophylaxis, diagnosis, or therapy for a disease, or for the modification of physiological function"[1]. ADRs are a developing and serious challenge for public health management due to multiple comorbidities, polypharmacy as well as arrival of new drugs on the market, and are considered a major cause of patient morbidity and

mortality[2]. It has been shown that ADRs account for 5%-10% of all hospital admissions[3,4] and cause a 9% increase in the length of hospital stay and a 20% increase in the variety of care costs[5].

The higher incidence of adverse drug reactions (ADRs) is a global health problem which requires the attention of all stakeholders, regardless of the practice settings. Spontaneous ADR reporting system is a global phenomenon, and the cornerstone of pharmacovigilance (PV) activities. Therefore, healthcare professionals, in any capacity, play a crucial role in the pharmacovigilance system, and as such they require considerable knowledge and expertise in the field of drug safety, especially in early recognition, detection, management and reporting of ADRs[6].

The rate of ADR reporting depends on many factors, such as national PV programs, regulations, and the knowledge and attitudes of healthcare professionals[7]. Evaluating the knowledge, attitudes, and practice of healthcare providers regarding PV and ADR reporting can help to devise strategies for improving reporting schemes in order to ensure patients' safety[8].

Given the fact that health workers play a crucial role in preventing and reporting adverse drug reactions, as well as the broad spectrum of pharmacotherapy used in everyday practice, the aim of our study was to evaluate the health workers' knowledge about pharmacovigilance in the Republic of North Macedonia.

Material and method

This study included 400 health workers (100 doctors of medicine, 100 doctors of dental medicine, 100 pharmacists and 100 medical nurses/technicians) employed in public and private healthcare institutions in the city of Skopje.

The research was conducted using an anonymous survey questionnaire intended for healthcare professionals. For this purpose, a modified version of the questionnaire according to Gupta *et al*.[7] was used.

Limitations of the study (possible risks and errors)

Measures were taken for two common limitations in this type of study:

- Selective bias. Doctors were selected from health institutions from different municipalities on the territory of the city of Skopje, in order to obtain a representative sample.
- Incomplete and involuntary disclosure of data when filling in the anonymous questionnaire by the subjects poses a risk of inadequate response.

The collected data were statistically analyzed by using SPSS Statistica v23 for Windows, with tests adequate to the sample characteristics.

Results

A total of 400 surveyed healthcare professionals (100 doctors of medicine, doctors of dentistry, pharmacists and nurses/technicians) participated in the study. The average age of respondents in the whole group was 48.4±13.1 years, 50% of respondents were younger than 52.0 years, for median IQR=52.0 (36-60). According to gender, the majority of respondents (87.0%) were women and 13.0% were men.

Table 1. Correct and incorrect answers of health workers on pharmacovigilance, in percentage

Question	Doctors of Medicine		Doctors of Dentistry		Pharmacists		Medical nurses / technicians	
	Correct answer	Incorrect answer	Correct answer	Incorrect answer	Correct answer	Incorrect answer	Correct answer	Incorrect answer
Q1. Define the term pharmacovigilance	38	62	12	88	74	26	7	93
Q2. What is the most important goal of pharmacovigilance?	40	60	27	73	69	31	6	94
Q3. Is there a mandatory obligation to report adverse drug reactions?	65	35	25	75	79	21	6	94
Q4. Which of the health professionals has the obligation to report adverse reactions to a drug that has been placed on the market?	50	50	22	78	67	33	19	81
Q5. Is there an established pharmacovigilance system in the Republic of North Macedonia?	75	25	70	30	88	12	20	80
Q6. Which regulatory body is responsible for monitoring adverse drug reactions in the Republic of North Macedonia?	66	34	58	42	71	29	12	88
Q7. Where is the International Center for Adverse Drug Reaction Monitoring located?	27	73	19	81	40	60	4	96
Q8. Have you seen the adverse drug reaction report form?	58	42	21	79	61	39	18	82
Q9. When is the deadline for reporting serious adverse reactions and events (without fatal outcome) from the use of a drug that has been placed on the market?	38	62	27	73	53	47	6	94
Q10. At what stage	68	32	42	58	75	25	20	80

of clinical drug trials can rare adverse drug reactions be detected?								
Q11. Which of the following methods is most commonly used to monitor adverse reactions to new drugs placed on the market?	55	45	45	55	70	30	12	88

