Journal of Thrombosis and Haemostasis, **12**: 1385–1387 DOI: 10.1111/jth.12622

FORUM

Reflections after the Diane affair

A. KANT,* E. VAN PUIJENBROEK*† and F. VAN HUNSEL*†
**Netherlands Pharmacovigilance Center Lareb, 's-Hertogenbosch; and †Department of Pharmacy: Pharmacotherapy and Pharmaceutical Care, University of Groningen, Groningen, the Netherlands*

To cite this article: Kant A, van Puijenbroek E, van Hunsel F. Reflections after the Diane affair. *J Thromb Haemost* 2014; **12**: 1385–7.

See also Emmerich J, Thomassin C, Zureik M. Contraceptive pills and thrombosis: effects of the French crisis on prescriptions and consequences for medicine agencies. This issue, pp 1388–90.

Summary. The Pharmacovigilance Centre Lareb received 621 reports of possible adverse drugs reactions on Diane-35®. Of all reports, 388 were received after media attention. Of the 309 reports of thromboembolic adverse drugs reactions, 18 cases were fatal. In 31 cases the thromboembolic adverse drugs reaction was initially not recognized as such. The analysis and the turmoil of the 'Diane affair' gave rise to the following reflections: Reflection 1. Continuous awareness and attention of risk of medicines is needed, also for known risks, for timely recognition of adverse drugs reactions. Reflection 2. Reporting side effects should be part of the professional attitude. Reports play a pivotal role in the detection of new adverse drugs reactions and the conditions under which known adverse drugs reactions occur. Reflection 3. Improvement of adequate use of drugs. Farmacovigilance not only has the aim to improve knowledge on risk of medicines, but also the aim of getting this knowledge into Health Care practice.

Keywords: adverse drug reaction; cyproterone acetate, ethinyl estradiol drug combination; Diane-35; embolism; thrombosis.

Introduction

Analysis of reports of thrombosis with a fatal outcome after the use of cyproterone/ethinylestradiol (Diane-35) led to extensive media attention in France and the request for a European review of the balance between the benefits and risks.

It was not surprising that the 'Diane affair' started in France, after the discussions initiated by the benfluorex (Mediator, French Drug Company Servier, Suresnes, France) case. Mediator was marketed to overweight diabetics, but was often prescribed off-label to healthy women. As many as 5 million people were given the drug between 1976 and November 2009, when it was withdrawn in France, years after being withdrawn in Spain and Italy, because of the risk, particularly of heart valve disease. The discussions focused on the role of the regulatory authority as being responsible for both approval and safety monitoring. In a report of the French inspectorate, it was mentioned that 'the pharmacovigilance chain functioned in such a way that the benefit of the doubt was not given to patients or the public, but to the pharmaceutical companies' [1].

After approval, independent monitoring of the safety and use in practice of a drug is crucial. Before drugs are marketed, they are extensively tested. However, the safety profile of a drug remains incomplete before its use in daily practice. Limitations of clinical trials in highlighting a drug's safety are homogeneous study populations, limited sample sizes, a limited duration, and an inability to replicate the real world [2]. After a drug has been granted marketing authorization, the number of users can greatly exceed the population on which the drug was tested during the trial phase. In addition, the group of patients can be more diverse than in premarketing studies. Also, as seen with Mediator and Diane, drugs can be used for purposes other than those originally intended (off-label use).

One of the most widely used methods for gaining information on a drug's safety after marketing authorization is the collection of case reports of clinical suspicion of adverse drug reactions (ADRs) [3]. In the case of Diane-35, the news spread to The Netherlands. As a result of the media attention, the Pharmacovigilance Center Lareb received a large number of reports of possible ADRs to Diane-35 and its generics containing cyproterone–ethiny-

Correspondence: Agnes Kant, Goudsbloemvallei 7, 5237 MH, 's-Hertogenbosch, the Netherlands.
Tel.: +31 736469700; fax: +31 736426136.
E-mail: a.kant@lareb.nl

Received 1 April 2014
Manuscript handled by: F. R. Rosendaal
Final decision F. R. Rosendaal, 30 May 2014

lestradiol. The analysis of these reports and the turmoil of the 'Diane affair' give rise to some reflections.

