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Stimulating Adverse Drug Reaction Reporting

Effect of a Drug Safety Bulletin and of Including Yellow Cards in Prescription Pads

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Abstract

Background: The effectiveness of voluntary reporting systems in pharmacovigilance highly depends on the number of assembled reports.

Aim: The aim of this study was to measure the effect of the periodical distribution of a bulletin on drug safety issues and of including yellow cards in prescription pads on the rate of adverse drug reaction (ADR) reporting.

Study Design and Methods: The Catalan Centre of Pharmacovigilance began its activities at the end of 1982. Since 1985, an ADR bulletin (ADRB) has been mailed approximately quarterly to all physicians in its catchment area, with one yellow card enclosed. Additionally, from 1991–1994, a yellow card was included in the prescription pads of the Catalan Health Service. Time series methodology, with adjustment of the monthly number of reports to an Auto-Regressive Integrated Moving Average (ARIMA) model, was used to evaluate the effect of these two measures.

Results: From January 1983–October 1995, 6240 spontaneous ADR reports were received, and 41 issues of the ADRB were sent out. Initially, the mean monthly spontaneous ADR reporting rate was 34.4 (SD = 14.1; n = 106 months). After the inclusion of yellow cards in prescription pads, the mean monthly spontaneous ADR reporting rate increased to 53.9 (SD = 14.4; n = 48 months). According to an ARIMA model, when a bulletin was send out (MONTH1), a mean increase of 9.4 reports was produced in that month, plus 12.3 additional reports in the following month (MONTH2), and 6.3 in the second month after sending the ADRB (MONTH3). A yellow card in the prescription pads elicits a monthly mean increase of 19.8 in the number of reports.

Conclusions: The present study suggests that ADRBs elicit a temporal increase of the ADR reporting rate. Including a yellow card in prescription pads was followed by an even greater increase in the reporting rate, possibly because it guarantees that yellow cards are available at the workplace.

Background

Spontaneous reporting is the most extensive method for hypothesis generation in pharmacovigilance. However, its effectiveness greatly depends on the number of assembled reports, particularly those dealing with new drugs and those describing serious and previously undescribed adverse drug reactions (ADRs). One of its main limitations is underreporting. In order to increase the reporting rate, measures aimed at stimulating reporting among prescribers should be implemented. Several actions, such as including a reporting form into prescription pads[1] or in national formularies, or paying a fee to reporters,[2] have been shown to be of value in increasing reporting rates.

In many of the countries participating in the WHO International Drug Monitoring Programme, adverse drug reaction bulletins (ADRBs) are regularly produced and distributed to prescribers and other health professionals.[3] Their main aim is to increase the reporting rate by providing feedback information to potential reporters. Some of them are viewed as helpful and informative amongst physicians.[4] However, their effect on the reporting rates of ADRs has not been evaluated.

The aim of the present study was to evaluate the effects on the rate of ADR reporting of distributing an ADRB, and the effect of including a reporting form in the prescription pad.

Study Design and Methods

A voluntary reporting system with a decentralised structure has been developed in Spain since 1983. There are 15 regional centres and a co-ordinating centre, which is part of the drug regulatory authority. The system receives approximately 9000 reports each year from physicians and pharmacists. The activities of the Spanish System of Pharmacovigilance started in Catalonia at the end of 1982. Since April 1984 the Catalan Centre of Pharmacovigilance – located in Barcelona and with a catchment population of 6 million inhabitants – has produced an ADRB (*Butlletí Groc*) which became approximately quarterly by the end of 1985.[5] The bulletin is sent by mail, free of charge, to all practising physicians (approximately 30 000), with one reporting form (yellow card) enclosed. Additionally, from January 1991–December 1994 a reporting form was included in all prescription pads of the main provider organisation for the Catalan Health Service (*Institut Català de la Salut*, ICS), with approximately 6500 prescribers.

