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Case Reports and Drug Safety

EP van Puijenbroek

Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, The Netherlands

Anecdotal case reports have proven to be of great value for drug safety. They play a pivotal role in signal detection and have served as a starting point for further confirmatory studies for many decades. Despite these virtues, there is also criticism that often focuses on their limited capability to provide objective information. In a recent publication, Loke and colleagues[1] studied the value of anecdotal reports of suspected adverse drug reactions (ADRs). They evaluated case reports published in 1997 in five main medical journals. The primary aim of the study was to determine whether these reports fulfilled their role as early warning signals that stimulated more detailed studies. From the 63 signals that were studied, 83% had not yet been subjected to further confirmatory investigations. Data from controlled studies were available in only three cases. They concluded that published case reports of suspected ADRs are of limited value as suspicions are seldom subjected to confirmatory studies. In addition, these signals appeared not to be amended in a systematic way in drug reference sources.

The discussion about the value of case reports is not new. Over the past few years, many others have commented on the value of case reports in journals and their place in drug safety. Some of them have even stated that anecdotal case reports are of extremely limited utility, that they are likely to do more harm than good and that it is not sensible to use this information in clinical practice.[2]

From an epidemiological point of view, it may be justified to conduct more detailed studies to confirm signals based on anecdotal case reports, but the question remains whether the critique on this valuable information source is adequate and justified. Case reports published in journals are a close representation of the events that occurred in clinical practice. Moreover, they provide insight in the decision-making process of the physician. They are the outcome of the interpretation of clinical events by the patient, the treating physician, the author and peer-review system of the journal.

Vandenbroucke[3] distinguishes two main categories of the function of case reports. First, they have a function in progress and medical science. Examples are the description of new diseases, aetiology and recognition of ADRs, and the study of mechanisms, therapy and prognosis. Secondly, case reports have a major function in education and quality assurance. In addition, they provide important information, which is needed for the design and conduct of more formal validation studies.[4] Case reports fulfil all these functions at low cost. The other side of the medal is that, in respect to the causal relationship of the reported events, as well as other (clinical) information provided, some false-positive signals may be expected.

1. What Type of Information Do We Need?

The information we need to make a reliable assessment in a clinical and regulatory setting differ to a certain extent. In the clinical setting, various factors are crucial in the assessment of the causal relationship between a suspected drug and an ADR. Next to the clinical picture and the course of the events, many other factors contribute. Some examples are the medical history of the patient involved, pharmaceutical properties of the suspected drug and information about whether the ADRs involved have been previously described or not. Paradoxically, numerical information from clinical studies, such as

incidence or relative risk, is not always of overriding importance for making decisions in a clinical setting.

On a regulatory level, there is a stronger need for numerical information. Nevertheless, the responsible authorities and marketing authorisation holders may sometimes be forced to base preliminary decisions about drug safety on sparse information. Arnaiz et al.[5] studied a total of 22 drugs withdrawn from the Spanish market. In 18 cases the evidence supporting the drug withdrawal came from case reports, case series or the combination of case reports and randomised clinical trials. In only four withdrawals, evidence from observational studies including a comparison group was used. The authors concluded that the quality of information required for the withdrawal of drugs needed to be improved. In reality, however, case reports are not the only source of information on which a decision is based. Data from (pre-) clinical studies and reports to voluntary reporting schemes of regulatory authorities and the marketing authorisation holders also make an important contribution. Additional information, such as periodic safety update reports and experiences with related drugs, will also be taken into account.

The true reason for the lack of epidemiological information when a (regulatory) decision has to be made is the absence of resources and especially the lack of time. For ADRs that occur rarely, it may be difficult to confirm the association within a reasonable time-span. Depending on the design, the studies that are needed would have to be very large and consequently expensive. When patients are at risk, it may be simply unethical to wait for an epidemiological confirmation of the suspected association. However, it is not clear under which circumstances additional formal studies are required for a balanced decision. A more consistent scheme of hypothesis-testing studies by the industry, regulators and third parties is therefore needed.[6] However, given the various interests of the parties that are at stake, a subjective element and a certain level of uncertainty may have to be accepted.

Will epidemiology provide the final solution? Many of the recent discussions take the need for an epidemiological proof of the signal that is provided by the case reports for granted. If we use epidemiological information, we still do not get rid of a certain subjective element. In many circumstances, a univocal interpretation of the results is not possible as a result of methodological issues. Even if the relationship between an ADR and a drug can be expressed in terms of an incidence or relative risk, the implementation of this knowledge in daily practice requires additional clinical information that only the description of the cases itself can provide. Therefore, the assumed discord between case reports and confirmatory studies is based on a wrong premise. Both systems have their own position. The suggestion of Loke et al.[1] to shift the current emphasis on spontaneous reporting to hypothesis-testing studies and to spend the resources on hypothesis-testing studies is a parochial point of view.

Aronson[7] noticed that many of the case reports that are published do not contain all the necessary information. Therefore, he calls for the development of guidelines. A uniform way cases are described should enable a more reliable assessment of the causal relationship by the readers of journals and would also facilitate a systematic review of the suspected reactions. This lack of transparency also applies to the use of information from case reports in the product information. In the event that certain information is missing in case reports, it should be clearly stated. Loke and colleagues[1] certainly have a point when they state that there is a haphazard manner in which ADRs are transmitted into the summary of product characteristics (SPC). This applies to the nature of information provided, but also to the reasons for the incorporation of ADRs in the SPC. It has been noted previously that a discrepancy exists between the SPC content, formal warnings and changes to the SPC, and the effect these factors have on the prescription and dispensing of the drugs involved.[8] Even for those involved in drug safety it is not clear why and when the SPC will be amended. Insight into these processes would enable health professionals to make a more balanced decision

when prescribing a certain drug and ensure more commitment with the content of the SPC.

2. The Value of the Case Report

Obviously, there are still no sound alternatives for case reports. The initial discovery of new ADRs and diseases is mainly based on the findings of clinicians and the possibility to share these experiences. The clinical lessons in the many journals are indicative of the need to exchange experiences in this format. If possible, numerical information should be available for decision making, but blaming the case report for not providing this level of evidence is not appropriate. It is evident that it will do more harm than good for drug safety if we do not publish our observations from clinical practice.

The last phrase of McBride's famous case report published in 1962,[9] which finally revealed the thalidomide disaster, dramatically illustrates the function and strength of the case report: "Have any of your readers seen similar abnormalities in babies of women who have taken this drug during pregnancy?" The primary goal of the publication of case reports is not to call for regulatory measures, but to share concerns with the readers about a possible safety issue.

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Correspondence and offprints: Dr *EP van Puijenbroek*, Netherlands Pharmacovigilance Centre Lareb, Goudsbloemvallei 7, 5237 MH 's-Hertogenbosch, The Netherlands.
E-mail: e.vanpuijenbroek@lareb.nl