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ADVERSE DRUG REACTIONS OF PSYCOPHARMACS

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SUMMARY

Background: *The objective of analysis of ADRs caused by drugs that pertain to the ATC group N (nervous system), as reported to the Croatian Agency for Medicinal Products and Medical Devices for the period from March 2005 to December 2008, was to examine the types of ADRs collected in said period, the profile of reporters and the possible impacts this could have on prescribing this group of medicinal products in the future.*

Subjects and methods: *A retrospective observational study of ADRs was performed. Drugs causing ADRs were grouped according to the ATC drug classification, and subsequently entered into a database. Data were analyzed in respect of total number, gender, age, type, seriousness, expectedness, outcome, system organ class, suspected drug and reporter.*

Results: *The findings showed that 15% of all reported ADRs were caused by drugs from the ATC group N. 60% of these were caused by drugs belonging to the ATC subgroups N05 (psycholeptics) and N06A (antidepressants). A significant increase in the percentage of serious ADRs in the examined groups of medicinal products was observed. Analysis of expectedness showed that the share of unexpected ADRs is very high.*

Conclusion: *The distribution of reporters is not satisfactory. The Agency, as regulatory authority, cannot undertake certain measures to improve the safe use of medicinal products without having reports. Only reporting of ADRs can result in changes to benefit all patient populations. Our joint aim should be avoiding a great number of ADRs and maintaining overall safe use of medicinal products.*

Key words: *adverse drug reaction - psycopharmacs - seriousness - safe use of medicinal products*

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INTRODUCTION

The importance of adverse drug reactions (ADRs) monitoring was recognized in Croatia more than 30 years ago. Back in 1974, the National Centre for Adverse Drug Reactions was established within Zagreb University Hospital. In March 2005, after new legislation came into force, the obligation of pre- and post-marketing drug surveillance was delegated to the Agency for Medicinal Products and Medical Devices.

We analyzed ADRs caused by drugs that pertain to the Anatomical-Therapeutic-Chemical drug classification (ATC) group N (nervous system), as reported to the Agency for the period from March 2005 to December 2008. Two subgroups of special interest were psycholeptics (N05) and antidepressants (N06A). The objective of this analysis was to examine the types of ADRs collected in said period, the profile of reporters and the possible impacts this could have on prescribing this group of medicinal products in the future. Furthermore, our aim was to see if the Agency should take action to ensure the safe use of group N medicinal products.

SUBJECTS AND METHODS

A retrospective observational study of ADRs reported to the Croatian Agency for Medicinal Products and Medical Devices for the period March 2005 to December 2008 was performed. ADR reporting is the legal obligation of every healthcare professional in Croatia. Reporters can be healthcare professionals (physicians and pharmacists), manufacturers, marketing authorisation holders, or healthcare professionals participating in a clinical study as an investigator. They must report ADRs in writing, namely by post, telefax or electronic post using the prescribed form. For drugs, reports are submitted to the Agency, while for vaccines, reports are submitted both to the Agency and the Croatian National Institute of Public Health.

Drugs causing ADRs were grouped according to the Anatomical-Therapeutic-Chemical drug classification (ATC), and subsequently entered into a database. Data were analyzed in respect of total number, gender, age, type, seriousness, expectedness, outcome, SOC (System Organ Class), suspected drug and reporter.

ADRs were considered only if the relatedness to the use of the suspected drug was evaluated as possible, probable or certain (Karch & Lasagna 1975).

The type of reaction was determined according to definitions of adverse drug reactions (Edwards & Aronson 2000). Adverse reactions can be divided into certain types. Characteristics of type A are following: they are common (≥1%), foreseeable, dose-dependent, with low mortality and may withdraw after a period of adaptation. They result from the excessive pharmacological effect of the drug. Characteristics of type B are the following: they are not expected, not dose-dependent, the mechanism is not always known, they

appear during the time of usage of the drug, with a low frequency (<1%), they have high mortality, usage of suspected drug must be discontinued and an appropriate anti-allergic treatment must be applied. They are independent of the main pharmacological effect of the drug. A type F adverse reaction means therapeutic failure.

ADRs were considered serious if one of the following criteria was met according to the ICH E 2A guideline: the ADR resulted in death, the ADR was life threatening, the ADR required inpatient hospitalization or prolongation of existing hospitalisation, the ADR resulted in persistent or significant disability/incapacity, the ADR was a congenital anomaly/birth defect, or the ADR was another important medical event in according to CIOMS V (Council for International Organizations of Medical Sciences) (CIOMS 2001).

