An approach to increase adverse drug events reports in Mercosur

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Risk communication associated with drug use is a critical point in post-marketing surveillance. Therefore, validation of strategies to minimize under-reporting of adverse drug events (ADE) are needed in order to contribute towards good pharmacovigilance practices. The present study aims to validate a multi-faceted educational intervention (MEI) in pharmacovigilance for Mercosur countries and assess its impact on particular attitudes, knowledge, and skills to correctly complete the ADE form to ensure quality of reports. The MEI was developed during four one-hour meetings. The following activities were carried out: a lecture regarding landscape; importance and concepts related to pharmacovigilance; classroom practice for elucidating the correct completion of ADE reports; distribution of an educational manual and completion of a questionnaire to assess knowledge, attitudes, and skills in pharmacovigilance. The answers of the questionnaire were analyzed using a content analysis technique. Definitions from the World Health Organization and the minimum and desired criteria to fill the ADE form, according to the Pan American Health Organization, were considered gold-standard answers. The impact of the MEI was analyzed by a Wilcoxon statistical test. 82 subjects were enrolled and sixteen returned questionnaires. Since after the methodology there were also fifteen reports of medication error, the MEI did contribute to the improvement of knowledge (p<0.002), skills (p=0.002) and attitude in pharmacovigilance. The proposed MEI may contribute to risk management, as it enhanced the quantity and quality of the reports. Furthermore, it can be used to effectively harmonize pharmacovigilance practices in Latin American countries.

Key words: Adverse drug reaction reporting systems, drug-related side effects and adverse reactions, pharmacovigilance, attitude of health personnel, risk management.

INTRODUCTION

The tradition of pharmacovigilance in Latin America is relatively recent, since most countries have initiated post-marketing drug surveillance systems in the 1990s (Pérez-Garcia and Figueiras, 2011). Therefore, actions may be considered preliminary, mainly because of adverse drug events (ADE) under-reporting and due to the lack of
motivation of healthcare professionals in the service (OPS, 2011).

The major cause of poor adherence of Latin American health professionals (Venezuela) in spontaneous reporting is the lack of knowledge; therefore, there is a need for development of interventions that clarify the concepts related to pharmacovigilance, and can be used to improve the ADE reporting rate (Pérez-Garcia and Figueiras, 2011). Brazilian physicians, pharmacists, and nurses consider their knowledge regarding adverse drug reactions (ADR) to be insufficient (Pinheiro and Pepe, 2011).

Educational interventions for health professionals have been shown to be effective for changing behavior/attitudes in clinical practice (Forsetlund et al., 2009). Studies performed in European countries show that continuing education in pharmacovigilance contributes to the increase of ADR reporting rates, and improves the quality of reports (López-González et al., 2015; González-González et al., 2013; Biagi et al, 2013; Herdeiro et al., 2012; Cereza et al., 2010; Pedrós et al., 2009; Herdeiro et al., 2008; Herdeiro et al., 2006; Figueiras et a., 2006; Herdeiro et al., 2005; Bäckström et al., 2002). Therefore, this study promotes signals detections, assessment of ADR causal association, analysis of quality of pharmaceutical products, prevention of medication errors, and in the risk management associated with drug use for market regulation.

In this setting, with the intention to harmonize the good pharmacovigilance practices within Mercosur members (Brazil, Paraguay, and Uruguay), the present study aimed to validate a multi-faceted educational intervention for health professionals who act in hospitals as well as to assess its impact on knowledge, skills and attitudes.

METHODOLOGY

Type of study

A multi-centric, longitudinal, prospective, uncontrolled, and no-blinded study was performed in six institutions in order to validate educational intervention for health professionals who act in tertiary levels of health care for Mercosur members.

Eligibility criteria and study population:

All health professionals with employment at the hospitals were invited to participate in the study, regardless of profession or whether they were full-time or part-time. Subjects who agreed to participate were made to sign an informed consent form which was considered eligible for the study. The exclusion criteria included professionals who were on sick leave, vacation, those who had not registered to carry out the intervention (although showed interest during invitation), and those who did not want to answer the questionnaire despite having shown interest in participating in the lecture and practical class. Study participants were recruited from three member countries of Mercosur. In Brazil, the study was carried out in a general, public hospital of medium complexity, with 108 beds. The Uruguayan hospital comprised a public, general, and teaching institution of high complexity, with 400 beds. All Paraguayan hospitals promote an assistance of high complexity: two are general with 100 beds, a maternity ward with 25 beds, and an institution specialized in cardiology care with 500 beds.

