Pharmacovigilance in Portugal: Activity of the Central Pharmacovigilance Unit

Farmacovigilância em Portugal: Atividade da Unidade Regional do Centro

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ABSTRACT

Introduction: The aim of this study was to characterize the spontaneous reports of adverse events that were received by the Central Portugal Regional Pharmacovigilance Unit.

Material and Methods: Spontaneous reports received between 01/2001 and 12/2013 were considered. The annual reporting ratios were estimated. The cases were characterized according to their seriousness, previous description, causality assessment, origin and professional group of the reporter, type of adverse event and pharmacotherapeutic groups of the suspected drugs most frequently reported.

Results: The Pharmacovigilance Unit received 2,408 reports that contained 5,749 adverse events. In 2013, the reporting rate was estimated at 171 reports per million inhabitants. Fifty-five percent of the reports were assessed as serious. Ninety percent of the cases were assessed as being at least possibly related with the suspected drug. The suspected drugs most frequently reported were anti-infectives for systemic use (n = 809, 33%). The most frequently reported adverse events were “Skin and subcutaneous tissue disorders” (n = 1,139, 20%). There were 154 (6.4%) reports resulting in life-threatening situations and/or death, and 88 (3.6%) containing at least one adverse event assessed as serious, unknown and certain or probable.

Discussion: The present results are in line with those found in other studies, namely the seriousness and type of the adverse events and the pharmacotherapeutic groups of the most frequently reported suspected drugs.

Conclusion: In the last years, the Central Portugal Regional Pharmacovigilance Unit has registered a growth in the reporting rate in general, as well as an increase in the reporting of unknown and serious adverse drug reactions.

Keywords: Adverse Drug Reaction Reporting Systems; Pharmacovigilance; Portugal.

RESUMO

Introdução: Caracterizar as notificações espontâneas de eventos adversos a medicamentos recebidas pela Unidade de Farmacovigilância do Centro.

Material e Métodos: Consideraram-se todas as notificações reportadas entre 01/2001 e 12/2013. Estimaram-se taxas de notificação anuais. Os casos foram caracterizados quanto à gravidade, conhecimento prévio, causalidade imputada, origem e grupo profissional do notificador, tipo de evento adverso e grupos farmacoterapêuticos onde se incluem os medicamentos suspeitos com maior prevalência de notificação.

Resultados: A Unidade recebeu 2408 notificações, que continham 5749 eventos adversos. No ano de 2013 foi registada uma taxa de notificação de 171 notificações/milhão de habitantes. Do total de notificações, 55% foram classificadas como graves. Das notificações com causalidade imputada, 90% tinham uma relação pelo menos possível com o medicamento suspeito. Os medicamentos que originaram maior número de notificações foram os anti-infeciosos para uso sistémico (n = 809; 33%), e os eventos adversos mais frequentemente notificados foram as “Afeções dos tecidos cutâneos e subcutâneos” (n = 1139; 20%). Registaram-se 154 (6,4%) casos de risco de vida e/ou morte e 88 (3,6%) continham pelo menos um evento adverso classificado simultaneamente como grave, desconhecido e definitivo ou provável.

Discussão: Os resultados deste estudo são consistentes com os de outros estudos, designadamente no que diz respeito à gravidade, aos grupos farmacoterapêuticos onde se incluem os medicamentos suspeitos e aos tipos de eventos adversos reportados.

Conclusão: Ao longo do período avaliado, a UFC solidificou a sua atividade, tendo verificado um crescimento da taxa de notificação em geral e um aumento da notificação de reações adversas graves e desconhecidas.

Palavras-chave: Farmacovigilância; Portugal; Sistemas de Notificação de Reações Adversas a Medicamentos.

