European Review for Medical and Pharmacological Sciences 2014; 18: 2237-2239

# The impact of pharmacovigilance on drug portfolio management

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**Abstract. – This review examines the influence of pharmacovigilance on drug portfolio. As a result of pharmacovigilance studies, actions are taken by national drug administrations and/or the World Health Organization (WHO) that have a strong impact on drug portfolio management: drug withdrawal from medical practice, discovery of new therapeutic indications, discovery of drug interactions, preference for specific pharmaceutical formulations, discovery of contraindications and change of drug prescription status.**

*Key Words:*
Drug portfolio, Pharmacovigilance, Pharmacoepidemiology, Clinical studies, National drug agency, World Health Organization (WHO).

## Introduction

### Pharmacovigilance Objectives and Organization

The purpose of pharmacovigilance is tracking, examining, recording, validating and systematic evaluation of drug side effects. The main objectives of drug monitoring are precocious tracking of severe and unexpected side effects, tracking of rare or delayed side effects, establishing the frequency and gravity of side effects, study of mechanisms and consequences of side effects, technical counseling through experts commissions of measures that need to be taken to assure the safety of patients and informing healthcare specialists about side effects.

Pharmacovigilance studies are part of phase IV clinical studies. Drug monitoring is non-structured and structured. Non-structured, i.e. non-organized monitoring refers to spontaneous reporting of some presumed side effects observed by practitioners to pharmacovigilance centers and/or to medical representatives. This reporting is important as a signal, but observations are often inaccurate. Structured, i.e. organized monitoring refers to the study of side effects using pharmacoepidemiology techniques. All side effects that occur while a drug is in use are reported by physicians to pharmacovigilance centers. Pharmacovigilance centers verify these effects through prospective (i.e. cohort) or retrospective (i.e. case control) clinical studies.

Cohort studies monitor a patient group taking a drug in comparison with a population control group that is not taking the drug. Upon enrollment, these two groups are monitored prospective over a certain period of time until a side effect occurs. These studies are difficult to implement because they require a large number of study subjects (i.e. patients and healthy individuals), a long period of monitoring time, and a constant compliance of physicians as well as patients to study protocol.

Case control studies compare a group of patients taking a drug with a group of healthy individuals. Upon enrollment, these two groups are analyzed retrospectively for the link between a side effect and a certain drug use. Case control studies have an advantage over cohort studies because they require a small number of study subjects, a shorter period of monitoring time and a higher compliance of physicians and patients due to a shorter study period.

The pharmacovigilance activity is very well organized. There is a World Pharmacovigilance Center belonging to the World Health Organization (WHO) and National Centers in almost every country. Reference offices exist in all universities of medicine and pharmacy and large hospitals. National Pharmacovigilance Centers receive, analyze, save and forward reports on drug side effects to the WHO. The WHO publishes information received from national centers (WHO Pharmaceuticals Newsletter). National Pharmacovigilance Centers also decide whether action must be taken immediately or only after reports on drug side effects are verified through pharmacovigilance studies[1].

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### Pharmacovigilance Reporting and Results

In 1998, the Spanish Health Authority has suspended the marketing authorization for EbrocitR (Ebrotidine), because of several reports regarding liver toxicity. Ebrotidine, a drug used to treat ulcer, acts by blocking H2 receptors, was put on the market in 1997. No sign of liver toxicity were observed during clinical trials. After EbrocitR was put on market, the Spanish Pharmacovigilance System has received several reports regarding severe cases of liver injury, most of them in patients treated longer than 6 weeks (50% of cases) or treated concomitantly with other hepatotoxic medications (57%). The Spanish Health Authority and the manufacturing company Laboratorios Robert have reached an agreement to withdraw the product from market since other antiulcers are safe[2].

