SHORT COMMUNICATION

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Evaluation of Completeness of Suspected Adverse Drug Reaction Reports Submitted to the Mexican National Pharmacovigilance Centre

A Cross-Sectional Period-Prevalence Study

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Abstract

Background: The Mexican National Centre of Pharmacovigilance (CNFV) receives suspected adverse drug reaction (ADR) reports from the pharmaceutical industry, Federal States Centre of Pharmacovigilance (CEFV) and Healthcare Institution Centres of Pharmacovigilance (CIFV). The completeness of these suspected ADR reports is particularly important for the proper evaluation of drug safety.

Objective: The aim of the study was to evaluate the completeness of the information reported in a representative sample of suspected ADR reports submitted to the CNFV during 2007 and 2008, to evaluate the completeness of the suspected ADR reports submitted to the CNFV from different sources during these 2 years and to identify the therapeutic subgroups with the highest number of suspected ADR reports during the study years.

Methods: A cross-sectional period-prevalence study was conducted at the CNFV. Only reports of suspected ADRs submitted by the CEFV, pharmaceutical industry and CIFV during 2007 and 2008 were included in the present study (reports related to vaccines were excluded). The sample sizes to be used for each year were determined using the formula for population rate at 95% significance level. The samples for each year were randomly selected from the reports related to synthetic drugs submitted that year. The suspected ADR reports were classified according to the standing Mexican Official Norm (Norma Oficial Mexicana [NOM]) guidelines, which were used to divide the reports into four categories (0, 1, 2 and 3) based on their completeness. The seriousness of the suspected ADRs reported was also evaluated; a suspected ADR was classified as 'non-serious' when signs and symptoms are likely to be tolerated, 'moderate' when ADR is not life threatening and needs pharmacological treatment, 'serious'

when ADR is life threatening and leads to hospitalization and 'fatal' when ADR contributes directly or indirectly to the patient's death.

Results: A total sample size of 370 and 371suspected ADR reports from 2007 and 2008, respectively, were examined. Our analysis revealed that the pharmaceutical industry sent the highest number of suspected ADR reports for both years (58% and 63%, respectively). Results of the information completeness analysis by using the NOM categories showed that, in both study years, among the total suspected ADR reports about 32% (119) and 40% (148), respectively, were categorized as grade 0 (information insufficient to generate risk signals). Analyses of the seriousness of all suspected ADR reports revealed that 2% of reports were classified as fatal each year, whereas 6% and 5% were classified as serious and 25% and 29% were classified as moderate in 2007 and 2008, respectively. The therapeutic subgroups, according to the Anatomical Therapeutic Chemical classification, with the highest frequencies of suspected ADR reports in both study years were sex hormones and modulators of the genital system, antibacterial for systemic use, antiepileptics and psychoanaleptics, and antihypertensives.

Conclusions: The completeness of the information provided in the suspected ADR reports submitted during the sample study years was incomplete and, in general, did not fulfil the requirements established by the NOM guidelines. Among the pharmaceutical industry, CEFV and CIFV, the suspected ADR reports were mainly provided by the pharmaceutical industry. It is necessary to improve the pharmacovigilance system in Mexico to achieve a high level of completeness of suspected ADR reports that totally fulfil the standing regulations.

Background

Nearly 50 years ago, researchers began testing pharmacovigilance methods to facilitate efforts toward enhancing the voluntary notification of adverse reactions. Adverse drug reaction (ADR) notifications continue to be a useful tool for identifying the risks associated with taking certain drugs that are in the postmarketing phase. Health professionals play a key role in the process of reporting suspected ADRs as they typically have regular contact with the medications and potentially affected patients.[1-5]

In 1989, the Government of Mexico initiated a voluntary notification programme regarding suspected ADRs that follows the WHO concept and definition of pharmacovigilance. The Health Ministry (abbreviated SSa, from the Spanish name) implemented the first National Pharmacovigilance System, in which drug manufacturers were given the option to provide voluntary notifications of suspected ADRs. In 1997, one of the articles of the General Health Law was amended, establishing the obligation for all pharmaceutical laboratories to report all suspected ADRs. Since 2001, the Mexican National Centre of Pharmacovigilance (CNFV) has been integrated with the Federal Commission for the Protection against Sanitary Risks (COFEPRIS), with the purpose of coordinating and integrating all Mexican pharmacovigilance programmes and centres. The ADR notification system is now compulsory for all health institutions and health professionals throughout the country, as well as for the clinical research entities that carry out drug studies.[1,6,7]

