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An Intervention to Improve Spontaneous Adverse Drug Reaction Reporting by Hospital Physicians

A Time Series Analysis in Spain

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Abstract

Background: Spontaneous reporting of adverse drug reactions (ADRs) in hospitals is scarce and several obstacles to such reporting have been identified previously.

Objective: To assess the effectiveness of a multifaceted intervention based on healthcare management agreements for improving spontaneous reporting of ADRs by physicians in a hospital setting.

Methods: In 2003, the spontaneous reporting of ADRs was included as one of the objectives of hospital physicians at the Vall d'Hebron Hospital, Barcelona, Spain, within the context of management agreements between clinical services and hospital managers. A continuous intervention related to these management agreements, including periodic educational meetings and economic incentives, was then initiated. We carried out an ecological time series analysis and assessed the change in the total number of spontaneous reports of ADRs, and the number of serious ADRs, unexpected ADRs, and ADRs associated with new drugs between a period previous to the intervention (from 1998 to 2002) and the period during the intervention (from 2003 to 2005). A time series analysis with ARIMA (Auto-Regressive Integrated Moving Average) models was performed.

Results: The median number of reported ADRs per year increased from 40 (range 23–55) in the first period to 224 (range 98–248) in the second period. In the first period, the monthly number of reported ADRs was stable (3.47 per month; 95% CI 1.90, 5.03), but in the second period the number increased progressively (increase of 0.74 per month; 95% CI 0.62, 0.86). In the

second period, the proportion of reported serious ADRs increased nearly 2-fold (63.1% vs 32.5% in the first period). The absolute number of previously unknown or poorly known ADRs increased 4-fold in the second period (54 vs 13 in the first period). There was also an increase in the absolute number of suspected pharmacological exposures to new drugs (97 vs 28) and in the number of different new drugs suspected of causing ADRs (50 vs 19).

Conclusion: A continuous intervention based on healthcare management agreements with economic incentives and educational activities is associated with a quantitative and qualitative improvement of spontaneous reporting of ADRs by hospital physicians.

Background

Spontaneous reporting of adverse drug reactions (ADRs) is the most commonly used method leading to the generation of hypotheses relating to newly recognized ADRs in pharmacovigilance. However, one of its main limitations is that underreporting, which decreases sensitivity, may delay detection of new signals and make the system sensitive to selective reporting.[1,2] Several studies have indicated a variety of obstacles to the spontaneous reporting of ADRs, such as physicians having an inadequate knowledge of ADRs, a lack of time because of clinical workload due to other healthcare priorities, uncertainty that the drug caused a particular ADR, difficulty in accessing reporting forms, lack of awareness of the requirements for reporting and lack of understanding of the purposes of spontaneous reporting systems, as well as having attitudes that are associated with a high degree of underreporting.[3-12] Other studies have evaluated the effectiveness of educational interventions or other interventions aimed at increasing reporting by physicians.[13-22]

In our hospital, the Vall d'Hebron Hospital, Barcelona, Spain, we have been developing and running a pharmacovigilance programme (PhVP) for more than 20 years. Our PhVP records cases of ADRs identified by a systematic and daily review of hospital admission diagnoses and cases of ADRs spontaneously reported by physicians.[23,24] Following causality evaluation, all of these ADR reports are included in the Spanish Pharmacovigilance System (SPhVS) database. During recent years, healthcare management agreements aimed at stimulating physicians to report ADRs have been developed in the hospital.

The aim of this study was to assess the effect of this multifaceted intervention, based on healthcare management agreements in the hospital, on stimulating ADR reporting by physicians.

Methods

Study Design and Data Collection

From 1998 to 2005 an ecological time series study was carried out in the general area of the Vall d'Hebron Hospital, a Spanish tertiary care teaching hospital. The general area of the hospital has approximately 700 beds, with more than 500 staff physicians and pharmacists, and more than 200 physicians and pharmacists in training. Data were collected from the hospital PhVP database and spontaneous reports of ADRs were selected and included in the study. The variables analysed were the number of spontaneous reports of ADRs, their date of reporting, seriousness, previous knowledge about the ADR, as well as the time since marketing authorization of the suspected drugs. The causality assessment methods of the SPhVS were used for the evaluation of individual reports of ADRs; these methods have been described in detail elsewhere.[25] The seriousness of the ADRs was classified according to EU criteria and cases were classified as serious (ADRs that result in death, are life-threatening,

