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Strategies to increase the sensitivity of pharmacovigilance in Portugal

ABSTRACT

OBJECTIVE: To evaluate the results of an intervention to improve the number and relevance of reports of adverse drug reactions.

METHODS: A cluster-randomized controlled trial was conducted with pharmacists working in Northern Portugal, in 2007. After randomization, 364 individuals were placed into the intervention group (261 in telephone interviews and 103 in workshops), while the control group was comprised of 1,103 pharmacists. The following were approached in the educational intervention: the problem of adverse drug reaction, the impact on public health and spontaneous reporting. With regard to relevance, adverse reactions were classified into severe and unexpected. Statistical analysis was performed, based on the intention-to-treat principle; generalized linear mixed models were applied, using the penalized quasi-likelihood method. The pharmacists studied were followed during a period of 20 months.

RESULTS: The intervention increased the rate of spontaneous reporting of adverse reactions three times (RR = 3.22; 95% CI 1.33;7.80), when compared to the control group. The relevance of reporting rose, with an increase in severe adverse reactions by approximately four times (RR = 3.87; 95% CI 1.29;11.61) and in unexpected adverse reactions by five times (RR = 5.02; 95% CI 1.33;18.93), compared to the control group.

CONCLUSIONS: During a period of up to four months, educational interventions significantly increased the number and relevance of spontaneous reporting of adverse drug reactions by pharmacists in Northern Portugal.

DESCRIPTORS: Pharmaceutical Preparations, adverse effects. Adverse Drug Reaction Reporting Systems. Drug Toxicity, prevention & control. Adverse Drug Reaction Reporting Systems. Intervention Studies. Health Education. Health Surveillance.

INTRODUCTION

Adverse drug reactions (ADR) are a public health problem worldwide and an important cause of death and hospitalizations in developed countries, representing approximately 6.5% of all hospitalizations.[3,13,15]

In effect, in the pre-commercialization phase, it is difficult to detect the majority of adverse reactions, namely those that are rare and those that are manifested in the long term. It is estimated that most serious adverse reactions are identified after approval of commercialization.[12]

Thus, it is essential to put into effect constant surveillance of drugs, after they are placed into the market, using pharmacovigilance activities. Following other

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European countries, the Portuguese Pharmacovigilance System covers all commercialized drugs, including vaccines, and it is particularly based on spontaneous (voluntary) reporting of suspected ADR by health professionals.

Spontaneous reporting is considered to be weak, scientifically speaking, when compared to the following post-commercialization surveillance methods: monitoring of prescription-event, cohort or case-control studies, and cluster-randomized controlled trials. However, spontaneous reporting of ADR is effective as it generates a safety sign, once each report is a source of information about the risk of commercialized drugs.

A major limitation of spontaneous reporting of ADR results from its being under-reported. In contrast with the proposed objectives of the World Health Organization (WHO) of 250 million reports/million inhabitants,[a] there were 175 reports/million inhabitants in Portugal, in 2008. Thus, information about ADR is scarce and it does not represent the reality of adverse events resulting from drug use. This problem is not exclusively found in Portugal and several studies suggest that less than 10% of ADR are reported to regulatory authorities.[14,17]

This problem persists, even with the regular qualification/sensitization activities that regional pharmacovigilance units (such as the Northern Pharmacovigilance Unit – UFN) perform with health professionals, approaching the theme of pharmacovigilance and spontaneous reporting of ADR.

Based on the results of a study that had been previously conducted,[8,9] a program for pharmacists of Northern Portugal was developed in 2007, using educational interventions. This program aimed to prevent the trend towards under-reporting, increasing the amount and relevance of the information about drug safety that was made available to the regulatory authorities.

Based on the reasons proposed by Inman[11] for under-reporting of ADR (Inman's seven deadly sins), it was concluded that the main obstacles to ADR reporting among pharmacists were as follows:

Complacency – very severe ADR are well documented in terms of drug commercialization;

Ignorance – only severe and unexpected ADR are reported;

Diffidence – only ADR that are positively associated with a certain drug are reported.

Educational interventions were designed, based on the attitudes of health professionals towards spontaneous reporting of ADR, identified by Herdeiro et al.,[7,8] using telephone interviews and workshops. The present study aimed to evaluate the results of an educational intervention, used to improve the number and relevance of reports of adverse drug reactions.

METHODS

A cluster-randomized controlled trial was conducted with pharmacists of Northern Portugal, in 2007. A control group was formed to eliminate potential sources of bias, caused by seasonal variations or vaccination campaigns that could result in an abnormal increase in the number of spontaneous reports of ADR.