Mabthera (Rituximab) is a monoclonal antibody indicated for the treatment of patients with follicular lymphoma stage III-IV, for chemo-resistant tumors or second or third relapse after chemotherapy. This drug was approved in 1997 in the United States of America and in 1998 in the European Union. The European Medicine Evaluation Agency (EMEA) in Great Britain has received information regarding severe side effects in patients treated with Rituximab, including eight deaths due to cytokines releasing syndrome. At least three cases appeared in patients treated for other diseases, not follicular lymphoma. A common feature of these lethal evolutions was the appearance of early severe side effects (i.e. dyspnoea, bronchospasm and/or hypoxia) at the first administration. As a result of these reports EMEA asked Roche to inform patients and physicians about these severe side effects and to offer new recommendations for their prevention and treatment. EMEA also emphasized that Rituximab should not be administered for other therapeutic indications except those approved, exceptions should be only controlled clinical studies. Roche asked for rapid approval for changing instructions for clinical use. The request was approved and Roche informed physicians using a "Dear Doctor" letter[3].

The Pharmaceutical Affairs Bureau of Japan has received reports about the occurrence of epileptic seizures in patients treated with Valproic acid who were concomitantly treated with Panipenem/Betamipron or Meropenem. These antibiotics induced a rapid decrease of plasmatic levels of Valproic acid and subsequently the occurrence of epileptic seizures in epileptic patients that were previously seizures free. Cessation of carbapenem drugs administration was followed by a rapid increase of Valproic acid plasmatic levels and disappearance of epileptic seizures. This drug interaction was reproduced by experiments on monkeys. The Bureau has decided that concomitant administration of Valproic acid and Panipenem/Betamipron or Meropenem is contraindicated and has changed instructions for clinical use[4].

As a result of studies regarding mortality increase in patients with ischaemic coronary heart disease treated with immediate release calcium channel blockers including Nifedipine, The Therapeutic Division of the Ministry of Health of New Zealand has realized a study on immediate versus slow release drugs containing calcium channel blockers. The study has concluded that data indicating a possible link between slow release dihydropyridine drugs (calcium channel blockers) and cardiovascular mortality increase can not be extrapolated to Verapamil, Diltiazem or slow release dihydropyridine drugs. Single therapy with immediate release calcium channel blockers is not recommended for patients with angina or clinical signs of coronary heart disease. They should be used in single therapy only in patients that do not tolerate other medications. Therapy with immediate release calcium channel blockers can be used however in hypertension treatment, in accordance to national or international therapeutic guidelines[5].

The Pharmaceutical Affairs Bureau of Japan has revised the pharmaceutical documentation for calcium channel blockers (Nifedipine) used in patients with ischaemic coronary heart disease due to safety concerns. Nifedipine is contraindicated in patients with acute myocardial infarction. Precaution should be exercised in patients with unstable angina pectoris since symptoms can be aggravated by acute changes in haemodinamics[6].

The United States Food and Drug Administration (USFDA) has changed the drug dispensing status from over the counter to prescription only medicine for drugs containing colloidal silver or silver salts for internal and external use. The USFDA has changed the dispensing status because there is not sufficient scientific evidence proving safe use of colloidal silver or silver salts in severe diseases, including infections with human immunodeficiency virus (HIV) and AIDS, cancer, and many other infectious diseases. Phar-

maceutical manufacturers have been invited to send to the USFDA all existing data and information that supports the safety and efficiency of colloidal silver or silver salts for uses other than those as astringent (e.g. silver nitrate) or as ophthalmic antiinfectious[7].

## Conclusions

As a result of pharmacovigilance reporting and studies pharmaceutical companies can be forced to take following measures: drug withdrawal from portfolio (i.e. market withdrawal), changing drug pre-clinical and clinical files (e.g. pharmacological pre-clinical, toxicological pre-clinical, clinical file), changing drug information documents (e.g. summary of product characteristics, instructions for clinical use, drug master file etc.), changing drug concentration or pharmaceutical formulation and changing drug dispensing status (from over the counter to prescription only medicine).

**Conflict of Interest**

The Authors declare that there are no conflicts of interest.

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