require hospitalization or prolongation of existing hospitalization, result in persistent or significant disability or incapacity, result in a congenital anomaly or birth defect, or are important medical events) or as non-serious (the remaining cases).[26] Previous knowledge of ADRs was classified according to the SPhVS's causality algorithm for ADRs as well known ADRs, poorly known or known from anecdotal reports, and unknown or unexpected ADRs.[27] New drugs were defined as those that had been marketed for less than 5 years at the time of onset of the ADR. The educational intervention was based on the identification of different obstacles to spontaneous reporting of ADR in the same centre.[10]

Intervention

A multifaceted intervention based on healthcare management agreements between hospital managers and clinical services was initiated in 2003. A framework agreement between hospital managers and physicians included different commitments linked to economic incentives. One of the objectives for physicians was to increase the number of spontaneous reports of ADRs. The economic incentives for ADR reporting were integrated with other clinical objectives at three levels: (i) institution or whole hospital; (ii) clinical department or clinical team; and (iii) physician. The financial incentive was variable according to the objectives achieved, and was approximately 5–7% of the physician's salary. The size of the financial payment to physicians for ADR reporting was not fixed, instead being variable depending on the prioritization of other commitments, and accounted for less than 10% of the total of agreed incentives. Therefore, the financial incentive obtained for reporting was, on average, less than 1% of the physician's salary. In each clinical service, an initial meeting between physicians and the hospital pharmacovigilance team was held. The objective of spontaneous reporting of ADRs, a summary of the hospital's pharmacovigilance activities, the way to report ADRs, and the changes in the pharmacovigilance legal rules recently established in the EU and Spain[26,28] were presented. To reinforce this, twice-yearly educational meetings were held in each clinical service, offering information about pharmacovigilance and emphasizing the selection of serious ADRs, unexpected ADRs, and those ADRs associated with new drugs as the priorities for spontaneous reporting. These meetings lasted 45–60 minutes, and the general agenda consisted of a brief explanation of the results from the PhVP (the number of ADRs detected in the whole hospital and in the specific clinical service and discussion of their main characteristics). Signals identified by the PhVP and news about ADRs released by regulatory agencies (the Spanish Agency of Medicines, European Medicines Agency [EMEA], US FDA and others) or identified by published studies were also discussed. In addition, reminder cards containing the contact telephone number of the pharmacovigilance team in charge of the hospital PhVP and a list of the most important ADRs to be reported (serious, unexpected and those associated with new drugs) were distributed to the hospital wards.

Statistical Analysis

The change in the numbers of reported ADRs between two periods was analysed: the first period was defined as prior to the intervention (from 1998 to 2002) and the second period as during the intervention (from 2003 to 2005). The intervention was put in place during December 2002. In addition, changes in the numbers of reported serious ADRs, unexpected ADRs and ADRs associated with new drugs were also analysed. Although the PhVP was set up more than 20 years ago, only the 5-year period prior to the intervention was selected for comparison. A time series approach with ARIMA (Auto-Regressive Integrated Moving Average) models for intervention analysis was used in order to quantify the impact of the intervention. The number of reports in each month from January 1998 to December 2005 was analysed, with a total of 96 observations. In order to set up the pattern series, the seasonality, homogeneity of observations, variances and trends for both periods were studied. The presence of autoregressive errors

and moving averages structures was explored. The goodness of the adjustment of the estimations was checked by the Ljung-Box and Dickey-Fuller statistics.[29] Descriptive analysis of report counts was performed by means of median and range. Categorical variables were described with percentages; statistical differences were assessed by means of Chi-square (χ^2) test. The statistical analysis was performed using the SAS version 9.1 (SAS Institute, Cary, NC, USA) statistical package. Significance was set at a level of 0.05 for two-tailed tests.

Results

Number of Spontaneous Reports

Of the total number of cases identified by the PhVP, the proportion of spontaneous ADR reports increased from 29.5% (n = 200) during the first period to 71.5% (n = 631) during the second period. Expressed as a median number of spontaneous reports per year, the increase was from 40 (range 23–55) to 224 (range 98–248). The analysis showed an absence of seasonality and it was therefore adjusted by applying a model of first-order moving average ($R^2 = 0.74$). Figure 1 shows the sustained increase in the monthly number of spontaneous reports since 2003. In the first period there was a monthly constant mean of 3.47 reports (95% CI 1.90, 5.03), while in the second period there was an increasing trend with a monthly increase of 0.74 reports (95% CI 0.62, 0.86).