INTRODUCTION

An adverse event is defined as any undesired harmful effect resulting from the use of a medication.[1] These events may arise when a drug is used according to its marketing introduction authorization, drug abuse or misuse situations, therapeutic errors or off-label use (outside approved therapeutic indications). Those situations related to therapeutic ineffectiveness are also included in the definition of an adverse event and should be notified to the regulatory authorities. The term “adverse reaction” is used when a causal relationship between the use of the

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medication and an adverse event may be established, i.e. when this association is considered in the least possible, by the notifier or through a causality imputation method.[2]

Iatrogenic drug effects have a significant impact on public health, are responsible for relevant morbidity and mortality.[3] and their incidence has been assessed through several studies. An adverse event incidence between 4 and 91/1,000 persons-month has been estimated in patients attending an outpatient setting.[4] About 5% of hospital admissions are due to adverse drug reactions.[5-7] The incidence of adverse events varies according to the age group: the percentage of elderly patients admitted to the hospital is higher when compared to other adult and children patients (10.7% *vs*. 6.3% *vs*. 4.1%, respectively).[6] It is estimated that about 0.3 to 5% of patients die due to suspected drug-related adverse reactions.[8-11]

The identification of adverse drug effects and the monitoring of its impact in the population led to the development of Pharmacovigilance,[12] a specific discipline originating in Pharmacoepidemiology, , aimed at ensuring that medication risks are not beyond benefits.[1] The Portuguese *Sistema Nacional de Farmacovigilância* was started in 1992, embedded into the *Despacho Normativo n.º 107/92*, from 27th June and subsequently decentralised in 2000 with the creation of the *Unidades Regionais de Farmacovigilância* (URF) (Pharmacovigilance Regional Units) and distributed according to the *Administrações Regionais de Saúde* (Health Regional Administrations).[13] Patients, beyond health professionals, have also been allowed to notify suspected drug-related adverse reactions, since the entrance into force of the more recent European legislation regarding Pharmacovigilance in 2012.[14]

The URF implementation allowed for higher interaction with notifiers and higher disclosure of the *Sistema Nacional de Farmacovigilância* (Pharmacovigilance National System), which represented a significant contribution to a stepwise increase in the number of notified suspected adverse reactions over the years.[15] The URF works on research within drug safety, augmenting Pharmacovigilance, beyond the validation, data processing and assessment of notifications performed by health professionals and patients.[16]

Our study aimed to characterise spontaneous notifications received by the UFC (*Unidade de Farmacovigilância do Centro* – Pharmacovigilance Unit of the Centre of Portugal) according to its source, to the place of professional activity of notifiers, to the pharmacotherapeutic group of suspicious medication, seriousness, previous knowledge and causality nature of the notified adverse events.

MATERIAL AND METHODS

This was an observational, cross-sectional and descriptive study involving all spontaneous notifications of adverse events reported to the *Unidade de Farmacovigilância do Centro* between 1 January 2001 and 31 December 2013. Spontaneous notifications meeting primary validation criteria (patient's identification, suspicious medication, adverse event and notifier) were included.

The number of notifications per million inhabitants per year in 2011, 2012 and 2013 was calculated. The population covered by the *Administração Regional de Saúde do Centro de Portugal* was obtained from the *Anuário Estatístico da Região Centro* and 1,719,973 inhabitants were identified.[17]

Spontaneous notifications were characterised according to its source (hospital, outpatient, pharmacy or other) and to the notifier's professional group (physician, pharmacist, nurse, other health professional or user). The term 'Outpatient' was used to identify notified cases with an origin in primary healthcare network institutions.

Each spontaneous notification refers to one single case (one patient) although it may include one or more adverse events associated to the use of one of more suspicious drugs. Patient's demographic characteristics were analysed (gender and age).

Suspicious drugs were classified according to the WHO (World Health Organization) ATC (Anatomical Therapeutic Chemical Code) Classification System at the first (anatomical main group) and the third level (pharmacological subgroup). According to this classification system, active substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties.[18]

Since each spontaneous notification contains at least one adverse event, each event was isolated and coded according to the MedDRA (Medical Dictionary for Regulatory Activities), version 17.0 [Maintenance and Support Services Organization (MSSO) McLean, VA, USA] dictionary, under the System Organ Class (SOC) and the Preferred Term (PT) levels.[19-21] The MedDRA coding system uses a specific and standardized terminology developed by the International Conference of Harmonisation to facilitate sharing of regulatory information between regulatory authorities and pharmaceutical industry regarding medical products (pharmaceuticals and medical devices) used by humans. It is used for the registration, documentation and safety monitoring of medical products both before and after a product has been authorised for sale (research, development and post-marketing monitoring).[22]

