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# Studies on 4 $\beta$ -hydroxycholesterol, a marker of CYP3A activity, and its association with 25-hydroxyvitamin D

AKADEMISK AVHANDLING

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## ABSTRACT

Cholesterol is a vital compound that can undergo cytochrome P450 (CYP) mediated conversion into steroid hormones, bile acids and oxysterols. CYP enzymes are present in all human tissues and mediate the metabolism of several endogenous and exogenous compounds such as steroids and drugs. Vitamin D status has been shown to be important for several biological processes such as drug metabolism, modulation of the immune system and bone health. Enzymes in subfamily CYP3A (CYP3A4, CYP3A5, CYP3A7 and CYP3A43) are present in liver and intestine and metabolize about 50% of all prescribed drugs. Genetic factors, age, sex, ethnicity and environmental factors influence the activity and expression of CYP3A enzymes. This cause wide inter-patient variability in CYP3A mediated drug response. There are a number of clinical markers to assess the CYP3A activity, e.g. plasma midazolam clearance, quinine metabolic ratio and 4 $\beta$ -hydroxycholesterol/cholesterol ratio.

In the present study we have evaluated the plasma levels of 4 $\beta$ -hydroxycholesterol and the 4 $\beta$ -hydroxycholesterol/cholesterol ratio as markers of CYP3A activity during enzyme induction by a number of drugs (carbamazepine in Papers I and III, rifampicin in Papers IV-V and efavirenz in Paper V) and by pregnancy (Paper III). We have also studied the association between CYP3A activity and vitamin D status (Paper IV-V). In Paper I, carbamazepine treatment in children with epilepsy doubled the plasma levels of 4 $\beta$ -hydroxycholesterol within two weeks of treatment. The increase was 5 to 10-fold within eight weeks treatment. In Paper III, pregnancy increased the 4 $\beta$ -hydroxycholesterol/cholesterol ratio and the plasma levels of cholesterol. Newborn children had similar CYP3A activity as adults as indicated by similar 4 $\beta$ -hydroxycholesterol/cholesterol ratios. Carbamazepine treatment during pregnancy further increased the CYP3A activity in one mother and child. In Papers IV-V, rifampicin-mediated CYP3A induction did not affect the plasma levels of 25-hydroxyvitamin D in healthy volunteers or in tuberculosis-HIV co-infected patients. In tuberculosis-HIV co-infected patients there was a significant negative correlation between the plasma levels of 25-hydroxyvitamin D and the 4 $\beta$ -hydroxycholesterol/cholesterol ratio already at initiation of treatment (Paper V). Efavirenz treatment caused a transient decrease in the plasma levels of 25-hydroxyvitamin D in HIV-infected patients (Paper V).

To summarize, 4 $\beta$ -hydroxycholesterol and the 4 $\beta$ -hydroxycholesterol/cholesterol ratio are useful as markers of CYP3A induction. 4 $\beta$ -Hydroxycholesterol is a non-invasive endogenous clinical marker that is easy to use also in children and vulnerable patient groups. The blood samples can be taken any time of the day regardless of food intake.