Seriousness

In the second period, the proportion of serious cases reported increased nearly 2-fold (63.1% vs 32.5% in the first period; $p < 0.001$). Of note, the median number per year of serious cases increased by more than 10-fold (153 vs 11 in the first period). Figure 2 illustrates trends in proportions of reported serious ADRs per year.

New Drugs Suspected of Causing ADRs

Overall, 285 and 877 suspected pharmacological exposures were included in the reports received in the first and second period, respectively. Approximately 10% of these exposures were to new drugs (9.8% in the first period and 11.1% in the second one; $p = 0.559$). Nevertheless, both the median number of suspected exposures to new drugs per year and the median number of different new drugs per year increased in the second period (33 vs 6 and 24 vs 5, respectively). Trends in reporting ADRs associated with new drugs per year are illustrated in figure 2.

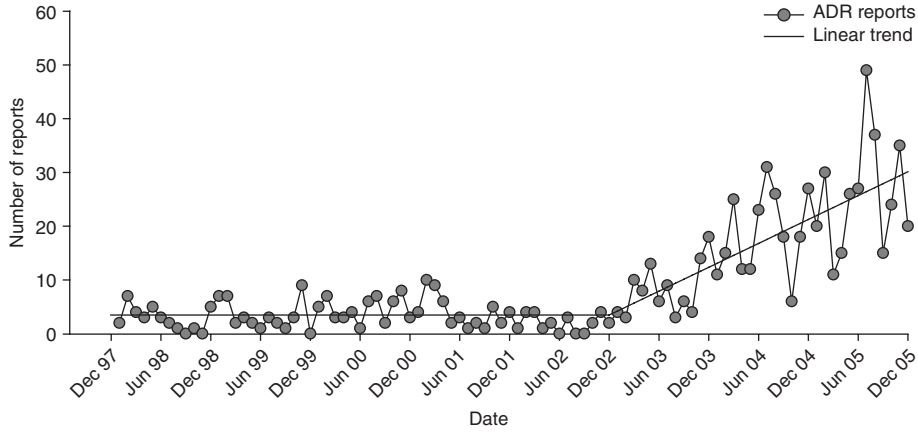

Fig. 1. Monthly numbers of spontaneous reports of adverse drug reactions (ADRs) to the pharmacovigilance programme (PhVP).

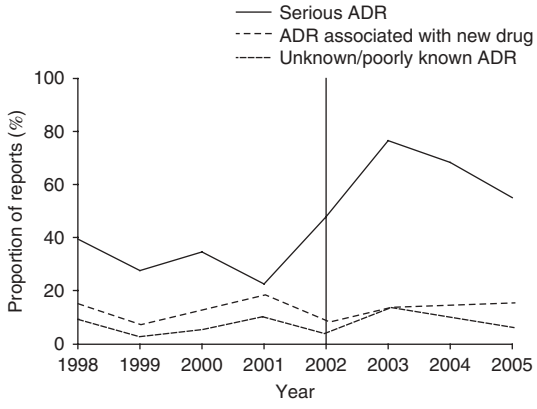

Fig. 2. Yearly proportion (percentages) of serious adverse drug reactions (ADRs), unknown or poorly known ADRs and ADRs associated with new drugs. Dates before the vertical dividing line are within the period prior to the intervention and those after are within the period during the intervention.

Previous Knowledge

Most reports described previously known drug-reaction associations (93.5% in the first period and 91.4% in the second period; $p = 0.376$). However, the median number of previously unknown or poorly known drug-reaction associations per year increased 6-fold in the second period (20 vs 3 in the first period); most of these were serious cases (5 of 13 in the first period and 40 of 54 in the second period). Figure 2 illustrates trends in reporting unknown or poorly known drug-reaction associations per year.

Discussion

The results of our study indicate that a multifaceted intervention based on healthcare management agreements between hospital directives and physicians improves the spontaneous reporting of ADRs. The effect was continued and progressive while the intervention was being developed. Not only did the quantity increase (the total number of reports of ADRs), but also the quality of reports increased (the number of reports of serious ADRs, unexpected ADRs and ADRs associated with new drugs.

