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From signal to clinical practice

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Pharmacovigilance is the science dedicated to the safety of drugs as used in daily practice and generates knowledge on harmful effects of drugs, both at the individual and the population level. This knowledge will eventually be applied in clinical practice and thus lead to a safer use of drugs. Drugs are extensively researched prior to their marketing. The majority of adverse drug reactions (ADRs) will be detected during these trials and are included in the Summary of Product Characteristics (SmPC). However, preregistration clinical research is usually limited to relatively small groups of selected patients. Once these medicines are prescribed to large numbers of patients in daily practice, relatively rare adverse drug reactions, interactions with other medicines or specific user-group effects may emerge. After the thalidomide (Softenon/Distaval) affair in the 1960s, national and international legislation was introduced for the registration and monitoring of adverse drug reactions.

In the Netherlands the Netherlands Pharmacovigilance Centre Lareb is responsible for the processing and analysis of the spontaneous adverse drug reaction reports received from health professionals and patients. Lareb informs both government and health professionals about important new signals. Moreover, Lareb tries to increase health professionals' involvement in pharmacovigilance, so they will be motivated to report adverse drug reactions in daily practice. In 2003, the Netherlands became one of the first countries in the world to allow patients to report adverse drug reactions. The number of reports submitted by patients has been gradually increasing over the years.

Lareb evaluates all the reports of adverse drug reactions separately. Lareb informs the regulatory authorities on all submissions and highlights the exceptional signals in quarterly reports. On the basis of reported adverse drug reactions, measures may be taken. On occasion, adverse drug reactions are added to the drug's SmPC. In serious cases the regulatory authorities on a national either European level (EMA) may decide to withdraw the product from

the market. The implications that spontaneous reports of adverse drug reactions may have are illustrated by some examples.

Doxycycline and onycholysis

Lareb received five reports concerning photo-onycholysis associated with the use of doxycycline. All five patients used 200 mg doxycycline a day for the prophylactic treatment of Lyme disease after tick bite. In all cases the affected nails had been exposed to the sun during the summer. Considering the relatively good health of the patients using doxycycline for the given indication, exposure to the sunlight was the likely cause of onycholysis. Onycholysis was considered to be the sole expression of a photosensitivity reaction. In a Lareb publication in the BMJ in 2004, it was concluded that patients should avoid sun exposure of their nails to the sun shortly after using doxycycline.¹

Rofecoxib (Vioxx) and cardiovascular risk

Rofecoxib was marketed in the Netherlands in 2000. Shortly after its introduction, Lareb received five reports of death by possible cardiovascular causes, associated with rofecoxib. On the basis of these reports, Lareb informed the Medicines Evaluation Board and published this possible signal in the Dutch Drug Bulletin in 2001.² A few years later, it was shown that patients using rofecoxib had an increased risk of cardiovascular accidents including myocardial infarction en cerebrovasculair accident, compared to the placebo group. By the end of 2004, Vioxx was withdrawn from from all markets worldwide by the market authorization holder.

Cisapride and prolonged QT interval

Cisapride was marketed in 1993 in the US for nocturnal heartburn and reflux. In 1996, a publication in the NEJM revealed 34 cases of torsade de pointes and 23 reports of prolonged QT interval.³ As a consequence, regulatory action was taken: cisapride was contraindicated in patients using drugs that can inhibit its metabolism. In the US, the number of prescriptions continued to grow. In 1998, the contraindication was expanded to all patients with heart disease and patients using other medication with possible QT-prolonging action. Eventually, in 2000, the market authorization holder terminated the marketing of cisapride in the US. In Europe, its use is very much restricted.

Thalidomide

The consequences of use of thalidomide in pregnant women are well known all over the world. As soon as the teratogenic effects of thalidomide became clear in the late sixties, this drug was no longer prescribed. However, several decades later, thalidomide is back on the market, for restricted use in patients with for example Morbus Kahler. This example shows the crucial importance of individual risk – benefit assessment by the prescribing physician..

These are just a few examples to illustrate the fact that case by case reports have an important role in the revelation of yet unknown adverse drug reactions, often leading to regulatory implications. Spontaneous reporting of adverse drug reactions can be considered indispensable in pharmacovigilance. The acquisition of knowledge as derived from the experiences form individual patients is needed and can be used to improve the pharmacotherapy to individual patients. More awareness among physicians and pharmacists regarding the appearance of adverse drug reactions and their clinical impact would prevent many unnecessary medical examinations and decrease costs.⁴ Additional information about these

and other cases and the complete Dutch database can be found at www.lareb.nl. This website is a rich source of interesting information in English language about adverse drug reactions.

References

1. BMJ 2004; 329: 265.
2. Dutch Drug Bulletin 2001(mrt); 35.
3. N Engl J Med. 1996 Jul 25; 335(4): 290-1.
4. Arch Inter Med 2008; 168: 1890-96.