Reports

On 3 April 2013, Lareb had received 621 reports about cyproterone–ethinylestradiol, including 309 reports of thromboembolic ADRs.

In 291 of 309 reports, the reporter was a consumer. Of all reports, 388 were received after the media attention. Most of the reported reactions had occurred in the past.

Analysis on reports of cyproterone–ethinylestradiol

Reported possible ADRs consisted of arterial thrombosis ($N = 52$), venous thrombosis ($N = 40$), pulmonary embolism ($N = 155$), and thrombosis with an unspecified location ($N = 128$). Medical validation was not always possible, as the vast majority of the reports were submitted by patients. It is possible that not all reported cases were venous thromboembolisms (VTEs) that were actually verified by a physician. A total of 299 reports of thromboembolic ADRs were classified as serious, including 18 cases with a fatal outcome. Patients' mean age was 30.5 years, and the mean body mass index was 24.3 kg m^{-2}. The primary indications for use were acne ($N = 147$), oral contraceptives ($N = 122$), hirsutism ($N = 10$), and other reported indications, e.g. menopausal complaints or alopecia ($N = 15$); in some cases, the indication was unknown ($N = 15$). Of the 309 patients with a thromboembolic ADR, 261 were known to have been treated with anticoagulant drugs. In 31 cases, the thromboembolic ADR was initially not recognized as such by either the patient or the healthcare professional.

The median time to onset was 5.0 years. In 25% of cases, the latency was <1 year and, in 40% of cases it was < 3 years. Patients also reported a very long latency, sometimes > 10 years.

There was no distinction between the time of onset with respect to the reported ADR. There were were 97 patients with one risk factor and 34 patients with multiple risk factors for VTE, such as smoking (15.5% of patients were known smokers) or a family history of VTE (8.7%). In 14 cases (4.5% of the total), a factor V Leiden deficiency was reported to be present. There were also 11 patients who reported that they were tested for coagulation disorders, without any abnormalities being found.

Reflection 1. Continuous awareness of and attention to the risk of medicines

Although the increased risk of thrombosis and embolism is known, it is very understandable that it is shocking when stories appear in the media of young, healthy women who have died, possibly as a result of the use of Diane-35.

The possible ADRs are mentioned in the official Summary of Product Characteristics (SmPC) and patient information leaflets. Apparently, there is not a continuous awareness of this risk. Abundant marketing focusing on the presumed advantages of this drug instead of the potential risks could be an issue here. The lack of awareness of this ADR and thereby an incorrect perception of the safety of the drugs poses a potential danger, because this ADR is initially not recognized. It is striking that, in 31 of the reports, it was mentioned that there was a delay in the diagnosis of VTE, leading to a potentially dangerous delay in treatment. Both general practitioners and patients tend to focus on the most probable diagnosis, and do not, like a medical specialist, tend to exclude alternative diagnoses. Especially in rare conditions such as VTEs, the risk of a wrong diagnosis is quite possible. The knowledge that VTE in young women has a low incidence carries the risk that the initial diagnosis will not be recognized, e.g. because the prior probability of bronchitis in this age group is simply higher than that of a VTE.

How can awareness and attention to, and thereby timely recognition of, ADRs be improved?

It should be normal practice that, before drugs are prescribed, possible ADRs constitute an important part of the consultation. Awareness of potential risks should continue after initiation of the drug, during subsequent contacts between the patient and the healthcare providers, as this will enable them to anticipate the occurrence of the initial symptoms of ADRs.

Our analysis showed that a substantial proportion of the patients did have extra risk factors. Regular checks for women using oral anticoagulants are no longer common. However, periodic checks on the development of potential risk factors and mentioning of the risk are recommended.

