Drug Saf (2016) 39:1189–1195
DOI 10.1007/s40264-016-0463-4

SHORT COMMUNICATION

Completeness of Spontaneous Adverse Drug Reaction Reports Sent by General Practitioners to a Regional Pharmacovigilance Centre: A Descriptive Study

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Published online: 29 September 2016

Abstract

Introduction Spontaneous reporting of adverse drug reactions (ADRs) remains the cornerstone of postmarketing drug safety surveillance (pharmacovigilance); however, one of its main limitations is incomplete data, thus limiting conclusions about causality assessment.

Objective The primary aim of this study was to assess the completeness of ADR reports sent by general practitioners (GPs) to regional pharmacovigilance centres and the secondary objective was to identify factors associated with complete ADR reports.

Methods All ADR reports sent by GPs to the Midi-Pyrénées Regional Pharmacovigilance Center (Toulouse, France) from 1 January 2010 to 31 December 2013 were reviewed. Healthcare professionals and patients can forward an ADR using either an online form through the Pharmacology Information Bulletin website (http://www.bip31.fr) or 'traditional' ADR reports (i.e. email, letter or fax). According to information provided in ADR reports (i.e. patient identification, ADR, date of occurrence, clinical description, drugs, etc.), reports were classified into three groups: 'well-documented', 'slightly documented' or 'poorly documented'. A multivariate logistic regression was performed to investigate potential factors associated with a 'well-documented' ADR report.

Results During the study period, 613 ADR reports were analysed. Among these reports, only 12.7 % were classified as 'well-documented', 68.5 % as 'slightly documented' and 18.8 % as 'poorly documented'. An association between a 'well-documented' ADR report and its 'seriousness' was found (odds ratio = 1.70 [95 % CI 1.04–2.76], $p = 0.01$). No association between report completeness ('well-documented' report) and GP practice location or mode of ADR reporting was found.

Conclusions The study shows that only one out of eight ADR reports from GPs was 'well-documented'. Therefore, it appears to be important to promote further information being available regarding the data required in ADR reports to optimise the evaluation of drug causality.

Key Points

Spontaneous reporting of adverse drug reactions (ADRs) remains the cornerstone of postmarketing drug safety surveillance (pharmacovigilance). However, one of its main limitation is incomplete data, thus limiting conclusions about causality assessment.

To our knowledge, there are very few data available on this important topic of general practitioner (GP) ADR reports.

We found that only one out of eight ADR reports from GPs was 'well-documented'; thus, it appears to be important to provide more information about the data required in ADR reports to optimize evaluation of drug causality.

Electronic supplementary material The online version of this article (doi:10.1007/s40264-016-0463-4) contains supplementary material, which is available to authorized users.

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1 Introduction

Since knowledge about real-life benefits and harms of drugs is limited at launch, gathering and analysing relevant clinical patient data throughout the life-cycle of a drug is required. Spontaneous reporting of adverse drug reactions (ADRs) to pharmacovigilance centres remains the cornerstone of postmarketing drug safety surveillance. Despite ADR under-reporting [1], spontaneous reporting allows the emergence of safety signals and is one of the main sources of drug withdrawal decisions [2]. Other advantages of this reporting system are its low cost and easy implementation.

Spontaneous reports can be sent to pharmacovigilance centres via paper forms, telephone, emails or online forms. These reports describe an adverse event apparently caused by a drug. The value of individual case ADR reports is directly proportional to the amount of clinically relevant information they include [3, 4]. Reports with few or no clinical data are of limited value because without these data, the relationship between a drug and a suspected ADR cannot be assessed. Regulatory agencies have pointed out the need for quality management systems as an essential component of good pharmacovigilance practices (GVPs) [5–7]. The completeness of ADR reports—are all critical items included? Are they recorded in a usable way?—is one of the quality parameters that should be considered [7].

