Pharmacovigilance or patient safety: analysis from a patient safety program

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Abstract

Purpose: drugs are the common point of pharmacovigilance and patient safety programs. Despite using a common language, the same epidemiological method and legislation that requires the operation of the two programs, there does not seem to be a clear relationship between them.

Methodology: observational descriptive cross sectional study of the reports database from an institutional patient safety program. Medication errors were classified according to the document *The Conceptual Framework for the International Classification for Patient Safety* (ICPS) WHO 2009. Adverse Reactions (ADR) were classified according to Uppsala Monitoring Center.

Results: the omission of drugs or doses was the most frequent error with 42.8% followed by ADRs (20.9%). No harm incidents corresponded to 61.2% and the remaining 38.8% was represented in near missincidents and no harm incidents. There were included 41 ADR and 15 therapeutic failures corresponding to a point-prevalence of 57 ADR/10,000 patients-year and 28.6% (56/196) of reports related to drugs. Phlebitis is the most frequently reported with 23, 7% followed by hypersensitivity reactions with 18.4% and excessive neuromuscular blockade with 13.1%.

Conclusions: considering time, level of care and number of bed, ADR prevalence seem low. A very important proportion of reports corresponding to near miss incidents or no harm incidents is not taken into account by the security managers, losing a valuable risk management opportunity in the patient safety programs.

Keywords: Pharmacovigilance, Patient Safety, Drug-Related Side Effects and Adverse Reactions, Medication Errors

Introduction

Although by 1848 an attempt had already been made to report adverse drug reaction (ADR) suspicions because of a young woman died by the administration of chloroform during surgery in England (1), it was only up to 1960 when the first pharmacovigilance (PV) systems were originated as a result of the outbreak of phocomelia caused by the administration of thalidomide (2). After this, a series of articles have been published showing the harm caused by drugs: Talley identified in 1974 that 2,9% of admissions to the medical service were for this cause and 6, 2% of these patients died (3). Subsequently, Manasse stated that by 1987 drug mortality affected 12,000 Americans and morbidity reached 15,000 hospitalizations. He also coined the term *Drug misadventuring* to describe negative drug experiences that he considered a public policy problem derived from the excessive use of drugs and error-prone preparation and distribution systems (4, 5). Lazarou affirm in 1998 that ADR were between the fourth and sixth leading cause of death (6).

According to the current definition of the World Health Organization (WHO), PV is "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems…". (7). By 2012, the national pharmacovigilance program in Colombia considered that PV should study the problems related with the use of drugs and its effects in society for preventing and resolving them (8, 9). Today, regulatory agencies work to balance access to drugs with safety concerns, in line with their mission to protect the public health. However, in the first years of the 21st century, the safety of prescribed drugs caught the attention of the public because of some drugs withdrawal, delays in warning the public about important risks and the approval of drugs without enough attention to safety. (10)

Not only ADRs are part of daily concerns of health professionals, there is also interest in others risks of health care such as nosocomial infections, complications of the clinical course and medication errors (ME). There have been numerous studies where it was estimated that the incidence rate of adverse events in Spanish hospitals were 9.3%, 46.6 were considered preventable; 37.4% were related with medication which 34.8% were preventable. (11).

The document *To err is human* identified that about 98,000 people die in a year because of errors in health care occurring in hospitals. After this document, the WHO in 2004 pointed out to the governments of the world the need to establish programs that guarantee safe actions in the patient care and suggests a global strategy to fulfill this purpose (12, 13). Colombia has not been unaware of this situation and through the Ministry of Social Protection urges institutions to implement and continuously validate a Patient Safety Program (PSP), which guarantees the best conditions for the healthcare of Colombian people and for which it has issued specific regulations (14, 15).

PSPs in their philosophy extend the approach of safety in patient care and include in their objectives the inspection of activities related to healthcare, such as skin integrity, prevention of falls, control of medical devices, and surveillance of blood derivatives, among others. These programs incorporate in their concept the inherent risk of health care service and part of their analysis includes the evaluation of the causes of errors or failures in the system that will allow establishing corrective actions in future risk situations for the patient. IBEAS study identified that a 10.5% of the patients presented an adverse event and at least half of these adverse events to drugs could be prevent (16).

Despite these two programs led by the WHO, the negative consequences for the patients' health are still far from being controlled or minimized due, among other reasons, to the current biomedical model that aims to solve health issues with medical interventions, in which drugs are an essential part, and a neoliberal economy that turned health into a business model (17, 18).