The sample was comprised of 1,467 pharmacists, of which 92% worked in pharmacies and 8% in hospitals. In addition, the proportion of females predominated in this sample (79%).

The target population consisted of all community and hospital pharmacists working in the area covered by the Northern Regional Health Management (ARS-Norte). To achieve this, the database made available by the Portuguese Association of Pharmacies and the Portuguese Association of Hospital Pharmacists was consulted, in 2002. According to this database, there was information about a total of 1,446 pharmacists, belonging to 15 spatial groups that served as randomization unit. Throughout the study, corrections were made to the initial database, excluding inactive and deceased individuals (84), while including those who became active (105), totaling 1,467 pharmacists. In addition, a correction was made for individuals who had moved from the control group to the intervention group and vice-versa.

Professionals who were performing any of the following activities were excluded: exclusive teaching, administrative areas, pharmaceutical industry and pharmaceutical distribution companies; the northern pharmacovigilance unit; specialized hospitals; specific clinical services, such as medical genetic or histocompatibility centers.

The randomization unit was comprised of geographic spatial groups to eliminate cross-contamination between the control and intervention groups. Each spatial group consisted of pharmacists performing activities in a referral hospital and in community pharmacies in their area of influence.

The present study was designed before the reorganization of the Portuguese hospital model, with the creation of hospital centers, beginning in 2007. In this way, groups are based on individualized hospitals, rather than clustered in hospital centers. Such groups were created according to the five health sub-regions subject

[a] Ministério da Saúde. Instituto Nacional da Farmácia e do Medicamento. Farmacovigilância em Portugal. Lisboa; 2004.

to ARS-Norte and having the smallest size possible, so as to minimize contamination between community pharmacies and hospitals. A total of five hospitals out of the 25 existing in the area of study were excluded as they were specialized. This could represent a contamination factor, once their area of influence includes the entire Northern region of Portugal. Of all 20 remaining hospitals, five were grouped because they were geographically very close to one another or because they were very small, resulting in 15 groups.

Differently from the majority of studies that form control and intervention groups at a ratio of 1:1, the present study opted for the inclusion of fewer groups in the intervention group, compared to the control one, due to economic reasons, thus obtaining an unequal randomization, at a ratio of 1:3, approximately.[19]

Next, the 15 groups were randomly distributed to form an intervention group (four groups) and a control group (11 groups). The intervention group was subsequently divided into two sub-groups, according to the intervention performed: telephone interview and workshop. Health professionals belonging to the 11 groups of the control group did not receive any of the previously mentioned interventions.

Workshop intervention

Interventions were performed between May 29 and June 26, 2007, in the regions of Vila Real, Macedo de Cavaleiros and Mirandela, including 48 (52%) pharmacists. Each session lasted approximately one hour, with a brief introduction about the problem of ADR and its impact on public health, followed by an approach of spontaneous reporting of ADR. Some of the attitudes and knowledge that pharmacists have about this issue were reported, based on the results of Herdeiro et al.[8] Guidance on how to complete the ADR spontaneous report file, discussion about a practical case with participants, and completion of this file with the actual case by participants were performed. After the session, each participant was provided the following support materials, so that the process was established and facilitated: copy of the practical case, copy of the ADR spontaneous report file to be completed with the actual case, report file, UFN presentation pamphlet, and certificate of presence.

Telephone intervention

The telephone interview script was pre-tested in the region of Ovar (out of the intervention and control areas) with eight pharmacists (seven of whom performed community pharmacy activities and one, hospital pharmacy activities). The script was found to be efficient, enabling a flowing conversation between interviewer and pharmacist, and its initial format did not undergo changes.

Telephone interventions occurred between July 2 and 20, 2007, with pharmacists of the Porto and Bragança regions. Telephone calls lasted between four and 12 minutes, according to the pharmacist's participation. For each one, three attempts of contact were made, after which such contact was considered impossible, resulting in 36% of all contacted individuals. After the call, the following support materials were sent to participants: a thank-you letter, ADR spontaneous report file and UFN presentation pamphlet.

In all, 141 individuals effectively had an educational intervention. Thus, the global rate of participation obtained was 39%. The rate of participation in workshops was 46%, whereas telephone intervention totaled 36%.

Criteria of relevance of reported adverse reactions were established and those that were severe and unexpected and had a high level of probability were considered more relevant. A severe adverse reaction is that which causes death, poses risk to life, leads to or prolongs hospitalization, increases temporary or permanent incapacity and/or causes congenital anomalies. Unexpected adverse reactions are those not described in the respective summary of drug characteristics.[b]

After validation, reports are evaluated by the regulatory authorities, when one of the following levels of probability is attributed to them: certain, probable, possible, improbable, conditional or non-classifiable.[c] In the present study, reports to which the probable or certain levels were attributed were considered relevant.