General practitioners (GPs) are the main actors of primary healthcare and often the first health professional to take care of a patient. However, ADR reports from GPs only represent a small proportion of the ADR forms sent to pharmacovigilance centres: 7 % in 2014 in France [8]. Different reasons for under-reporting have been described by Inman [9], such as *complacency*, i.e., the belief that very serious ADRs are well documented by the time a drug is marketed; *insecurity*, i.e., the belief that it is nearly impossible to determine whether a drug is responsible for a particular adverse reaction or *diffidence*, i.e., the belief that reporting an ADR should only be done if there is certainty that it is related to the use of a particular drug or indifference. Lack of time to complete the ADR form has also been put forward as a factor associated with under-reporting [10]. Several interventions to improve ADR reporting have been proposed, including education, practice-based training, distribution of drug safety bulletins, detailed drug-specific feedback to the reporting doctor and online reporting [11, 12]. In the Midi-Pyrénées area (in the South-West of France), the regional pharmacovigilance centre has also implemented methods to improve ADR reporting: education, drug safety bulletins, feedback to the reporter, online reporting, smartphone applications and Clinical Research Assistant (CRA) visits in hospitals (Pharmacovigilance in Midi-Pyrénées Region [PharmacoMIP] network). The PharmacoMIP network had already shown that regular visits by a CRA increase the number of ADR reports [13]. Therefore, we have developed a similar action for Midi-Pyrénées GPs [14]. In this context, in order to enhance the effectiveness of these visits, it was relevant to review ADR reports submitted by GPs prior to the CRA visits.

To the best of our knowledge, studies assessing the completeness of ADR reports from GPs have not been published. Thus, the primary aim of this study was to assess the completeness of ADR reports sent by GPs to a regional pharmacovigilance centre and the secondary objective was to identify factors associated with a 'well-documented' ADR report.

2 Methods

The French pharmacovigilance system is based on a network of regional pharmacovigilance centres located in medical pharmacology departments in university hospitals and coordinated by the French Medicines Agency. Regional Pharmacovigilance Centres (RPVCs) collect, document and review the ADR reports case-by-case in their defined geographical area. In particular, they evaluate the causal relationship between drug exposure and occurrence of ADRs in each report. Since 1984, RPVCs have shared a common database of spontaneously reported ADRs: the French Pharmacovigilance Database (FPVD). In France, prescribers of drugs (physicians, dental surgeons and midwives) and pharmacists are legally required to report ADRs immediately to their RPVC. Other healthcare professionals and, more recently, patients (decree of 10 June 2011) can also report ADRs [15, 16]. The RPVC of Midi-Pyrénées covers a population of more than 2.9 million inhabitants and includes around 3500 GPs [17].

In this study, a query in the FPVD to identify the ADRs spontaneously reported to the Midi-Pyrénées RPVC by GPs between 1 January 2010 and 31 December 2013 was performed. ADRs reported by telephone to the RPVC were excluded from the analysis, since intervention by a pharmacovigilance professional could introduce bias in the filling out of the pharmacovigilance form. Data on the practice location of the GPs and ADR reporting modality were also collected. ADR report modes included online reporting via the Pharmacology Information Bulletin website (http://www.bip31.fr) or sending an ADR form via postal mail, email or fax to the RPVC. Paper reporting forms and e-forms are managed in the same way: if important data are missing, the Midi-Pyrénées RPVC contacts the reporter to complete the reporting form before assessing drug causality and entering the case report in the

FPVD. The paper form and e-form are shown in Electronic Supplementary Material 1 and 2, respectively.

An ADR was considered to be 'serious' if it resulted in one of the following: death, life-threatening illness, hospitalisation or prolongation of hospitalisation, persistent or significant disability, an congenital anomaly or birth defect [3].

To assess the completeness of GP ADR reports, data required for drug causality assessment were collected in pre-coded and free fields of ADR reporting forms sent by GPs (primary source). According to the European Medicines Agency guideline on GVP [18], an ADR report is valid if it includes one identifiable reporter (primary source), one single identifiable patient (characterised by initials, patient identification number, date of birth, age, age group or gender), one or more suspected substance/medicinal product and one or more suspected ADR. The lack of any of these four elements means that the case is considered incomplete and does not qualify for reporting. In addition to these required or 'mandatory' elements, a well-documented ADR report should also include baseline medical condition, co-morbidities, use of concomitant medications, documentation of the diagnosis of the effects, clinical course and outcome of the patient, relevant therapeutic measures, laboratory data and information about response to dechallenge and rechallenge [5].

