Daria SCHETZ[1,2]
Piotr KABATA[2]
Jacek SEIN ANAND[1,2]

Pharmacovigilance and toxicovigilance system in Pomeranian province in 2015

System farmakowigilancji i toksykowigilancji w województwie pomorskim w 2015 roku

[1]Zakład Toksykologii Klinicznej, Gdański Uniwersytet Medyczny, Polska
Kierownik: dr hab. n. med. Jacek Sein Anand

[2]Pomorskie Centrum Toksykologii, Gdańsk, Polska
Kierownik: dr n. med. Wojciech Waldman

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In Pomeranian Centre of Toxicology (PCT) pharmacovigilance (PhV) system is organized simultaneously with toxicovigilance system (ToxV).

The purpose of the study was to explore the effectiveness and usefulness of the adverse reactions monitoring system in which PhV and ToxV are organized according to a common scheme.

We evaluated the effectiveness of our PhV and ToxV system and investigated the frequency and the nature of adverse reactions after drugs and other chemical substances administration.

All ADRs were designated as "A-type reactions" or "B-type reactions" according to their nature.

The study has shown also some limitations of the standard form for ADRs monitoring (known as "yellow card") in case of reporting of adverse drug reactions after drug intoxication.

W Pomorskim Centrum Toksykologii system monitorowania działań niepożądanych leków jest połączony z systemem monitorowania powikłań występujących na skutek przedawkowania substancji chemicznych. Celem badania było zbadanie efektywności oraz przydatności tak skonstruowanego systemu. W badaniu oceniono częstość oraz rodzaj działań niepożądanych, które wystąpiły po przyjęciu leków. Dla celów badania wprowadzone zostały terminy: ADRsDTox – w przypadku wszystkich reakcji, które wystąpiły w konsekwencji przedawkowania leków oraz ADRsCU – dla reakcji, które wg charakterystyki produktu leczniczego występowały w czasie prawidłowego stosowania farmaceutyków. Wszystkie działania niepożądane zostały sklasyfikowane jako reakcje A lub B. Badanie pokazało ponadto wady i ograniczenia standardowo używanego formularza tzw. „żółtej karty" stosowanego w przypadku zgłaszania działań niepożądanych będących przyczyną przedawkowania leków.

Introduction

According to a new definition, formulated in EU directive 2010/84/UE, an adverse drug reaction (ADR) is understood as a harmful and undesirable reaction after drug administration that occurs regardless whether given dose was pharmacological or higher than recommended. Such approach enables prediction of consequences of both, irrational and rational drug uses.

ADRs can be divided into two major groups – "A type reactions" and "B type reactions" [1,2].

A type reactions are dose and action mechanism dependent, and therefore preventable.

B type reactions are often life-threatening and often unpredictable because they are independent on the dose nor mechanism of action of a drug.

The most common are idiosyncratic and allergic reactions, thus even smaller than recommended dose may cause life-threating symptoms.

Pharmacovigilance (PhV) is focused on both types, as they are relevant in certain circumstances. In some cases, individual differences between patients exist. Pharmacokinetics variabilities that may be the cause of ADRs also may occur, even when a drug is used correctly in recommended dose [3,4].

In some patients a small change in dosing can provoke serious ADRs, whilst dose reduction minimizes the risk of health-complications [5].

Given the above facts, ADRs monitoring is an important tool in toxicological departments. From the toxicological point of view it is essential to know the hazards associated with use of drugs. Knowledge of early symptoms can help recognize the reason of acute intoxication and predict its consequences that leads to improvement of patients outcome.

In case of poisonings it is very important to know whether the symptoms were caused by administration of normal, higher or lower that recommended doses of a drug.

In Poland PhV is organized in decentralized pattern. It was established that in each province regional PhV centre should be created.

As for the time of writing this paper only in 5 among 16 provinces such centres were created (Poznań, Kraków, Wrocław, Szczecin, Gdańsk) [6].

In Pomeranian region, PhV system is organized simultaneously with toxicovigilance (ToxV) in Pomeranian Centre of Toxicology (PCT) and is called: Adverse Drug & Chemical Substances Reaction Monitoring Centre" (ADChMC).

