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Completeness of Published Case Reports on Suspected Adverse Drug Reactions

Evaluation of 100 Reports from a Company Safety Database

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Abstract

Background: Case reports of suspected adverse drug reactions (ADRs) are common in the biomedical literature. Standards for authors and editors for writing, submitting and publishing ADR case reports have been empirically established since the 1980s; however, these recommendations have not been widely disseminated or incorporated into practice. Comprehensive and standardized guidelines on good publication practice have recently been proposed. No study has been performed so far to assess the adherence of published ADR case reports to these guidelines.

Objective: To describe the current situation with regards to the reliability and completeness of published ADR case reports.

Methods: A random sample of 100 single ADR case reports published between 2005 and 2008 (25 for each year) was retrieved from Pfizer's pharmacovigilance database. Reliability and completeness were assessed by comparing the relevant information contained in the retrieved ADR case reports against the recommendations prescribed by the guidelines. Descriptive statistics and correlation analysis using the Statistical Package for Social Science (SPSS) were undertaken.

Results: The patient's medical history relevant to the ADR was reported in 92% of the case reports. Concerning the suspected drug, 11% of the reports included the proprietary name; duration, dosage, route and formulation were reported in 87%, 85%, 37% and 21% of the reports, respectively. Information on concomitant therapies was included in 71% of the reports. The description of the ADR contained details on management (99%), time-course (97%) and diagnostic tests (95%), while final outcome and seriousness were reported in 73% and 52% of the reports, respectively. A discussion on the possible mechanism for the ADR was present in 70% of the case reports. The possible implications for clinical practice of the reported drug-event association were described in 75% of the cases. Causality assessment was reported in 81%, and rating scales to support the causal link were used in 20% of the reports. The major predictive factor for the presence of an objective causality assessment was found to be publication in specialized pharmacoepidemiology or clinical

pharmacology journals: 47% specialized versus 11% non-specialized (odds ratio = 6.93; 95% CI 2.37, 20.26).

Conclusions: The findings of this study show that published ADR case reports, especially those coming from non-specialized journals, still lack important information necessary for comprehensive evaluation. As published ADR case reports are expected to be reported to regulatory authorities using the same approach as for spontaneous cases, it is paramount for their effective integration in the pharmacovigilance system that pharmaceutical companies and learned societies actively promote a culture of good publication practices.

Background

Postmarketing safety reporting most often occurs via direct reporting by healthcare providers to the responsible drug manufacturer or to the local regulatory agencies. Less frequently, a healthcare provider may elect to submit the observations to a biomedical journal for publication if a potential causal relationship between a medicinal product and an adverse event is suspected.[1] Published case reports are more reliable than spontaneous reports, since publication implies the occurrence of clear-cut reactions, which have been evaluated by the critical peer-review system.[2]

Most specialist pharmacoepidemiology and clinical pharmacology journals and some generalist medical journals publish case reports on adverse drug reactions (ADRs) on a routine basis. Publication of adverse event reports represents an important part of the postmarketing safety surveillance of medicinal products. About 30% of the primary published literature on ADRs is in the form of case reports.[3]

Careful descriptions of the relevant clinical features in published case reports can contribute to the growth of understanding on the safety of medicinal products. The information is essential for the manufacturer, as well as for the prescribing physicians and patients, for evaluation of potential risks and benefits.[4] With this information, hypotheses on product-associated effects can be developed, which can be further formally evaluated and quantified in clinical or observational studies. Such studies have limited value, or can even be misleading, when they lack relevant information about the patient, the event(s), all of the potentially relevant concomitant drug exposures, the clinical decision-making processes and, most importantly, the possible alternative aetiologies.[5]

Since the 1980s, various authors have proposed quality standards for publishing case reports on ADRs.[6-8] In 2003, Aronson[9] proposed a set of recommendations, the PHARMA guidelines, that listed the essential pieces of information that should be contained in a case report, including those required for the title and the abstract.

More recently, guidelines on publishing ADR case reports were proposed by the International Society for Pharmacoepidemiology (ISPE) and the International Society of Pharmacovigilance (ISoP). These guidelines describe three tiers of key information about the affected patient, the administered drugs and the suspected adverse event that potential authors of case reports should consider when explaining their case, performing the causality assessment and constructing an adverse event report for publication.[10]

A total of 100 single ADR literature case reports were retrieved from a pharmaceutical company's safety database. The objective of this study is to describe, analyse and discuss the completeness of these published case reports on ADRs in relation to the recently proposed guidelines on good publication practices.