Adverse events were considered as serious when the patient outcome is one of the following: 'death', 'life-threatening', 'hospitalisation (initial or prolonged', 'temporary and/or definitive disability' and/or 'congenital anomaly'. Other adverse events that, despite not life-threatening or not having caused any hospitalisation, were associated to major clinical consequences and/or required any medical intervention to be reversed were also considered as serious.[23] Adverse events were considered as expected

when these were described in the Summary of Product Characteristics of the suspected medication. The causal relationship between exposure to the suspected medication and the occurrence of the adverse events was assessed by the UFC's Scientific Council according to the global introspection method. An adverse event may be ranked as definitely, probably, possibly or not related, conditional / not classified or unavailable / unclassifiable.[24] The global introspection method involves the assessment of causality between the exposure to a medication and the occurrence of an adverse event by an expert panel, considering the Bradford Hill criteria: strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence and analogy.[25] This method resembles the clinical diagnosis process and depends on the expert's knowledge and expertise.[26] It has a moderate to high degree of correspondence with decision algorithms for adverse reactions most probably related to the suspected medication.[16]

Analyses were carried out aimed to characterise two subgroups of spontaneous notifications of adverse events: life-threatening events and/or those related to patient's death, regardless of the causal relationship with suspected medication and those simultaneously ranked as serious, unexpected and definitely or probably related to the suspected medications.

The Microsoft Excel® 2010 (Microsoft Corporation, Santa Rosa, CA, USA) software was used for statistical processing of data.

RESULTS

In total, 2,408 spontaneous notifications of adverse events were reported to the UFC between January 2001 and December 2013.

Notification rate

A notification rate of 101, 123 and 171 notifications/million inhabitant/year was found in 2011, 2012 and 2013, respectively.

Notification source and type of notifier

The distribution of reported spontaneous notifications by source of notification and type of notifier is shown in Table 1. From all the cases, 943 (40%) originated in outpatient settings, 778 (32%) in the hospital, 502 (21%) in community pharmacies and 185 (8%) in other workplaces or, in the case of users, in their home address. The health professionals that more frequently notified were physicians (1,457; 61%), followed by pharmacists (693; 29%) and nurses (239; 10%). Thirteen cases (0.5%) were notified by users.

Demographic characteristics of patients

Most spontaneous notifications regarded female patients (n = 1,594; 66%). Median age of patients was 53 (minimum 2 months, maximum 96 years) at the time when the adverse event took place. Most patients were aged between 15 and 65 (n = 1,385; 58%). In total, 269 (11%) and 683 (28%) patients were below 15 and above 65 years of age, respectively. The patient's age was unavailable in 72 cases.

Suspected medications

In thirty cases reported to the UFC (1%) more than medication was suspected. In total, 2,448 medications were suspected. The ATC classes more frequently related to suspected medications are shown in Table 2. According to the 1st level ATC, the medications that were mostly related to spontaneous notifications were anti-infectious agents for systemic use (n = 809; 33%), those acting in the musculoskeletal system (n = 322; 13%) and in the nervous system (n = 312; 13%).

The suspected medications included in the group of vaccines were the most frequently notified, involving patients aged 0-15 (n = 191; 69%). In the remaining age groups, non-steroid anti-inflammatory drugs were the most frequently notified (n = 209; 10%).

Adverse Events

From the 2,408 cases reported to the UFC, 1,540 (64%)

Table 1 – Spontaneous notifications distribution according to notifier and the source of notification

Type of notifier	Source of Notification[§]				
	Outpatient	Pharmacy	Hospital	Other	Total
Nurse	166	0	73	0	239
Pharmacist	0	499	175	19	693
Physician	777	0	528	152	1,457
Other health professional	0	3	2	1	6
Patient Self-report[¶]	0	0	0	13	13
Total	943	502	778	185	2,408

[§] Outpatient: Primary Healthcare (Cuidados de Saúde Primários). Pharmacy: Community Pharmacy. Other: other workplace or personal address.

[¶] Patients were only allowed to notify from July 2012.