Nevertheless, some aspects still require further investigation and development to reach the completeness levels required at the global level.[8-13]

The qualitative and quantitative assessment of the potential risk associated with the suspected ADR reports, and consequently the designation of ADRs, have not been adequately evaluated to date.

The main objective of the present investigation is to evaluate the completeness of the information reported in a representative sample of the suspected ADR reports submitted to the CNFV during 2007 and 2008. The specific objectives were as follows: (i) to evaluate the completeness of the suspected ADR reports submitted to the CNFV from different sources during these 2 years; and (ii) to identify the therapeutic subgroups with the highest number of suspected ADR reports during the study years.

Methodology

This research was carried out at the CNFV. The method used in this study was to compare and verify the information reported in each of the selected sample of suspected ADR reports against the information required in the Mexican Official Norm (Norma Oficial Mexicana [NOM]; NOM-220-SSA1-2002) guidelines. A cross-sectional period-prevalence study was conducted. The selected sample was compounded by all the suspected ADR reports received by the CNFV during 2007 and 2008 from the Federal States Centre of Pharmacovigilance (CEFV), pharmaceutical industry and Healthcare Institution Centres of Pharmacovigilance (CIFV).

Inclusion Criteria

The suspected ADR reports received by the CNFV during the study period from the CEFV, pharmaceutical industry and CIFV that were readable and that reported suspected ADRs related to synthetic drugs were included in this study.

Exclusion and Elimination Criteria

Suspected ADR reports on vaccines, food supplements, herbal products, antiseptics, antiserum and milk products, contrast media and medical devices, as well as suspected ADR reports from clinical trials, were excluded from this study.

Calculation of Sample Size

The sample size was calculated considering the total number of reports that fulfilled the inclusion criteria for each study year (2007 and 2008). In 2007, the CNFV received 15 726 suspected ADR reports, but only 10 150 fulfilled the inclusion criteria. In 2008, CNFV received 17 826 suspected ADR reports but only 10 269 met the inclusion criteria.

A pilot test was conducted to calculate the sample size by report (complete and incomplete). Overall, 100 suspected ADR reports were taken randomly from the total number of suspected ADR reports. The results of the pilot test were as follows: (i) 49% of the suspected ADR reports were considered complete, that is the information contained in them corresponded to the NOM classification grades 2 and 3; and (ii) 51% of the suspected ADR reports were incomplete (grades 0 and 1 according to the NOM classification). Based on these data, we calculated the sample sizes to be used for each year by using the formula for population rate at 95% significance level.[14,15] This calculation determined that we would examine 370 and 371 suspected ADR reports between 2007 and 2008, respectively. Subsequently, the precise sample selection for each year was carried out by using a random number table using the existing numbering system for all suspected ADR reports per year.

Information Analysis

After the random selection of the suspected ADR reports to be studied, the different sources of each of these reports (CEFV, pharmaceutical industry and CIFV) were analysed.

Table I shows the NOM criteria to evaluate the completeness of the information contained in each suspected ADR report.

The seriousness of the suspected ADRs was also assessed using the classification system of the NOM, as shown in table II. Due to ambiguity in the NOM definitions of the last two categories (c and d), we classified the suspected ADR reports reporting only death, as in the 'd' category, as a fatal suspected ADR.

We also analysed the suspected ADR frequencies for each therapeutic subgroup. In particular, the

Table I. Mexican Official Norm criteria for classification of the completeness of the information contained in the suspected adverse drug reaction reports

Grade	Description
0	The date of the suspected ADR is presented, but the dates of treatment are unknown
1	Both the initial dates of the suspected ADR and the treatment dates are specified
2	In addition to the grade 1 data being present, the involved drug, its indication and posology, as well as the final outcome are also described
3	In addition to the previous data (grades 1 and 2) being present, the suspected ADR report also contains data about the reappearance of clinical manifestations after drug re-administration

ADR = adverse drug reaction.

