

Laboratory markers in drug safety research: studies on drug-induced thrombocytopenia

It regularly happens that medications are found to cause severe adverse effects that remained undetected during premarketing research. From the perspective of the patient, the public and drug manufacturers there is a need for better tools for earlier detection, quantification and mechanistic unraveling of associations between drug exposure and adverse health outcomes in patient populations. A tool that is considered to be valuable for this purpose is a database with patient-oriented data on medication exposure and laboratory test results collected in clinical care. The objective of this thesis was to investigate the value of laboratory data collected in patient care for drug safety research. We focused on drug-induced thrombocytopenia as an example. First, we investigated the association between thrombocytopenia and exposure to drugs most often reported to cause thrombocytopenia. For this study we used data from the PHARMO Record Linkage System. To identify patients with thrombocytopenia hospital discharge diagnoses were used. An increased risk for thrombocytopenia following exposure to beta-lactam antibiotics was found. The expected increase in risk for thrombocytopenia could not be confirmed for the other medications investigated. This may be the result of limited statistical power, in which incomplete identification of patients with drug-induced thrombocytopenia by using hospital discharge diagnoses could play a role. Following-up this study we compared the use of hospital discharge diagnoses for thrombocytopenia with the use of platelet measurements as strategy for case-finding potential drug-induced thrombocytopenia from health care data. We found that using platelet measurements is a more sensitive approach for this purpose. However a low platelet count was observed to be non-specific for potential drug-induced thrombocytopenia. For this study we used data from the Utrecht Patient Oriented Database (UPOD). UPOD is a recently established database for (pharmaco-)epidemiological research, encompassing automated data on laboratory test results, medication exposure, hospital discharge diagnoses, medical procedures and patient demographics for all patients treated at the UMC Utrecht. By using data from UPOD we performed three studies concerning different aspects of drug-induced thrombocytopenia: the incidence and relative risk of chemotherapy-induced thrombocytopenia, a biomarker for the mechanism of chemotherapy-induced thrombocytopenia and compliance with recommendations for monitoring the platelet count for heparin-induced thrombocytopenia. We respectively found that the cytostatic drugs carboplatin, gemcitabine and paclitaxel are associated with the highest risk for thrombocytopenia in oncology patients treated in clinical practice, platelet size indices can not be used to distinguish bone marrow and immune-related causes of chemotherapy-induced thrombocytopenia and compliance to recommendations to monitor for heparin-induced thrombocytopenia in patients treated with low molecular weight heparin is low. We concluded that linking laboratory and medication data within a research database is a valuable tool for investigating the safety of drugs in patient populations, including the investigation of the incidence, risk factors and monitoring for adverse drug reactions that can be detected with a biochemical test (such as drug-induced blood disorders) and the identification of potential biomarkers for adverse drug reactions. The knowledge from this research is valuable in maximizing the benefits of effective medications in patients treated in clinical practice.

Laboratoriumparameters bij de bestudering van bijwerkingen van geneesmiddelen: onderzoeken naar geneesmiddel-geïnduceerde trombocytopenie

Regelmatig blijkt dat een geregistreerd geneesmiddel schadelijke neveneffecten heeft welke niet zijn ontdekt in het pre-marketing onderzoek. Er is behoefte aan onderzoeksinstrumenten om bijwerkingen van geneesmiddelen tijdig te ontdekken, het risico op de bijwerking te kwantificeren en het mechanisme van de bijwerking te duiden. Een instrument dat nog weinig wordt gebruikt, maar waarvan wordt verondersteld dat het meerwaarde heeft voor deze doeleinden, is een databank met geautomatiseerde zorggegevens over medicatieblootstelling en laboratoriumuitslagen. Veel typen bijwerkingen kunnen namelijk met laboratoriumparameters worden gedetecteerd, bijvoorbeeld bloedbeeldafwijkingen. Het doel van dit promotieonderzoek was het bepalen van de meerwaarde van dit instrument voor het bestuderen van de veiligheid van geneesmiddelen in patiëntenpopulaties. In dit kader is een databank met gekoppelde laboratorium- en medicatiegegevens, de Utrecht Patient Oriented Database (UPOD), gerealiseerd. Met gegevens uit UPOD zijn een aantal epidemiologische onderzoeken gedaan die betrekking hadden op de bijwerking geneesmiddel-geïnduceerde trombocytopenie, waaronder de frequentie van trombocytopenie tijdens chemotherapiebehandeling, een biomarker voor het onderliggende mechanisme van chemotherapie-geïnduceerde trombocytopenie en het opvolgen van adviezen om heparine-geïnduceerde trombocytopenie te detecteren. Databanken zoals UPOD zijn een waardevol instrument om te leren over incidentie, mechanismen en monitoring van bijwerkingen die biochemisch kunnen worden gedetecteerd, alsook het bestuderen van mogelijke biomarkers voor bijwerkingen.