In the present study, based on the GVP criteria and expertise of the regional centre, data were classified into 'mandatory' and 'non-mandatory' criteria. The 'mandatory' criteria included (1) patient identification (at least the first three letters of their last name and first letter of their first name); (2) full date of birth; (3) gender; (4) ADR and date of occurrence; and (5) suspected drug(s) and administration date. 'Mandatory' criteria (4) and (5) were considered documented if the two elements of the criteria were met. A full date of birth was required because it is important not only to prevent duplicate reporting of the same case, but also to permit follow-up for additional information.

The 'non-mandatory' criteria included (1) the patient's medical history; (2) concomitant medications; (3) clinical course and/or ADR outcome; and (4) documentation of the diagnosis of the adverse effects (non-drug aetiology) and/or results of medical examination and/or laboratory data (biology). 'Non-mandatory' criteria (3) and (4) were considered documented if at least one element of the criteria was available.

Three categories of ADR reports were determined by two pharmacovigilance experts with medical training depending on the presence or absence of the 'mandatory' and 'non-mandatory' criteria:

- 'well documented': if the five 'mandatory' and four 'non-mandatory' criteria were all documented;
- 'slightly documented': if the five 'mandatory' criteria were all documented and at least one 'non-mandatory' criterion was missing; or
- 'poorly documented': all other situations.

Potential factors associated with 'well-documented' ADR reports were assessed using a multivariate logistic regression. In order to perform this analysis, the three categories of ADR reports, defined above, were merged into two classes: complete ('well-documented') and incomplete ('slightly' and 'poorly documented') ADR reports. To perform the logistic regression, the characteristics of ADR reports (reporting year, ADR seriousness, patient age, practice location of GPs and tool of ADR reporting) were classified into two or more categories. Patient ages were divided into three classes: 'children' (i.e. under 18 years), 'adults' (between 18 and 65 years) and 'elderly' (over 65 years). Two groups—urban (Toulouse city, the capital of Midi-Pyrénées region and its suburbs) and rural (other parts of the Midi-Pyrénées region)—were defined for the practice location of GPs. ADR reporting tools were also classified as 'online' (if submitted via http://www.bip31.fr) and 'non-online' reporting. Unlike fax, mail or email ADR reporting, some fields are mandatory in the online form: last name (the first three letters), gender, birth year, hospitalisation, suspect drug, ADR description, start date of ADR, outcome of the ADR and reporter identification [18]. Correlations between the characteristics of the ADR reports were calculated using a Chi-squared test. A p value <0.05 was considered to be statistically significant. Statistical analyses were performed with SAS® software version 9.4 (SAS Institute, Cary, NC, USA).

3 Results

3.1 Description of Adverse Drug Reaction (ADR) Reports

A total of 755 ADR reports notified by Midi-Pyrénées GPs between 1 January 2010 and 31 December 2013 were extracted from the FPVD. Among these reports, 131 (17.4 %) met at least one criterion of non-inclusion (ADRs reported by telephone to the RPVC or collected during a visit by a CRA) and 11 (1.8 %) were excluded due to incomplete information on physician specialty. The 613 selected ADR reports involved more women than men (58.0 vs. 41.4 %, $p = 0.01$; missing data: 0.6 %). The mean age (± SD) of patients was 57.1 ± 20.9 years (range 0–94 years), mainly being adults and elderly patients (51.7 and 41.1 %, respectively). A total of 228 reports (37.2 %) were considered to be 'serious'.

During the study period, from 2010 to 2013, 293 GPs sent at least one ADR report to Midi-Pyrénées RPVC. A total of

180 (61.4 %) GPs submitted a single ADR report during this 4-year period, while one GP (0.3 %) reported 50 ADRs. On average (mean ± SD), GPs notified 2.1 ± 3.4 (range 1–50) ADR reports during this 4-year period.

