4β-Hydroxycholesterol – a New Marker for Drug Metabolism

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We have recently shown that cytochrome P450 3A4 (CYP3A4) can convert cholesterol into the oxysterol 4β-hydroxycholesterol. Patients treated with drugs known to induce CYP3A4 had significantly increased plasma levels of 4β-hydroxycholesterol. Three weeks treatment with the weak inducer ursodeoxycholic acid resulted in a 50% increase while treatment with the strong inducer carbamazepine caused a 10-20-fold increase in 4β-hydroxycholesterol. Infusion experiments with deuterium labeled 4β-hydroxycholesterol revealed a half-life of 60 hours. These results prompted us to suggest 4β-hydroxychoelsterol as a potential clinical marker of CYP3A4 activity. In vitro experiments indicated that also CYP3A5 could convert cholesterol into 4β-hydroxycholesterol. Studies in different populations showed that the mean plasma concentration was low in black Africans, intermediate in Caucasians and high in Asians. Genotyping of the most important polymorphisms in CYP3A5 showed that in all three populations the number of active CYP3A5 alleles was an important determinant of plasma 4β-hydroxycholesterol concentrations. Furthermore, a clear sex difference was observed with higher levels of 4β-hydroxycholesterol in females compared to males. The endogenous marker 4β-hydroxycholesterol showed a good correlation to the exogenous CYP3A-marker quinine. No diurnal variation was observed for 4β-hydroxycholesterol.

It is concluded that 4β-hydroxycholesterol is a promising new marker of CYP3A4/A5 activity that can be used for individualized drug treatment as well as screening of new drug candidates.