Methods

Published reports referring to a single individual patient were considered eligible for inclusion in this study. ADR case reports published from January 2005 to December 2008 were retrieved from Pfizer's safety database. A random selection of 25 publications for each of the 4 years considered in the study was performed using www.random.org, the random number service freely available on the Internet. An appraisal form was specifically developed for capturing all of the relevant information from the content of the original full publication of the 100 ADR case reports that constituted the study sample.

All of the data elements listed in the ISPE/ISoP guidelines were taken into account. Patient details included demographics (age and sex) and medical and family histories relevant to the adverse event. Data on the suspect drug included the generic and proprietary names, approximate dosage and duration of therapy, therapeutic indication, route of administration, formulation and plasma concentration. The presence of information on the potential contribution of concomitant therapies was also assessed, as well as data on their approximate dosage and duration of treatment. Data on the suspected adverse reaction included seriousness (evidence of patient's death, life-threatening circumstances, hospitalization required or prolonged, presence of persistent or significant disability), time-course in relation to the administration of the suspect drug, diagnostic tests and procedures performed to confirm the final diagnosis, measures taken to treat the adverse event, clinical course and final outcome.

With reference to the data elements required by the guidelines for the assessment of a causal relationship, the presence of the following items was verified: evidence of the authors' causality assessment; the evaluation of possible alternative causes; the use of objective methods for the causality assessment; and the review of previously published similar cases and of relevant data from preclinical studies. In addition, the presence in the published report of information on the putative mechanisms behind the adverse reaction and on the hypothesis generated by the report, as well as of a description of the implications for the clinical practice, was assessed.

With reference to the information to be included in the title and in the abstract that was not described in the ISPE/ISoP guidelines, the key elements suggested by Aronson[11] in the PHARMA guidelines were considered in the analysis. Based on the PHARMA guidelines, the title should include patient's demographics, the suspect drug, the suspected adverse reaction and its seriousness, as well as any important risk factors for its occurrence. Moreover, when available, the abstract should also include, in addition to all the data elements that are required for an informative title as described, the authors' causality assessment.

Thirty-nine dichotomous variables refer to the presence or the absence of the key elements described in the guidelines; in particular 28 variables concerned the key elements required for the body of the paper, 5 variables regarded the title and 6 were related to the abstract. The 28 key elements related to the body of the paper were considered for constructing a quality score for the case report (table I). The quality score was constructed by assigning the value of 1 or 0, based on the presence or absence, respectively, of each of the 28 key elements required by the guidelines. A cut-off score was established at the 75th percentile value for identifying published case reports that were acceptably complete.

For the purpose of this study, in addition to the data elements recommended by the guidelines, the features relative to the authorship and to the publishing journal were also collected and considered in the data analysis. In particular, authors' details included their clinical specialties, the country of affiliation and the presence in the paper of information for expedited contact with the corresponding author. Journal details included the nature of the readership, if generalist or specialist, as well as whether a journal was specialized in pharmacoepidemiology or clinical pharmacology as opposed to other healthcare disciplines. The type of publication, e.g. a major publication or a letter to the editor, was also considered in the analysis.

Moreover, given the importance of published case reports on the discovery of new and un-

Table I. Key elements considered for assessing the quality score

Patient's details
Demography
Medical history
Family history
Administered drugs
Suspected drug
generic name
trade name
indication
dosage
duration
route
formulation
plasma concentrations
Information on concomitant drugs
Concomitant drugs' names
Concomitant drugs' dosage
Duration of concomitant therapies
Suspected adverse reaction
Information on seriousness of the adverse event
Time-course in relation to the administration of the suspected drug
Results of diagnostic tests and procedures
Measures taken to treat the adverse reaction and management
Clinical course of the reaction
Final outcome
Causality assessment/clinical implications
Authors' assessment of the causality
Evaluation of other possible causes
Objective assessment of causality (use of a rating scale)
Review of previous cases
Evaluation of data from preclinical studies
Possible mechanisms/hypothesis generated by the report
Implications of the report for clinical practice/therapy

expected ADRs, it was also verified whether the drug adverse event association described in the case report was already included in the product label of the implicated drug in use at the time of publication (e.g. the Summary of Product Characteristics for medicinal products marketed in Europe, the US package insert for products marketed in the US but not in Europe).

All of the retrieved published case reports were independently assessed by both of the authors of this article; in case of disagreement, the opinion of a third assessor (a colleague physician from the same pharmacovigilance department) was sought.

