

Results: During the study period, 19,173 reports were registered in the database, among which were: 908 bleeding cases, 361 headache cases, 548 hepatitis cases, 49 TEN, 369 myalgia cases, 53 myocardial infarction cases and 321 stroke cases. For bleeding, the number of reports of interest (detection threshold) for new drugs with 50 reports all events considered, was estimated at 6 when compared to all other drugs and at 3 after excluding reports concerning the main drugs already associated with bleeding. These thresholds were decreased for all reporting frequencies studied for bleeding and stroke. They were not modified for headache, hepatitis, TEN, myalgia or myocardial infarction. Thresholds were similar whether they were evaluated for a new drug or for an existing one.

Conclusions: The choice of the comparator is of great importance for signal generation and has great influence on detection thresholds. The inability to define a specific comparator might limit the performance of data mining when it is used to generate signals without prior hypotheses. For orientated signal exploration, the comparator must be defined, especially for serious, specific and frequent adverse events.

530. Hypoglycaemia Associated with the Use of Angiotensin II Receptor Antagonists: A Safety Signal Generated by Confounding

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Background: Automated disproportionality analysis of spontaneous reporting is increasingly used routinely in pharmacovigilance systems, but most of these methods are unable to fully investigate potential biases such as confounding ones. The potential role of confounding in signal generation has been demonstrated in situations where the prior publicization of a possible association was also involved (angiotensin converting enzyme (ACE) inhibitors and hypoglycaemia).

Objectives: To study the potential effect of confounding on automated signal generation in a situation where no notoriety effect would be expected.

Methods: The French Pharmacovigilance database was analysed for an association between adverse drug reaction reports mentioning hypoglycaemia and angiotensin II receptor antagonists using the case non-case method. The association between angiotensin II receptor antagonists or other chosen drugs and hypoglycaemia was also tested in the subgroups of patients taking or not antidiabetic agents.

Results: Hypoglycaemia was found in 807 of all 174595 reports in the database and in 589 of 6909 reports with antidiabetic agents (OR 69.2; 95%CI 59.2–81.1). It was found in

33 of the 4155 reports involving angiotensin II receptor antagonists (OR 1.8; 1.2–2.5). Other study drugs associated with hypoglycaemia were ACE inhibitors (OR 3.0; 2.2–4.2), disopyramide (OR 17.4; 10.4–29.1), cibenzoline (OR 107.3; 77.8–148.1), atenolol (OR 2.0; 1.2–3.6), dihydropyridines (OR 1.9; 1.2–3.0), frusemide (OR 2.8; 2.3–3.5), but not diazepam, verapamil, combination thiazide diuretics. However, angiotensin II receptor antagonists and other drugs were associated with antidiabetic agents. The association of angiotensin II receptor antagonists with hypoglycaemia disappeared in the subgroups of patients taking or not antidiabetic agents, (OR 0.4; 0.2–0.8 and OR 1.4; 0.8–2.7). Association of hypoglycaemia with disopyramide or cibenzoline was not affected.

Conclusions: Although there is no evidence in the literature supporting an association between hypoglycaemia and the use of angiotensin II receptor antagonists, a signal was generated in the French pharmacovigilance database. This signal disappeared after stratification on antidiabetic agents use, demonstrating the role of confounding by indication in its generation.

531. Lareb Intensive Monitoring, a Web Based System for Monitoring ADRs in the Postmarketing Phase

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Background: There is an increased awareness for the safety of new drugs. Regulators are sometimes requesting specific post-marketing information about the first period of use in daily practice. Intensive monitoring offers the possibility to monitor drugs actively after introduction on the market. While other systems are based on information received from physicians *Lareb Intensive Monitoring* (LIM) is based on information from patients.

Objectives: Our aim is to describe the feasibility of a web-based and patient-based system of intensive monitoring, using the Pharmacy Information System to identify eligible patients.

Methods: Patients receive information about LIM when he or she collects the drug under investigation in the pharmacy for the first time. After on-line registration, the patient will receive questionnaires via e-mail at specific points in time asking for his experiences with the drug, including adverse drug reactions (ADRs).

