Scholars Academic Journal of Pharmacy (SAJP) **ISSN 2320-4206 (Online)**
Sch. Acad. J. Pharm., 2015; 4(2): 117-123 **ISSN 2347-9531 (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublisher.com

Research Article

Analysis of Reports Received by the Pharmacovigilance Unit of National University of San Luis, Argentine

Alicia del C. Panini[1], Mauricio R. Teves[2], Marisa H. Garraza[3], Emiliano Giraudo[4], Claudia P. Calderón[5*]
[1]Teaching Assistant of Hygiene and First Aid, Faculty of Chemistry, Biochemistry and Pharmacy, National University of San Luis. San Luis, Argentina
[2]Teaching Assistant of Pharmacology, Faculty of Chemistry, Biochemistry and Pharmacy, National University of San Luis. San Luis, Argentina
[3] Associate Professor of Physiology, Faculty of Chemistry, Biochemistry and Pharmacy, National University of San Luis. San Luis, Argentina
[4] Research fellow in Pharmacology, National University of San Luis, San Luis, Argentina
[5]Adjunct Professor of Pharmacology, Faculty of Chemistry, Biochemistry and Pharmacy, National University of San Luis. San Luis, Argentina

***Corresponding author**
Dr. Claudia P. Calderón
Email: cpcalderon2000@gmail.com; ccal@unsl.edu.ar

Abstract: Pharmacology of the National University of San Luis was designated as Peripheral Effector of the National Pharmacovigilance System of the National Administration of Drug, Food and Medical Technology in September 2010. The spontaneous reports received of adverse events, medication errors, and lack of efficacy, were analyzed since its conformation until November 2013. The reports were mainly Adverse Events, mostly preventable, possible and mild. Adverse effects were disorders mainly gastrointestinal, general disorders of the organism, of skin and appendages, and psychiatric disorders; while the accused drugs mostly corresponded to the nervous, musculoskeletal and cardiovascular systems. Female gender and patients aged 20-39 years were most affected. Duplication of efforts for greater professional and community formation in Pharmacovigilance, would allow us to increase the quality and quantity of notifications, all for the benefit of the health of the population.
Keywords: Adverse drug reaction, adverse event, Pharmacovigilance, spontaneous reports, peripheral effector.

INTRODUCTION

Medications currently offer many advantages, which are offset by adverse drug reactions (ADR) which generate, which can lead to disease, disability and death in many cases preventable.

An ADR is the undesired effect attributable to the administration of a drug at doses normally used in humans to prevent, diagnose or treat a disease or to modify any biologic function [1]. On the other hand, an ADR must be differentiated of an event or adverse event (AE), the latter being any unfortunate medical event that may occur during treatment with a drug, but has no necessary causal relationship with this treatment. Although coincidence in time is observed, that exists relationship causal is not suspected [2].

The World Health Organization (WHO) defines Pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects of medications or other health problems related to them [1]. The Pharmacovigilance studies the unwanted effects of drugs, mainly produced by drugs, as well as by herbs, complementary medicines, biologics, blood products, vaccines and medical devices, medication errors, efficacy lack, and others [3]. The use of drugs in indications unapproved and without scientific justification, in lower doses; acute and chronic intoxications with drugs; evaluations of drug-related mortality; abuse and misuse of drugs; and drug interactions with other medicines, chemicals, food and drinks, are added to it [1].

Pharmacovigilance has its beginnings in Germany in the 60s, with the occurrence of the "tragedy of thalidomide", drug that after being launched commercially, brought serious consequences in newborns due to its teratogenic effects. This led to that several countries began stricter monitoring, and established the regulatory mechanisms of control to ensure the safety, quality and efficacy of drugs available in the market for consumption.

WHO established an international program of monitoring of drugs, which since 1978 is conducted by the Uppsala Monitoring Centre in Sweden (UMC, Uppsala Monitoring Centre).