WHO Anatomical Therapeutic Chemical classification was used for categorization; drugs were classified at the first and second levels (anatomical main group and subgroup).[16] For each study year, all suspected ADR reports making up our sample set were classified by their therapeutic subgroup, and the frequency (percentage) of each was calculated.

The ethical board of the CNFV that maintains the database containing the suspected ADR reports gave their consent to conduct the present study.

Results

Our analysis revealed that in the study years 2007 and 2008, the highest number of suspected ADR reports sent to the CNFV by pharmaceutical industries was 58% (215) and 63% (234), respectively, followed by 26% (96) and 25% (93) for the CEFV and, finally, 16% (59) and 12% (44) for the CIFV.

Results from the information completeness analysis using the NOM categories (grades 0, 1, 2 and 3) showed that in 2007 and 2008, among a total of 370 and 371 suspected ADR reports sent to the CNFV, 32.2% (119) and 40% (148), respectively, were grade 0; 25.9% (96) and 13% (48) were grade 1; 41.6% (154) and 44% (163) were grade 2; and 0.3% (1) and 3% (12) were grade 3.

Table III shows the comparison of the NOM completeness grade between the sources (CEFV, pharmaceutical industry and CIFV) of the suspected ADR reports sent to the CNFV during the study period. In 2007 and 2008, pharmaceutical industries submitted most reports of suspected ADRs, whereas the CIFV submitted the least number of reports in both study years.

Based on the seriousness analysis of the information contained in the suspected ADR reports, it was determined that, among the 370 and 371 suspected ADR reports that we examined and that were submitted to the CNFV in 2007 and 2008, respectively, by the CEFV, pharmaceutical industry and CIFV, approximately 67% (249) and 64% (236) were classified as non-serious, 25% (93) and 29% (106) as moderate, 6% (23) and 5% (20) as serious, and 2% (5) and 2% (9) as fatal.

Table IV shows the comparison of the NOM seriousness categories between the sources (CEFV, pharmaceutical industry and CIFV) of the suspected ADR reports during the study period. In

Table II. Mexican Official Norm criteria for the classification of the seriousness of the information contained in the suspected adverse drug reaction reports

Seriousness categories	Description
Non-serious	The patient presents signs and symptoms that are likely to be tolerated, do not require treatment, do not prolong hospital stay and may or may not require discontinuation of the drug
Moderate	The suspected ADR interferes with the patient's daily activities (it may cause work or school absences), is not life threatening, needs pharmacological treatment and may or may not require discontinuation of the drug
Serious	The suspected ADR is a morbid manifestation after the administration of any drug dose, and the suspected ADR is life threatening, leads to hospitalization or prolongs hospital stay, and causes patient death, significant disability or other alterations or malformations in a newborn
Fatal	The suspected ADR contributes directly or indirectly to patient death

ADR = adverse drug reaction.

Table III. Comparison of the Mexican Official Norm completeness grade between the sources of the suspected adverse drug reaction reports during the study years

Completeness grade	2007 (N = 370)			2008 (N = 371)		
	CEFV [n (%)]	PhI [n (%)]	CIFV [n (%)]	CEFV [n (%)]	PhI [n (%)]	CIFV [n (%)]
0	17 (18)	102 (47)	0 (0)	20 (22)	127 (54)	1 (2)
1	30 (31)	40 (19)	26 (44)	16 (17)	24 (11)	8 (18)
2	48 (50)	73 (34)	33 (56)	53 (57)	78 (33)	32 (73)
3	1 (1)	0 (0)	0 (0)	4 (4)	5 (2)	3 (7)
Total	**96 (100)**	**215 (100)**	**59 (100)**	**93 (100)**	**234 (100)**	**44 (100)**

CEFV = Federal States Centre of Pharmacovigilance; **CIFV** = Healthcare Institution Centres of Pharmacovigilance; **PhI** = pharmaceutical industry.

both study years, only pharmaceutical industries sent suspected ADR reports that were categorized as fatal. Also, in both years, most of the suspected ADR reports that were categorized as serious were sent by the pharmaceutical industry.