Discussion

In order to determine the knowledge of health professionals about the term "pharmacovigilance", we asked health professionals to define the term pharmacovigilance by choosing one of the offered answers in the questionnaire. Our results showed that 74.0% of surveyed pharmacists, 38.0% of surveyed doctors of medicine, 12.0% of doctors of dentistry and 7.0% of nurses/technicians gave the correct answer to question no. 1, that is, they knew the definition of the term "pharmacovigilance". The percentage difference between pharmacists and other health professionals was statistically significant for $p<0.05$ (Difference test, p=.0000). In addition, in order to obtain a more detailed understanding of the knowledge of healthcare workers, we asked them to determine the most important goal of the pharmacovigilance system - determination of hitherto unknown adverse drug reactions. To question no. 2, 69.0% of surveyed pharmacists, 40.0% of doctors of medicine, 27.0% of doctors of dentistry and 6.0% of nurses/technicians gave the correct answer. The percentage difference between pharmacists and other health professionals was statistically significant for $p<0.05$ (Difference test, p=.0000). The results obtained from the survey regarding question no. 1 and question no. 2, and which refer to the assessment of the knowledge of healthcare workers about the concept and purpose of pharmacovigilance, indicated that pharmacists had the highest level of knowledge, followed by doctors of medicine, doctors of dentistry and, finally, nurses/technicians. We believe that this is due to the different educational profile of health workers provided by the curricula. Namely, the largest number of courses on pharmacovigilance in the study programs published on the websites of the Faculty of Pharmacy[9], the Faculty of Medicine[10] and the Faculty of Dentistry[11] at the Ss. Cyril and Methodius University in Skopje, is provided in integrated study program for masters in pharmacy, followed by the study program for doctors of medicine. Numerous studies in literature indicate that to ensure the safe use of medicines, PV and ADRs reporting educations are important competencies for all healthcare students, and incorporating the PV course in their curriculum is mandatory[12-14]. It is also very important to ensure that they are well trained and have adequate knowledge about PV and ADR reporting to reduce the under-reporting of ADRs, to minimize the incidence of ADR, and to provide quality of care to patients[15].

Our data are consistent with literature data indicating that pharmacists are the healthcare professionals who have the best knowledge about the pharmacovigilance system[16, 17]. On the other hand, our results showed that pharmacists in our study had a higher level of knowledge than pharmacists in Japan[18], China[19], Turkey[20], Jordan[21], Nigeria[22], and Nepal[23]. Research conducted by Chopta *et al*.[24], including a sample of 100 medical doctors, employed at the tertiary level in India, showed that 38% of medical doctors gave a correct answer to the question about the concept of pharmacovigilance, which is identical to the data obtained in our study. The data on the knowledge of doctors of medicine obtained in

other studies are similar[25,26]. In contrast to these studies, the study conducted in Romania found that only 22.6% of medical doctors knew about the pharmacovigilance system[27]. One research carried out in the Netherlands found that 90% of respondents knew the purpose of pharmacovigilance[28].

The results obtained about the knowledge of dentists in our survey compared to other surveys[28-30] indicated that dentists did not know enough about the concept and purpose of pharmacovigilance. The lack of knowledge about the pharmacovigilance system by nurses/technicians, which we also registered, is in line with the literature data[31, 32]. However, a study conducted in Turkey[33] showed that nurses/technicians had a higher level of knowledge about adverse drug reactions compared to respondents in our study.

Our survey showed that 79.0% of pharmacists, 65.0% of surveyed medical doctors, 25.0% of dental doctors and 6.0% of nurses/technicians know that there is a mandatory obligation to report adverse drug reactions. The percentage difference between pharmacists *versus* other health professionals was statistically significant for $p<0.05$ (Difference test, p=.0000) (question no. 3). In order to obtain more detailed information about the knowledge of healthcare professionals regarding the obligation for reporting adverse drug reactions, the survey questionnaire also contained a question on the exact determination of healthcare professionals who have the obligation to report adverse drug reactions (question no. 4). The results showed that 67.0% of pharmacists, 50.0% of surveyed doctors of medicine, 22.0% of doctors of dentistry and 19.0% of nurses/technicians gave a positive response that all health professionals had an obligation to report an adverse reaction to a drug. The percentage difference between pharmacists *versus* other health professionals was statistically significant for $p<0.05$ (Difference test, p=.000). The obtained data indicated that a large number of health professionals knew the obligations for reporting an adverse reaction to drugs, which was in accordance with the research available in the literature, especially with the research in the European Union countries[34-37]. In the literature available to us, the largest number of health professionals stated that reporting adverse drug reactions was a professional obligation and they recognized it as such[27, 38-42].

In other studies, the attitude of health workers was examined, whether registration should be mandatory or on a voluntary basis. Thus, in Romania, majority of doctors of medicine (60.1%) believed that reporting should be mandatory[27], similar to doctors from the United Arab Emirates 66.7% [43], Pakistan 80%[44], while in a study conducted in India, the range of healthcare professionals who believed that reporting ADRs was from 51% to 95%[45-50].

The results obtained in our study have indicated that the largest number of health professionals know that a system of pharmacovigilance has been established in the Republic of North Macedonia (question no. 5) and that the Agency for Medicines and Medical Devices (MALMED) is the regulatory body responsible for monitoring adverse drug reactions (question no. 6). However, in our survey, a small number of respondents answered correctly to the question that the International Centre for Monitoring Adverse Drug Reactions was located in Uppsala, Sweden (question no. 7). Similar results were obtained in the study by Gupta[7] and Nisa[51].