In Argentina, on 21 September 1993, the National System of Pharmacovigilance(NSPV) was created by Resolution 706/1993 of the Ministry of Health and Social Action of the Nation, considering it as "an indispensable tool for control and supervision of medicinal specialties, allowing early detection of adverse and/or unexpected effects of drugs during their stage of widespread use, also facilitating the perception of failures in the therapeutic response due to quality deficiencies" [4]. From 1994, the NSPV of Argentina was recognized by the UMC as country member [5].

This NSPV is organized on a central effector that is located in the Pharmacovigilance Department, belonging the National Administration of Drugs, Food and Medical Technology (ANMAT) and receives the participation of the Peripheral effectors operating in different parts of our country.

The Department of Pharmacology del Department of Pharmacy, Faculty of Chemistry, Biochemistry and Pharmacy, National University of San Luis (UNSL) was designated as Peripheral Effector of this NSPV in September 2010. Moreover, the UNSL protocolized its operation through the creation of the Unit of Pharmacovigilance (UPV-UNSL) in 2011, according to Resolution 858/11.

This work has as purpose to present of our initial experience as peripheral effector, analyze the spontaneous reports received during the first years of our establishment and determining the association between submission of ADR and the variables age and sex.

EXPERIMENTAL SECTION

A retrospective evaluation of spontaneous communications received at the UFV-UNSL was performed from designation as Peripheral effector (September 2010) to June 2013. Spontaneous reports were recorded in the notification forms of the UFV-UNSL, which are similar to ones of the NSPV of ANMAT [6]. The spontaneous reports that correspond to suspicions to AE, Medication Errors (ME) and reports of Events Supposedly Attributable to Vaccination and Immunization (ESAVI) were stored in Excel spreadsheets (Microsoft Office 2010). Notifications of suspected ADRs were classified in turn, according to the intensity of the clinical manifestations in Mild, Moderate, Severe, and Lethal or Fatales [7].

The Classification of the Naranjo algorithm to assign causality or attribution of ADR as Proven, Probable, Possible and Improbable, was used [8].

In turn, to establish whether the ADR was avoidable or unavoidable was used as tool the algorithm Hallas et al. [9]. The suspected drugs were coded by the classification system Anatomical Therapeutic-Chemical (ATC) proposed by the WHO [10], while the Terminology Adverse Reactions of the WHO was used for the coding of ADR [11].

The distribution of the ADR was determined by sex (male and Female) and age (separated into the following groups: <20 years, 20-39 years 40-59 years 60-79 years, and ≥80 years).

RESULTS

Of a total of 73 notifications received, the 97.26% (n = 71) correspond to AE, to ESAVI a 1.37% (n = 1), and a 1.37% to MS (n = 1). Most of the notifications were of the Female sex (n = 50; 68.49%).

The distribution of notifications by sex and the discrimination of the notification types according to sex are shown in Table 1.

Table 1: Proportion of reports by gender and type of report.

Character	Male n (%)	Female n (%)	Total *n* (%)
Reports	23 (31.51)	50 (68.49)	73 (100)
ReportType			
ESAVI	1 (100)	0 (0)	1 (100)
ME	1 (100)	0 (0)	1 (100)
AE	21 (29.58)	50 (70.42)	71 (100)

Referring to the reports AE, classified according to clinical manifestations proposed by ANMAT, it was observed that the vast majority were Mild intensity (n = 48; 67.61%) and to a lesser extent Moderate (n = 19; 26.76%) and Grave (n = 4; 5.63%); while notifications of intensity Fatal or Lethal were not found.

In Table 2, the intensity of the AE and its impact in relation to sex are shown.

Table 2: Effect of the intensity of the AE according to sex.

Character	Male n (%)	Female n (%)	Total *n* (%)
Intensity of AE			
Leve	12 (25)	36 (75)	48 (100)
Moderate	7 (36.84)	12 (63.16)	19 (100)
Grave	2 (50)	2 (50)	4 (100)
Lethal	0	0	0

Regarding the preventability of the ADR, it were determined that the majority were preventable and 17 (23.3%) were not avoidable.