One of the common points of PVP and PSP are drugs. Despite the use of common language such as ADR, ME and the same epidemiological method (risk approach) added to the fact that in Colombian legislation it is required to have the two programs in order to achieve the certification of institutions for provision of health services to the population, there seems to be no clear articulation between them and it has even been identified that there is a significant variability in PVP, which limits the comparability between different information systems(19). From an institutional PSP, this study

80 characterized the drug related reports sent to the program, identified the differences of their
81 classification.

82 Materials and methods

83 An observational descriptive cross sectional study was carried out with a retrospective collection of
84 information, reports of the institutional PSP application were included during 2015, and there were
85 excluded duplicate reports, invalid (report presenting any inconsistency), tests (information is
86 introduced to verify the integrity of the application), related to the infrastructure of the hospital, and
87 personal complaints. The reports were classified according to the categories established in the
88 document *The Conceptual Framework for the International Classification for Patient Safety* (ICPS)
89 of WHO 2009 (20). For the ADR classification, the tools suggested by the Uppsala Monitoring Center
90 were used, such system/organ affected and seriousness (21).

91 The ethics committee approved the study conforms to the Declaration of Helsinki and resolution
92 008430 of 1993 according to the specified in the article 11 of chapter I. The present study is a risk-
93 free investigation therefore written informed consent is not required.

94 Results

95 According to the database used in the study, 1481 safety cases were reported in 2015. After the
96 preliminary analysis, 439 (29.6%) reports were discarded, because they fulfilled some excluded
97 criteria, leaving 1042 total valid reports of which 196 (18.8%) were identified and are related to drugs
98 and make up the common nucleus between PSP and PVP. Fig 1 shows the process and the results of
99 the initial evaluation.

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Figure 1. Flow diagram of the selection and classification of the reports. Steps for the selection of the reports included in the present study. Only those related to medications were included.

PSP: medication errors.

Table 1 shows the distribution of reports according to ICPS, where it can be observed that 42.8% (84/196) correspond to omission of drugs or dose (category 9), followed by 20.9% (41/196) related to ADR (category 11). Sixteen reports could not be classified in any category so it was necessary to create two additional categories: "therapeutic failure" (TF) (category 12) in which 15 reports were identified, and "unclassifiable" (category 20) corresponding to an event of wrong adjustment.

Table 1. Distribution of errors according to ICPS

Error	**Category**	**N**	**%**
Wrong drug	1	14	7,14
Wrong patient	2	3	1,53
Wrong dose/strength of frequency	3	10	5,10
Wrong formulation or presentation	4	4	2,04
Wrong route or quantity	5	1	0,51
Wrong Dispensing Label/Instruction	6	8	4,08
Contraindication	7	2	1,02
Wrong storage	8	13	6,63
Omitted medicine or dose	9	84	42,86
Expired medicine	10	0	0
Adverse drug reaction	11	41	20,92
Therapeutic failure	12	15	7,65
Not classifiable	20	1	0,51
	Total	196	100

110 Classification of medication errors according to ICPS. The last two classifications (12 and 20) were
111 created for the present study.

112

113 Reports were constituted by 61.2% (120/196) of harmful incidents and the remaining 38.8% (76/196)
114 of the reports were represented near miss incidents and no harm incidents. Harmful incidents were
115 distributed in ADRs (41/120), TF (15/120) and harm related to surgery delay, additional tests, drug
116 rupture or harm or strict monitoring (64/120) are included. Of these events, 68% (82/120)
117 corresponded to moderate harm.

118 *PVP: Adverse drug reactions*

119 There were identified 41 ADRs and 15 TF that correspond to 5.4% (56/1040) of total reports and to
120 28.6% (56/196) of reports related to drugs. Table 2 shows that the most affected organ-system was
121 the skin with a 42.8% (24/56), followed by the central nervous system with a 23.2% (13/56)

122 **Table 2. Distribution of ADR according to WHO**

Drug	ADR	Classification	Affected System	N
Dexmedetomidine	Agitation, anxiety	Moderate	Nervous	1
Rocuronium	Neuromuscular block	Serious	Musculoskeletal	5
Oxygen	hypertensive crisis	Serious	Cardiovascular	1
Noradrenaline	Emesis	Moderate	Gastrointestinal	1
No medication related	Emesis	Moderate	Gastrointestinal	2
Haloperidol	Extrapyramidalism	Moderate	Nervous	1
No medication related	Phlebitis	Moderate	Skin and its appendages	11
Polymyxin B	Phlebitis	Moderate	Skin and its appendages	1
Vancomycin	Phlebitis	Moderate	Skin and its appendages	2