Table 2 – Suspected medications, classified in the 3rd level ATC, more frequently notified (frequency ≥ 0.5%)

Suspected medications	n	%
J07B Viral vaccines	236	9.64%
M01A Anti-inflammatory and anti-rheumatic products, non-steroids	218	8.91%
J07A Bacterial vaccines	173	7.07%
N06A Antidepressants	102	4.17%
L01X Other antineoplastic agents	97	3.96%
J01C Beta-lactam antibacterials: penicillins	96	3.92%
C10A Lipid modifying agents, plain	86	3.51%
J01M Quinolone antibacterials	82	3.35%
L01C Plant alkaloids and other natural products	70	2.86%
J01D Other beta-lactam antibacterials	59	2.41%
C09A ACE inhibitors, plain	51	2.08%
B01A Antithrombotic agents	50	2.04%
J01F Macrolides, lincosamide and streptogramins	47	1.92%
N03A Anti-epileptics	47	1.92%
N02B Other analgesics and antipyretics	46	1.88%
A02B Drugs for peptic ulcer and gastro-oesophageal reflux disease	43	1.76%
M05B Drugs affecting bone structure and mineralization	43	1.76%
M04A Anti-gout preparations	36	1.47%
J01X Other antibacterials	30	1.23%
G03A Hormonal contraceptive for systemic use	29	1.18%
J01E Sulphonamides and trimethoprim	27	1.10%
C08C Selective calcium channel blockers with mainly vascular effects	26	1.06%
L01B Antimetabolites	25	1.02%
L04A Immunosuppressants	25	1.02%
N02A Opioids	23	0.94%
N05A Antipsychotics	22	0.90%
L02B Hormone antagonists and related agents	20	0.82%
V08A X-ray contrast media, iodinated	20	0.82%
N05B Anxiolytics	19	0.78%
N05C Hypnotics and sedatives	17	0.69%
C09B ACE inhibitors, combinations	16	0.65%
C09C Angiotensin II antagonists. plain	16	0.65%
L03A Immunostimulants	16	0.65%
R05C Expectorants, excluding combinations with cough suppressants	16	0.65%
J07C Bacterial and viral vaccines, combined	15	0.61%
R06A Antihistamines for systemic use	14	0.57%
G04C Drugs used in benign prostatic hypertrophy	13	0.53%
H02A Corticosteroids for systemic use, plain	13	0.53%
M03B Muscle relaxants, centrally acting agents	13	0.53%
Others	448	18.30%
Total	**2,448**	100.00%

concerned more than one adverse event. In total, 5,749 adverse events were reported. The most frequently notified adverse events, coded according to the PT and grouped by SOC, are shown in Table 3. 'Skin and subcutaneous tissue disorders' was the SOC most frequently related to adverse events (n = 1,139; 20%), followed by 'General disorders and administration site conditions' (n = 1,084; 19%) and 'Gastrointestinal disorders' (n = 1,034; 18%). These three groups were related to 57% of the reported adverse events.

The more frequently reported adverse events in patients aged 0-15 were related to vaccination, namely to 'vaccination failure', 'parotid gland enlargement' and 'pyrexia'. 'Pruritus', 'diarrhoea' and 'vomiting' were the most frequent adverse events in patients aged ≥ 65.

Life-threatening and/or death-related adverse events

From the 2,408 spontaneous notifications, 1,316 (55%) were classified as serious. From these, 154 (6.4%) were life-threatening and/or death related and 118 (76.6%) were notified by physicians, 20 (13%) by pharmacists, 15 (9.7%) by nurses and 1 (0.6%) by the user (pulmonary embolism). Most spontaneous notifications were related to female patients (n = 97; 63%). Median age of patients was 56 (minimum 2 months, maximum 93 years) at the time when the adverse event took place. The most frequently reported ATC classes regarding suspected medications and life-threatening and/or death-related adverse events are shown in Table 4 and 5, respectively. The medications used in oncological diseases, including antineoplastic agents (n = 21; 13%), alkaloid (n = 10; 6%), antimetabolite drugs (n = 4; 3%) and alkylating agents (n = 4; 3%), were the most frequently associated to these cases. Anaphylaxis events, which may include 'anaphylactic reaction' (n = 21; 5%), 'anaphylactic shock' (n = 16; 4%), 'dyspnoea' (n = 15; 4%), 'hypotension' (n = 11; 3%) and 'larynx oedema' (n = 9; 2%) were the most frequently related to life-threatening and/or death-related events.

