ORIGINAL RESEARCH ARTICLE

Drug Safety 2005; 28 (9): 825-833
0114-5916/05/0009-0825/$34.95/0

Physicians' Attitudes and Adverse Drug Reaction Reporting

A Case-Control Study in Portugal

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Abstract

Objectives: Voluntary adverse drug reaction (ADR) reporting is fundamental to medical drug safety surveillance; however, substantial under-reporting exists and is the main limitation of the system. This study sought to identify the knowledge- and attitude-related factors associated with ADR reporting by physicians in Northern Portugal.

Methods: Case-control study covering a population of National Health Service medical practitioners. The 88 cases comprised physicians who had reported at least one ADR to the drug surveillance unit from the year 2000 to the date of enrolment in the study. The 771 controls were randomly selected from among the remaining physicians. All interviews were conducted using a self-administered questionnaire. Knowledge and attitudes regarding spontaneous ADR reporting were based on Inman's 'seven deadly sins'. Agreement with the questions included in the questionnaire was measured using a horizontal, continuous visual analogue scale, which was unnumbered. Recorded answers were read in a range from zero (total disagreement) to ten (total agreement). We used logistic regression to determine the ADR reporting adjusted odds ratio (OR_{adj}) for a change in exposure corresponding to the interquartile range for each attitude.

Results: A total of 397 questionnaires were received from 731 eligible practitioners (54.3%). Physicians who worked in primary versus hospital care (OR_{adj} 7.74 [95% CI 1.85, 32.30]) and in general medicine (OR_{adj} 1.05 [95% CI 0.30, 3.69]) versus medical specialities were more likely to report ADRs. In contrast, physicians working in the medical-surgical/surgical fields were significantly less likely to report ADRs compared with medical specialists (OR_{adj} 0.10 [95% CI 0.02, 0.46]). Attitudes to ADRs were strongly associated with reporting probability. Hence, an interquartile decrease in any of the following attitudes increased the probability of reporting by: (i) 87% ($p < 0.05$) for *complacency* (the belief that really serious ADRs are well documented by the time a drug is marketed); (ii) 109% ($p < 0.01$) for *insecurity* (the belief that it is nearly impossible to determine whether a drug is responsible for a particular adverse reaction); (iii) 143% ($p < 0.001$) for *diffidence* (the belief that one would only report an ADR if one were sure that it was related to the use of a particular drug); (iv) 220% ($p < 0.001$) for *indifference* (the belief that the one case an individual doctor might see could not

contribute to medical knowledge); and (v) 71% ($p < 0.05$) for *ignorance* (the belief that it is only necessary to report serious or unexpected ADRs).
Conclusion: This study shows that there are attitudes strongly associated with under-reporting. The implementation of purpose-designed educational interventions based on the attitudes identified in this study may serve to improve reporting substantially.

Background

Spontaneous adverse drug reaction (ADR) reporting systems are the basic components for comprehensive postmarketing surveillance of drug-induced risks. They are primarily designed for rapid detection of uncommon or unexpected ADRs, thereby creating hypotheses to be tested in subsequent studies.[1-3] Nevertheless, low voluntary reporting rates greatly limit the advantages offered by this surveillance method.[4-6] Indeed, it is estimated that only 10% of all adverse reactions are reported.[7-11] In Portugal, where an ADR system was introduced in 1992, under-reporting is even higher than that found in other countries, e.g. the European average is 250 notifications per million population versus 134 per million for Portugal.[12]

Despite the fact that under-reporting is the principal limitation of ADR reporting systems in all countries, the reasons for this are not clear. Factors such as failing to perceive the importance of the individual contribution to the overall knowledge of drug treatment safety, lack of certainty about the diagnosis of a particular ADR, uncommunicative doctor-patient relationship, lack of time, lack of interest, lack of report forms and fear of involvement in litigation have all been described as potential causes of under-reporting behaviour.[13-17] In 1976, Inman[14] first proposed a list of seven attitudes as potential causes of ADR under-reporting; however, even though various other studies have looked at these relationships,[13,14,18-22] the majority of studies have either failed to find an association or found only one or two attitudes to be associated with under-reporting.[2,20,22]

The aim of this study was to assess the knowledge, attitudes and reporting behaviour of medical practitioners' vis-à-vis the voluntary reporting system in Northern Portugal. Identification of the factors that influence under-reporting in Portugal enables specific intervention strategies to be purpose-designed to address this problem.