Results: Nineteen pharmacies participated in a pilot early 2006. During the pilot 280 information flyers were handed out of which 72 (26%) patients registered on the LIM website.

In August 2006 the LIM-system started officially and since then two drugs are monitored. More than 500 patients

were included in the first half year and the first experiences show that patients are willing to register and fill in the questionnaires that were sent to them at the start and at fixed moments afterwards.

Conclusions: The pilot study and the experiences in the first year show that LIM is a promising system in gathering information about new drugs. By using the first prescription signal in the pharmacy it will be possible to monitor the drug from the first day of use. Since the patient using the drug provides the information, this system enables us not only to identify new ADRs but also other problems related to drug use. Patients and pharmacists are willing to participate in LIM. Enduring encouragement is needed to stimulate pharmacy personnel to include patients who get the drug under investigation for the first time. Web based intensive monitoring can be a valuable addition to our existing spontaneous reporting system in order to detect new signals in an early stage.

532. Design Issues in Active Surveillance Studies: Experience from the EURAS Studies

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Background: EURAS-OC and EURAS-HRT are examples of large-scale, long-term active surveillance studies that were successfully applied to investigate the safety of new oral contraceptives and hormone replacement therapies under real-life conditions in Europe. In this type of multinational, controlled, prospective, non-interventional cohort study we enrolled up to 60,000 women and compiled up to 145,000 years of observation. A similar design was also used successfully for an OC and an HRT study in the USA despite some obvious differences in the respective health care systems. It is conceivable that the design of the EURAS studies can also be applied to other therapeutic areas.

Objectives: To analyze which of the design features of the EURAS studies were important for their success and which could be applied to other therapeutic areas.

Methods: The EURAS studies were characterized among other things by comprehensive documentation of risk factors and medical history, inclusion of only new users (starters or switchers), patient-reported adverse events validated via the attending physicians, blinded adjudication of outcomes of interest, and a multifaceted, 4-level follow-up procedure. The impact of these characteristics on the study results were analyzed.

Results: In the EURAS-HRT study the comprehensive documentation of baseline risks revealed significant regional differences between central European and Mediterranean countries and enabled an adequate stratification of the ana-

lyses. The patient-reported adverse events were a very sensitive tool for capturing serious clinical outcomes of interest, and showed – after validation via the attending physicians – that the true incidence of venous thromboembolism among users and non-users of OCs is higher than previously reported. Blinded adjudication of clinical outcomes by independent experts led to a reclassification of approx. 2% of the reported outcomes of interest. The comprehensive 4-level follow-up procedure yielded loss to follow-up rates of 2–3%.

Conclusions: Comprehensive documentation of baseline risks, patient-reported clinical outcomes, and a comprehensive follow-up procedure were essential for the quality of the EURAS studies. Blinded adjudication further improved the quality. These features are also applicable to active surveillance studies in other therapeutic fields.

533. Smile Plots to Identify Adverse Drug Reactions

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Background: The current system in place to study safety of medicines after their introduction on the market relies predominantly on spontaneous reports. Here we propose a new approach to systematically identify adverse events utilising a large primary care database.

Objectives: To investigate whether the ‘Smile Plot’ method identifies known associations between prescription drugs and risk of Systemic Lupus Erythematosus (SLE).

Methods: We utilised the UK-based General Practice Research Database (GPRD) to conduct a matched case-control study. Incident cases of SLE diagnosed between 1987 and 2001 were matched to 5 non-autoimmune disease controls on age, practice, sex and calendar time. Cases with comorbid autoimmune disease were excluded. Exposures of interest took place one year or more before index date. We investigated risk for all drugs in the British National Formulary (BNF), grouped by BNF subchapter. Odds Ratios (OR) and corresponding P-values for risk of SLE were calculated using conditional logistic regression. ORs and P-values were then plotted in a graph and P-values were corrected for multiple comparisons using the Yekutieli method.

Results: We identified 875 cases and 3632 matched controls. After correction for multiple comparisons the following subchapters were associated with risk of SLE: Sunscreens and camouflagers (OR = 15.4, 95% Confidence Interval (CI) 6.74 - 35.4), Topical local corticosteroids (OR = 1.80, 95% CI 1.51 - 2.16), Antihistamines