ADRs were coded and classified according to the Medical Dictionary for Regulatory Activities (MedDRA); the suspect drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system. Descriptive statistics were performed for all variables. Bivariate analyses were performed to identify factors that may influence the completeness and quality of the case reports. The publication type (major publication), co-authorship involving multiple specialties and publication in a journal of pharmacoepidemiology or clinical pharmacology were considered as independent variables. The strength of the association and its statistical significance were assessed by using odds ratios (OR) and 95% confidence intervals (CIs). All statistical analyses were performed using the Statistical Package for Social Science (SPSS, Chicago, IL, USA).

Results

Most of the 100 published ADR case reports originated in Europe (40%) and North America (32%); the balance were from Asia and other parts of the world. Overall, 28 countries contributed, with the greatest number of case reports coming from the US (29 reports).

The case reports were published in 81 different biomedical journals: the great majority of the journals (71) contributed only one report. Fourteen journals were specialized in pharmacoepidemiology or clinical pharmacology and contributed a total of 23 case reports. Most reports (63) appeared as major publications, and 57 also included an abstract; the remaining 37 reports were published as letters to the editor. Concerning the authorship, five reports were single-authored, while the vast majority had two or more authors; in 31 reports with more than one author, the different authors had different specialties. Information permitting expedited contact with the corresponding author was present in 75% of the reports.

Seventy-six different ADRs were described in the reports; they concerned 20 different MedDRA system organ classes (SOCs), with skin and subcutaneous tissue disorders (21 cases) and nervous system disorders (17) being the most

represented. Forty-nine different drugs were suspected of having caused the adverse event(s). These drugs belonged to 12 different ATC groups, the most frequent being nervous system agents (33 cases) and anti-infectives (26 cases). In 40% of the cases, the described drug-event association was not included in the relevant drug-labelling document. All reports contained the patient's demographics, while the relevant medical history was reported in 92% of the cases and the relevant family history was reported in 9%.

While the generic name of the suspect drug was mentioned in all reports, 11% also included the proprietary name. The indication for which the suspect drug was administered was reported in 99% of the cases. Treatment duration and the dosage of the suspect drug were reported in 87% and 85% of the cases, respectively. The route of administration and the formulation of the suspected drug were reported in 37% and 21% of the cases, respectively. The plasma concentration of the suspect medication was reported in 6% of the cases. Information on whether or not concomitant medications had been prescribed was reported in 71% of the cases; in 61 of these 71 cases (86%), the affected patient had received concomitant medications. The duration of treatment with concomitant medications and the approximate dosage were reported in 36 (59%) and 34 (56%) of these 61 cases, respectively.

ADRs contained details on the clinical management of the patient in 99% of the reports and on the clinical course in 97%. The temporal relationship between the occurrence of the reaction and the administration of the suspected medication was described in 95% of the reports. Description of the tests and procedures performed to confirm the diagnosis was also present in 95% of the reports. The final outcome of the ADR was reported in 73% of the cases. Information for assessing the seriousness was present in 52% of the reports.

The author's causality assessment was expressed in 81% of the reports, but an objective probability assessment to support the causal link was present in only 20%. Alternative causes for the ADR were discussed in 61% of the reports. In 85% of the reports, the authors had performed a review of previously published similar cases. A discussion on the possible mechanism for the ADR was present in 70% of the case reports; however, data from preclinical studies (animal or *in vitro* studies) in support of the proposed mechanism were present in only 18%. The possible implications for clinical practice of the reported drug-event association were described in 75% of the cases.

In none of the published case reports did the main body of the paper contain all 28 key elements suggested by the guidelines and used for constructing the quality score. In particular, the quality score ranged from 10 to 25, with a median value of 18; 32 cases had a score of 20 or higher, while 22 case reports had a score of 15 or lower. A score of 20 (75th percentile) or higher was considered as the outcome variable in the bivariate analysis. The quality score did not change over the years 2005–8; the average score was 17.83 for reports published in 2005, 17.94 for reports published in 2006 and 17.93 for reports published in 2007 and 2008.

The suspected adverse reaction was provided in the title of the report in 96% of the cases, the generic name of the suspect drug in 95%, important risk factors for the occurrence of the ADR in 22%, patient demographics in 14% and information on seriousness in 11% of the cases.

Regarding the required data elements for the abstract, while the generic name of the suspect drug and the adverse reaction were always reported, 41% of the abstracts reported the causality assessment. The important risk factors were mentioned in 35% of the abstracts and the patient's demographics in 32%, while 19% of the abstracts included information on the seriousness.