From analysis of notifications segregated by age group, the following percentages are observed: <20 years: 15.07%; 20-39 years: 31.51%; 40-59 years: 26.03%; 60-79 years: 21.92%; ≥80 years: 1.37%. In Table 3, these values were differentiated by sex. Furthermore, in Table 4 the relationship between intensity of the AE and age are shown.

Table 3: Distribution of notifications by age group and sex.

Character	Male n (%)	Female n (%)	Total *n* (%)
Age Group			
<20	6 (54.55)	5 (45.45)	11 (100)
20-39	3 (13.04)	20 (86.96)	23 (100)
40-59	7 (36.84)	12 (63.16)	19 (100)
60-79	5 (31.25)	11 (68.75)	16 (100)
≥80	0 (0)	1 (100)	1 (100)
Empty	-	-	3

Table 4: Intensity of the AE by age.

		Intensity of the EA							
		Mild		Moderate		Severe		Lethal	
		n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
AgeRange	*<20 years*	5	(50)	5	(50)	0	(0)	0	(0)
	20-39 years	17	(73.9)	5	(21.7)	1	(4.4)	0	(0)
	40-59 years	10	(52.6)	6	(31.6)	3	(15.8)	0	(0)
	60-79 years	13	(81.2)	3	(18.8)	0	(0)	0	(0)
	≥80 years	1	(100)	0	(0)	0	(0)	0	(0)

By comparing Tables 2 and 4 arises a difference of 2 mild AE. This is due to lack of records of age corresponding to Table 4.

Notification of a single ESAVI was from the group of people under age 20, while the report of EM, lacked age.

The causality of ADR determined by the Naranjo algorithm produced the following results: Possible 65% Probable 35%. The empty records corresponded to reports of ME and ESAVI. In Table 5, the causality was differenced by sex.

Table 5: Differentiation of causality of ADR according to sex.

Character	Male n (%)	Female n (%)	Total *n* (%)
Imputability of ADR			
Possible	16 (30.19)	37 (69.81)	53 (100)
Probable	5 (27.78)	13 (72.22)	18 (100)
Empty	2 (100)	0 (0)	2 (100)

The Gastrointestinal System was the more affected by ADR, such as nausea, diarrhea and vomiting (32.35%, n = 33). Following to the notifications corresponding to general disorders of the body, mainly headache, fever, fatigue, pain and anaphylactic shock, with the 22.55% (n = 23). Finally, a 15.69% (n = 16) of the ADR were different disorders of the skin and appendages, such as rash, pruritus, dermatitis and urticaria. The other body disorders caused by ADR had less impact on communications received by our UPV-UNSL and are characterized in the Table 6, differing unitarily sex.

It is noteworthy that several of communications reported on the incidence of more than a disorder of the body.

Table 6: Disorders caused by ADR differentiated by sex.

Character	Male n (%)	Female n (%)	Total *n* (%)
Disorders			
Gastrointestinal System	10 (30.30)	23 (69.70)	33 (100)
General whole-body	8 (34.78)	15 (65.22)	23 (100)
Skin and appendages	5 (31.25)	11 (68.75)	16 (100)
Psychiatric	1 (11.11)	8 (88.89)	9 (100)
Peripheral and Central Nervous System	0 (0)	7 (100)	7 (100)
Respiratory System	2 (33.33)	4 (66.67)	6 (100)
Musculo-Skeletal System	1 (33.33)	2 (66.67)	3 (100)
Liver and Biliary System	1 (33.33)	2 (66.67)	3 (100)
Reproduction (women)	0 (0)	3 (100)	3 (100)
Cardiovascular, general	0 (0)	2 (100)	2 (100)
Metabolism and Nutrition	0 (0)	1 (100)	1 (100)
Erythrocytes	1 (100)	0 (0)	1 (100)
Urinary System	1 (100)	0 (0)	1 (100)

The drugs belonging to the group N (Nervous System: 17.81%; 13/73) of the ATC classification were mostly involved, followed by Group M (Musculoskeletal System: 15.07%; 11/73) and Group C (cardiovascular system: 13.70 %; 10/73).