Methods

Design, Population, Sample and Settings

Data were supplied by the Northern Region Health Authority of Portugal (an area divided into five sub-regions) and included the name and workplace of medical practitioners affiliated to the National Health Service (NHS) in the region at the date of commencement of the study. Despite the fact that Portugal has a very small private healthcare sector, virtually the entire population enjoys healthcare coverage under the NHS.

We designed a case-control study, in which the study population comprised NHS physicians engaged in clinical work in Northern Portugal in 2002. The 88 cases were physicians who had reported at least one ADR to the regional drug surveillance unit between the year 2000 and their date of enrolment in the study. Approximately eight controls were selected for each case (there being a small number of cases), with the 771 controls being randomly selected from among the remaining physicians stratified by sub-region; we thus selected approximately 10% of the total physician population per sub-region.

Data Collection

A self-administered questionnaire was mailed to cases and controls alike, accompanied by a letter describing the objectives of the study and the importance of participating, plus a prepaid addressed envelope for returning the completed questionnaire. Questionnaires were first mailed in December 2002 and then resent at intervals of 8 weeks. In the case of non-respondents, it was resent a maximum of four times.[18,20]

The questionnaire was designed to be short and easy to complete and comprised 27 items spread over two pages. Data were sought in three areas: (i) personal and professional information, such as age, sex, medical specialisation, patient load and prescription volume; (ii) 15 questions about the subjects' knowledge and attitudes regarding spontaneous ADR reporting; and (iii) three questions relating to the physician's use of the voluntary reporting system during the first 3 years of operation of regional drug surveillance in Northern Portugal. Responses to these final three questions will not be discussed further in this paper.

The 15 questions from section (ii) were based on Inman's 'seven deadly sins' and other previous studies.[13,14,16,20-27] Agreement with the questions included in the questionnaire was measured using a horizontal, continuous visual analogue scale, 8cm long and unnumbered.[28] Recorded answers were read in a range from zero (total disagreement) to ten (total agreement), with a precision of 0.5.[18] Physicians were assured of confidentiality in their answers and all forms were coded to facilitate resending.

Questionnaire Validation and Study

Both the questionnaire and letters of invitation (a different letter per each mailing) were evaluated in linguistic and interpretative terms by experts, resulting in small changes in the order and wording of the text. Thereafter, the questionnaire was validated by experts in pharmacology and pharmacovigilance. To assess reproducibility, a pilot test was performed at a regional health authority centre on a sample of 30 medical doctors (10 general practitioners, 10 surgeons and 10 general medicine specialists). The questionnaire was mailed twice, with an intervening period of 4 weeks.

Statistical Analyses

The questionnaire's reproducibility was evaluated using the intraclass correlation coefficient, based on the results obtained for the first and second answers, for each physician.

Logistic regression analysis was used to model the associations between independent variables and the outcome of having reported an ADR. Two sets of statistical models were created: (i) we evaluated all of the personal and professional variables using crude and adjusted analyses; and (ii) we evaluated the influence of attitudes related to ADR reporting, such as those quantified in the questionnaire, adjusting for personal and professional variables that proved significant in the first model. Results were expressed as odds ratios (ORs) with their 95% confidence intervals (CIs), which indicated the increase/decrease in the probability of being a responder for an increase of one unit on the continuous visual analogue scale (score range 0 = total disagreement to 10 = total agreement). To take into account the independent variable's distribution among the study subjects, we calculated the interquartile OR (IqOR), which is based on an incremental exposure corresponding to the interquartile range of these attitude measures. Since most ORs assume values lower than unity, we calculated the inverse of the IqOR (1/IqOR), which can be interpreted as the increase in the probability of being a responder when exposure decreases from the 75th to the 25th percentile of the distribution.