Phenytoin	Phlebitis	Moderate	Skin and its appendages	1
Insulin glargine	hypoglycemia	Moderate	Endocrine	1
Prazosin	Hypotension	Moderate	Cardiovascular	1
Certolizumab	Reverse psoriasis	Moderate	Skin and its appendages	1
Cefazolin	Skin rash	Moderate	Skin and its appendages	1
Dipyrone	Hypersensitivity reaction	Moderate	Skin and its appendages	1
Phenytoin	Hypersensitivity reaction	Moderate	Skin and its appendages	1
Hyoscine	Hypersensitivity reaction	Moderate	Skin and its appendages	1
Levetiracetam	Hypersensitivity reaction	Moderate	Skin and its appendages	1
Morphine	Hypersensitivity reaction	Moderate	Skin and its appendages	1
Piperacillin tazobactam	Hypersensitivity reaction	Moderate	Skin and its appendages	1
Rituximab	Hypersensitivity reaction	Moderate	Skin and its appendages	1
Heparin	Overanticoagulation	Serious	Blood	1
Warfarin	Overanticoagulation	Serious	Blood	3
Midazolam	Therapeutic failure	Moderate	Nervous	6
Dexmedetomidine	Therapeutic failure	Moderate	Nervous	1
Fentanyl	Therapeutic failure	Moderate	Nervous	4
Labetalol	Therapeutic failure	Moderate	Cardiovascular	4
			Total	56

123 Classification of the ADR according to the Uppsala Monitoring Center, taking into account the
124 severity and the affected organ-system

125

126 During the study period, 9900 patients were attended, which shows an incidence of ADR of 0.56%
127 (456/9900). According to the organ-system affected, the skin and appendages disorders occupy the

first place with 42.8% (24/56) followed by the nervous system with 23.2% (13/56). According to the seriousness of ADR, most of them were moderate with 82.2% (46/56) and the remaining 17.8% (10/56) were serious.

In the results of the causality analysis with the Naranjo algorithm (68), a score of 7 was obtained in all cases, with the exception of rocuronium, which was assigned an additional point (+8) because of the fact that sugammadex was used to reverse the blockade, however, they all go into the PROBABLE category.

Drugs involved in the reports

The drugs classification by anatomical group was carried out according to the Anatomical Therapeutical Chemic (ATC) classification (22), in which the group of drugs most frequently involved in the reports were those of the N group with 30.4% (17/56) followed by the group M and C each with 10.7% (6/56). Other groups with low percentage were L and A. It was necessary to create "category X" (without specific drug), which corresponds to the report of an event where a problem is mentioned without specifically describing the international common denomination.

Discussion

The present study identified that 1 out of 4 reports were rejected, this can be explained by some of the following reasons: incomplete socialization of the program, high healthcare burden, high professionals and students turnover (university hospital). These invalid reports have a negative impact on the program, because the classification of the reports is done manually and increases the reading time**.**

Another finding was a higher frequency of incidents reports related with care (70.8%), followed by those related to drugs (18.8%) and, finally, with medical devices (10.4%). Given that the interest of this work corresponds to drugs, it can be mentioned that the frequency of reports related to this supply

151 is within the numbers identified in studies such as ENEAS (adverse events in hospitals in Spain, with
152 37.4%) (11), IBEAS (adverse events in hospitals in Latin America, with 8.23%) (16) and SYREC
153 (adverse events in Spanish intensive care units, with 24.6%) (23).

154 Regarding the reports classification, it can be affirmed that about half correspond to category 9 of the
155 ICPS (drugs omission) and another important percentage is related to categories 1 and 7 (inadequate
156 conservation conditions and wrong medication). These findings may be a reflection of the lack of a
157 drug distribution system, whose purpose is, precisely, to reduce these errors (24).

158 A study conducted in the hospitalization service of a clinic in Cali (Colombia) identified that in a
159 period of 20 days the drugs omission was the most common error, although it does not mention which
160 classification was used (25). Another study conducted by Machado et al. during 8 years in ambulatory
161 pharmacies in different cities of Colombia identified that most of the errors were related to
162 dispensation (26). However, it is necessary to emphasize that the comparison of these results with
163 other studies is complicated by the use of different types of classification and different settings of
164 study (community, hospital, ambulatory, etc.). For example, a recent report in England identifies the
165 potentially inappropriate prescription as an error, as well as administration, monitoring and
166 dispensing errors (27).

167 According to the typology of the reportable events, it is identified that more than half of the reports
168 correspond to harmful incidents. Regarding the harmful incidents, it is necessary to clarify that from
169 the perspective of PSP, these harms are not always related to the affectation of human biology (which
170 in PV would be called ADR), but also include another type of harm that affects other areas of the
171 person or the health system (surgery delay, intensive monitoring, pharmaceutical product damage,
172 etc.). The development and consolidation of the program may lead to the predominance of the near
173 miss incidents report, since they are closer to prevention and constitute the first sign of incidents that
174 may or not lead to harm. This high proportion of harmful incidents reports may be related to the fact
175 that people tend to report those events that cause harm, since those that do not bring consequences

176 can be considered "normal", not worthy of notification or a combination of the "seven capital sins of
177 underreporting", which will be discussed later (28).