In the Table 7, the suspected drug groups, according to ATC classification and gender differentiation, were individualized. Considering the drugs individually, the most commonly involved in the notifications received corresponded to paracetamol, which caused four AE, while cephalexin, diclofenac and ibuprofen caused three AE each.

Table-7: Major drugs suspects to produce ADR, grouped according to ATC classification.

ATC Group	Drugs	Male *n* (%)	Female *n* (%)	Total *n* (%)
N		0 (0)	13 (100)	13 (100)
	Paracetamol	0	4	4
	Alprazolam	0	2	2
	Carbamazepine	0	1	1
	Dextropropoxyphene + Dipyrone	0	1	1
	Dimenhydrinate	0	1	1
	Dipyrone	0	1	1
	Fluoxetine	0	1	1
	Lamotrigine	0	1	1
	Paracetamol + Chlorpheniramine + Bromhexine + Pseudoephedrine	0	1	1
M		5 (45.45)	6 (54.55)	11 (100)
	Diclofenac	1	2	3
	Ibuprofen	2	1	3
	Ibandronate	0	1	1
	Ketoralac	0	1	1
	Meloxicam	1	0	1
	Meloxicam + Glucosamine	0	1	1
	Piroxicam	1	0	1
C		3 (30)	7 (70)	10 (100)
	Amlodipine	1	1	2
	Enalapril	0	2	2
	Atenolol	1	0	1
	Carvedilol	0	1	1
	Fenofibrate	0	1	1
	Lisinopril	0	1	1
	Metoprolol	1	0	1
	Simvastatin + Ezetimibe	0	1	1
J		4 (44.44)	5 (55.56)	9 (100)

	Cephalexin	1	2	3
	Amoxicillin	1	1	2
	Amoxicillin + Clavulanicacid	0	2	2
	Metronidazole	1	0	1
	Varicella	1	0	1
A		2 (25)	6 (75)	8 (100)
	Metformin	0	2	2
	Ranitidine	1	1	2
	Mesalazine	0	1	1
	Pantoprazole	0	1	1
	Sibutramine	1	0	1
	Vitamins + Minerals	0	1	1
G		0 (0)	4 (100)	4 (100)
	Cyproterone + Ethinylestradiol	0	1	1
	Drospirenone + Ethinylestradiol	0	1	1
	Levonorgestrel + Ethinyl	0	1	1
	Miconazole + Metronidazole + Hydrocortisone	0	1	1
R		3 (75)	1 (25)	4 (100)
	Budesonide	1	0	1
	Mometasone	0	1	1
	Salbutamol	1	0	1
	Tiotropium	1	0	1
L		0 (0)	3 (100)	3 (100)
	Methotrexate	0	2	2
	Capecitabine	0	1	1
D		2 (100)	0 (0)	2 (100)
	Betamethasone + gentamicin + Micomazol	1	0	1
	Chlorhexidinedigluconate	1	0	1
H		0 (0)	2 (100)	2 (100)
	Levothyroxine	0	1	1
	Meprednisone	0	1	1
B		2 (100)	0 (0)	2 (100)
	Aspirin	2	0	2
S		0 (0)	1 (100)	1 (100)
	Hydroxypropylmethylcellulose	0	1	1
V		0 (0)	1 (100)	1 (100)
	Iodine	0	1	1
Vacuum		2 (66.67)	1 (33.33)	3 (100)

N: nervous system, M: musculoskeletal system, C: cardiovascular system, J: antimicrobial, A: Alimentary tract and metabolism, G: genitourinary and sexual hormones, R: respiratory system, L: antineoplastic and immunomodulating, D: dermatological, H: hormones for systemic use, B: blood, S: organs, V: Other

DISCUSSION AND CONCLUSIONS

The ADRs are a major health problem, with high worldwide prevalence, and generate high costs in health systems. Therefore, the Pharmacovigilance is keyto identify, evaluate, analyze and prevent risks of using drugs marketed. In this analysis of spontaneous reports received by the UPV-UNSL, we have been able to detect and analyze retrospectively, a small part of the ADR that take place in our reference population. This is mainly due to the low participation of health professionals in the notification of AE, ME and ESAVI detected in our peripheral effector, as well as by a significant lack of know about of the existence of the notification system.