All data were obtained from the UFN, coordinated by the Portuguese Authority of Drugs and Health Products and certified according to WHO directives. The expert responsible for the evaluation of adverse reactions was not aware of the study group to which each pharmacist belonged. Confidentiality was maintained during the entire study and data on those who made reports were changed into number codes. The UFN guaranteed that all ADR reports were followed in the study population, without losses during this follow-up. Post-intervention results were analyzed in four-month periods.

Statistical analysis was performed based on the intention-to-treat principle.[10] Generalized linear mixed models were applied, using the penalized quasi-likelihood method,[6] on three levels of observation: level

[b] Committee for Medicinal Products for Human Use. The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use. London; 2007. (The Rules Governing Medicinal Products in the European Union, 9A).

[c] World Health Organization. The Uppsala Monitoring Center. Geneva; 1978[cited 2009 Jul 23]. Available from: http://www.who-umc.org

1 – the number of monthly spontaneous reports of ADR per pharmacist (dependent variable); level 2 – the individuals; and level 3 – spatial groups.

Randomization effects were considered both for individuals and spatial groups.

Due to the characteristics of the dependent variable, a Poisson generalized linear mixed model, adjusted according to the overdispersion parameter.[6] To measure the intervention effect, a dichotomous variable (period) was created, with values ranging from 0 (for the basal period) to 1 (for the months between the beginning of the intervention and the end of the follow-up time). The intervention effect was evaluated by interacting the period variable with the group variable (with a value of 0 for the control group, 1 for the workshop intervention group and 2 for the telephone intervention group). This interaction enables the quantification of possible contamination of the control group by intervention, in addition to the basal differences among study groups.

Another variable with six categories (value of 0 for the basal period, value of 1 for the period of four months after intervention and values of 2, 3, 4 and 5 for the subsequent four-month periods) was created to analyze the duration of the intervention effect.

The SPSS® software, version 14.0, was used to generate the database. Subsequently, the statistical analysis was conducted with the S-Plus® software.

The results are expressed as relative risk (RR), with respective 95% confidence intervals (CI), indicating the number of times when the probability of reporting ADR increases.

The results are shown in terms of the number of times when the intervention increased the number and relevance of the ADR reports made in the UFN.

A previous authorization was requested to perform educational interventions in the ARS-Norte and Hospital Management Councils involved. The present study was approved by the Ethics Committees of each hospital (Processes 005015, from 13/03/2007, and 1539, from 25/05/2007). The ARS-Norte was informed about the interventions in all institutions involved.

RESULTS

There was a global increase in the number of ADR reports in the months of intervention, although this increase was not maintained throughout time. There was an increase in the rate of reporting in all four-month periods, except for the last one (Table 1).

The intervention increased the rate of spontaneous reporting of ADR three times (RR = 3.22; 95%CI 1.33;7.80), adjusted for basal values and place of work, compared to the control group. With regard to the reports, there was an increase in severe (RR = 3.87; 95%CI 1.29;11.61) and unexpected ADR reports (RR = 5.02; 95%CI 1.33;18.93) in the groups involved with interventions, compared to the control group.

Reports with a high level of probability did not have a statistically significant increase (Table 2).

Table 1. Effect of intervention on the rate and type of intervention. Northern Portugal. 2007-2008.

Type of report/Group	Rate of reporting per one thousand pharmacists-month					
	Basal period	Post-intervention period (four-month period)				
		1º	2º	3º	4º	5º
Total						
Control	1.76	3.85	2.49	2.27	4.53	1.59
Workshop	7.65	48.54	12.14	16.99	12.14	4.85
Telephone	1.69	12.45	7.66	6.70	11.49	0.96
Severe						
Control	0.92	1.59	1.36	0.91	2.27	0.91
Workshop	3.92	29.13	7.28	7.28	7.28	2.43
Telephone	0.66	6.70	1.92	2.87	3.83	0.96
High level of probability						
Control	1.04	2.72	1.13	2.04	3.40	1.13
Workshop	5.60	33.98	7.28	14.56	12.14	4.85
Telephone	1.18	6.70	5.75	3.83	8.62	0.96
Unexpected						
Control	0.57	0.91	0.68	0.91	0.45	0.45
Workshop	1.68	12.14	4.85	12.14	2.43	-
Telephone	0.52	-	3.83	4.79	2.87	-

Table 2. Results of the intervention in the number and quality of adverse drug reactions reported to the Northern Pharmacovigilance Unit. Northern Portugal, 2007-2008.

