Institutionen för laboratoriemedicin, Avd. för klinisk farmakologi

Drug-drug interactions – from knowledge base to clinical impact

AKADEMISK AVHANDLING
Som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras på engelska språket i föreläsningssal R64, Karolinska universitetssjukhuset Huddinge.

Fredagen den 25 april 2014, kl. 09.00

av

Marine Andersson
farmacie magister

Huvudhandledare
Docent Ylva Böttiger
Karolinska Institutet
Institutionen för laboratoriemedicin
Avd. för klinisk farmakologi

Bihandledare
Medicine doktor Jonatan Lindh
Karolinska Institutet
Institutionen för laboratoriemedicin
Avd. för klinisk farmakologi

Bihandledare
Farmacie doktor Birgit Eiermann
Karolinska Institutet
Institutionen för laboratoriemedicin
Avd. för klinisk farmakologi

Fakultetsopponent
Robert Vander Stichele
University of Gent
Heymans Institute of Pharmacology, Belgium

Betygsnämnd
Docent Eva Wikström Jonsson
Karolinska Institutet
Institutionen för medicin

Docent Ellen Vinge
Lunds Universitet, Institutionen för laboratoriemedicin

Docent Anders Carlsten
Göteborgs Universitet, Avd. för samhällsmedicin och folkhälsa

ABSTRACT

Drug usage has increased steadily, and the more drugs used, the higher the risk for adverse effects or loss of effect due to drug-drug interactions. For drug prescribers it is difficult to know what drugs a patient is taking and whether they interact. Computerizing of health care records has made it possible to connect patients' drug lists to clinical decision support systems giving the prescriber information about e.g. drug-drug interactions, duplicated prescriptions and drugs in pregnancy. The aim of this thesis is to create a knowledge base suitable for usage in decision support systems, to evaluate the database in clinical practice, and to use existing clinical databases to create new knowledge about possible drug-drug interactions and their mechanisms.

Paper I is a description of how the knowledge base SFINX was created. The publication describes handling of substances and drug formulations. Standardization of literature searches and text formulations, classification of interactions, structuring of interaction texts, basis for recommendations and the process of approval is also discussed.

In paper II, the interaction between lamotrigine and quetiapine was studied using therapeutic drug monitoring data. Patients exposed to both quetiapine and lamotrigine were matched with controls exposed to quetiapine alone. The dose-corrected quetiapine concentration was 58% lower in patients co-treated with lamotrigine than in patients treated with quetiapine alone, possibly due to induction of quetiapine metabolism by lamotrigine.

In paper III, the influence of mutations in the CYP2C9 gene on the interaction between simvastatin and warfarin was studied. In patients with a CYP2C9*3 allele, the warfarin maintenance dose was 25% lower if treated with simvastatin, according to the results from multiple regression. No significant interaction could be observed in patients lacking the *3 allele.

Paper IV was a questionnaire study where we collected information about how SFINX is used and how the database is perceived by the users of the web version. We found that the database is often used when the prescriber/pharmacist sees the patient, that the information influences the treatment of the patient, and that the database is used to learn more about interactions.

In paper V, we investigated if integration of SFINX into electronic health care records prevented the prescribing of drug combinations leading to potentially serious drug-drug interactions in primary health care. When comparing prescriptions between a period before integration of SFINX and a period after integration, we found that the prevalence of potentially serious drug-drug interactions decreased significantly by 17%.

ISBN 978-91-7549-536-1