Serious, unknown and definitive or probably-related adverse events

The UFC received 88 spontaneous notifications involving at least one adverse event classified as serious, unexpected and definitely or probably-related. The reported suspected medications are shown in Table 6. Anti-infectious agents for systemic use (n = 27; 30%), antineoplastics (n = 21; 23%) and medications acting in the musculoskeletal system (n = 12; 13%) were the most prevalent suspected medications.

DISCUSSION

Spontaneous notification is a type of pharmacovigilance methodology which allows for the identification of adverse events, involving all the medications on the market used for all patients, particularly those included in populations under-represented in clinical trials, such as the elderly, pregnant mothers and children. Spontaneous notification also enables the detection of rare adverse events including those with long-term latency.[27-29]

The notification rate is one of the indicators of the activity of the URF. When compared to the results obtained in a previous study, we found an increase in the number of spontaneous notifications per million inhabitants per year reaching the UFC over the last 3 years (maximum of 171 cases/million inhabitants/year in 2013).[24] This result approaches the WHO recommendation (≥ 200 cases/million inhabitants/year).[24,30]

More than half of the cases (55%) that reached the UFC were classified as serious. This result is in line with the proportion of serious iatrogenic events found in other URFs in Portugal and also with the results obtained by studies assessing the pharmacovigilance systems in other European countries.[15,31,32] Every adverse events should be notified to the regulatory authorities. It is tempting to speculate that a bias may result from the fact that health professionals are particularly prompted to only report serious adverse events, as these are associated to an increase in morbidity and in health costs.[32]

Most spontaneous notifications received by the UFC during its period of activity were reported by physicians, in line with the results found in other studies,[15,31-34] followed by the pharmacists and the nurses. When compared to a previous study, with the same design and involving the spontaneous notifications reported to the UFC between 2001 and 2011, the percentage of cases notified by nurses has considerably increased.[24] This is partly due to the awareness actions carried out by the UFC with these health professionals aimed at increasing their knowledge regarding the relevance of reporting iatrogenic events and notification procedures.[35] Within their professional practice, nurses are in close contact with patients.[35] These professionals are responsible for therapy administration and monitoring, and especially in the case of elderly patients, are in a unique position to identify any adverse reactions.[35-39]

Although the new legislation of Pharmacovigilance allows health professionals as well as patients themselves to notify suspected adverse reactions, patient contribution has been minimal.[40] Patients have been allowed to notify suspected adverse reactions for some years in other countries, for instance in Denmark, Holland and in the UK.[41,42] Although the first studies aimed to assess the contribution of patient-self notifications of suspected adverse reactions to Pharmacovigilance have suggested a low sensibility for the notification of suspected adverse reactions, the latest evidence considers that patients' contribution to the identification of iatrogenic drug reactions is valuable, as these may report previously unknown suspected adverse reactions.[41-43] Health professionals and patients have different perspectives regarding the

Table 3 – More frequently notified adverse events (frequency ≥ 0.5%), classified under the PT of the MedDRA classification

Adverse events	n	%
Cardiac diseases	104	1.81%
Tachycardia	53	0.92%
Others	51	0.89%
Gastrointestinal Diseases	1,034	17.99%
Vomiting	164	2.85%
Nausea	153	2.66%
Parotid gland swelling	137	2.38%
Diarrhoea	134	2.33%
Abdominal pain	111	1.93%
Dyspepsia	42	0.73%
Other	293	5.10%
General disorders and local reactions in the administration site	1,084	18.86%
Pyrexia	197	3.43%
General malaise	81	1.41%
Facial oedema	64	1.11%
Swelling in the injection site	60	1.04%
Erythema in the injection site	54	0.94%
Oedema in the injection site	50	0.87%
Peripheral oedema	48	0.83%
Asthenia	46	0.80%
Oedema	43	0.75%
Ineffective drug	39	0.68%
Pain in the injection site	36	0.63%
Heat in the injection site	35	0.61%
Heat sensation	30	0.52%
Others	218	3.79%
Immune diseases	82	1.43%
Anaphylactic reactions	30	0.52%
Others	52	0.90%
Infections and infestations	151	2.63%
Mumps	74	1.29%
Others	77	1.34%
Complications in procedures related to injuries and intoxications	161	2.80%
Ineffective vaccination	140	2.44%
Outros	21	0.37%
Musculoskeletal and connective tissue disorders	215	3.74%
Myalgia	56	0.97%
Dorsalgia	45	0.78%
Others	114	1.98%