Results

In the pilot study, the correlation coefficients yielded by assessment of the questionnaire's reproducibility exceeded 0.75 for all 15 attitudes and opinions, save the attitudes "it is only necessary to report serious or unexpected ADRs" and "when I read medical literature I am interested in articles about ADRs", in which the coefficients were 0.65 and 0.70, respectively ($p < 0.005$).

Of the total 859 questionnaires mailed, 110 were returned by the postal service because of errors in the postal addresses (100 from controls and 10 from cases) and 18 were excluded because the physicians concerned were engaged in specialisations such as anatomy or pathology, in which they neither prescribed nor administered drugs (all from controls). A total of 397 questionnaires were completed by 731 eligible practitioners (54.3%), 66 by cases (84.6%) and 331 by controls (50.7%).

Table I shows the personal and professional characteristics of responding practitioners for cases as well as controls. Although the probability of reporting any ADR was higher for women than for men (OR 1.82 [95% CI 1.06, 3.11]), this was no longer

Table I. Influence of personal and professional characteristics on voluntary adverse drug reaction (ADR) reporting

	Ever reported an ADR (n)[a]		Crude analysis		Adjusted analysis[b]		
	Yes	No	OR	95% CI	OR	95% CI	p-Value
Sex							
Male	26	176	1.00		1.00		
Female	40	150	1.82	1.06, 3.11	1.23	0.61, 2.48	0.565
Age							
<40	21	116	1.00		1.00		
40–48	28	112	1.38	0.74, 2.57	0.81	0.35, 1.86	0.619
>48	17	94	1.00	0.50, 2.00	0.67	0.27, 1.67	0.393
Type of medical specialisation							
Medical	30	167	1.00		1.00		
Medical-surgical/surgical	2	80	0.14	0.03, 0.60	0.10	0.02, 0.46	0.003
General medicine	33	69	2.68	1.52, 4.78	1.05	0.30, 3.69	0.942
Other	1	5	1.12	0.13, 9.93	7.20	0.35, 148.73	0.201
Number of patients seen/day							
<12	20	101	1.00		1.00		
12–18	20	64	1.50	0.76, 2.99	1.82	0.73, 4.55	0.197
>18	17	83	1.04	0.52, 2.09	0.64	0.23, 1.79	0.391
Number of prescriptions written/day							
<10	18	120	1.00		1.00		
10–23	13	57	1.52	0.70, 3.32	0.79	0.32, 1.95	0.613
>23	23	81	1.89	0.96, 3.73	0.68	0.24, 1.90	0.465
Workplace							
Hospital	12	127	1.00		1.00		
Primary care	31	59	5.56	2.67, 11.59	7.74	1.85, 32.30	0.005
Both	23	139	1.74	0.83, 3.64	2.71	0.97, 7.55	0.057

a Continuous variables categorised in tertiles for all participants.

b Adjusted for the effects of the other variables included in the table.

OR = odds ratio.

significant after adjustment for the remaining variables. Age failed to have any influence on ADR reporting. In terms of specialisations, although the crude analysis showed that general medical practitioners are two and a half times more likely to report ADRs than other specialists (OR 2.68 [95% CI 1.52, 4.78]), this relationship nevertheless disappeared in the adjusted analysis. Surgical specialists registered the lowest probability of reporting in both the crude (OR 0.14 [95% CI 0.03, 0.60]) and adjusted analyses (OR_{adj} 0.10 [95% CI 0.02, 0.46]). Physicians' workplace appeared to exert an influence on reporting probability. Practitioners who worked in primary care were over seven times more likely to report an ADR (OR_{adj} 7.74 [95% CI 1.85, 32.30]) than those who worked exclusively in hospitals.

Since our results might have been affected by the professional and personal characteristics of non-responders, data were collected *a posteriori* on aspects such as age, sex, specialty and workplace for non-responders and a new logistic regression model for both responders and non-responders was constructed. The results of this model (data not shown) are in line with the results in table I and indicate that, whereas age and sex are not related to notification, specialty and workplace do indeed influence reporting.