As shown in table V, 15 therapeutic subgroups in 2007 and 2008 represented 87.9% and 91.8%, respectively, of the suspected ADR reports in the study sample; the therapeutic subgroup with the highest number of suspected ADR reports filed in both study years was 'sex hormones and modulators of the genital system'. In contrast, the therapeutic subgroups with the least number of suspected ADR reports filed were 'antihistamines for systemic use' in 2007 and 'immunostimulants' and 'immunosuppressants' in 2008.

In addition, it is worth mentioning that the three drugs (sodium dipyrone, pregabalin and drospirenone-ethinylestradiol) that were among the most frequently used drugs in Mexico during the study years were included in the top 15 therapeutic subgroups with suspected ADR reports.[17,18]

Discussion

Discussion of Results

In spite of the fact that it is mandatory for the institutions (CEFV, pharmaceutical industry and CIFV) to report suspected ADRs in Mexico, there are no consequences (i.e. sanctions and fines) for not carrying out this requirement. As reported by the WHO, the Mexican CNFV received >10 000 reports in 2008,[19] which is in good accordance with our findings. Nevertheless, our findings show that most of the suspected ADR reports were incomplete.

Most of the suspected ADR reports for both study years (2007 and 2008) were grade 2, which was an assignment based on the completeness of the information contained in each report compared with the NOM requirements. Although grade 2 reports predominated, if the frequencies of grades 0 and 1 (table III) are added together (per study year), the resultant total percentages are 58% and 53% in 2007 and 2008, respectively. Thus, most of the suspected ADR reports received in the study period contained incomplete

Table IV. Comparison of the Mexican Official Norm seriousness categories between the sources of the suspected adverse drug reaction reports during the study years

Seriousness categories	2007 (N = 370)			2008 (N = 371)		
	CEFV [n (%)]	PhI [n (%)]	CIFV [n (%)]	CEFV [n (%)]	PhI [n (%)]	CIFV [n (%)]
Non-serious	62 (65)	142 (66)	45 (76)	71 (76)	135 (58)	30 (68)
Moderate	26 (27)	57 (27)	10 (17)	19 (21)	76 (32)	11 (25)
Serious	8 (8)	11 (5)	4 (7)	3 (3)	14 (6)	3 (7)
Fatal	0 (0)	5 (2)	0 (0)	0 (0)	9 (4)	0 (0)
Total	**96 (100)**	**215 (100)**	**59 (100)**	**93 (100)**	**234 (100)**	**44 (100)**

CEFV = Federal States Centre of Pharmacovigilance; **CIFV** = Healthcare Institution Centres of Pharmacovigilance; **PhI** = pharmaceutical industry.

Table V. Suspected adverse drug reaction report frequencies by ATC therapeutic subgroups during the study years

No.	ATC classification[16]	Therapeutic subgroups	2007 (N = 370)		2008 (N = 371)	
			n	Frequency (%)	N	Frequency (%)
1	G03	Sex hormones and modulators of the genital system	68	18.4	51	13.7
2	J01	Antibacterials for systemic use	46	12.4	48	12.9
3	N03, N06	Antiepileptics and psychoanaleptics	45	12.1	26	7
4	C02	Antihypertensives	40	10.8	35	9.5
5	M01	Antiinflammatory and antirheumatic products	30	8.1	25	6.7
6	N07	Other nervous system drugs (smoking cessation drugs)	20	5.4	33	8.9
7	A03	Drugs for functional gastrointestinal disorders	18	4.9	13	3.5
8	M05	Drugs for treatment of bone diseases	18	4.9	22	5.9
9	L01	Antineoplastic agents	15	4.1	13	3.5
10	R03	Drugs for obstructive airway diseases	14	3.8	NA	NA
11	R06	Antihistamines for systemic use	11	3	NA	NA
12	A08	Antiobesity preparations, excl. diet products	NA	NA	35	9.5
13	A10	Drugs used in diabetes	NA	NA	15	4
14	N01	Anesthetics	NA	NA	13	3.5
15	L03, L04	Immunostimulants; Immunosuppressants	NA	NA	12	3.2
16		Other therapeutic subgroups	45	12.1	30	8.2
		Total	**370**	**100**	**371**	**100**

