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CYP2C-dependent drug metabolism *in vivo*; influence of genetics and drug interactions

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ABSTRACT

Cytochrome P450 enzymes (CYPs) are responsible for the metabolism of the majority of therapeutic drugs. This thesis focuses on one of the CYP subfamilies, CYP2C, especially CYP2C9 and CYP2C19, which are responsible for the metabolism of 15–20% of all drugs. All CYP2C enzymes are polymorphic, i.e. there are genetic variants, which have functional consequences for drug metabolism. Individuals can be classified according to their CYP2C metabolic capacity in extensive (EMs), intermediate (IMs) and poor metabolisers (PMs). Recently, a novel variant of the CYP2C19 gene was described in individuals with high metabolic capacity. This allele, CYP2C19*17, has been claimed to cause ultrarapid metabolism (UM) of CYP2C19 substrates.

The aim of this thesis is to explore some of the aspects underlying varying metabolic capacity between, and within, individuals with the focus on genetics and drug–drug interactions. The thesis is based on five published papers.

In Paper I we explored the influence of the genetic variant CYP2C9*3 on the CYP2C9 dependent metabolism of the anti-inflammatory and analgesic drug celecoxib. We found a seven-fold higher median exposure at steady-state in homozygous carriers of the CYP2C9*3 allele compared to homozygous wild-type subjects. This might be one factor behind the increased risk of cardiovascular events that has been observed in long-term users of celecoxib in a dose-dependent fashion.

Paper II and III focused on the CYP2C19*17 allele that has been associated with extensive metabolism of CYP2C19 substrates. We showed a 52% lower exposure of omeprazole in homozygous *17 carriers compared to homozygous wild-type subjects after a single dose of 40 mg. Regarding steady-state levels of escitalopram (5 mg twice daily for a week), we noted a trend towards a 21% lower exposure in CYP2C19*17 homozygous individuals. However, this did not reach statistical significance in this study that was powered for a 40% difference. The clinical impact (or lack of impact) of this allele for various clinically important CYP2C19 substrates will be discussed in the thesis.

A clinical consultation was the starting point for Paper IV in which we described eight cases of increased anticoagulant effect of warfarin in connection with concomitant use of noscapine; a cough medicine available over-the-counter. These cases were reported to the Swedish adverse drug reactions (ADR) register and we could show that they yielded a statistically significant signal worthy of further investigation. In vitro experiments were performed, showing that noscapine strongly inhibited CYP2C9 and CYP3A4, the key enzymes in warfarin metabolism.

Besides noscapine, another OTC drug, glucosamine, has attracted interest for suspected interaction with warfarin. In Paper V we addressed the pharmacokinetic aspect of these interactions by giving a cocktail of four probe drugs before and during noscapine or glucosamine. Compared to baseline phenotyping, significant inhibition of both CYP2C9 (4.9-fold increase in the urinary losartan/E3174 ratio; 95% CI 2.8 - 8.4) and CYP2C19 (3.6-fold increase in the plasma omeprazole/5-hydroxyomeprazole ratio; 95% CI 2.6 - 4.8) was seen during noscapine treatment. This is likely to explain the observed interaction with warfarin. No enzyme inhibition was seen with glucosamine and a metabolic interaction between warfarin and glucosamine seems highly unlikely.

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