The study period was January 1983–October 1995, and only spontaneous reports were included. The main outcome variable was the monthly number of spontaneous reports received at the Catalan Centre during this time. Reports from special surveillance schemes, phase IV clinical studies and those sent by the pharmaceutical industry were not included. The reporting rate was related to the date of distribution of the ADRB and to the time that a reporting form was included in each prescription pad of ICS. The effect of both measures on the reporting rate was analysed by means of time series methodology,[6] by adjusting the monthly number of reports to an Auto-Regressive Integrated Moving Average (ARIMA) model.[7-9] Since the bulletins were sent at approximately quarterly intervals, an intervention model was designed where the month when the ADRB was sent out (MONTH1) and the two following months (MONTH2, MONTH3) were included as parameters. The reporting rate in these periods was compared with the reporting rate prior to sending the bulletin or, after starting sending it, in months without the effect of the bulletin (i.e. other than MONTH1, MONTH2 or MONTH3 whenever the bulletin was not sent regularly). It was considered that the inclusion of the yellow card in the prescription pads would produce a 'step' effect on the reporting rate during the period in which the intervention was carried out.

In order to identify the ARIMA model that was most appropriate for our data, we used the 'Akaike Information Criterion' (AIC) for goodness-of-fit, the residual variance, and the significance of the parameters estimated in the model.[10] Among the models tested to explain our data, the one with no self-correlation of its residuals (Durbin-Watson statistics) and with smaller AIC and residual variance was chosen (table I). To avoid over-fitting of the

Table I. Influence of the intervention variables on the adverse drug reaction reporting rate. Coefficients, 95% CI and significance were based on the an Auto-Regressive Integrated Moving Average (1,0,0) $(1,0,0)_{12}$ model[a,b]

	Coefficient	95% CI of coefficient	p-Value
AR	0.31	0.16–0.47	<0.0001
SAR	0.29	0.13–0.45	0.0004
MONTH1	9.39	5.12–13.89	<0.0001
MONTH2	12.31	7.19–17.42	<0.0001
MONTH3	6.27	1.72–10.82	0.007
PAD	19.76	12.53–26.99	<0.0001
Constant mean	27.03	21.80–32.23	<0.0001

a Residual: mean = –0.054; variance = 159.55.

b Durbin-Watson statistics = 1.94.

AR = auto-regressive parameter; **MONTH1** = month of bulletin mailing; **MONTH2** = next month of bulletin mailing; **MONTH3** = second month after bulletin mailing; **PAD** = yellow card in the prescription pads of the National Health Service's provider organisation; **SAR** = seasonal autoregressive parameter.

model, the most parsimonious was chosen.[10] To evaluate the time trend of the ADR reporting rate and the combined effect of both interventions, the data were adjusted to a linear ARIMA (1,0,0) $(1,0,0)_{12}$ model, an autoregressive model of first order with monthly seasonality component. This model can be expressed in the following way (equation 1):

$$X_t = \mu + \varphi X_{t-1} + \Phi X_{t-12} - \varphi\Phi X_{t-13} + I_1 + ... + I_n + a_t$$

where μ is the constant mean of the process, φ is a first order autoregressive parameter, Φ is a seasonal parameter of 12th order and a_t is the random component of the series, represented by the residuals of the model. The month when the bulletin was sent (MONTH1) and the 2 consecutive months (MONTH2 and MONTH3), as well as the period when yellow cards were included into the prescription pads (PAD), were added to the model as intervention variables (in the form of dummy variables). The intervention variables are represented in the general formulation by coefficients I_1,.., I_n. As the interventions evaluated in this study can interact between them, the interaction coefficients (MONTH1 × PAD, MONTH2 × PAD, and MONTH3 × PAD) were also estimated.

The statistical analysis was performed with SPSS 6.0.1 for Windows.[10]

Results

Trend of Report Series

During the study period, 6240 spontaneous ADR reports were received in our regional centre and 41 issues of the bulletin were sent out. The bulletin started to be sent out regularly in September 1985. Before this date only one bulletin was sent in March 1984, thus leaving 29 months without the effect of any intervention. After September 1985, 40 bulletins were distributed leaving 22 additional months without any supposed effect of the bulletin as there was an overlapping influence in 19 months, because the bulletin was sent monthly or bimonthly. The mean monthly number of reports was 40.5 (SD = 17.7; range 7–105), the median was 38, and the mode 35. The monthly reporting rate showed marked seasonal variability, with a maximum of 56 (SD = 19) reports in March, and a minimum of 23 (SD = 13) in August (see figure 1). Figure 2 represents the trend of spontaneous reporting, by month, in relation to the distribution of the ADRB and to the inclusion of yellow cards in the prescription pads of the ICS. Initially, the monthly reporting rate immediately reached a steady-state, without any trend, with a mean monthly reporting rate of 34.4 (SD = 14.1; n = 106 months). After the inclusion of yellow cards in ICS prescription pads, the mean monthly reporting rate reached a new steady-state, with a mean monthly reporting rate of 53.9 (SD = 17.4; n = 48