Regarding question no. 8, that is, have you seen the form for adverse drug reaction reporting, 61.0% of pharmacists, 58.0% of doctors of medicine, 21.0% of doctors of dentistry, and 18.0% of nurses/technicians answered affirmatively. The percentage difference registered between health professionals - doctors of medicine and pharmacists *versus* doctors of dentistry and nurses/technicians was statistically significant for $p<0.05$ (Difference test, p=.0000). This form is part of the legal regulations of our country and is provided as a mandatory form of reporting adverse drug reactions in accordance with the Rulebook on the

method of reporting, the content of the form for reporting adverse drug reactions and the manner of organization of the pharmacovigilance system[52]. In literature, the question regarding the knowledge of the procedure and form for reporting adverse drug reactions is frequent in survey questionnaires, but the results obtained indicate different knowledge of the procedure and the form for reporting. Namely, in different studies conducted in different countries, pharmacists answered in a range from 45% to 100%[53-55]. Regarding the literature review on doctors of medicine, 71% of doctors of medicine in the UAE did not know how to report an adverse drug reaction [43]. This data is similar to the results obtained in India, where, in the study, the percentage of medical doctors who did not know how to report the adverse event was 92.5%[46], 55.6% in Malesia[56], 95.1% in Nigeria[57], 68% in Romania[58]. A study from Pakistan indicated that only 9.7% of respondents knew about the reporting procedure. Other studies from India showed that different rates of knowledge of the procedure for reporting adverse drug reactions varied from 6 to 75%[24, 26, 50, 59-62]. Belton's study found that the majority of healthcare professionals in the European Union did not know how to report an adverse drug reaction [63]. In literature, we did not find any data on the knowledge of dentists about the method of reporting adverse drug reactions. Santosh's research found that 83% of nurses/technicians did not know the method of reporting adverse drug reactions[64, 65].

In order to assess the knowledge of healthcare professionals, we asked them whether they know the deadline for reporting serious adverse reactions and events (without fatal outcome) from using a drug placed on the market. Regarding question no. 9, the correct answer, that is, that these adverse reactions and events should be reported within 15 days, was given by 38.0% of surveyed doctors of medicine, 27.0% of doctors of dentistry, and the highest percentage of correct answers (53.0%) was given by pharmacists. In contrast, only 6.0% of nurses/technicians gave the correct answer. The percentage difference between pharmacists *versus* other health professionals was statistically significant for $p<0.05$ (Difference test, p=.00). The Law on Medicines and Medical Devices of the Republic of North Macedonia provides for different deadlines for reporting adverse drug reactions[66]. According to the regulation, the deadline for submitting an ADRs report depends on the severity and anticipation of the ADR. Thus, some unexpected or serious ADRs must be reported within 15 days, those leading to death must be reported immediately, and others must be reported within 30 days, and this time accommodation may have led to a lag in reporting or non-detection of some ADRs, making the effect of the intervention decrease over time. In different countries, the deadline for reporting ADRs is different. According to the regulation of the People's Republic of China, identical deadlines for reporting ADRs are provided[67].

Adverse drug reactions can occur both in clinical trials of the drug and after the drug has been placed on the market. Therefore, we asked health professionals at what stage of clinical trials can rare adverse drug reactions be detected (question no. 10). 68.0% of surveyed doctors of medicine, 42.0% of doctors of dentistry gave the correct answer to this question, i.e., that rare adverse reactions to the drug can be detected during phase 4 of the clinical trial; the majority of them gave the correct answer, that is, 75.0% of pharmacists and 20.0% nurses/technicians. The percentage difference between doctors of medicine and pharmacists *versus* other health professionals was statistically significant for $p<0.05$ (Difference test, p=.00). In the study conducted in Sikkim, India, it was determined that 60% of health professionals knew that rare ADRs could be identified in phase-4 clinical trials[68]. Considering that phase IV of clinical trials are often used to investigate drug safety after approval, it is very important to have appropriate sample size with safety surveillance as a main task[69].

Regarding question no. 11, which referred to the knowledge of healthcare workers about the most common method used for monitoring adverse reactions to new drugs placed on the market, 70.0% of pharmacists, 55.0% of doctors of medicine, 45.0% of doctors of dentistry and 12.0% of nurses/technicians gave the correct answer. Spontaneous reporting system (SRS) is the most widely used system globally to report adverse reactions by health care professionals, drug companies, or patients themselves to the national authorities regulating PV activities in the country. SRS could improve the safety profile of a particular drug by detecting and reporting ADRs that may not have been detected during premarketing clinical trials or even during postmarketing surveillance. Therefore, it could serve as a method for detection of new, rare, or serious ADR events. One of the main advantages of SRS is that it applies to all drugs during its lifetime and is not limited to a period of study [70]. Datta S *et al*. in the research conducted in India found that 63% of health workers correctly identified spontaneous reporting system as the most commonly employed method to monitor ADR's [68].

Conclusion

The results obtained in this study showed that pharmacists' knowledge was significantly better than that of other healthcare professionals. In our research, doctors of medicine, although with weaker knowledge than pharmacists, showed a good level of knowledge of the pharmacovigilance system, while doctors of dentistry and nurses/ technicians had the least knowledge of this system.

We believe that by predicting the curricula on pharmacovigilance and the adverse drug reactions in the undergraduate studies, adequate knowledge of this system will be provided which will contribute to improving the quality of care for patients and reducing the under-reporting of ADRs.

Conflict of interest statement. None declared.

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