Adres do korespondencji:
Dr n. med. Daria Schetz
Pomorskie Centrum Toksykologii
ul. Kartuska 4/6
80 - 104 Gdańsk
E-mail: dariaschetz@gumed.edu.pl
Tel.: +48 58 682 19 39

The ADChMC is involved in early detection of all hazards associated with drugs and other chemical substances. The latter include diet supplements, household chemicals, novel psychoactive substances (NPS) and recreational drugs.

The purpose of the study was to explore the effectiveness and usefulness of a monitoring system in which PhV and ToxV are organized according to a common scheme.

We would like to present a new approach and alternative solution for drug-safety system model and show its importance. However, such system requires a lot of changes in the existing manner of ADRs reporting.

Methods

We evaluated the effectiveness of our PhV and ToxV system and investigated the frequency and the nature of adverse reactions (ARs) after drugs and other chemical substances administration.

Adverse drug reactions (ADRs) were divided into two groups: "ADRs as a result of drug intoxication" (ADRsDTox) and "ADRs as a result of correct use of a drug" (ADRsCU).

As ADRsDTox are understood reactions that were caused by incorrect use of drugs (overdose), whilst as ADRsCU are understood as reactions that were seen in case of correct use of drugs in normal doses (according to a drug label).

All ADRs were designated as "A-type reactions" or "B-type reactions" according to their nature and current knowledge. "A type reactions" when reactions are dose and mechanism of action dependent, and therefore preventable; and "B type reactions" when reactions are not dose and mechanism action dependent, and difficult to predict.

In the study we evaluated the standard form for ADRs monitoring (known as "yellow card") in case of ADRsDTox reporting.

Results

From the 31.12.2015 to 01.01.2016 there were 1293 ADRs of which 797 were seen after drug administration (Tab. I). Based on established classification, it was found that 168 accounted for ADRsCU, and 629 for ADRsDTox. Out of this cohort women constituted 73% and 69% population respectively (Tab. II).

The average age of the patients in case of ADRsCU and ADRsDTox were: 36 and 43 years respectively.

We found that in case of ADRsCU as many as 65 cases (38.69%) were serious, life-threatening or requiring hospitalization (Tab. II). Owing to the fact, that all ADRsDTox required hospitalization in PCT and very often were life-threatening, we established that all of them were serious.

Among ADRsCU 53.57% were "type--A reactions" while 46.42% were B-type reactions.

In contrast, ADRsDTox were generally classified as "A-type reactions" (96.50%) and merely 3.49% were categorized as "B--type reactions" (Tab. III).

The most common group of drugs that caused ADRsCU were: analgesics (23.46%), hypnotics and anxiolytics (20.67%), cytostatics (16.20%), drugs affecting cardiovascular system (11.17%), neuroleptics (8.93%), antidepressants (7.26%), respiratory tract affecting agents (7.26%), antibiotics (3.91%), and other (1.11%) (Tab. IV).

The most common symptoms were: gastrointestinal reactions (36%), CNS symptoms such as dizziness, drowsiness, memory problems (29%), hypotension (22%), tachycardia (20%), and rash (10%).

According to our data, four most frequently reported drugs that were responsible for the majority of ADRsCU were: acetylsalicylic acid (ASA) (n=17), simvastatin (n=13), cisplatin in combination with etoposide (n=10), and alprazolam (n=8).

The most common group of drugs that caused ADRsDTox were: drugs that affect CNS (59.78%), mainly neuroleptics (18.66%) and antidepressants (17.16%). Subsequently, there were analgesics (27.94%) among which the most frequently mentioned were drugs with minimal anti-inflammatory effects like paracetamol (12.57%) (Tab. V).

It has been observed, that the most frequent symptoms were: laboratory abnormalities (74%), central nervous system symptoms such as dizziness, deep sedation or even a coma, excitation, confusion (63%), cardiovascular symptoms including tachycardia, bradycardia, rise or drop in blood pressure (47%), and gastrointestinal disturbances (34%).

According to data, four most frequently reported drugs that were responsible for the majority of ADRsDTox were: paracetamol (125 patients), ibuprofen (51 patients) and quetiapine (41 patients).

The study has shown also some limitations of the standard form for ADRs monitoring (known as "yellow card") in case of ADRsDTox reporting. First of all, in case of ADRsDTox form was lacking some essential information:

1. Information whether ingested drug belonged to the affected patient.
2. How many hours have passed from administration of first to last dose of the drug and how high was the total dose (duration of administration from first to last dose).
3. Description of poisoning circumstances (eg. shortly after dose escalation).
4. A drug-plasma concentration when known.