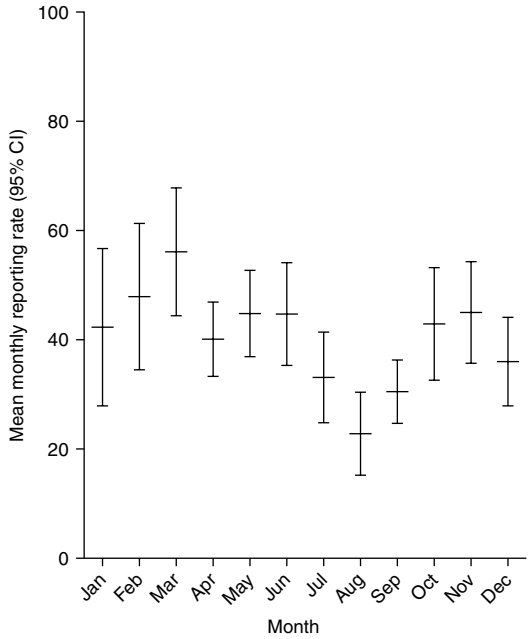

Fig. 1. Mean monthly reporting rate, by month, from 1983 to 1995. The total number of spontaneous adverse drug reaction reports was 6240.

months) [see figure 3]. Cyclical seasonal variations in the series were recorded (see figure 1). August was the month with the lowest reporting rate. However, in the years when an issue of the ADR bulletin was mailed in July (5 years), the mean number of reports received in August was 37; this compares with a mean reporting rate of 14 in the 8 years when no bulletin was sent out in July.

Intervention Analysis

The ARIMA (1,0,0) $(1,0,0)_{12}$ model coefficients, 95% CI and their statistical significance are shown in table I. The model in the table is the one with the best pattern of adjustment to the data. The mean absolute percent error of the estimate was 28.7% with a 95% CI of 24.1–33.3%. This means that the model explains about 70% of the variability of the data series. The constant mean of the model was 27 (95% CI 21.8–32.2) monthly reports. The autoregressive model assumes a temporary dependence of the values observed in a certain moment, i.e. that the number of reports received in a given month partly depends on the number received in the previous month (AR) and in the same period of the previous year (SAR).

Effect of Bulletin Distribution and Yellow Card Inclusion in the Prescription Pads

MONTH1 (month of bulletin dispatch), MONTH2 (first month after sending the bulletin), MONTH3 (second month after sending the bulletin) and PAD (yellow cards in the prescription pads) coefficients reflect the effect of the study interventions and should be interpreted as the mean increase in the ADR reporting rate attributable to such interventions. According to our model, when a bulletin was sent out (MONTH1), a mean increase of 9.4 (95% CI 5.1–13.9) reports was produced in the same month, plus 12.3 (95% CI 7.2–17.4) additional reports in the following month (MONTH2), and 6.3 (95% CI 1.7–10.8) in the second month following such mailing (MONTH3). The combined effect of these three factors (MONTH1, MONTH 2, MONTH3) produced a monthly mean increase of 11.7 reports.

In the period in which yellow cards were included in the prescription pads (PAD), the increase in the monthly reporting rate was 19.8 (95% CI 12.5–27).

We evaluated the possible interaction of the studied interventions. The corresponding coefficients were nonsignificant and were not included in the model because they did not improve its fitting.

Discussion

Our centre implemented two different interventions with the aim of increasing the reporting rate. One was the publication and free mail distribution of an ADR bulletin, whose aim was not only to stimulate ADR reporting, but also to increase knowledge and general culture on drug prescribing, in the context of other information, teaching and continuing education interventions.[5] The second consisted in the inclusion of a yellow card in every National Health System prescription pad in order to increase the availability of reporting forms. The present study suggests that in our milieu, editing and distributing a bulletin on drug safety produces a mean

