Quantifying the dynamics of the modulatory effect of CYP3A perpetrators on hepatic CYP3A activity using a nonlinear mixed-effects model of microdosed midazolam and its metabolite 1-hydroxymidazolam

Yomna M. Nassar (1,2), Gerd Mikus (1,3), Wilhelm Huisinga (4), Robin Michelet (1), and Charlotte Kloft (1)

(1) Department of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Germany
(2) Graduate Research Training program PharMetrX, Berlin/Potsdam, Germany
(3) Department of Clinical Pharmacology and Pharmacoepidemiology University Hospital Heidelberg, Heidelberg, Germany
(4) Institute of Mathematics, University of Potsdam, Germany

Background

- Modulators of CYP3A activity (perpetrators) can **alter exposure** of CYP3A substrates [1].
- Effects of perpetrators are usually evaluated by time-independent end-points [2,3].
- For CYP3A, midazolam (MDZ) is the specific substrate; **92%** of MDZ is metabolised by CYP3A [4].
- The clearance (CL) of non-pharmacological microgram intravenous (i.v.) dosing of midazolam (MDZ) can quantify [5]:
  1) In vivo activity of ***hepatic*** CYP3A
  2) Extent of CYP3A modulation over time in response to perpetrators

Objective

- To ***quantify*** the modulatory impact of different types of CYP3A perpetrators ***over time***, on hepatic CYP3A activity, by developing an NLME model of MDZ and its metabolite, 1-hydroxymidazolam (1_OHMDZ)

Methods

Study design

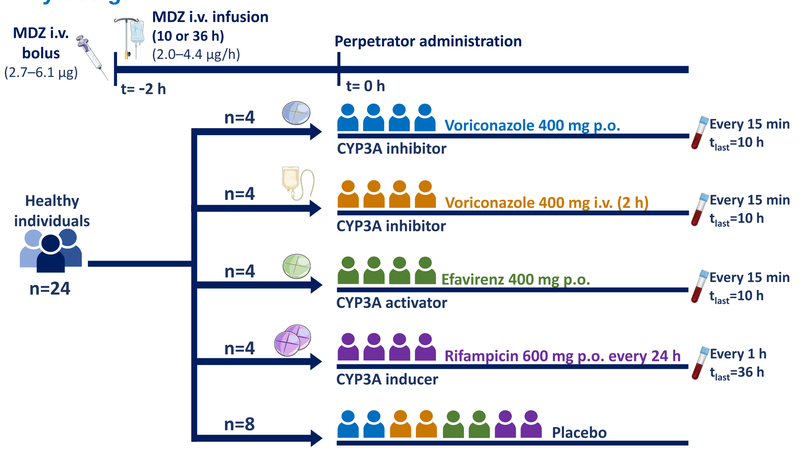

Figure 1. Clinical study design. EudraCT No: 2013-004869-14

MDZ/1_OHMDZ NLME PK model development

- NONMEM 7.4.3 and PsN 4.8.1 with FOCE+I method

Methods (Cont.)

Quantification of CYP3A modulation

- Perpetrator drug effect on CYP3A activity was quantified as change in MDZ CL compared to placebo group, along the sampling duration of MDZ.
- The sampling duration of each study arm was split into discrete time intervals.
- For each time interval, $$CL = \theta_1 \cdot (1 + \theta_i) \cdot e^{\eta_1}$$ **Eq 1**

  CL: Individual MDZ CL; θ_1: Population MDZ CL; θ_i: Fractional change in population MDZ CL as a result of perpetrator administration unique per time interval and study group. **For the placebo group, θ_i was set to zero.**
- Relative change in CL (RelCL) was calculated as in eq 2,

$$RelCL = \frac{CL_{TV} - CL_{pop}}{CL_{pop}} \cdot 100$$ **Eq 2**

CL_{TV}: Typical MDZ CL unique per time interval and study group; CL_{pop}: Population MDZ CL