The ADRs were mostly avoidable possible and mild, and the patients recovered fully. Only one of the patients of 51 years old was hospitalized for a ADR caused by dipyrone.

While most of notifications correspond to patients who are between 20-39 years, the ranges 40-59 and 60-79 years were also significantly affected, which could be a result of the major consumption of drugs that frequently exists by adults and seniors.

Of analysis of spontaneous reports received by the UPV-UNSL, Female gender was mainly affected, corresponding approximately to twice the male gender. In concordance with other authors, who reported that

the occurrence of ADR is more common in Female sex [12-13].

Various Drugs caused ADR, those who act on the nervous system, caused more ADR, followed by those acting on the musculoskeletal system and the cardiovascular system; paracetamol, cephalexin, diclofenac and ibuprofen were the most involved. Most studies agree that the drugs most frequently involved in the emergence of ADR are those belonging to the non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics [14-17]; coincident circumstances with the results obtained in our analysis of spontaneous reports that were received in the UPV-UNSL.

Adverse effects were mainly gastrointestinal disorders, general disorders of the organism, of skin and appendages, and psychiatric disorders. These results are consistent with studies indicating that the organs of the gastrointestinal system and skin are often the most affected [14,16,18-20].

Given the prevalence of adverse reactions, is considered of great importance to public health that is promoted the provision of new peripheral effectors. It is also necessary encourage the realization of an active Pharmacovigilance, and the constitution of groups of trained professionals and with specific roles in this area. This would contribute greatly favor the strengthening of the National System of Pharmacovigilance. Moreover, would allow thus promoting better use of medicines, avoiding unnecessary risks to the health of the population.

It is essential that health professionals receive specific training in Pharmacovigilance, allowing them is aware of how they can contribute to the safe use of medicines.

The Pharmacovigilance should be included in the curricula of all health related careers both undergraduate and graduate such as Medicine, Pharmacy, Nursing, Dentistry, Biochemistry, Nutrition, Kinesiology, etc. It also must be implement the dictation of courses, workshops and seminars on the subject, aimed at health professionals and various sectors of the population. The aims of these activities are to give known the existing system of notification, the importance of their participation in it, and how and where to notify.

CONCLUSIONS

It is necessary the commitment of professionals in the field of health and of population in general for this activity. When the same is successful, results in a reduction of costs related to the use of drugs, and also results in an increase prudent prescription thereof. This could improve the manufacture, the use and changing of excipients of pharmaceuticals. Also allow drug withdrawal or the change of its prospect. The discovery of adverse events, in some cases serious and previously unknown, would allow improve the use of drugs, and also the prospects to do better medicines.

Therefore, our goal is the ranking of our UPV-UNSL, establishing continuity in the program, and for this, an adequate university capacitation, of undergraduate and graduate, to different professionals working in the field of health is provided. In addition, brochures, newsletters, trainings, seminars, and publishing of articles for the general population are implemented. [21].

These activities would allow us to increase the quality and quantity of notifications, all for the benefit of the health of the population.