3.2 Completeness of General Practitioner ADR Reports

Table 1 describes the completion rate of the 'mandatory' and 'non-mandatory' criteria in the three categories of ADR reports. The three criteria most often completed were 'mandatory' (patient identification, gender and ADR with date of onset) and the two least often completed criteria were 'non-mandatory' (concomitant drugs [37.0 %] and non-drug aetiology and/or results of medical examination and/or biology [27.7 %]).

According to the three previously defined categories of information completeness, only 12.7 % ($n = 78$) of ADR reports from GPs were 'well-documented', 68.5 % ($n = 420$) were 'slightly documented' and 18.8 % ($n = 115$) were 'poorly documented'. In the 'slightly documented' group, the most frequently missing information in the 'non-mandatory' criteria were concomitant drugs (completion rate: $n = 114$ [27.1 %]) and non-drug aetiology and/or results of medical examination and/or biology ($n = 67$ [15.9 %]). In the 'poorly documented' group, the most frequently missing information in the 'non-mandatory' criteria was birth date ($n = 35$ [30.4 %]). Among the non-mandatory criteria, the missing information were mainly concomitant drugs ($n = 35$ [30.4 %]) and non-drug aetiology and/or results of medical examination and/or biology ($n = 25$ [21.7 %]).

3.3 Factors Associated with Complete ADR Reports

An association between a 'well-documented' ADR report and its 'seriousness' (odds ratio [OR] = 1.70 [95 % CI 1.04–2.76], $p = 0.03$, multivariate logistic regression) was found (Table 2). In contrast, there was no association between the information quality ('well documented') and GP practice location or mode of ADR reporting. Moreover, a statistical analysis was performed excluding the 50 reports sent by one GP and an association between a 'well-documented' ADR and its 'seriousness' (OR = 1.85 [95 % CI 1.13–3.04], $p = 0.01$) was also found.

4 Discussion

This study assessed the completeness of ADR reports sent by GPs to the Midi-Pyrénées RPVC during a 4-year period (2010–2013). Firstly, it shows that only one in eight ADR reports (12.7 %) from GPs was 'well-documented' as defined in this study. The most poorly documented criteria were concomitant medications and non-drug aetiology, with a completeness of 37.0 and 27.7 %, respectively. An association was found between a 'well documented' report and the 'seriousness' of ADRs, but no association was observed with the mode of ADR reporting.

Our study suggests that documentation of ADR reports submitted by GPs could be further improved. Low information quality or completeness have long been identified as important factors hampering the usefulness of individual case report data. But, as far as we know, there are very few available data on this important topic regarding GP ADR

Table 1 Completion rate of the nine criteria in the 613 adverse drug reaction reports sent by general practitioners to the Midi-Pyrénées Regional Pharmacovigilance Center according to the three categories of reports ('well-documented', 'slightly documented' and 'poorly documented') between January 2010 and December 2013

	Well-documented [*n* (%)]	Slightly documented [*n* (%)]	Poorly documented [*n* (%)]	Total criteria [*n* (%)]
'Mandatory' criteria				
Patient identification	78 (100)	420 (100)	103 (89.5)	601 (98.0)
Birth date	78 (100)	420 (100)	35 (30.4)	533 (86.9)
Gender	78 (100)	420 (100)	102 (88.6)	600 (97.9)
ADR with date of onset	78 (100)	420 (100)	97 (84.3)	595 (97.1)
Suspected drug and administration date	78 (100)	420 (100)	93 (80.8)	591 (96.4)
'Non-mandatory' criteria				
Medical history	78 (100)	330 (78.5)	90 (78.2)	498 (81.2)
Concomitant medications	78 (100)	114 (27.1)	35 (30.4)	227 (37.0)
Clinical description and/or ADR outcome	78 (100)	383 (91.2)	106 (92.2)	567 (92.5)
Non-drug aetiology and/or medical examination and/or biology	78 (100)	67 (15.9)	25 (21.7)	170 (27.7)
ADR reports ($n = 613$)	78 (12.7)	420 (68.5)	115 (18.8)	

