Assessment of potential induction of CYP3A4 after a single-dose of efavirenz using midazolam pharmacokinetics as a marker

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INTRODUCTION

- The importance of CYP3A4 in the metabolism of many regular used drugs and therefore also in drug interactions is well known.
- Many substances can influence the activity of CYP3A4 either to an increased (induction) or decreased activity (inhibition). Whereas inhibition is an almost immediate response induction is a slow and regulatory process [1] which involves an increased rate of enzyme synthesis.
- The non-nucleoside reverse transcriptase inhibitor efavirenz (EFV) is known to act both as an inducer and inhibitor of CYP3A4.
- This study was carried out to investigate the possible inductive effect on CYP3A4 after a single-dose of EFV.

METHODS

- 12 healthy volunteers (6 male, 6 female) were included in this controlled, open label study (Fig. 1).
- The benzodiazepine midazolam (MDZ) was used as a marker to assess CYP3A4 activity in liver and gut wall, it is primarily metabolized by CYP3A4 to 1-hydroxy midazolam (1-OH-MDZ).
- MDZ was administered p.o. (4 mg) and 6 hours later i.v. (2 mg) on each study day. Blood samples were collected over 14 hours and urine was collected over 24 hours with 3 collection periods.
- The pharmacokinetics of MDZ and 1-OH-MDZ before and after administration of EFV were determined using WinNonlin 5.2 and a Friedman ANOVA with Dunn's post-hoc tes (InStat 3) was used to test for differences between the study days.

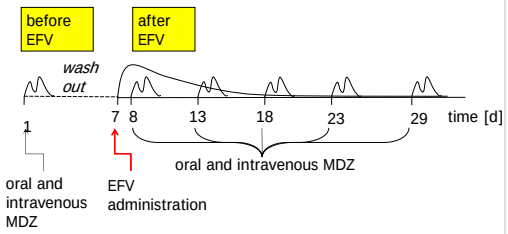

Fig. 1: study flow chart

RESULTS

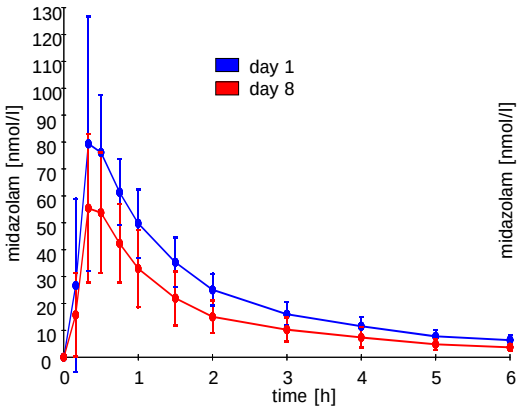

Fig. 2: mean plasmaconcentrations after oral MDZ (4 mg)

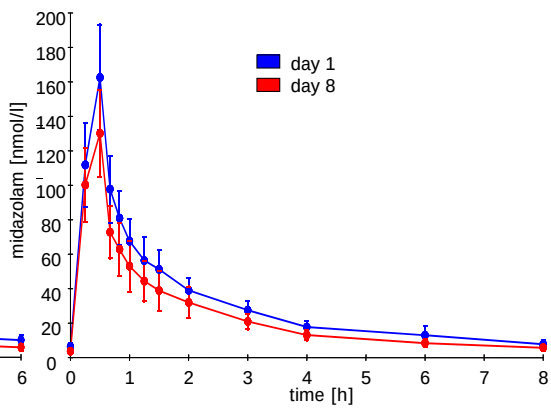

Fig. 3: mean plasmaconcentrations after i.v. MDZ (2 mg)

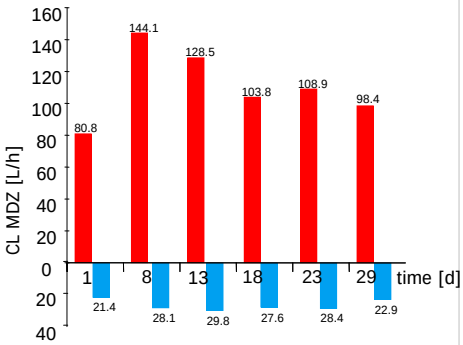

Fig. 4: CL after oral and intravenous MDZ administration

	parameters	before EFV	7	8	13	18	23	29
4 mg MDZ p.o.	$AUC_{0-\infty}$ (hr*nmol/l)	163.07 ± 41.12	400 mg efavirenz	100.04 ± 40.04	100.32 ± 22.25	125.33 ± 31.22	122.47 ± 34.99	142.35 ± 58.28
	$t_{½}$ (hr)	2.17 ± 0.32		1.68 ± 0.28	1.74 ± 0.37	1.93 ± 0.30	1.83 ± 0.39	1.98 ± 0.44
	CL (ml/min)	1346.33 ± 404.81		2401.28 ± 1064.09	2140.98 ± 511.04	1729.79 ± 441.95	1815.00 ± 597.7	1639.66 ± 575.46
2 mg MDZ i.v.	$AUC_{0-\infty}$ (hr*nmol/l)	276.01 ± 54.90		220.26 ± 76.92	209.62 ± 50.32	240.88 ± 86.63	222.66 ± 58.18	250.47 ± 95.64
	$t_{½}$ (hr)	3.35 ± 0.94		3.28 ± 1.11	3.47 ± 1.64	3.19 ± 1.87	3.19 ± 1.14	3.57 ± 1.57
	CL (ml/min)	382.55 ± 66.56		488.91 ± 182.67	515.16 ± 133.74	483.14 ± 199.39	519.07 ± 217.06	433.74 ± 161.97

Tab. 1: pharmacokinetic parameters of midazolam before and after EFV administration
significant ($p<0.05$) differences in comparison with the data before EFV administration

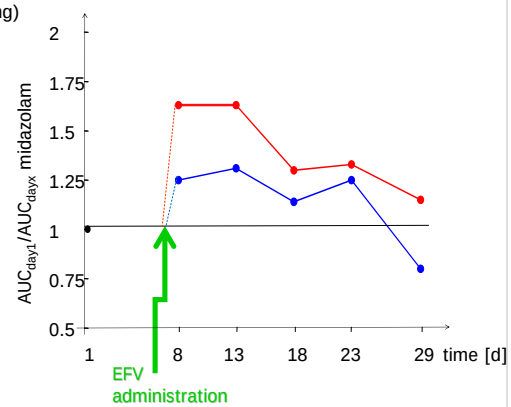

Fig. 5: AUC_{day1}/AUC_{dayX} of midazolam after oral and intravenous administration

CONCLUSION

- A single dose application of EFV (400 mg) leads to time dependent alterations in MDZ pharmacokinetics.
- EFV has are more pronounced effect of orally administered MDZ, the increase in MDZ clearance indicates mainly an induction of CYP3A4-mediated metabolism. The MDZ AUC shows a clear relationship to the partial metabolic clearance to 1-OH-midazolam (personal communication).
- A direct interaction of EFV can be excluded since a 12 h interval was chosen between EFV and the first MDZ administration.
- It is unclear, if the observed effect already after 12 h is a true induction of CYP3A4 or possibly an enzyme activation.

REFERENCES

[1] Lin JH, Lu AYH. Inhibition and Induction of Cytochrome P450 and the Clinical Implications. Clin Pharmacokinet. 1998; 35(5): 361-390