Educational intervention

A multi-faceted educational intervention was developed by applying four different techniques: lecture regarding pharmacovigilance concepts and landscape; practical class to clarify how to correctly fill out the ADE report; educational material distribution and questionnaire addressed to health professionals before and after educational intervention. These activities were carried out during four, one-hour meetings. In the first meeting, a questionnaire was given to assess knowledge, skills and attitudes in pharmacovigilance prior to intervention. The instrument was elaborated based on previous studies (Pinheiro and Pepe, 2011; Mcgettigan et al., 1997; Figueiras et al., 1999; Green et al., 2001; Herdeiro et al., 2005; Herdeiro et al., 2006; Passier et al., 2009; Gerritsen et al., 2011) and included essay questions regarding concepts related to ADE (example, ADR, medication errors, quality deviations of drugs, and suspicions of therapeutic ineffectiveness) and post-marketing surveillance.

The second meeting comprised a lecture (Pedrós, et a., 2009; Figueiras et al., 2006) regarding the following: the theoretical framework and importance of pharmacovigilance; spontaneous ADE reporting; causes and consequences of under-reporting and distribution of educational material (Herdeiro et al., 2008). In the third meeting, a practical class (Ribeiro-Vaz et al., 2011; Herdeiro et al., 2012) was performed with the participants to promote a discussion of a fictitious case of ADR (Farcas and Bojita, 2009). The essential, necessary, and recommended information to be filled out from the form were explained to ensure better quality of reports made by health professionals.

In the last meeting, another questionnaire was given to assess the impact of the educational intervention on the knowledge, skills, and attitudes of health professionals.

Outcome measures

Knowledge assessment was performed by comparison of gold-standard definitions from the World Health Organization (WHO; Table 1) with the answers obtained from questionnaire. Scores from zero to ten were assigned according to the degree of appropriateness of concepts reported by health professionals from those established by the WHO (2002). A skills evaluation was carried out according to the perception of the subject regarding the

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relevant degree of the information to be filled in from the ADE form. Therefore, they were asked to highlight the fields in the ADE form whose data were considered recommended, necessary, or essential to be reported. The answers were compared with the minimal and desirable criteria to be filled in as recognized by the Pan-American Health Organization that were considered widely accepted definitions (Table 1). Scores from zero to ten were assigned according to the degree of appropriateness of information reported by health professionals from those established by OPS (2011). For both variables (knowledge and skills), scores below five were classified as unsatisfactory, scores between five and 7.5 were considered regular, and scores above 7.6 were considered a satisfactory improvement. Findings were expressed as median (minimum and maximum) due to its non-normal distribution. Change behavior (attitudes) of health professionals was evaluated by comparison of the absolute numbers of the ADE reported before and after the educational intervention.

Sample size

During the period of data collection, there were 3,264 health professionals working in the hospitals under study. Of them, 421 belonged to the Brazilian hospital, 920 to Paraguayan hospitals and 923 to Uruguayan hospitals. None of the three institutions have deployed pharmacovigilance service; therefore, this study did not apply statistical methods to calculate sample size. Instead, all health professionals were recruited to participate in the study in order to raise awareness regarding pharmacovigilance and to begin the cultural changing related to drug safety analysis with the aid of adverse drug events reports.

Statistical analysis

To assess the impact of the educational intervention on knowledge, skills, and attitudes on pharmacovigilance, this study used the Wilcoxon statistical test. Significance was accepted when p<0.05.

RESULTS

After the recruitment of the 3264 health professionals, 3182 were excluded; because 120 did not meet the inclusion criteria, and 3062 did not carry out the registration required to participate in the intervention (even though they had demonstrated interest when invited). The 82 subjects enrolled consisted of a multidisciplinary health team consisting of pharmacists (n=32), physicians (n=30), pharmacy auxiliaries (n=16), nurses (n=2), a biomedical specialist (n=1) and a nutritionist (n=1). Of them, only 16 participated in all four of the meetings and returned the questionnaires. Therefore, a low return-rate was observed in all institutions: Brazil (n=14), Uruguay (n=2), and Paraguay (n=0).