Several studies have analysed the effect of educational intervention on the spontaneous reporting of ADRs.[13-20] Those studies have used multiple interventions, such as mailings, newsletters, ADR bulletins, oral presentations, educational programmes linked to educational credits, verbal reminders, advertisements, and coordination between physicians and hospital pharmacists. Moreover, some studies have assessed the effect of some kind of economic inducement on the reporting rate of ADRs.[21,22] However, our study has some specific and differential characteristics. First, we assessed the effect of a continuous multifaceted intervention that included not only educational activities but also economic incentives over time for 3 years. Secondly, our methodology was different from other studies because, although our study was observational, we used a time series as the method of analysis. Only one previous study has used this method.[20] In spite of these differences in the type of intervention and study methodology, our results are similar to those of other studies that showed an improvement in the spontaneous reporting of ADRs. However, we do not know the different intensity effect of each facet of the intervention (i.e. economic incentives and educational activities). Future studies should compare different strategies for improving reporting of ADRs.

The duration of the effect of the intervention is another important key to bear in mind. The magnitude of changes in reporting was lower than those found in some other studies,[15,16,18] but in our study these changes were constant and progressive over the time during which the intervention was being developed. Although we cannot be certain, we believe that these changes would reverse if the intervention activities were abandoned. In other studies, the effect of educational interventions began to attenuate after 1 year and lasted for no more than 2 years.[15,17-19] Economic incentives have also shown to be associated with a temporary initial increase in the number of reports, although the reporting rate returned to baseline after this initial increase.[21,22]

Moreover, it must be emphasized that not only did the quality of spontaneous reports not decrease but in fact increased. Some studies have shown that educational or economic stimuli

can influence both the rate of spontaneous reporting and the proportion of reports of serious ADRs[18,22] or reports of special interest (e.g. unexpected ADRs, those ADRs with high causality assessment scores and ADRs associated with new drugs).[18,19] In our study, the increased number of reports was not due to the addition of trivial cases; on the contrary, there was an important increase in the proportion of reports of serious ADRs or in the absolute number of reports of special interest. These findings may be related to the reminder given of the most important ADRs that should be reported. Whether the improvement of reporting in our hospital had an impact on patient care or signal identification is now under study.

Our study had limitations that are worth noting. Firstly, the generalizability of these findings may be limited because the intervention was carried out in a specific hospital with particular characteristics (the largest teaching hospital in our geographical area) and it may not be effective in other hospitals with different characteristics. Secondly, a greater number of spontaneous reports do not necessarily imply more efficient signal identification. Since the main objective of spontaneous reporting systems is the prompt detection of new drug safety issues, it is crucial that the increase in the number of reports does not occur at the expense of an increase in the ratio of signal to noise.[30,31] Other studies should analyse the effect of reporting increases on the number of signals identified and the speed of their recognition. Thirdly, the response variable consists of count data (the number of monthly reports); therefore, the suitability of the ARIMA model could be questioned, as other approaches (e.g. Poisson or negative binomial regression) may be appropriate. However, the results obtained by using these alternative methods are similar to those presented (data not shown), and our analysis yields more conservative effect estimates. In order to keep the most simple model and interpretation we elected to retain the results from the ARIMA model. Fourthly, we did not include a control group in our study. Nevertheless, as a control group was unavailable, time series analysis was the most appropriate method for the evaluation of the influence of the interventions on the reporting rate trend. The use of time series methodology served to eliminate potential sources of bias, such as seasonal variation, and to minimize the effects of changes in behaviour over long periods of time. Finally, we did not have information on other potentially relevant factors such as years since graduation, medical speciality, postgraduate degrees or previous training of physicians, each of which may be related to the observed effects. Future studies should analyse the effect of these and other factors.

Conclusion

An intervention based on healthcare management agreements led to a quantitative and qualitative improvement of spontaneous reporting of ADRs by hospital physicians. In our study, this intervention was based on economic incentives and regular educational activities in pharmacovigilance. The absolute number of spontaneous reports and also the number of reports of serious, unexpected and ADRs associated with new drugs increased. Future studies should analyse whether these activities or other activities in pharmacovigilance increase the number of signals identified and shorten the time to be recognized, and also how these activities could be used at a local level to achieve the safer use of medicines.

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