(Continuation)

Table 3 – More frequently notified adverse events (frequency ≥ 0.5%), classified under the PT of the MedDRA classification

Adverse events	n	%
Diseases of the nervous system	601	10.45%
Headache	132	2.30%
Dizziness	120	2.09%
Shivering	62	1.08%
Drowsiness	35	0.61%
Paraesthesia	30	0.52%
Others	222	3.86%
Psychiatric disorders	122	2.12%
Insomnia	42	0.73%
Others	80	1.39%
Respiratory and mediastinal diseases	282	4.91%
Dyspnoea	90	1.57%
Cough	56	0.97%
Others	136	2.37%
Skin disorders	1,139	19.81%
Pruritus	196	3.41%
Rash	136	2.37%
Erythema	101	1.76%
Maculopapular rash	85	1.48%
Urticaria	82	1.43%
Erythematous rash	71	1.23%
Hiperhydrosis	43	0.75%
Generalized rash	43	0.75%
Generalized pruritus	39	0.68%
Angioedema	36	0.63%
Others	307	5.34%
Vasculopathies	193	3.36%
Hot flushes	91	1.58%
Hypotension	37	0.64%
Hypertension	29	0.50%
Others	36	0.63%
Other SOC	581	10.11%
Total	5,749	100.00%

notification of suspected adverse reactions, in which the former are more focused in causality and the latter in seriousness and impact on their quality of life. As such, it is important to receive notifications from both groups in order to obtain a better assessment of the event's nature.[44]

The outpatient setting was the most frequently source of spontaneous notifications, followed by the hospitals and the community pharmacy. The hospital was described in other studies as the most frequent source for spontaneous notifications.[32-34] The incidence of adverse drug reactions in In-hospital patients is considered as high.[9] However, it is recognized that most adverse events taking place in hospi-tals are not reported to the regulatory authorities.[45] Some of the reasons identified as possible causes for under-notification in the hospital are the lack of an organised system of hospital pharmacovigilance, health professional lack of

time or problems related to data confidentiality.[46]

The most frequently notified suspected medications reaching the UFC were anti-infectious drugs for systemic use, including vaccines and antibiotics, followed by medications acting in the musculoskeletal system, mostly non-steroid inflammatory drugs and medications acting on the nervous system, mainly antidepressant, antipsychotic and anxiolytic agents. These results are in line with national data.[15] It must be said that, over the last two years, the UFC has received a relevant number of spontaneous notifications regarding the mumps vaccine, an outbreak of this disease having occurred in the central region of Portugal.[47] However, despite the increase in this particular case, the results found for the UFC are still in line with those obtained by other studies.[32,48] The medications included in these therapeutic classes are amongst the mostly used in clinical practice, which may explain their involvement in such high percentage of suspected cases reported to the UFC.[49] There are medications with a more disadvantageous risk/benefit balance when compared to the most frequently reported suspected medications involved in this study with a therapeutic indication for more serious pathologies such as cancer or autoimmune diseases. Therefore, when we limited our analysis to life-threatening or death-related serious cases, the medications used for the treatment of oncological diseases were the most frequently notified. These results were somewhat expectable as tolerance to the risk of serious adverse event occurrence generally tends to be higher if the medication is used in the treatment of serious diseases.[50] The fact that these medications are administered in the hospital setting under close supervision of health professionals allows for the detection of adverse events from a very early stage and for an immediate action aimed to revert these. Despite the presence and application of procedures aimed to prevent the occurrence of adverse events associated to antineoplastic therapy, including the previous administration of steroids and antihistamines, anaphylactic-type reactions continue to occur in oncology patients.[51] The efficacy of preventive measures is worthy of a deeper future research effort.