The results showed that most of the health professionals who concluded the intervention were female (n=15) and almost half of the subjects had post-graduation courses (n=6) and had already been trained in pharmacovigilance (n=6). However, most participants (n=12) had not been able to detect ADE during clinical practice, and none had reported them in the appropriate form.

Results from the questionnaire answers showed that the degree of appropriateness of definitions and concepts related to pharmacovigilance increased after the educational intervention. An unsatisfactory level in knowledge and skills was verified before the educational intervention, and this level was changed to the regular level after the methodology development (Table 2). Therefore, there is a trend that educational intervention contributes towards post-marketing surveillance practices.

Therefore, the approach was successful because it raised the awareness regarding the importance to report any suspicious of ADE (expected and unexpected) and drug related problems (effectiveness, safety, quality). The approach also improved the definition of post-marketing surveillance (phase IV studies) and allowed the detection of etiologies of medication errors (Table 3).

Furthermore, educational intervention also contributed to developing the skills of health professionals to ensure the quality of reports, since the relevant information for causal assessment was inserted on the form after educational intervention, such as data of the event, description of evolution and causes that may be related to the event, alternative causes related to the event, and characteristics of patients and their clinical histories. Considering the impact of educational intervention on attitudes of health professionals, a 15-fold increase in the absolute number of medication errors reporting was noted. The medication errors reported included dispensing (n=12), transcription (n=3), and prescription (n=1).

Regarding the adaptation of the questionnaire, no changes were suggested for the knowledge and attitude sections. However, terminology changes regarding degree of relevance of information to be filled in from the form were proposed in the skill section ("recommended" to "unnecessary"). Changes in the ADE form were also recommended, in particular, in the topic "other important information to describe ADR". It was suggested to change the following: "The event was not serious?" to "The event was serious?" In addition, three volunteers suggested that the course load was insufficient; however, they did not propose any changes.

DISCUSSION

There is evidence that our multi-faceted educational intervention was effective, since it improved the knowledge, skills, and attitudes of health professionals in pharmacovigilance, even with poor adherence observed.
Table 1. Criteria considered as the 'gold standard' for knowledge and skill assessment in pharmacovigilance.

<table>
<thead>
<tr>
<th>Knowledge</th>
<th>Gold-standard answers(^1)</th>
<th>Skills</th>
<th>Gold-standard answers(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knowledge</td>
<td>It is the monitoring of the medicine uses for the detection, assessment and prevention of adverse drug reaction and any issues related to medicines</td>
<td>About patients: name initial, medical record number, bed, gender, clinical history (illness, comorbidities, drug allergies)</td>
<td>About ADR: clinical manifestations (treatment initiation and finalization), evolution (outcomes), laboratorial exams, treatment (hospitalization, discontinuation of drugs, prescription of drugs). About suspected drug: drug, dose, route of administration, indication, date of treatment initiation and finalization, expiry date, lot number and manufacturer)</td>
</tr>
<tr>
<td>What is pharmacovigilance?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the practice of pharmacovigilance promote benefits? Whether positive, what are the benefits and who are the beneficiaries?</td>
<td>The practice of pharmacovigilance promotes benefits for drug users, professionals and healthcare institutions. The benefits are: contribution to patient safety, to improving the quality of care in health facilities, for the rational use of drugs the maintenance of safe, effective and quality medicines in the pharmaceutical market</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Who may notify?</td>
<td>Drug users, health professionals and the pharmaceutical industry</td>
<td></td>
<td>About polypharmacy: drugs, dose, route of administration, date of treatment initiation and finalization, expiry date, lot number and manufacturer)</td>
</tr>
<tr>
<td>What can you notify?</td>
<td>Any drug related problems, especially adverse drug reaction, medication errors, therapeutic ineffectiveness and drug quality deviations</td>
<td>About reporter: name, profession, telephone number or e-mail and date that the report was made</td>
<td>About patient: risk factors for ADR occurrence (kidney and/or hepatic failure, previous exposition to the drug, alcoholic consumption or smoking habit). About ADR: clinical evolution (outcomes), event’s diagnoses documentation, including procedures applied, data of laboratorial exams and pharmacological treatment</td>
</tr>
<tr>
<td>What do you mean by: a) Adverse drug event? b) Adverse drug reaction?</td>
<td>It is any damage or harm caused to patient, arising from drug use.</td>
<td>Desirable criteria</td>
<td></td>
</tr>
<tr>
<td>Medication errors?</td>
<td>A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer</td>
<td>Medication errors reporting</td>
<td>About the product: the product involved in the error (dose, route of administration, expire date, lot number, type of types of packaging, label, among others)</td>
</tr>
<tr>
<td>Quality drug deviations?</td>
<td>It is the departure of the quality parameters established for a product or process. In pharmacovigilance can be: changes organoleptic, physico-chemical and / or general (leaks, inadequate labeling, and foreign particles, among others)</td>
<td>Desirable criteria</td>
<td></td>
</tr>
</tbody>
</table>
in the study (only 2.5% of volunteers were eligible). The number of professionals who were engaged in the interventions is important information, according to González et al. (2013), since it determines the reporting rate per professional-time unit; therefore, this study could not calculate the initial reporting rate and its influence in the observed relative reporting increases. Knowing the number of professionals engaged in interventions is also important because it can be used to calculate the absolute increases in the reporting rate. Furthermore, this study finding suggests that the culture of ADE reporting in developing countries should be encouraged in order to motivate and change behavior in drug surveillance activities.