In the bivariate analysis, case reports that appeared as a major publication more often had a high quality score: 43% compared with 14% of the case reports published as a letter to the editor (OR = 4.80; 95% CI 1.66, 13.94). In addition, the case reports that appeared as major publications more frequently included the author's assessment of the causality (89% vs 68%) [OR = 3.84; 95% CI 1.31, 10.91] and information for expedited contact with the corresponding author (87% vs 54%) [OR = 5.84; 95% CI 2.18, 15.63].

The results of the bivariate analysis also showed that case reports published in journals on pharmacoepidemiology or clinical pharmacology more often contained an objective causality assessment (47% vs 11%) [OR = 6.93; 95% CI 2.37, 20.26] compared with those published in other journals.

Finally, the results of the bivariate analysis showed that the case reports with a co-authorship involving multiple healthcare specialties more frequently had a high quality score compared with those with author(s) from a single healthcare speciality (52% vs 24%) [OR = 3.42; 95% CI 1.34, 8.33].

Discussion

Previous reviews and editorials have expressed concern about the quality of case reports of ADRs published in biomedical journals.[12] Our study showed that 13% of the screened published case reports did not include information on treatment duration and 15% even neglected to mention the dosage of the incriminated drug. Moreover, in about 30% of the reports no information was reported on patient's concomitant drug exposures. Although the finding that published ADR case reports may lack crucial information is unsettling, this was not completely unexpected. Ferguson et al.[13] analysed published ADR case reports involving Eli Lilly pharmaceutical products that were received by the company during 1999. They found that only 45% of the analysed case reports provided all of the data elements necessary to adequately assess the individual case reports.[13] More recently, Kelly[14] reported an analysis of ADR case reports published over a 20-year period. He found that complete patient variables were reported in less than 25% of the cases and formal methods for casualty assessment were applied in less than 1%.

In the case reports analysed in our study there was great emphasis on describing the clinical management, the tests and the procedures utilized for confirming the diagnosis, as well as the clinical evolution of the adverse reactions; all of these items of information were reported in 95% or more of the cases. In addition, in 75% of the reports the authors also discussed the possible implications for clinical practice of the reported drug-event associations. However, much less attention, and often no attention at all, was devoted to discussing the factors that may have contributed to the occurrence of the adverse reaction or the putative mechanism(s) behind development of the reaction: about 40% of the published case reports did not relay information on other possible alternative causes for the event, and in more than 80% of the reports there was no mention whatsoever of any relevant preclinical studies.

This imbalance towards the clinical elements of case description may be due, at least in part, to the fact that ADR case reports are mostly prepared by doctors with training in clinical specialties who are, therefore, likely to write manuscripts with clinical case descriptions for submission to journals specializing in clinical medicine. Such journals often lack specific requirements for descriptive ADR case reports, or, more usually, lack an emphasis on the specialty of pharmacovigilance.[15,16]

The data elements recommended by the ISPE/ISoP guidelines should be taken into consideration when constructing ADR case reports for publication in light of their clinical and academic implications. First, well documented ADR case reports can alert practitioners to the possibility of a suspected medicinal product-associated event and increase their awareness of it. This heightened sensitivity may allow earlier diagnoses in subsequent cases, with better prognoses through earlier therapy, potentially including suspension of the suspect offending agent. Second, the guideline framework can contribute to clinical teaching since the recognition (and ultimately the reporting) of an ADR is rarely given priority in most medical, nursing and pharmacy schools' curricula nor is it required in postgraduate education. This guideline framework highlights the need for healthcare professionals to include a possible adverse drug effect in their differential diagnosis of any new medical event, and it outlines the important elements to consider when evaluating a suspected adverse reaction to a medicinal product.

In order to establish its regulatory reporting status, the most important component of a

published case report is the seriousness of the ADR, as it determines the timeframe within which the case report should be submitted by the manufacturer to the relevant health regulatory authorities. The results of this study revealed that only about half of the published case reports contained the information required for a clear assessment of seriousness in the main body of the paper. Moreover, these data elements were present in only 19% of the abstracts and in only 11% of the titles of the case reports.

The importance of the title and the abstract should not be underestimated in terms of regulatory reportability. They can provide helpful information for safety professionals working in the pharmaceutical industry who may not always have immediate full access to the journal or the full publication. In addition, in those instances where highly significant and/or rare ADRs are published in local languages, the title and the abstract are often the only elements readily available in English. Moreover, since the titles and abstracts of the case reports are searchable fields in the main bibliographic databases, the lack of sufficient information in these fields may hamper efficient monitoring of the biomedical literature and, consequently, the prompt identification of ADRs that may require expedited reporting to regulatory authorities.[17] In the case reports analysed in this study, the titles fail to mention the name of the implicated drug in 5% of cases and the suspected adverse reaction in 4%.