ADR adverse drug reaction

Table 2 Factors associated with complete adverse drug reaction reports sent by the general practitioners to the Midi-Pyrénées Regional Pharmacovigilance Center between January 2010 and December 2013 (logistic regression model, $n = 613$)

	Complete [*n* (%)]	Incomplete [*n* (%)]	Total [*n* (%)]	Univariate			Multivariate		
				p	OR	95 % CI	*p*	OR	95 % CI
Year of report									
2010	15 (19.2)	72 (13.5)	87 (14.2)	0.49	Ref			[a]	
2011	14 (17.9)	101 (18.9)	115 (18.8)		0.67	0.30–1.46			
2012	15 (19.2)	132 (24.7)	147 (24.0)		0.55	0.25–1.18			
2013	34 (43.6)	230 (43.0)	264 (43.1)		0.71	0.37–1.38			
'Serious' ADR									
No	37 (47.4)	348 (65.0)	385 (62.8)	0.003	Ref		0.03	Ref	
Yes	41 (52.6)	187 (35.0)	228 (37.2)		2.06	1.28–3.33		1.70	1.04–2.76
Age									
Children	8 (10.3)	36 (6.7)	44 (7.2)	0.52	Ref			[a]	
Adults	38 (48.7)	279 (52.1)	317 (51.7)		0.61	0.27–1.42			
Elderly	32 (41.0)	220 (41.1)	252 (41.1)		0.66	0.28–1.53			
GP practice location									
Rural	47 (60.3)	212 (39.6)	259 (42.3)	0.0007	Ref			NS	
Urban	31 (39.7)	323 (60.4)	354 (57.7)		0.43	0.27–0.70			
Online ADR reporting									
No	44 (56.4)	262 (49.0)	306 (49.9)	0.22	Ref			NS	
Yes	34 (43.6)	273 (51.0)	307 (50.1)		0.74	0.46–1.20			
Mail ADR reporting									
No	53 (67.9)	404 (75.5)	457 (74.6)	0.15	Ref			[b]	
Yes	25 (32.1)	131 (24.5)	156 (25.4)		1.46	0.87–2.44			
Email ADR reporting									
No	75 (96.2)	503 (94.0)	578 (94.3)	0.45	Ref			[b]	
Yes	3 (3.8)	32 (6.0)	35 (5.7)		0.63	0.19–2.10			
Fax ADR reporting									
No	63 (80.8)	436 (81.5)	499 (81.4)	0.88	Ref			[b]	
Yes	15 (19.2)	99 (18.5)	114 (18.6)		1.05	0.57–1.92			

ADR adverse drug reaction, *CI* confidence interval, *GP* general practitioner, *NS* not significant, *OR* odds ratio, *Ref* reference

[a] Not entered in the multivariate logistic regression model

[b] Variables combined in one class: 'non-online' reporting

reports. The characteristics of a 'well-documented' ADR report should include a description of the adverse effect with time to onset of symptoms, suspected and concomitant drug details, patient characteristics including demographic information, baseline medical condition, co-morbidities, documentation of the diagnosis of the effects, clinical course and outcome of the patient, relevant therapeutic measures, laboratory data and information about the response to dechallenge and rechallenge [5]. A study conducted in 2000 showed that less than half of the reports in VigiBase® contained basic information such as reaction onset and drug treatment dates, and only a small fraction (11.5 and 10.6 % in 1995 and 2000, respectively) included dates as well as the indication for treatment and patient outcome [20]. An evaluation of completeness of suspected ADR reports submitted to the Mexican National Pharmacovigilance Centre [21] showed that, in 2008, most of the reports contained incomplete information according to their national guidelines; about 40 % were categorised as grade 0 (i.e. date of suspected ADR present but dates of treatment unknown). More recently, the Uppsala Monitoring Centre used the vigiGrade completeness score (*C*) to measure the amount of clinically relevant information in the WHO global individual case safety reports registered in the World Health Organization (WHO) VigiBase® database. This score starts at 1 for reports with information on time-to-onset, age, sex, indication, outcome, report type, dose, country, primary reporter and comments. vigiGrade classifies reports with $C > 0.8$ as well -documented. From 2007 to January 2012, this study found that, altogether,

only 13 % of the studied reports achieved $C > 0.8$ in VigiBase® [7]. Finally, our findings reinforce the results of these previous studies and indicate that information quality in ADR reports still remains of concern.

