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Clinical study on the dose-dependency of cytochrome P450 3A4 inhibition by ritonavir and the effect of an additional CYP3A4 induction

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This is the first study to systematically evaluate the dose-dependency of CYP3A4 inhibition by rising doses of ritonavir in the same study population. In the 12 healthy subjects included in the study a significant inhibition was observed starting at ritonavir doses as low as 1 and 3 mg. While 300 mg of the potent inhibitor led to a maximum effect of about 90% activity reduction of CYP3A4, the half maximum inhibiting dose was observed in a dose as low as 3.4 mg.
Pharmacokinetics of ritonavir was found to be non-linear when comparing the different dose steps and the built-up concentration in the serum of the subjects. The dose-corrected exposure varied 900-fold within the dose range of 0.1 to 300 mg of ritonavir. The non-linear effect was attributed to the previously described mechanism of auto-inhibition: Ritonavir is a potent irreversible inhibitor of CYP3A4, which might inhibit its own metabolism by the same enzyme. The auto-inhibitory effect will consequently be lower at lower ritonavir doses and result in enhanced drug elimination and thus lower drug exposure than at higher ritonavir doses.

Further, we investigated which effect the administration of a low dose of ritonavir, causing half maximal inhibition, has on the induced state of CYP3A4. A net induction of the enzyme's activity was observed when the inducing substance St. John's wort was co-administered with 3 mg of ritonavir. Considering the net inhibiting effect observed at higher doses of ritonavir, our study might reveal a dose-dependent response in the common interaction between St. Johns wort and ritonavir on CYP3A4 where the predominance of the inhibition requires higher doses than 1 to 3 mg.

In conclusion, ritonavir is able to significantly inhibit CYP3A4 in considerably lower doses than those previously reported.

The findings in this study could be relevant in a research setting with a more specific use of ritonavir to inhibit the most important cytochrome in the human liver.
Moreover, lower doses than the currently used standard doses in treatment of HIV could be used to booster other antiretroviral substances metabolized by CYP3A4 lowering pill burden and occurrence of adverse drug events.