Table I
Causes of ADRs.
Przyczyny występowania działań niepożądanych leków.

Agents	ADRs
Drugs	79 7
Diet supplements	15
Household chemicals	72
NPS	159
Drugs of abuse	82
Total	**1293**

Table II
Incorrect or correct use of drugs/supplements based on label of an agent.
Prawidłowe lub nieprawidłowe stosowanie leków/suplementów diety w oparciu o charakterystykę produktu leczniczego.

Agent	Total	ADRsDTox		ADRsCU			
		N	%	N	%	Severe reactions	
						N	ADRsCU [%]
Drugs	797	629	78.92	168	21.07	65	38.69
Diet supplements	15	4	26.66	11	73.33	0	0
Total	**965**	**633**		**179**		**65**	**38.69**

Table III
Classification according to type of ADRs.
Podział według rodzaju działania niepożądanego leków.

	Types of reaction			
	A-type		B-type	
	N	%	N	%
ADRsCU	90	53.57	78	46.42
ADRsDTox	607	96.50	22	3.49

Table IV
ADRsCU.
Działania niepożądane leków występujące w przebiegu ich prawidłowego stosowania.

Group of drugs	N	%
analgesics	42	23.46
sedatives and anxiolytics	37	20.67
cytostatics	29	16.20
Cardiovascular system	20	11.17
Neuroleptics	16	8.93
Antidepressants	13	7.26
Respiratory tract	13	7.26
Antibiotics	7	3.91
Other	2	1.11

Table V
Information about drugs that causes ADRsDTox.
Informacje na temat leków, które były przyczyną występowania ADRsDTox.

Target system	Group of drugs	Type of drugs	Agent	Number	Total (%)	(%)
CNS	Neuroleptics		levomepromazine	19	187 (18.66%)	
			chlorprothixene	35		
			perazine	18		
			aripiprazole	4		
			haloperidol	7		
			quetiapine	41		
			olanzapine	25		
			amisulpiride	3		
			sulpiride	5		
			risperidone	10		
			clozapine	20		
	Benzodiazepines		diazepam	28	85 (8.48%)	
			alprazolam	16		
			clonazepam	15		
			estazolam	12		
			lorazepam	6		
			nitrazepam	5		
			unknown	3		
	Anxiolytics	Antihistamines	hydroxyzine	35	35 (3.49%)	
	Z-drugs		zolpidem	24	24 (2.39%)	
	Antidepressants	Tricyclic antidepressants	opipramol	18	37 (3.69)	172 (17.16%)
			doxepin	11		
			amitriptyline	8		
		SSRI	sertraline	31	89 (8.88%)	
			fluoxetine	18		
			escitalopram	18		
			paroxetine	11		
			citalopram	7		
			fluvoxamine	4		
		SNRI	venlafaxine	10	10 (0.99%)	
		NaSSA	mianserin	16	16 (1.59%)	
		SARIs	trazodone	20	20 (1.99%)	
	Stimulants		methylphenidat	2	2	2 (0.19%)
	Antiepileptics		carbamazepine	43	93 (9.28%)	
			valproic acid	41		
			lamotrigine	6		
			topiramate	3		
	AChE inhibitors		donepezil	1	1 (0.09%)	
	Analgesics	Minimal anti-inflammatory effects	paracetamol	125	126 (12.57%)	280 (27.94%)
			metamizole	1		
		NSAIDs	ibuprofen	51	104 (10.37%)	
			ketoprofen	30		
			asa	17		
			diclofenac	4		
			naproxen	2		
		Opioids	tramadol		50 (4.99%)	
			codeine	23		
			methadone	9		
			mixed opioids	7		
			morphine	6		
			pethidine	4		

Table V
Information about drugs that causes ADRsDTox (Part II).
Informacje na temat leków, które były przyczyną występowania ADRsDTox (Część II).