Although Latin American contributions in the pharmacovigilance field have increased in the last years (González et al., 2006), a systematic review demonstrated that in countries within Mercosur members none or few studies have attempted to make health professionals aware of the importance of adherence in phase IV clinical trials (González et al., 2013). Therefore, studies that attempt to inform health professionals about drug surveillance assessment and risk communication in transitional economies are necessary, since 28% of adverse events detected in the hospitals of Argentina, Colombia, Costa Rica, Mexico and Peru have caused disability and another 6% were associated with the death of the patient (Aranaz-Andrés et al., 2011). Educational interventions that target ADE reporting may allow early detection of ADE, prevent avoidable harms, and contribute for patient safety.

Since pharmacovigilance knowledge is constructed...
### Table 3. Comparison of answers obtained from the questionnaire before and after the educational intervention (n = 16).

<table>
<thead>
<tr>
<th>Knowledge variables</th>
<th>Educational Intervention (Qualitative analysis of answers)</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) What is the concept of pharmacovigilance?</td>
<td></td>
<td>The last stage of clinical research. This aims to identify adverse</td>
<td>Follow-up of drug use on the market, in order to promote safety for</td>
</tr>
<tr>
<td></td>
<td></td>
<td>drug reaction during clinical trials.</td>
<td>the patients.</td>
</tr>
<tr>
<td>(2) Does the practice of Pharmacovigilance promote benefits? Whether positive, what</td>
<td>This promotes benefits for drug users. The benefits most frequently</td>
<td>Drug users and health professionals</td>
<td></td>
</tr>
<tr>
<td>and for whom?</td>
<td>cited were: improvement of knowledge and professional customer</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>service.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3) Who may notify?</td>
<td>Health professionals</td>
<td>Health professionals, drug users.</td>
<td></td>
</tr>
<tr>
<td>(4) What can you notify?</td>
<td>Adverse drug reaction</td>
<td>Any kind of drug related problems (adverse drug reaction, quality</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>deviations of drug, therapeutic ineffectiveness and medication errors)</td>
<td></td>
</tr>
<tr>
<td>(5) What do you mean by:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Adverse drug event?</td>
<td>Unexpected situations related to drug use or adverse drug</td>
<td>Problems caused to patients due to adverse reactions, medication</td>
<td></td>
</tr>
<tr>
<td></td>
<td>reaction synonymous.</td>
<td>errors, ineffectiveness therapy and diversion of drug quality.</td>
<td></td>
</tr>
<tr>
<td>b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) Adverse drug reaction?</td>
<td>Manifestation caused by drug over-dosage.</td>
<td>Unwanted reaction that is described or not in the leaflet.</td>
<td></td>
</tr>
<tr>
<td>C) Medication errors?</td>
<td>Medication errors are incorrect administration of drug,</td>
<td>Medication errors arising from lack of professional attention and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>resulting in therapeutic failure</td>
<td>can occur at any stage of drug use.</td>
<td></td>
</tr>
<tr>
<td>e) Variances drug quality (technical defects)?</td>
<td>The drug does not have the expected effects. Examples of</td>
<td>Non-conformance to quality standards expected.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>technical complaints (general changes).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e) Suspected therapeutic ineffectiveness?</td>
<td>Therapeutic ineffectiveness occurs due to drug overdose or</td>
<td>The drug did not have the expected effect.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>drug interaction.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(6) What is the correlation between Pharmacovigilance and drug safety?</td>
<td>Ensuring safety in the use of the drug by the population.</td>
<td>Monitoring the quality and safety of medicines.</td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Cont’d.