Voluntary ADR reporting attitudes and opinions, and their influence on reporting are shown in table II. The attitudes in respect of which doctors showed the highest agreement were the following: "I would only report an ADR if I were sure that it was related to the use of a particular drug" (median 9.0) and "I have a professional obligation to report ADRs" (median 10). The attitudes in respect of which doctors showed the least agreement were as follows: "I

Table II. Influence of several attitudes and opinions[a] on voluntary adverse drug reaction (ADR) reporting

Attitude or opinion[a]	Percentile			Adjusted analysis[b]				
	25	50	75	OR[c]		1/lqOR[d]		
				OR	95% CI	1/lqOR	95% CI	p-Value
Really serious ADRs are well documented by the time a drug is marketed	3.0	6.5	8.5	0.89	0.81, 0.98	1.87	1.13, 3.10	0.015
It is nearly impossible to determine whether a drug is responsible for a particular adverse reaction	1.5	3.0	5.5	0.83	0.74, 0.94	2.09	1.27, 3.41	0.004
I would only report an ADR if I were sure that it was related to the use of a particular drug	5.0	9.0	10.0	0.84	0.77, 0.91	2.43	1.63, 3.65	<0.001
The one case an individual doctor might see could not contribute to medical knowledge	1.5	4.0	8.0	0.84	0.76, 0.92	3.20	1.73, 5.85	<0.001
When I read medical literature I am interested in articles about ADRs	5.5	8.0	9.5	1.13	1.00, 1.27	0.61	0.38, 0.99	0.046
I would be more likely to report ADRs if there were an easier method	3.5	7.5	9.0	0.80	0.73, 0.87	3.46	2.10, 5.69	<0.001
I think that the most correct way to report an ADR is in medical literature	1.0	3.0	7.0	0.89	0.81, 0.99	1.96	1.06, 3.62	0.031
I should be financially reimbursed for providing the ADR service	0.5	0.5	1.5	0.99	0.88, 1.12	1.01	0.89, 1.13	0.937
I have a professional obligation to report ADRs	9.0	10.0	10.0	1.04	0.83, 1.29	0.97	0.78, 1.20	0.751
Reporting ADRs puts my career at risk	0.5	1.0	4.5	0.91	0.81, 1.02	1.44	0.91, 2.28	0.120
It is only necessary to report serious or unexpected ADRs	0.5	2.0	5.5	0.90	0.81, 0.99	1.71	1.02, 2.89	0.044
I do not have time to complete the yellow card	1.0	3.5	6.0	0.88	0.80, 0.97	1.91	1.17, 3.09	0.010
I do not have time to think about the involvement of the drug or the other causes in ADRs	1.0	2.5	5.5	0.87	0.77, 0.97	1.90	1.14, 3.19	0.014
I do not know how the information reported in the yellow card is used	2.5	6.5	9.5	0.81	0.74, 0.88	4.49	2.43, 8.23	<0.001
I talk with pharmaceutical companies about possible ADRs with their drugs	6.0	8.5	9.5	0.94	0.85, 1.04	1.26	0.89, 1.80	0.196

a Measured using a continuous, horizontal visual analogue scale. Recorded answers were read in a range from zero (total disagreement) to ten (total agreement), with a precision of 0.5.

b OR adjusted for specialisation and workplace.

c OR indicates the increase/decrease in the probability of being a responder for every one-unit rise in the value of the visual analogue scale (score range 0–10).

d The 1/lqOR based on an change corresponding to the interquartile range of attitude or opinion measures.

1/lqOR = inverse of the interquartile OR; **OR** = odds ratio.

should be financially reimbursed for providing the ADR service" (median 0.5), "reporting ADRs puts my career at risk" (median 1.0), "it is only necessary to report serious and unexpected ADRs" (median 2.0) and "I do not have time to think about the involvement of the drug or other causes in ADRs" (median 2.5). Some of the practitioners' attitudes displayed certain discrepancies, with some doctors being in total agreement and others in total disagreement, e.g. "really serious ADRs are well documented by the time a drug is marketed", "the one case an individual doctor might see cannot contribute to medical knowledge" and "I do not have time to think about the involvement of the drug or the other causes in ADRs" (see percentiles in table II).