Target system	Group of drugs	Type of drugs	Agent	Number	Total (%)	(%)
Cardiovascular system	Beta-blockers		propranolol	9	19 (1.89%)	68 (6.78%)
			bisoprolol	5		
			metoprolol	4		
			atenolol	1		
	Antihypertensive agents or/and diuretics	Ca blockers	amlodipine	12	12 (1.19%)	
		ACE inhibitors	ramipril	10	19 (1.89%)	
			captopril	7		
			enalapril	2		
		Diuretics	indapamide	5	9 (0.89%)	
			hydrochlorothiazide	3		
			furosemide	1		
		AT1 antagonists	valsartan	2	3 (0.29%)	
			candesartan	1		
	Cholesterol-lowering agents	Statines	simvastatin	3	6 (0.59%)	
			atorvastatin	2		
			rosuvastatin	1		
Infections	Infections		ciprofloxacin	6	14 (1.39%)	
			amoxicilin	5		
			clindamycin	2		
			metronidazole	2		
			nifuroxazide	1		
Others			levothyroxine	19	59 (5.88%)	
			dextromethorphan	12		
			metformin	10		
			baclofen	5		
			omeprazole	4		
			prednisone	3		
			cetirizine	3		
			loratadine	2		
			drotaverine	1		
				1002		

5. Information about any ADRs following administration of antidote.

In the analyzed period ADRsCU monitoring led to detection 2 new and previously undescribed in the medical literature reactions after drug administration.

Discussion

It was stated above, that a new approach to definition of ADRs enables to predict consequences of irrational and rational uses of drugs. From this point of view it is worth to emphasize that ADRs are reported by the doctors and pharmacists on the one established form ("yellow card" or electronic form) [6].

In our study as many as 629 reports were associated with administration of toxic doses of drugs.

In this case all reactions were severe, because according to the definition "severe reactions" are life-threating and need hospitalization or medical observation [7].

In contrast, in case of ADRsCU, 38.69% were severe. Based on this these conclusions, we confirm that introduction of different terms such as ADRsCU and ADRsDTox in the study is valid. Such division can prevent misinterpretation of the data. It is important that in case of normal use of drugs almost 39% reactions were severe.

In our study it was also visible that there are significant differences in the occurrence of a particular type of ADRs: "A-type reactions" and "B-type reactions" in case of ADRsCU and ADRsDTox.

While in case of ADRsDTox the most common were "A-type reactions (96.50%), in case of ADRsCU they occurred with similar frequency ("A-type reactions" were seen in 53.57% of the population). It can be assumed, that in cases of recommended use of drugs, 53.57% of the population suffered from drug complications that were preventable.

It is worth highlighting that ADRsCU can talk about toxicity even when a drug is used correctly, in doses that are accepted by rest of population.

According to our study such situation was seen often in case of antineoplastic agents, and this conclusion is supported by other researchers [8].

The study has shown also some limitations of the standard form for ADRs monitoring (known as "yellow card") in case of ADRsDTox reporting.

This limitations were solved by suggesting a new form for ADRsDTox monitoring and indication an important issues in case of ADRsDTox.

In many conditions drug absorption after drug intoxication can be modified [4], and as a result its bioavability changes. Based on these observations it should be noted, that in toxicology it is very important to know not only administrated dose of a drug, but also its serum concentration of a drug if it is known. This issue should be included separately in reporting form for ADRs monitoring. In our study we could observe, that in case of drug poisoning, the information obtained from the patient on the number of tablets ingested would frequently vastly vary from real plasma concentration of a drug.

From the toxicological point of view it is also necessary to know whether a drug belonged to a patient, since symptoms after overdose may vary significantly depending on whether the patient has developed tolerance or not. Such information should also be included in reporting form.

This is another one justification that supports the notion, that terms ADRsDTox and ADRsCU are very important from the toxicological and pharmacological point of view.

The study has shown that in case of ADRsDTox majority of suicide poisonings were caused by drugs that affecting CNS system, especially neuroleptics and antidepressants that were paradoxically prescribed to treat mental diseases.

The most frequently reported drug, that was responsible for the majority of ADRsCU was acetylsalicylic acid (ASA). The agent is very popular not only because is available as OTC medicine, but also widely used in prevention of myocardial infarction. Owing to its pharmacological properties ADRs, such as: bleeding, gastrointestinal (GIT) symptoms, idiosyncratic reactions (eg. aspirin-induced asthma) are very probable [9].

Conclusions

ADRs monitoring is an important tool in toxicological departments. We confirm the validity of introduction different terms such as ADRsCU and ADRsDTox in the study. The study has shown also some limitations of the standard form for ADRs monitoring (known as “yellow card”) in case of ADRsDTox reporting. The first of all is that in case of ADRsDTox form should be adjusted and contain additional information that are essential in case of intoxication.

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