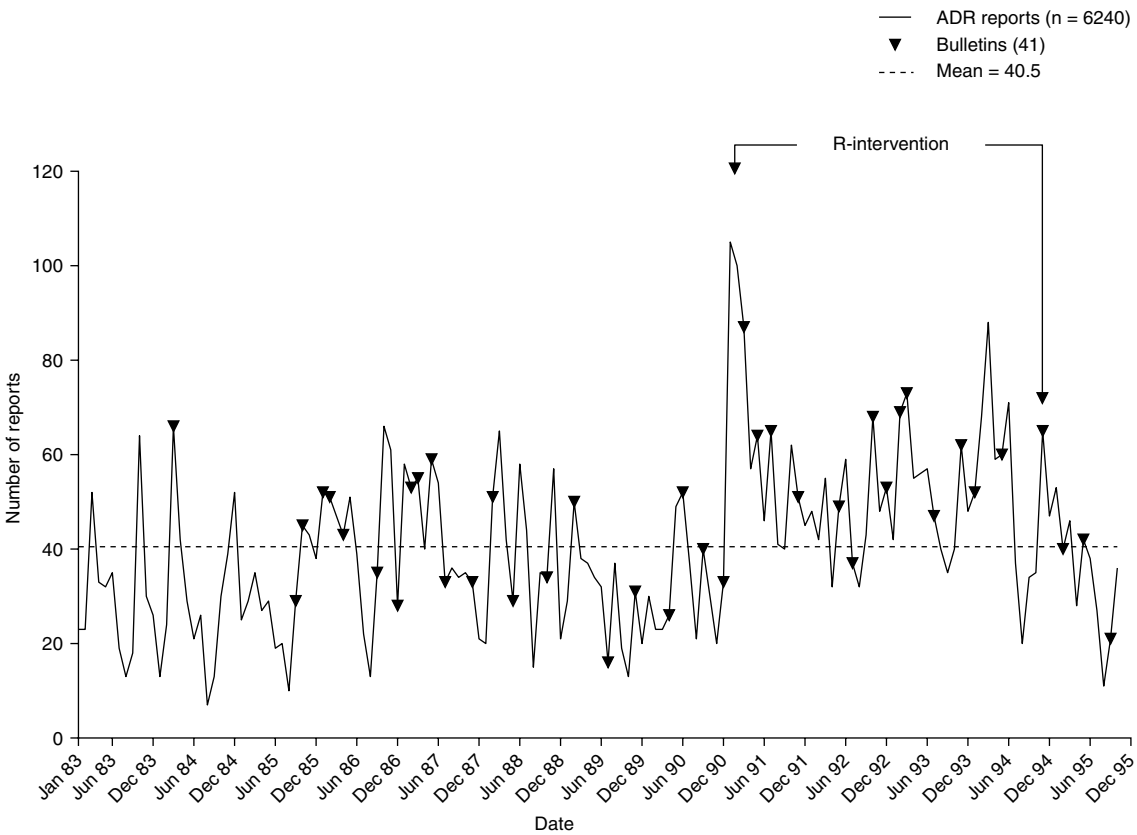

Fig. 2. Frequency-distribution of 6240 spontaneous reports of adverse drug reactions (ADRs) [January 1983–October 1995], in relation to the mailing of 41 ADR bulletins and inclusion period of yellow cards in the prescription pads of the Catalan Health Service's provider organisation (R-intervention).

increase in the reporting rate of 11.7 in the 3 months following its mailing. It also suggests that the inclusion of a yellow card in the prescription pads of the National Health System will produce a mean monthly increase in the reporting rate of 19.8.

As a control group was unavailable, time series analysis was the most appropriate method for the evaluation of the influence of different interventions on the reporting rate trend of ADRs. Although more complex models could be applied, the one used in this study explains >70% of data variability and adjusts to trends explained by means of other models and to previous observations made by ourselves.[11] The fact that 30% of data were not explained by this model is probably due to the influence of variables, other than those tested in the present study, on the reporting rate (e.g. changes in the population of potential reporters, in the pharmaceutical market or in the pattern of drug consumption, or availability of other sources of information). It is not possible to rule out that some of these or other effects have acted as confounders.