The results of this study also show that the published case reports with a high quality score were more frequently those that appeared as a major publication (not as a letter to the editor) and with a co-authorship that involves multiple healthcare specialties. The association of these editorial variables to the quality of the published case reports, although not surprising, has not been reported before. Letters to the editor have strict word limitations, and this may mean that critical elements are not included in the case report or are eliminated during editing to meet space requirements. As an example, this study found that the author's causality assessment was missing in about one-third of the case reports published as a letter to the editor. While the value of journal space is widely recognized, nevertheless the editors should carefully balance the need to be concise with the importance of an adequate case description, especially for letters to the editor, which may not be exposed to the peer-review system of the journal concerned. In addition, about half of the case reports published as letters to the editor did not contain any information for expedited contact with the corresponding author, thus preventing expedited requests for follow-up information by the manufacturer. This is particularly unfortunate because, as shown by the present study, these are more often the case reports in which the key information required for a comprehensive assessment of the case and for the appropriate definition of its regulatory reportability is missing.

The finding that a co-authorship involving multiple healthcare specialties had a positive influence on the quality of the published case report clearly reflects the essence of the discipline of pharmacovigilance. Pharmacovigilance is more than just the reporting of ADRs; it is a truly multidisciplinary activity covering the diagnosis, prevention and treatment of ADRs, and the investigation of their causes and mechanisms, as well as of any regulatory implications.[18] The results of this study are clear evidence that a multidiscipline approach is associated with a good quality standard of the published ADR case reports and therefore every effort should be made by editors of biomedical journals and learned societies to promote and stimulate such a multidisciplinary approach.

A multidisciplinary approach is also essential for assessing the need to translate any suggested drug event association that emerges from a published case report into the product's labelling document. The results of this study showed that 40% of the case reports concerned drug event associations that were not included in the relevant drug labelling document. Published case reports on ADRs may serve as a starting point for further confirmatory studies, but they are of limited value if the suspicions are not subjected to confirmatory investigation. It is therefore particularly important to stress the need for further studies to test hypotheses and to confirm or

refute the suggested associations.[19] The results of a recently published study show that in most cases anecdotal reports are not subjected to formal validation studies, although the adverse events may nevertheless be subsequently mentioned as adverse reactions in the product's labelling document.[20]

Limitations

The ADR case reports considered in this study do not constitute a truly representative sample, being relative to products of just one pharmaceutical company. However, their general characteristics are not expected to differ significantly from the standard case reports currently published in the biomedical literature. Pfizer products are used in all branches of medicine all over the world and the drugs implicated in the case reports belonged to 12 of the 14 main ATC groups. Moreover, the ADRs described in the case reports included in the study sample involved 20 of the 26 MedDRA SOCs. A further limitation of this study is the relatively small number of case reports included in the sample that may limit the precision of the estimates. Nevertheless, this study has identified general patterns in the quality of the published ADR case reports, which have implications for future reporting.

Conclusion

Publication of these anecdotal ADR case reports is important to facilitate identification of new and rare reactions, generate and test hypotheses, describe mechanisms of the ADRs and their management, and provide information and education about drug safety and pharmaceutical risk management.[21]

The current marked variation in the quality of ADR reports, as shown by the results of this study, creates challenges both for healthcare professionals reading the reports and for safety professionals working in the pharmaceutical industry: the former need to decide whether to, or in which ways to revise their treatment plans in response to a report of suspected ADRs and the latter need to evaluate the contribution of published case reports to the overall evidence of risk of a medicinal product and to determine the need to have this information included in the product label. A uniform approach to the way in which cases are described would enable the readers to apply a more dependable assessment of the drug-event causal relationship and would also facilitate the interpretation of clinical events by the peer-review system of the journal.[22]

It is of paramount importance for editors of biomedical journals that publish anecdotal reports of suspected ADRs to require authors to follow the guidelines as closely as possible. This is particularly relevant for journals in clinical medicine from which clinicians acquire most of their knowledge on adverse drug effects. However, where such reports are frequently published as a letter to the editor, they often fail to include many of the key elements recommended by the guidelines, as shown by the results presented here. Moreover, since published ADR case reports are also expected to be reported to regulatory authorities using the same approach as that for spontaneously reported cases, it is essential for their effective integration in the pharmacovigilance systems that pharmaceutical companies and the drug regulatory authorities cooperate with professional bodies and journal editors to actively promote a culture of good publication practice.

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