Reflection 2. Reporting side effects: part of the professional attitude

ADR reporting has proven to be of great value for drug safety. Reports play a pivotal role in the detection of new ADRs and the conditions under which they occur. They provide important information, which is needed for the design and conduct of more formal validation studies [4,5]. Vandenbroucke distinguishes two categories of the function of case reports. First, case reports play an important role in progress and medical science. They are important in the description of new diseases, the etiology and recognition of ADRs, and the study of mechanisms, therapy, and prognosis. Second, case reports fulfill a major function in education and quality assurance [6].

The information that is needed for making a reliable assessment in clinical and regulatory settings may differ. In the clinical setting, various factors are crucial in the assessment of causality between a suspected drug and an ADR. Not only the clinical picture and the course of the

events but also many other factors contribute. Examples are the medical history, the pharmaceutical properties of the drug, and whether ADRs have been previously described. If the relationship between an ADR and drug can be expressed in terms of an incidence or relative risk, the implementation of this knowledge in the doctor's office requires additional clinical information. Case reports can provide this type of information. Case descriptions and epidemiologic studies both have their own uses [7].

The goal of reporting ADRs is to share concerns with other healthcare professionals about a possible safety issue, and reporting these circumstances should be part of the professional attitude. It is remarkable that all of the reports of deaths after a thrombosis and embolism were submitted after the media attention of early 2013. Of course, Lareb had received these reports previously. Although the risk of thrombosis and embolism is known, the reports give insights into the impact in daily practice, the indications for use, the recognition and diagnosis process, and the course and consequences. Probably, patients were not sufficiently aware of the possibility and importance of reporting. Healthcare professionals are probably more aware of both, but are not aware that reporting about known ADRs can provide additional insights into the risks associated with drug use. Reporting ADRs should be a professional attitude.

Reflection 3. Improvement in the adequate use of drugs

Cyproterone–ethinylestradiol was indicated for the treatment of acne, seborrhea or light hirsutism, when hormonal treatment was needed in cases of androgen-dependent disorders. Although it also has contraceptive properties, it was not indicated for this purpose.

Nevertheless, the use in daily practice was wider than originally intended. It was no longer primarily used only for severe acne in patients who also profited from the contraceptive properties, but gradually acquired the character of 'the contraceptive in situations where users may also profit from anti-androgenic properties'. A substantial number of women in the reports on Diane-35 mentioned an oral contraceptive as the primary indication for the prescription. Also, the duration of use was often much longer than advised in the SmPC, in which the period of use is limited to a maximum of 3 months.

The use of medicines without risks is impossible, but we should aim at minimizing this risk. Before registration, the risk–benefit balance of a drug is assessed. After registration, permanent reviews on this are important. Therefore, good insights into the use in practice and actually occurring ADRs are crucial. A high quality of independent postauthorization safety studies is needed, and so is an effective reporting system for ADRs. A good reporting system needs reports from both patients and healthcare professionals.

In addition, it is a substantial challenge to ensure that adequate use of medicines is improved. Pharmacovigilance not only has the aim of improving knowledge on the risk of medicines, but also has the aim of getting this knowledge to the right place: in the doctor's office, where it plays an important part in the conversation between doctor and patient.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

References

1 Prescrire In English. France's Mediator scandal: take the high road. http://english.prescrire.org/en/81/168/46752/0/NewsDetails.aspx. Accessed 31 March 2014.
2 Stricker BH, Psaty BM. Detection, verification, and quantification of adverse drug reactions. *BMJ* 2004; **329**: 44–7.
3 Waller PC. Making the most of spontaneous adverse drug reaction reporting. *Basic Clin Pharmacol Toxicol* 2006; **98**: 320–3.
4 Russmann S. Case reports of suspected adverse drug reactions: case reports generate signals efficiently. *BMJ* 2006; **332**: 488.
5 Ishiguro C, Hall M, Neyarapally GA, Dal PG. Post-market drug safety evidence sources: an analysis of FDA drug safety communications. *Pharmacoepidemiol Drug Saf* 2012; **21**: 1134–6.
6 Vandenbroucke JP. Case reports in an evidence-based world. *J R Soc Med* 1999; **92**: 159–63.
7 van Puijenbroek EP. Case reports and drug safety. *Drug Saf* 2006; **29**: 643–5.