Results

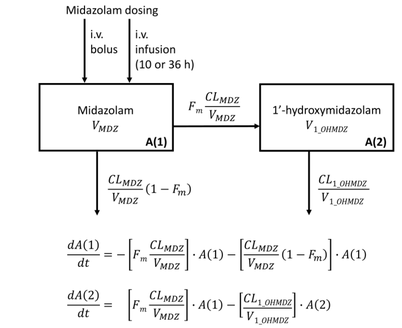

Figure 2. Schematic diagram of MDZ/1_OHMDZ model

Table 1. Parameter estimates of MDZ/1_OHMDZ model

Parameter	Final model		Parameter uncertainty
	Value	RSE [%] [a]	95% CI [a] [lower–upper]
Structural parameters			
CL_{MDZ} [L/h]	43.9	4.37	40.0–47.5
V_{MDZ} [L]	56.7	6.84	49.9–65.1
CL_{1_OHMDZ} [L/h]	264	7.68	224–305
V_{1_OHMDZ} [L]	300	8.87	250–353
F_m	0.92 [b]		
Interindividual variability [%CV]			
ω^2 CL_{MDZ}	21.9	27.4	16.8–28.5
ω^2 V_{MDZ}	29.9	32.9	22.3–40.7
ω^2 CL_{1_OHMDZ}	42.0	25.7	33.1–53.2
ω^2 V_{1_OHMDZ}	39.9	37.5	28.5–56.5
Residual variability [proportional, %CV]			
MDZ	12.6	4.93	12.1–13.3
1_OHMDZ	22.6	4.84	21.6–23.8

[a] Obtained from SIR; [b] Fixed [4]
- SIR-reported RSE (for all parameters): 4.37%–43.5%.

CI: Confidence interval; CL: Clearance; CV: Coefficient of variation; F_m: Fraction of MDZ metabolised; MDZ: Midazolam; 1_OHMDZ: 1-hydroxymidazolam; RSE: Relative standard error; V: Volume of distribution; ω^2: Variance

Quantification of CYP3A modulation

Table 2. Modulatory effects of different perpetrators visualised in **fig 3**

Perpetrator	Maximum modulatory effect		Time of significant modulatory effect* [h]
	Time [h]	Relative change in CL (%)	
Voriconazole p.o.	6–8	-70.6	0
Voriconazole i.v.	6–8	-61.1	4
Efavirenz	2–3	+59.1	2
Rifampicin	28–30	+46.8	22

* Outside bioequivalence limit: 80%–125%, corresponds to CL_{MDZ} <35.1 L/h and >54.9 L/h

No perpetrator effect was estimated for:
- Placebo group
- First 2 hours of each group
- Last efavirenz time interval
- First 24 h of rifampicin

Results (Cont.)

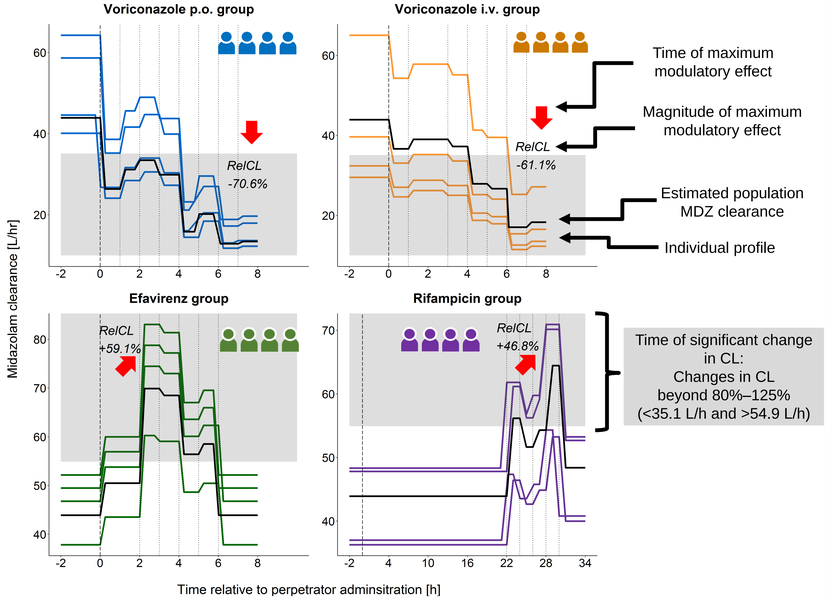

Figure 3. Midazolam clearance-time profiles showing modulatory effects of different perpetrators per time intervals, within each study group (n=4)
The following time intervals' clearance was fixed to the placebo value: 6-8 h (efavirenz), 0-22 h (rifampicin).
Dashed vertical line: Time of perpetrator administration; **Dotted vertical lines:** Time intervals

Conclusion

- Knowledge of the dynamic modulatory profile of each perpetrator
- Clinical and analytical framework can be applied to:
  - **Distinguish** different mechanisms of CYP3A modulation by time of onset *(Activators versus Inducers)*
  - **Identify** monitoring time for a significant modulatory effect *(change in CL beyond 80%–125%)*
  - **Screen** for perpetrators in drug development *(use of microdosed CYP substrates)*
  - **Support** the design of future DDI studies *(decide times of intensified sampling)*

References

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[4] Y. Ohno *et al*. Clin. Pharmacokinet. 47: 669–680 (2008).
[5] N. Hohmann *et al*. Br. J. Clin. Pharmacol. 79: 278–285 (2015).

For additional information, please contact
Yomna M. Nassar
yomna.nassar@fu-berlin.de

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