A = Alimentary tract and metabolism; **ATC** = Anatomical Therapeutic Chemical; **C** = Cardiovascular system; **G** = Genito-urinary system and sex hormones; **J** = Antiinfectives for systemic use; **L** = Antineoplastic and immunomodulating agents; **M** = Musculo-skeletal system; **N** = Nervous system; **NA** = not applicable; **R** = Respiratory system.

information, limiting the effectiveness and full potential of analysis of those reports.

Upon analysing the suspected ADR reports with respect to their origin (CEFV, pharmaceutical industry and CIFV), we found a high percentage (>60%) of reports with incomplete information that came from pharmaceutical industries. As mentioned, the pharmaceutical industry not only sent the highest number of suspected ADR reports for both years but also the highest number of incomplete ADR reports. In contrast, in 2007 and 2008, the CIFV (hospitals) sent the least number of suspected ADR reports but most (56% and 80%, respectively) were categorized as complete reports. The Mexican Regulatory Agency should focus on encouraging the pharmaceutical industry to send complete reports and encouraging the CIFV to increase the number of reports.

Fatal suspected ADRs reported were sent only by the pharmaceutical industry for both study years, and were 2% and 4%, respectively, of the total reports sent by them. As the percentages of fatal suspected ADR reports found in our study sample are relatively high, more intense and urgent action is required in Mexico to ensure the completeness of each suspected ADR report and to avoid potential deaths due to the use of medications. In Mexico, effectiveness of the regulatory intervention in improving the completeness of the suspected ADR reports appears rather weak. Possible explanations are the lack of a database and insufficiently trained staff at the CNFV. In addition, during the present study period, the CNFV did not have a rejection policy for incomplete-suspected ADR reports. Timely evaluation of the received suspected ADR reports should be an immediate reaction to the result of the present study.

Interestingly, we found some therapeutic subgroups with a high number of suspected ADR reports from 2008 that were not reported in 2007 (table V). Examples of this include anesthetics, drugs used in diabetes and antiobesity preparations.

The therapeutic subgroup frequency patterns of the suspected ADR reports, for both study years, is similar to the general Mexican consumption pattern of medicines.[17,18] Fifteen therapeutic subgroups in 2007 and 2008 (table V) represented

87.9% and 91.8%, respectively, of suspected ADR reports in the study sample, and nine (sex hormones and modulators of the genital system, antibacterials for systemic use, antiepileptics/psychoanaleptics, antihypertensives, antiinflammatory and antirheumatic products, drugs for functional gastrointestinal disorders, drugs for treatment of bone diseases, antiobesity preparations and drugs used in diabetes) were among the top 15 most consumed therapeutic subgroups in Mexico during the same period of time.[17,18]

In our study, we found in the top 15 therapeutic subgroups with suspected ADR reports three drugs (sodium dipyrone, pregabalin and drospirenone-ethinylestradiol) that were also among the top 15 consumed medicines in Mexico in the study years.[17,18] The drugs belonging to the frequently reported therapeutic subgroups should likely be treated with more caution and their use should be monitored more closely.

Thus, Mexican health authorities should focus their attention and surveillance on the aforementioned therapeutic subgroups. Furthermore, a lack of completeness analysis of suspected ADR reports might compromise the health of the Mexican population.

Study Limitations

The main limitation of this study is inherent to the study design. The results are only useful for implementing future pharmacovigilance actions. The present results are only a statistical sample size of the reports of only 2 years (2007 and 2008), and it is not intended that any generalizations beyond Mexico are made.

Conclusions

In general, information in the study samples of the suspected ADR reports submitted to the CNFV during 2007 and 2008 was incomplete and did not fulfill the requirements established by the NOM guidelines. Among the CEFV, pharmaceutical industry, and CIFV the suspected ADR reports were mainly provided by pharmaceutical industries.