Variable	p	RR	95%CI
Report of ADR*	0.010	3.22	1.33;7.80
Report of ADR with a high level of probability	0.168	2.02	0.74;5.49
Report of severe ADR	0.016	3.87	1.29;11.61
Report of unexpected ADR	0.017	5.02	1.33;18.93

*ADR: Adverse Drug Reaction

case, with the completion of an ADR report file in real time. The material provided to participants at the end of workshops and telephone interviews could also have had a key role in a successful intervention, contributing as a facilitating agent.[1]

The results of workshop interventions must be analyzed with caution, because there may be an effect of contamination from continuous qualification activities developed by the UFN. Although the intervention designed for this study had its own characteristics,

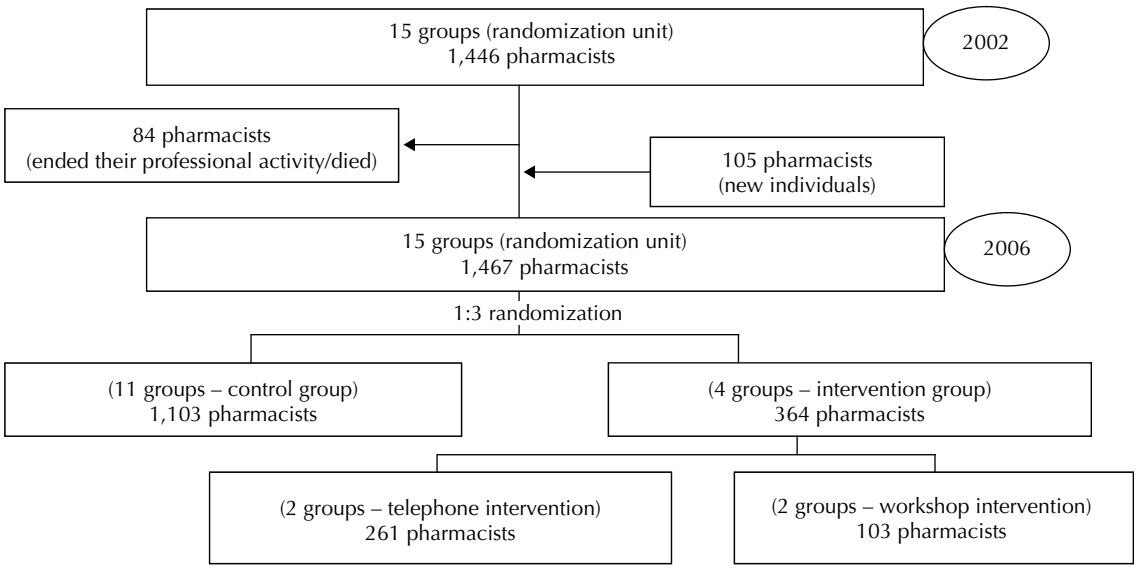

Figure. Study design. Northern Portugal, 2007-2008.

DISCUSSION

Educational interventions conducted in workshops or telephone interviews significantly increased the number and relevance of spontaneous ADR reports by pharmacists of Northern Portugal.

However, as shown in other studies,[4,5,16] this increase loses significance throughout time. The population that can potentially make reports needs regular qualification courses to remain participative in the Portuguese Pharmacovigilance System. Based on the results of the present study, sensitization at every four months could be proposed, when loss of influence of intervention is identified.

With regard to the content of interventions, the importance of focusing on the attitudes associated with under-reporting of ADR is observed, so that an effective change occurs.[2] In addition, their effectiveness in terms of results could be due to the fact that these interventions have a highly interactive nature,[18] especially because they include the discussion of a practical which distinguish it from common qualification courses developed by the UFN, the latter occurred in the sub-health area of Porto predominantly, which did not belong to the workshop intervention group.

It is believed that the only possible sources of error in the present study would be the cases of death or end of the professional activity of an individual who reported ADR during the study, whose information was not available. Nonetheless, these cases would not affect the accuracy of the number of ADR reports, although they could distort the rate of report per pharmacist.

In conclusion, a restructuring of regular activities of sensitization of health professionals is suggested, including telephone interview interventions, which had not been used until then. This aspect does not invalidate the continuity of normal in-person sensitization/qualification actions that the Regional Pharmacovigilance Unit regularly performs. Such actions must include the discussion about the attitudes of health professionals towards spontaneous reporting of ADR, in terms of the main reasons for under-reporting.

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