178 According to this consideration, it draws attention that a little less than half of these incidents
179 correspond to ADR and therefore were included in the activities of PVP, while the remaining
180 percentage of incidents that also caused harm were not considered. Additionally, reports of incidents
181 that did not cause harm (no harm incidents, near miss incidents) are not analyzed, mainly due to high
182 workload, which means that an important opportunity to manage the risk is lost, since it should not
183 wait for it to appear ADR to inform and then analyze. This is one of the most relevant findings of the
184 present study, since it demonstrates that PV should also deal with errors or infractions in order to be
185 corrected and prevented. Some authors have identified this need and make a call so that ME are taken
186 into account in PVP (29, 30). It is therefore necessary to visualize these findings as an opportunity
187 for improvement, first identifying that the scope of the two programs pose as a challenge the non-
188 duplicity of efforts, and, as an opportunity, not leaving problems unattended, specifically the near
189 miss incidents and no harm incidents.

190 In the referenced studies, it was not possible to identify the results in terms of no harm incidents or
191 near miss-incidents. Some of them describe the results in terms of ADR or ME without taking into
192 account the infractions and other reportable events mentioned at the beginning of the paragraph. It is
193 not possible to make a direct comparison with other studies related to the subject for the following
194 reasons: equal or very similar terms to refer different things (adverse event in PV vs. adverse event
195 in PS); different terms to refer the same (adverse event or preventable ADR in PV vs. ME in PS);
196 lack of knowledge by PV programs that only look at ADR and, finally, some discrepancies in the
197 harmonization of terms used in the Colombian regulation vs. WHO (incident related to patient safety
198 according to WHO 2009 and incident according to Minprotection 2008 and 2009).

199 In relation to the PVP and according to the institutional application, a 0.56% prevalence of ADR was
200 estimated during a year, a number that seems low for a fourth-level hospital with 223 hospital beds

and 9900 inpatients in the different services during a year, if it is considered that the studies indicate that in this type of hospitals it is presented between 10 to 20% of ADR, of which between a 10 to 20% are classified serious and the 0.5 to 0.9%% are mortal (11, 16). The results of the present study may also be related to underreporting, one of the main problems of passive pharmacovigilance (31). A document prepared by Varallos et al. explains that this, under report, occurs for what has been called "the seven capital sins of underreporting": 1) consider that serious ADR are well documented, 2) fear of being involved in legal proceedings, 3) guilty feeling for have been responsible for the harm to the patient, 4) ambition of a group for publish serious cases, 5) lack of knowledge about how to make the notification, 6) insecurity about the report of ADR and, 7) indifference, lack of interest, time or another excuse to postpone notification. The main causes of ADR underreporting found in the studies included in a systematic review were ignorance and insecurity, findings related to the low knowledge of professionals on the activities of drugs safety analysis; the authors propose that professional notifications can be promoted through educational interventions aimed to clarify their importance (28). For the present study, this could also be the cause of poor registration in the institutional application and invalid reports.

The drugs involved in the reports differ from the results found by Machado et al. in Colombia (32-33), De las Salas et al. in two pediatric hospitals for 6 months (34), Moscoso et al. in a second-level hospital in Bogotá for 3 months (35) and a study by Chaves in 31 second-level institutions in the city of Bogotá for a year (36), where antibiotics are among the drugs that report the most ADR, although they agree that the skin it is the most affected organ-system. Although some similarities are found in the afore mentioned, differences are also found in some of the results, this can be explained by the type of institution and the methodology used for the identification (passive vs. active).

Despite the wide dissemination and published studies related to patient safety, no similar studies were found in the bibliographic review carried out for this study that attempted to reflect on the articulation of PV and PS programs in specific hospitals. However, documents such as the one written by the

WHO in 2014 and the EMA in 2015 allow us to deduce that studying the real articulation of these programs is at the heart of the PV and PS programs (29, 37). For almost 20 years, several authors have discussed the need for a change in the scope, approach or methods used to perform PV. It is possible that these findings are the result of the movement on patient safety or of society's need to counteract the growing outbreak of drug-induced iatrogenic (38-44).

There is a need to broaden the vision of health surveillance systems to include aspects such as drug-related problems, ME and ADR. It has not yet been possible to integrate and incorporate these terms into a single program, perhaps for reasons that range from the purely philosophical, to a predominance of positivism, passing through political and economic causes whose analysis goes beyond the scope of this research (45-47).

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