REFERENCES

1. Organización Panamericana de la Salud. Buenas Prácticas de Farmacovigilancia. Washington, D.C. OPS, 2011. Red PARF Documento Técnico No. 5, 78 pág.
2. Uppsala Monitoring Centre. Vigilancia de la seguridad de los medicamentos. Guía para la instalación y puesta en funcionamiento de un centro de Farmacovigilancia. Uppsala: UMC/OMS; 2002.
3. Valsecia M; Farmacovigilancia y mecanismos de reacciones adversas a medicamentos. Available at: http://med.unne.edu.ar/catedras/farmacologia/temas_farma/volumen5/13_farmacovigi.pdf
4. Ministerio de Salud y Acción Social de la República Argentina; Resolución 706/1993, del: 21/09/1993; Boletín Oficial 04/10/1993.
5. Uppsala Monitoring Centre; Listado de Países que participan en el Programa de Seguridad de Medicamentos de la OMS, con el año de su incorporación. Available at: http://www.who-umc.org/DynPage.aspx?id=100653&mn1=7347&mn2=7252&mn3=7322&mn4=7442
6. Administración Nacional de Medicamentos Alimentos y Tecnología Médica. Formularios de notificación. Available at: http://www.anmat.gov.ar/farmacovigilancia/Notificar.asp
7. Administración Nacional de Medicamentos Alimentos y Tecnología Médica.Guía de buenas prácticas de Farmacovigilancia. Ministerio de Salud. Secretaría de Políticas, Regulación e Institutos, 2009.
8. Holloway K, Green T; Comités de farmacoterapia. Guía práctica. Organización Mundial de la Salud. Departamento de Medicamentos Esenciales y Política Farmacéutica, Ginebra, Suiza, 2003.
9. Hallas J, Harvard B, Gram L, Grodum E, et al. Drug related hospital admissions. The role of definitions and intensity of data collection, and the possibility of prevention. J Int Med 1990; 228:83-90.

10. World Health Organization. Introduction to Drug Utilization Research. Norway, 2003.
11. World Health Organization; Terminología de las reacciones adversas de la Organización Mundial de la Salud. The Uppsala Monitoring Centre, 2008.
12. Hoddinott BC; Drug reactions and errors in admission on a medical ward. Canadian Medical Association Journal, 1967; 97: 1001-1006.
13. Vervloet D, Durham S; ABC of allergies adverse reaction to drugs. BMJ, 1998; 316:1511-1514.
14. Vilá A, San José A, Roure C, Armadans L, Vilardell M,y Grupo para el estudio de las reacciones adversas a medicamentos en pacientes ancianos hospitalizados. Estudio multicéntrico prospectivo de reacciones adversas a medicamentos en pacientes ancianos hospitalizados. Médica Clínica (Barc), 2003; 120 (16): 613-618.
15. Major S, Badr S, Bahlawan L, Hassan G, Khogaoghlanian T, Khalil R, et al.; Drug-related hospitalization at a tertiary teaching center in Lebanon: Incidence, associations, and relation to self-medicating behavior. Clinical Pharmacology & Therapeutics , 1998; 64: 450-46.
16. Stoukides CA, D'Agostino PR, Kaufman MB; Adverse drug reaction surveillance in an emergency room. American Journal of Hospital Pharmacy, 1993; 50: 712-4.
17. González JL. Reacciones adversas a medicamentos como urgencias externas en el hospital clínico universitario de Valladolid. Médica Clínica (Barc), 1987; 89: 130-131.
18. Otero López MJ, Bajo Bajo A, Maderuelo Fernández JA, Domínguez Gil Hurlé A; Evitabilidad de los acontecimientos adversos inducidos por medicamentos detectados en un Servicio de Urgencias. Revista Clínica Española, 1999; 199: 796-805.
19. Garijo B, De Abajo FJ, Castro MAS, Lopo CR, Carcas A, Frías J; Hospitalizaciones motivadas por fármacos: un estudio prospectivo. Revista Clínica Española, 1991;188: 7-12.
20. Schneeweiss S, Hasford J, Gottler M, Hoffmann A, Riethling AK, Avorn J; Admissions caused by adverse drug events to internal medicine and emergency department in hospitals: a longitudinal population-based study. European Journal of Clinical Pharmacology, 2002; 58 (4): 285-291.
21. Panini A, Teves M, Garraza M, Calderón C; Farmacovigilancia: Conceptos básicos. Revista Ciencias de la Salud de la Universidad Nacional de San Luis, 2012; 1(1): 70-76.