On the other hand, we compared the effect of the bulletin on the reporting rate before the bulletin was sent out and the months without any intervention effect. As the bulletin was sent approximately quarterly, we assumed that the effect disappeared the third month after sending it. In order to rule out that this assumption overestimates the effect of the bulletin, a new factor was introduced to evaluate the effect on the third month after mailing the bulletin. The new coefficient was neither significant nor did

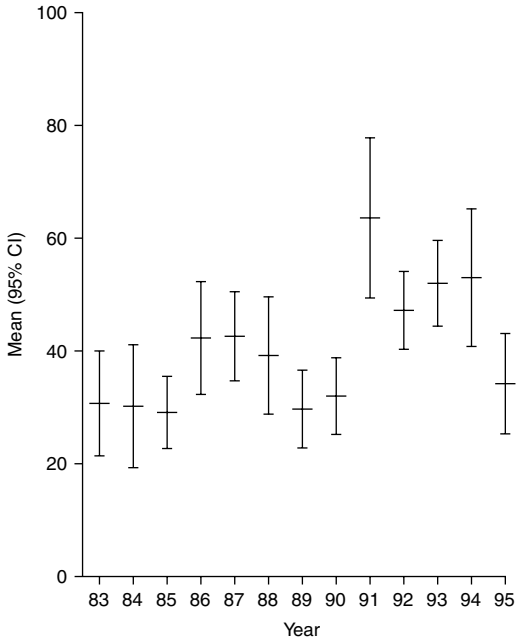

Fig. 3. Mean monthly reporting rate, by year, from 1983 to 1995. The total number of spontaneous adverse drug reaction reports was 6240.

it improve the fitting of the model. The rest of the coefficients remain practically unmodified.

The effect of including a yellow card in the prescription pads on the reporting rate was apparently smaller than that obtained with similar experiences in the UK in the 1970s.[1] This could be explained by the low number of prescribers who use these prescription pads (22% of all prescribers in the catchment area), and by the fact that yellow cards were included in the prescription pads at the time when other changes in the prescription forms were introduced, which were not well accepted by a proportion of the GPs.

As far as we know, the effect of an ADR bulletin on the reporting rate has never been studied. The aims of an ADR bulletin such as the one edited by our centre are to inform about news related to drug treatment, to feed the information produced by the programme back to the reporters in a digested manner and, last but not least, to remind potential reporters of the existence of the ADRs and the need to monitor them. The mere fact that mailing an issue of the bulletin in July, just before the summer holidays, was followed by a more than 2-fold increase in the usual reporting rate in August is illustrative in this respect. Time series analysis confirmed this impression on a more general perspective.

Our data suggest that the inclusion of a reporting form in the prescription pads produces a larger increase in the reporting rate than distributing an ADR bulletin, in spite of the fact that the bulletin was mailed to all 30 000 physicians, while the prescription pads were used only by 22% of them. The bulletin is mailed approximately quarterly to health professionals' homes with a yellow card enclosed, while every prescription pad had one yellow card for every 100 prescription forms – i.e. approximately every 2–3 days. Thus, the inclusion of a reporting form in each prescription pad seemed to produce a quantitatively higher effect, probably because this guarantees that yellow cards are available at the workplace, where and when ADRs are suspected and/or diagnosed, and it represents a more continuous reminder effect. This is compatible with recent evidence suggesting that nonavailability of reporting forms has been pointed by prescribers as one of main reasons that preclude reporting.[4]

In order to obtain a more accurate appraisal of the effect of the ADR bulletin on reporting, an approach aimed at knowing the effect of the contents of the bulletin on the reporting rate of reactions, which are specifically related to the content of an ADRB should ideally have been tried. Although the study period was quite long (13 years of follow-up), this approach was still not applicable because of the small number of reports relating to a specific drug-ADR association that were received after a bulletin dealing with that specific ADR had been sent. The same limitation applies when studying the effects of these interventions on the reporting rate of serious or unknown ADRs or on other outcomes, such as the number of new reporters, or the reporting rate among old reporters.

To overcome the limitations derived from an observational analysis (i.e. the lack of control group), a randomised controlled study could be carried out in future investigations. Notwithstanding, it

should be taken into account that the reasons that induce a health professional to voluntarily report a suspected ADR are not duly known, so the interpretation of the results of such a study could be difficult.

When considering the implementation of stimuli to improve reporting rates in spontaneous reporting systems, both the expected increase in the number of reports and the cost of each measure should be considered. Producing an ADR bulletin requires highly specialised writing, reviewing and editing activities. Instead, including yellow cards in prescription pads does not require any additional manpower. We conclude that easy actions, such as including yellow cards in prescription pads, are useful to stimulate spontaneous reporting. However, although the cultural, informative and updating values of ADR bulletins may be more difficult to evaluate, but they should be viewed as one of the many instruments aimed at improving prescription habits, and consequently at reducing the occurrence of ADRs, in particular those due to inappropriate drug prescribing.

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