As found in other studies, the reactions involving the skin and soft-tissues, gastrointestinal system and general disorders occurring in the administration site were the most frequently notified by health professionals.[15,32,52] The fact that dermatological adverse events were the most frequently reported is also expectable, as these are more easily identified by the patients and the health professionals.[32] Disorders such as diarrhoea, vomiting, generalized discomfort, fever and reactions in the administration site, involving injectable medications, are presumably the

Table 4 – Suspected medications notified in life-threatening and/or death related events

Suspected medications	n	%
L01X Other antineoplastic agents	21	13.29%
M01A Anti-inflammatory and anti-rheumatic products, non-steroids	17	10.76%
L01C Plant alkaloids and other natural products	10	6.33%
N02B Other analgesic and antipyretics	7	4.43%
B01A Antithrombotic agents	6	3.80%
J01D Other beta-lactam antibacterials	5	3.16%
M04A Anti-gout preparations	5	3.16%
J01E Sulphonamides and trimethoprim	5	3.16%
J07B Viral vaccines	5	3.16%
V08A X-ray contrast media, iodinated	4	2.53%
L01B Antimetabolites	4	2.53%
A10B Blood glucose lowering drugs, excluding insulins	4	2.53%
L04A Immunosuppressants	4	2.53%
L01A Alkylating agents	4	2.53%
Other	58	36.48%
Total	159	100.00%

Table 5 – Life-threatening and/or death-related notified adverse events

Adverse events	n	%
Anaphylactic reaction	21	5.33%
Anaphylactic shock	16	4.06%
Dyspnoea	15	3.81%
Hypotension	11	2.79%
Larynx oedema	9	2.28%
Vomiting	9	2.28%
Erythema	9	2.28%
Angioedema	8	2.03%
Urticaria	7	1.78%
Pruritus	7	1.78%
Other	282	71.57%
Total	394	100.00%

adverse events more frequently involved in clinical practice and correspond to a considerable percentage of the notifications reported to the UFC.

Eighty-eight notifications involved at least one adverse event simultaneously ranked as serious, unexpected and definitely or probably-related. The two selected levels of casualty mean a stronger association between the exposure to a suspected medication and the occurrence of an adverse event, with serious clinical consequences and unexpectedly occurring. These cases deserve special attention as they represent the new knowledge arising from the activity of the UFC. When compared to the results obtained in a previous study, the absolute number of cases with such characteristics more than doubled in about two and a half years.[24] Results suggest the increasing relevance and importance of UFC and notifier activity in the centre region of Portugal, working together to produce new knowledge regarding drug safety.

Evidence on the risks is mostly obtained from post-marketing data, including spontaneous notification, case reports and observational studies.[53] Most regulation decisions produced by the regulatory authorities regarding drug safety, including market withdrawal and safety alert disclosure, has been mostly based on spontaneous notifications.[49,53-58] More than half of the safety alerts issued by regulatory authorities between 2010 and 2012 were based on spontaneous notifications, from which 20% were exclusively based on this evidence.[49] These results suggest the importance of spontaneous notifications in producing new knowledge regarding drug safety. However,

Table 6 – Suspected medications notified in serious, unexpected and definitely or probably-related events

Suspected medications	n	%
J Anti-infectious agents for systemic use	27	29.67%
L Anti-neoplastic and immunomodulator agents	21	23.08%
M Musculoskeletal system	12	13.19%
N Nervous system	8	8.79%
C Cardiovascular system	5	5.49%
V Various	4	4.40%
A Alimentary tract and metabolism	4	4.40%
B Blood and blood forming organs	3	3.30%
R Respiratory system	2	2.20%
S Sensory organs	2	2.20%
G Genitourinary system and sex hormones	1	1.10%
D Dermatological preparations	1	1.10%
H Systemic hormonal preparations, excluding sex hormones and insulins	1	1.10%
Total	91	100.00%

the difficulty in recognizing, diagnosing and establishing a causal relationship between an adverse event and the use of a medication act as barriers to spontaneous notifications.[59] Under-notification by health professionals is a cross-cutting issue to every Pharmacovigilance system.[19,24,35,60]

CONCLUSIONS

Health professionals from the centre region of Portugal have increased their contribution to the production of new knowledge regarding drug safety. This fact suggests the importance and relevance of the UFC's activity, which has found an increasing global notification rate of adverse reactions simultaneously serious and unexpected. The increased rate of spontaneous notifications, based on a higher compliance of health professionals with this method of drug safety monitoring in clinical practice will allow for the production of more knowledge leading to a better assessment of risk/benefit balance of medications and to higher safety for patients.

CONFLICTS OF INTEREST

The authors declare there were no conflicts of interest in writing this manuscript.

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