(7) How would you explain why a drug does not produce the desired effect?

Owing to medication errors (mainly in prescribing incorrect dosage).

Owing to medication errors (prescription drugs that interact and dosing errors) and deviations drug quality (technical failures and degradation of the drug problems of storage and transportation).

(8) In which stages of drug use occur medication errors?

Prescription, storage and drug administration.

Manufacturing, prescription, distribution, preparation and drug administration.

from information arising from a voluntary report (Lindquist, 2004), and collaborative network development is associated with technical and scientific advancement (Catalá-López et al., 2014; Zwarenstein et al., 2009), this multicenter study was the first to harmonize and standardize a strategy to improve drug risk communication, patient safety, qualification of medicine suppliers, and regulation of the pharmaceutical market.

Poor participation of health professionals in this study can be explained in terms of lethargy and lack of interest, which have been causes of under-reporting of ADE described since 1976 (Inman, 1976). These limitations are inherent to the ADE spontaneous reporting system and may be more severe in countries where implementations of National Centers of Pharmacovigilance are recent, as is the case of Brazil, Uruguay, and Paraguay. Moreover, the lack of knowledge and experience can also justify why developing countries have a lower reporting rate when compared with developed countries (Aagaard et al., 2012). This fact was also observed in the present study and is corroborated by Pérez-García et al. (2011) and López-González et al. (2009).

Several studies are being developed to increase ADE reports, and their effectiveness is already clear and well documented. These studies investigate the association of different methods in pharmacovigilance (passive surveillance with intensive monitoring and/or passive surveillance with observational pharmacoepidemiological studies) (Pal et al., 2013; Edwards, 2012); screening of ADE in medical records with the aid of trigger tools (Rozich et al., 2003); safety assessment of medical prescriptions for elderly people (AGS, 2012), which comprise the age group most susceptible to undesirable effects; and the need to invest in academic training in pharmacovigilance in undergraduate of health courses and post-graduation programs (Hazell and Shakir, 2006).

Furthermore, it is impossible to state that there was no awareness of professionals who did not participate in all meetings of educational intervention, since the partial content they were exposed to may have increased, even perhaps very slightly, their interest in the service. The measurement of this impact can be assessed with a follow-up of ADE reporting after interventions as well as by the improvement of medical records, which have begun to contain information about ADR occurrence and descriptions of medication errors. Thus, elaboration of risk minimization plans should be proposed in order to promote patient safety.

Moreover, given that the study was carried out as a pilot study, there is a need to create new strategies to improve the adherence of Latin-American health professionals in educational interventions of pharmacovigilance. This study suggests that the extension of the period of the study and the promotion of interventions in the three on-duty periods could contribute to the increased rate of return of the questionnaires.

Study limitations

Findings should be assessed with cautions, since educational intervention was carried out in hospitals
of medium and high complexity. Furthermore, the current study had a 2.5% response rate for participation among those invited and a 0.5% response rate for completion of the evaluation. The results are unlikely to be representative of a larger population group.

Conclusion

The data suggest that a multi-faceted educational intervention is effective in harmonizing theoretical concepts and practices related to pharmacovigilance in the hospitals of Mercosur countries. The validated method can contribute towards good practices in drug-safety assessment, improved risk communication, and quantity and quality of reports of medication errors, as well as increased knowledge related to post-marketing surveillance. However, efforts should be made to make participating professionals aware of pharmacovigilance services.

Conflict of Interests

The authors have not declared any conflict of interests.

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