According to GVP [5], a 'good' report should also include description of concomitant medications and documentation of non-drug aetiology (or diagnosis of ADR). These two criteria have seldom been assessed in previous studies. Our analysis shows that these criteria were the most poorly documented, with a completeness of 37.0 % for concomitant medications and 27.7 % for non-drug aetiology. These results indicate that most of the GPs involved in the study were not aware of the relevance of this medical information. The assessment of the potential contribution of concomitant drugs is important to discover ADRs linked to potential drug interactions [4]. Moreover, pharmacovigilance databases have been shown to be an interesting approach for investigating drug–drug interactions in a real-life context as a complement to classic methods such as in vitro studies, case reports or clinical trials [22]. The second criterion of 'non-drug aetiology' enables us to discuss drug-induced disease and its diagnosis. ADRs are an important cause of hospitalisations, which account for about 5 % of all hospital admissions [23, 24]. In a study conducted in the UK, more than 2 % of patients admitted with an ADR died [23]. Physicians and other health professionals should be knowledgeable about the risk of drug-induced diseases. However, simply knowing that a given drug can cause a particular disease may not be enough. Every time a patient presents with a new disease or an exacerbation of an existing condition, someone needs to ask, 'Could this be drug-induced?'. Unfortunately, drug-induced diseases are often overlooked in medical training [25].

The secondary objective of the study was to identify factors associated with 'well-documented' ADR reports. The association observed between a 'well-documented' ADR report and its 'seriousness' is reassuring. This result suggests that GPs gave careful attention to 'serious' ADRs. To our knowledge, this issue has not been addressed in previously published studies. Only a recent study performed by the US Food and Drug Administration (FDA) [26] has assessed the completeness of serious ADR reports received in 2014. A completeness rate of 86.2 % was found according to the presence of age, gender, event date and at least one medical term describing the event.

Finally, in this study, the lack of association between the information quality and mode of ADR reporting was unexpected as online or electronic reporting tools are supposed to improve ADR reports. However, online reporting is not always a prerequisite for quality: in VigiBase®, the 'well-documented' reports come out of systems that are largely paper-based [7]. In our e-form, parameters such as drug administration date, concomitant medications or non-drug aetiology are not mandatory. This may explain the lack of positive association between information quality and e-reporting. Moreover, too many mandatory criteria could discourage reporting of ADRs and lead to a loss of signal.

4.1 Study Limitations

A limitation of the results is the sample representativeness of the GPs involved in our study. Further investigations including GPs from different geographical areas should be carried out. Another limitation could be the definition of a 'well-documented' ADR report that includes all of the criteria of a 'good' ADR report according to GVPs [5]. This approach could underestimate the rate of 'well-documented' reports and overestimate 'slightly documented' reports. Furthermore, the relevance of information would have been assessed to give a better estimation of data quality. However, assessment of quality information remains subjective as, to our knowledge, no sufficiently comprehensive and internationally validated tool exists.

5 Conclusion

The study shows that only one out of eight ADR reports spontaneously sent by GPs provided a good level of information. Therefore, it appears important to promote pharmacovigilance and to educate GPs both regarding the information required to accurately assess drug causality and about drug-induced diseases. Professional training of health students is also necessary. Moreover, too many mandatory criteria could discourage reporting of ADRs and lead to a loss of signal. This is an important challenge for pharmacovigilance today.

Compliance with Ethical Standards

Funding No funding was received for this study.

Conflict of interest Geneviève Durrieu, Julien Jacquot, Mathilde Mège, Emmanuelle Bondon-Guitton, Vanessa Rousseau, François Montastruc and Jean-Louis Montastruc have no conflicts of interest.

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