The expectedness of adverse reactions is assessed by criteria of its presence in the summary of product characteristics approved in Croatia, which is the expert basis on medicinal products for healthcare professionals. If a suspected ADR, in association with the specific medicinal product, is related to signs and symptoms of recognised reactions that are listed in the product information for that medicinal product, the adverse reaction is expected. If it is not the case, the adverse reaction is classified as unexpected.

There are six categories of ADR outcomes: recovered/resolved, unknown, not recovered/not resolved, recovering/resolving, recovered/resolved with recurrences, fatal - reaction may be contributory.

Data concerning the suspected ADRs were coded using the MedDRA (Medical Dictionary for Drug Regulatory Affairs) adverse drug reaction terminology into the related SOC (System Organ Class).

Reporters were classified into the following groups: hospital/non-hospital psychiatrist, general practitioner, hospital/non-hospital specialist other than psychiatrist, pharmacist, Marketing Authorisation Holder (MAH) and other healthcare professional.

The Statistical Package for the Social Sciences (SPSS), version 17.0 was used in the data analysis.

RESULTS

During the period May 2005 – December 2008, the Agency received a total of 168 reports of adverse drug reactions, whose relatedness to the use of suspected drugs of the ATC group N was evaluated as possible, probable or certain. In those reports, a total of 370 adverse reactions were reported.

The gender distribution of patients experiencing ADRs was 58.7% female and 48.3% male patients. The patient age range at the time the ADRs appeared was 17 to 86 years of age.

The distribution of types of reported ADRs is as follow: 89.4% of ADRs pertaining to type A, 7.6% pertaining to type B and 2.9% pertaining to type F.

The proportion of serious ADRs reported for the drug-groups N05A and N06A, both serious and non-serious, in comparison with all drugs is shown in Figure 1. Among the reported adverse reactions (370), 41.7% were unexpected.

The overview of the percentage of each group concerning the outcome of ADRs resulted in the following: 52.5% were recovered/resolved, 25.0% were unknown, 4.4% were not recovered/not resolved, 7.1% were recovering/resolving, 6.3% were recovered/resolved with recurrences, and 0.8% were fatal.

Table 1. Distribution of the most frequently reported ADRs by SOC

SOC	Percent (%)	ADR	Percent (%)
Nervous system disorders	20.7	Headache	3.8
		Tremor	2.5
		Dizziness	1.6
		Neuroleptic malignant syndrome	1.6
		Restless legs syndrome	1.6
		Parkinsonism	1.4
		Somnolence	1.4
Psychiatric disorders	19.1	Insomnia	3.6
		Restlessness	1.6
		Suicidal ideation	1.6
		Libido decreased	1.4
Gastrointestinal disorders	13.2	Nausea	3.3
		Dry mouth	1.4
		Salivary hypersecretion	1.4
General disorders and administration site conditions	10.5	Ashtenia	1.4
		Oedema peripheral	1.4
Investigations	8.9	Weight increased	5.2
Reproductive system and breast disorders	5.6	Erectile dysfunction	1.6

A distribution of the most frequently reported ADRs by SOC are shown in Table 1. The most frequently reported ADRs were weight gain (n=19), headache (n=14), insomnia (n=13), nausea (n=12), tremors (n=9) and restless leg syndrome, restlessness, neuroleptic malignant syndrome, dizziness, erectile dysfunction, and suicidal ideation with 6 reports (n=6).

Suspected drugs with the percent of reported ADRs and drug consumption score are shown in Table 2. The distribution of reporters is shown in Figure 2.

Table 2. List of the most common suspected drugs in comparison with their DDD per 1000 inhabitants per day in Croatia

Suspected drug	Percent of reported ADRs (N)	No.	DDD/1000inh/day	No.
N05A Antipsychotics				
olanzapine	17.1% (30)	1	3.174	8
clozapine	9.1% (16)	3	1.454	15
haloperidol	6.9% (12)	6	4.649	4
risperidone	5.1% (9)	7	3.956	6
sulpiride	4.0% (7)	8	1.342	16
ziprasidone	2.9% (5)	9	0.092	23
quetiapine	2.3% (4)	10	1.009	17
fluphenazine	0.6% (1)	13	2.920	9
levomepromazine	0.6% (1)	13	0.565	19
promazine	0.6% (1)	13	4.301	5
N06A Antidepressants				
sertraline	12.0% (21)	2	5.789	3
fluvoxamine	8.6% (15)	4	3.776	7
escitalopram	9.1% (16)	3	2.465	11
paroxetine	8.0% (14)	5	10.737	1
venlafaxine	2.9% (5)	9	0.463	20
tianeptine	2.3% (4)	10	2.754	10
citalopram	1.7% (3)	11	2.137	13
fluoxetine	1.7% (3)	11	5.940	2
mirtazapine	1.7% (3)	11	0.877	18
maprotiline	1.1% (2)	12	2.045	14
amitriptyline	0.6% (1)	13	2.206	12
moclobemide	0.6% (1)	13	0.381	22
reboxetine	0.6% (1)	13	0.400	21