The following attitudes and opinions registered a statistically significant inverse relationship with reporting probability (see table II), in as much as a lower degree of *complacency* (the belief that really serious ADRs are well documented by the time a drug is marketed), *insecurity* (the belief that it is nearly impossible to determine whether a drug is responsible for a particular adverse reaction), *diffidence* (the belief that one would only report an ADR if one were sure that it was related to the use of a particular drug), *indifference* (the belief that the one case an individual doctor might see, could not contribute to medical knowledge) and *ignorance* (the belief that it is only necessary to report serious or unexpected ADRs) were all associated with a higher probability of reporting. Hence, a one-unit decrease on the visual analogue scale (score range 0 = total disagreement to 10 = total agreement) increased the probability of reporting by 12% in the case of complacency and ignorance (1/OR = 1/0.89 = 1.12), rising to 20% in the case of insecurity (1/0.83 = 1.20), diffidence (1/0.84 = 1.19) and indifference (1/0.84 = 1.19).

The OR for a change in exposure corresponding to the interquartile range of these measures (see table II), indicates that a change from the 75th to the 25th percentile in assessments of the following attitudes or opinions would lead to reporting probability rising by 87% for complacency, 109% for insecurity, 143% for diffidence, 220% for indifference, and 71% for ignorance.

Other attitudes and opinions that showed an association with under-reporting were linked to: (i) lack of time, e.g. "I do not have time to complete the yellow card" and "I do not have time to think about the involvement of the drug or other causes in ADRs"; and (ii) method of reporting, e.g. "I would be more likely to report ADR if there were an easier method" and "I do not know how the information reported in the yellow card is used". Similarly, the variable "when I read medical literature, I am interested in articles about ADRs", also appeared to be associated with the probability of reporting (OR 1.13 [95% CI 1.00, 1.27]).

Discussion

The results yielded by our study seem to indicate that physicians' attitudes are an important determinant of ADR under-reporting. Since 1976, when Inman[14] proposed the 'seven deadly sins' as the principal reason for under-reporting, a number of studies have sought to pinpoint these relationships,[7,18-21] yet this is the first paper to report a strong association between all attitude-related 'deadly sins' and under-reporting. In addition, data yielded by this study suggest that the type of medical specialisation and workplace (hospital vs primary care) exert an influence on notification. In contrast to a number of other studies that observed differences in reporting probability for variables, such as gender,[7,18] number of prescriptions written/day[18,20] and number of patients consulted/day,[7,18,20] our research failed to establish any such differences.

It is well known that ADRs have a strong impact on hospital practice; indeed, some studies state that >6% of all hospital admissions are due to ADRs,[29] while others report that >30% of hospitalised patients suffer from ADRs,[30-33] thereby leading to increased costs[34,35] and excess mortality.[36] Nevertheless, in Portugal, physicians who work in hospitals are seven times less likely to report an ADR than physicians who work in primary care. These findings are similar to other studies conducted in Spain,[18] Germany,[24] the US[26] and the UK.[22] It might be thought that the reason for this is that there are some hospital-based specialities that are associated with a low number of prescriptions, yet our study reveals that this effect remains – and indeed increases – when adjustment is made for specialty and number of prescriptions. We observed that re-

porting probability is lower among surgical and medical-surgical specialities, a finding that is in agreement with other studies[18,20] and one that is perhaps due to differences in post-graduate education.[37] The inclusion of pharmacovigilance subjects in under- and post-graduate degree syllabuses is vital for medical knowledge.[38,39] However, this varies significantly, not only between countries but also between different universities in the same country.[27,40] In view of the lower probability of reporting in hospital environments, it could, therefore, be important to give priority to hospital interventions when these are designed.[41,42]

