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Institutionen för medicinsk epidemiologi och biostatistik

Mathematical Model Development to Investigate the Pharmacokinetic Variability of Two Anticancer Drugs

AKADEMISK AVHANDLING

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ABSTRACT

Pharmacokinetic variability in a population is the variability in plasma drug concentrations among individuals. It may, for instance, be caused by differences in genes coding for drug-transport proteins and metabolizing enzymes, amount of body fat, age, sex, patient compliance, diet or disease progression. For anticancer agents, the combination of a high variability and a narrow therapeutic window may cause adverse side events, with additional suffering for already afflicted patients and with high costs for society.

The work in this thesis aims to explore the possibilities for individualized treatment of two specific anticancer drugs, paclitaxel and imatinib, by developing mathematical models to investigate their pharmacokinetic variability.

In Paper I, two existing population pharmacokinetic models for paclitaxel are compared using a clinical study comprising thirty-three women treated for ovarian cancer. Using identifiability and sensitivity analysis, it is shown that a model describing the relation between total, unbound, and bound drug can be used with at least as good fit as a more empirical model, although only total plasma concentrations of paclitaxel are available.

In Paper II, the conclusions from Paper I are used to expand the mechanism-based model for paclitaxel to also include three metabolites. It is shown that the solubilizer Cremophor EL seems to have a strong effect on the kinetics of the two hydroxy-metabolites. Clearance of the main metabolite 6 α -hydroxypaclitaxel (fraction metabolized) was significantly correlated ($p < 0.05$) with the ABCB1 allele G2677T/A. Individuals carrying the polymorphisms G/A ($n = 3$) or G/G ($n = 5$) showed a 30% increase, whereas individuals with polymorphism T/T ($n = 8$) showed a 27% decrease relative to those with the polymorphism G/T ($n = 17$).

In Paper III, a population pharmacokinetic model for imatinib is developed using data from a clinical study including fifty men and women on long-term treatment for gastrointestinal stromal tumour. It is shown that the pharmacokinetics is best described using a model with time dependent apparent bioavailability and absorption rate, which are decreased by approximately 30% and 50%, respectively, after three months of treatment. In addition, apparent clearance of imatinib was associated with the size of the liver metastasis, and was decreased by almost 4% for every 100 cm³ of liver metastasis.

In Paper IV a semi-physiologically based pharmacokinetic model for paclitaxel and its metabolites is developed using existing models and data available in the literature. Sensitivity analysis of hepatic uptake, metabolism and efflux of the substances predicts systemic plasma concentrations of 6 α -hydroxypaclitaxel to be sensitive to changes in the capacity of the ABCB1 transporter.