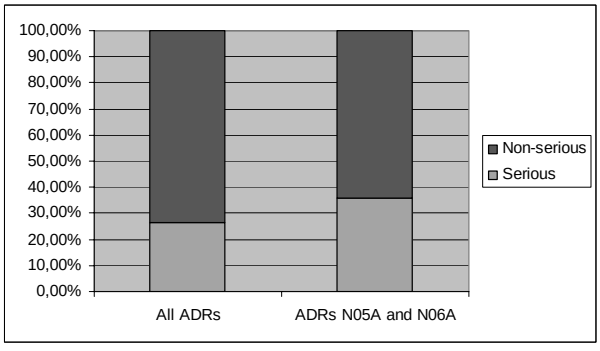

Figure 1. Comparison of seriousness for all medicinal products and drugs pertaining groups N05A and N06A (p=0.009)

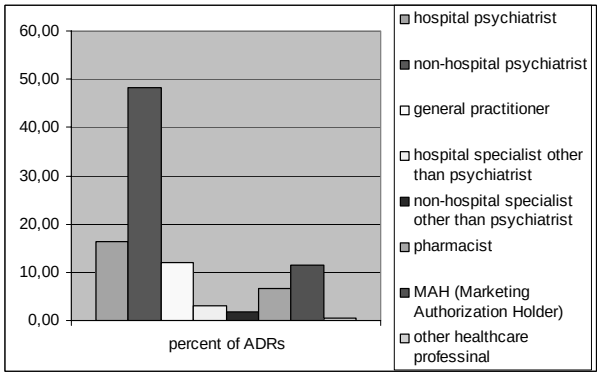

Figure 2. Profile of reporters

DISCUSSION

The results of the conducted retrospective observational study of reported ADRs show a typical pattern in respect of gender distribution (Macolić Šarinić 2008). It is well known that ADRs are slightly more common in females, and the present study showed no discrepancy in that regard. The age range is similar to other suspected medicinal products that the Agency has received in past years. The median age in targeted ADRs was 46.5 years of age. This median age is in compliance with the reported ADRs. Overall, the highest number of reports was received for the range of 41–64 years of age. Furthermore, an increasing trend was observed for this age range.

The review of distribution of ADRs by type showed a decrease in type B reactions and slight increase in type F reactions for the N group (ATK) of drugs. This decrease in type B reactions is in line with the decreased percentage of ADRs belonging to SOC Skin and subcutaneous tissue disorders, accounting for 3.8%, and SOC Immune system disorders, accounting for 0.3%, in comparison with the overall percentage for all other medicinal products of named SOCs, accounting for approximately 21.6% and 1.2%, respectively. The increase in type F is expected as many ADRs are indistinguishable among the symptoms of disease, and the efficacy of group N drugs is observed after longer use in comparison with other groups of drugs. With regard to SOCs, the distribution of the most common SOCs is expected for the reviewed group of drugs. As expected, the presence of SOC Nervous system disorders and SOC Psychiatric disorders exceeds their share in overall ADRs, accounting for 11.3% and 4.5% respectively.

A significant increase in the percentage of serious ADRs in the examined groups of medicinal products (35.71%) was observed in comparison with all medicinal products (26.51%). There is a statistically significant difference between the proportion of serious ADRs of psycopharmacs and the proportion of serious ADRs of all medicinal products (p=0.009). This is a very important and anticipatory finding.

Analysis of expectedness showed that the share of unexpected ADRs is very high. It is likely that the reporters are not aware of this classification and the importance of reviewing the approved summary of product characteristics. Reporting unexpected ADRs is very important as this is very valuable information which can be identified as signals.

The review of the outcome of ADRs showed that it was unknown for one fourth of cases. That is the usual number and indicates the shortcomings of the current ADR reporting form. It also emphasises the importance of workshops on the role of physicians and pharmacists in reporting adverse reactions and the pharmacovigilance system in Croatia. At these workshops, organised by the Agency, healthcare professionals learn how to fill out the reporting form. The fatal outcome of 0.8% will be discussed below.