Physicians' attitudes can be modelled by reference to the eight reasons proposed by Inman (initially he had proposed seven reasons,[14] but later added an eighth[43]). These reasons could be divided into two different groups:[44] (i) three linked to attitudes relating to professional activity (financial incentives, legal aspects and ambition to publish); and (ii) five linked to ADR-related attitudes and knowledge (insecurity, diffidence, indifference, complacency and ignorance). Our data indicate that Portuguese physicians do not see any need for additional financial recompense since they regard reporting as their duty and something that can in no way compromise their professional liability. These results are in line with studies conducted in Europe addressing the same topic,[21,22,27] but are different from other studies involving US physicians.[13,14] Another proposed reason was the ambition to publish;[14] nevertheless, this does not seem to be an important factor for Portuguese doctors, e.g. a bibliographic review found a reference to only one Portuguese paper on ADR reporting in MEDLINE review indices (April 2004).[45] This is in line with a European study undertaken by Belton[27] that included Portuguese doctors.

Our study is the first to find an association between reporting probability and all five of Inman's proposed ADR-related reasons (insecurity, diffidence, indifference, complacency and ignorance) in contrast with others that have found only one, two, three or four of these reporting-related reasons.[18,20-24,46] We believe that the discrepancies between our and other published results could be due to our use of a visual analogue scale. This scale would be able to detect small, albeit relevant, differences in medical practitioners' attitudes that are not discernible when using a categorical-type scale with three or four categories. Moreover, thanks to these scales,[18] we have detected a strong association between attitudes and reporting; thus, according to our data, potential changes equivalent to the interquartile range could lead to a rise in reporting probability of >100% for insecurity, diffidence and indifference, and of >50% for complacency and ignorance.

This strong association between knowledge/attitudes and under-reporting may well indicate that educational interventions that are purpose designed to change such beliefs could bring about important improvements in reporting (i.e. Knowledge-Attitude-Practice (KAP) model).[44] However, in order for this to occur it is also important that these educational strategies enhance the degree of balance between medical practitioners, their environment (patients, colleagues, health system administration and pharmaceutical industry: needs satisfaction theory)[44] and their ADR-related motivation. Not only must such education be undertaken by institutions involved in this field, such as universities, pharmacovigilance units and other health system institutions, but it must be furnished to all health system professionals having a duty to ensure that it becomes an activity that forms an integral part of their daily routines.

The main limitation of this study is the difference in the response rate between cases (84.6%) and controls (50.7%). However, one might reasonably think that the controls who participated are probably the best-motivated ADR non-reporters. Yet we nevertheless observed attitudinal differences between cases and controls and it is, therefore, reasonable to assume that such differences would be even more pronounced if cases were compared against the overall set of controls that included non-responders. The overall response rate (54.3%), although not high, was fairly satisfactory, especially if one considers a similar study undertaken in the EU by the European Pharmacovigilance Research Group,[27] in which a response rate of 37.0% was obtained for Portugal. A further limitation is that, because of the study design, we were unable to assess the influence of yellow card report form availability on notification − a factor that had been associated with ADR

reporting in an earlier study.[17] However, our data indicate that ADR-related attitudes seem to be an important determinant of reporting, despite the fact that all our study subjects enjoyed the same theoretical report form availability.

Conclusions

The results of our study suggest that ADR under-reporting could be greatly reduced by changing certain attitudes held by the medical profession. To create a 'reporting culture' it would be necessary for the education and training of practitioners to be enhanced with respect to ADRs and to increase their involvement in the system. Educational programmes need to be focused on changing those attitudes identified in the study as being associated with under-reporting. Our data indicated that hospital physicians must be a priority target for this intervention. Accordingly, we feel that this paper could provide a sound basis for designed educational interventions targeted at reducing under-reporting.

Acknowledgements

The authors wish to express their sincere thanks to the PRODEP (Program for the Educational Development in Portugal) for funding the study, the Northern Region Health Authority and all the medical practitioners who responded to the questionnaire. Dr Adolfo Figueiras' work on this project was in part funded by Health Research Fund (Fondo de Investigación Sanitaria) grants 99/1189 from the Spanish Ministry of Health.

The authors have no conflicts of interest that are directly relevant to the content of this review.

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