According to the information completeness classification categories used, most of the suspected ADR reports from the pharmaceutical industry were classified as grade 0 (provided information was insufficient to generate risk signals). The seriousness of most of the suspected ADR reports was classified as non-serious; however, about 2% were found to be fatal suspected ADRs.

All involved parties should work together to prevent serious and fatal ADRs. Based on our findings, it seems necessary to improve the pharmacovigilance system in Mexico and to promote submission of high completeness of suspected ADR reports that fully fulfill the NOM specifications. These measures are necessary to generate risk signals and prevent ADRs.

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References

1. Ashish K, Kuperman GJ, Rittemberg E, et al. Identifying hospital admissions due to adverse drug events using a computer based monitor. Pharmacoepidemiol Drug Saf 2001; 10: 113-9
2. Mirjam K, Rommers MK, Teepe-Twiss IM, et al. Preventing adverse drug events in hospital practice: an overview. Pharmacoepidemiol Drug Saf 2007; 10: 1-7
3. Laporte JR, Carné X. Epidemiological basic methodology in pharmacovigilance. In: Laporte JR, Tognoni G, editors. Drug epidemiology principles. 2nd ed. Barcelona: Masson-Salvat, 1993: 111-27
4. Emerson A, Martin MR, Tomlin M, et al. Prospective cohort study of adverse events monitored by hospital pharmacists. Pharmacoepidemiol Drug Saf 2001; 10: 95-103
5. Herrera CJ, Núñez LME. Pharmacovigilance. In: Herrera CJ, editors. Handbook of clinical pharmacy and pharmaceutical care. 1st ed. Madrid: Elsevier, 2003: 283-96
6. World Health Organization. The importance of pharmacovigilance: safety monitoring of medical products [online]. Available from URL: http://www.ops.org.bo/textocompleto/ime18633.pdf [Accessed 2011 Feb 28]
7. Anonymous. Pharmacovigilance in Mexico. Pharmacovigilance Bulletin 2006; 14 (4): 6
8. Bousquet PJ, Demoly P, Romano A, et al. Pharmacovigilance of drug allergy and hypersensitivity using the ENDA–DAHD database and the GA^{2}LEN platform. The Galenda Project. Allergy 2009; 64: 194-203
9. Funmilayo O, Ajayi Sun H, Perry J. Adverse drug reactions: a review of relevant factors. J Clin Pharmacol 2000; 40: 1093-101
10. Gislason GH, Jacobsen S, Rasmussen JN, et al. Risk of death or reinfarction associated with the use of selective cyclooxygenase 2 inhibitors and nonselective nonsteroidal

antiinflamatory drugs after acute myocardial infarction. Circulation 2007; 113: 2906-13

11. Guha M. Anti-epileptics to get suicide warning in the EU. Scrip 2008; 13: 3425-6
12. Grosso A, Douglas I, Hingorani A, et al. Post-marketing assessment of the safety of strontium ranelate; a novel case-only approach to the early detection of adverse drug reactions. Br J Clin Pharmacol 2008; 66 (5): 689-94
13. Blenkinsopp A, Wilkie P, Wang M, et al. Patient reporting of suspected adverse drug reactions: a review of published literature and international experience. Br J Clin Pharmacol 2007; 63 (2): 148-56
14. Dowson B, Trapp RG. Basic and clinical biostatistics. 4th ed.: New York: McGraw-Hill, 2004: 126-58
15. Lachin JM. Biostatistical methods: the assessment of relative risks. 2nd ed.: Hoboken (NJ): John Wiley & Sons, Inc., 2011: 85-95
16. World Health Organization, Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2010. Oslo: WHO, 2009
17. International Marketing Services-Health (IMS-Health Mexico). 2007 Mexican Pharmaceutical Market Statistics Database
18. International Marketing Services-Health (IMS-Health Mexico). 2008 Mexican Pharmaceutical Market Statistics Database
19. Olsson S, Pal SN, Stergachis A, et al. Pharmacovigilance activities in 55 low- and middle-income countries: a questionnaire-based analysis. Drug Saf 2010; 33 (8): 689-703

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