No significant correlation between the number of ADRs for each suspected drug and the pharmacoeconomic score (DDD/1000/day) of drug consumption was observed. There are few well known moments when analysing reported ADRs. Firstly, the Agency does not have access to the absolute number of ADRs. In accordance to the available data, only about 6% of all ADRs are reported (Francetić & Huić 2007). The percentage of serious ADRs reported is higher and accounts for about 10%. Healthcare professionals more frequently report ADRs for new medicinal products or new pharmaceutical formulations. An example in this study is olanzapine. It is presumed that more ADRs were reported because a new formulation is available on the Croatian market. Furthermore, there are medicinal products for which all prescribers are aware of the specific safety profile and thus implies more reports of ADRs (e.g., clozapine). The possible attribute in misinterpretation cause the medicinal products which are long on the market and for which the number of reported ADRs is decreasing. All the above mentioned causes impact the reporting of ADRs. The ADRs that most trouble patients and worry prescribers are more frequently reported. A pattern would be observed if the number of ADRs would be very high for a certain drug, and the drug consumption score low. As such, no strong conclusions can be made, though there are always indicators present among the reported ADRs.

Among the reported ADRs, a serious reaction neuroleptic malignant syndrome stands out, and was reported for haloperidol (n=3) and risperidone (n=3). The Agency presumes that neuroleptic malignant syndrome is even more frequent, but is not likely reported despite the legal obligation to do so in Croatia. The Agency is conducting particular promotion on reporting serious ADRs.

Also, an interesting finding is that some drugs show a grouping of ADRs. For olanzapine, reports were received of 2 cases of diabetes mellitus, 4 cases of oedema peripheral and even 8 cases of weight gain all of which can be also be part of a metabolic syndrome. The issues regarding reporting for olanzapine were listed above, namely: a new pharmaceutical formulation and increased perception of both patients and healthcare professionals. All reported cases of salivary hypersecretion were for clozapine as the suspected drug.

The ADRs that are worrisome are those related to cardiac disorders, as they are potentially fatal and markedly underreported (Hazell & Shakir 2006). For the group of antipsychotics, the following ADRs were reported: death (n=1), electrocardiogram QT prolonged (n=1), myocardial infarction (n=1), angina pectoris (n=1) and chest pain (n=1). For the group of antidepressants, the following ADRs were reported: tachycardia (n=3), chest discomfort (n=2), palpitations (n=1). It is necessary to emphasize the monitoring of patients in order to perceive cardiac disorders and prevent fatal cases.

The distribution of reporters is not satisfactory. It is evident that the share of hospital psychiatrists is very low in the total number of reporters. It is expected that they are first to observe serious and unexpected ADRs for the drug group N that are presumably underreported and, as such, they are crucial for benefit/risk assessment.

As previously mentioned, there are some limitations in reviewing the reported ADRs and in decision making. The Agency does not have access to absolutely all ADRs. Many ADRs are not reported as they are assessed by healthcare professionals as well known, non-serious, and not disabling, or a certain insecurity is present in the sense of a possible accusation for the inadequate treatment of patients. It is important to stress that every ADR is valuable and the information on reporters are confidential and available only to the Agency. These are not valid reasons for not reporting ADRs.

CONCLUSIONS

It is assumed that too few observed ADRs are actually being reported to the Agency. It is important to emphasise that the portion of hospital psychiatrists of the total number of reporters is pronouncedly low, when serious and severe ADRs are most commonly presented in hospitalised patients or patients are being hospitalised because of severe ADRs. The profile of ADRs for the analysed group N drugs differs in comparison with the profile of adverse reactions for other medicinal products. The group N drugs had a greater incidence of serious ADRs, exceeding the mean value of 25% which is usual for medicinal products. It is important to stress the signal of an appearance of cardiovascular ADRs, for example cardiac arrhythmia, QT interval prolongation and reports of sudden deaths that can be caused by malignant cardiac arrhythmia. It is necessary to pay greater attention to patients who have risk factors for developing these kinds of ADRs, and to report every suspicion that a medicinal product caused a sudden death. Also, it is important to note that there is a high share of unexpected ADRs among the spontaneous reports, which are very significant for further monitoring of the safety profile of N group drugs. In Croatia, psychiatrists are confronted with ADRs in their daily practice. It is evident that they are dealing with them frequently and that recommendations are given for individual cases (Jakovljević 2009, Uzun & Kozumplik 2009). The Agency, as regulatory authority, cannot undertake certain measures to improve the safe use of medicinal products without having reports on the reactions that occur in daily practice. Only reporting of ADRs can result in changes to benefit all patient populations. When adverse reactions are reported, some signals can be identified and can result in changes of posology (dose recommendations), special warnings and precautions for use, or recommendations for special patient groups. This then results in avoiding a great number of ADRs and maintaining overall safe use of medicinal products.

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