Pharmacovigilance of Contraceptives: Why Does it Take so Long to Take Action?

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Background: A spontaneous reporting system is meant to detect signals and the general idea is that signals need to be confirmed by a formal epidemiological studies. More and more we see a renewed appreciation of observational data, such as case series.

Objective: Different aspects of the value of signals detected through spontaneous reporting in relation to formal epidemiological studies will be discussed, using two examples in the field of contraceptives.

Methods: In 2003 the Netherlands Pharmacovigilance Centre Lareb published four cases of thromboembolism associated with the use of the oral contraceptive ethinylestradiol/drospirenone (Yasmin_).[1] On July 1st, 2011 Lareb had received 49 cases of thromboembolism in Yasmin_ use and a fatal outcome was reported 8 times. The safety of drospirenone containing oral contraceptive, final results from the European Active Surveillance study on oral contraceptives based on 142 475 women years of observation.[2] In 2011, 8 years after the initial signal was given, two epidemiological studies were published confirming an increased risk of thromboembolic events.[3,4] No regulatory action has been taken yet, however the risk of this contraceptive seems as double as high as with so called second generation pills. In 2010 four countries published a paper about the relation between a levonorgestrel containing intrauterine device (Mirena_) and uterine perforation in which more than 500 cases received through the spontaneous reporting system were analyzed. An epidemiological study, sponsored by the manufacturer, has been published. No independent research has been published and no regulatory action has been taken up to now.

Results: These two examples show that there is a long time between the publication of a new signal and signal confirmation by a formal epidemiological study. This leads to a delay in the regulatory decision making process.

Conclusion: Women could have been exposed to a greater risk than needed when searching for reliable contraception. Case reports have to be taken more seriously by regulators and marketing authorization holders in the benefit-harm assessment of a drug.

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