



# Pharmacokinetics of midazolam and its metabolites in terminally ill adult patients

Linda Franken<sup>1</sup>: l.franken@erasmusmc.nl

B.C.M de Winter<sup>1</sup>, A.D. Masman<sup>2,3</sup>, F.P.M. Baar<sup>2</sup>, D. Tibboel<sup>3</sup>, T. van Gelder<sup>1</sup>, B.C.P. Koch<sup>1</sup> and R.A.A. Mathot<sup>4</sup>

## Aim

Developing a population pharmacokinetic model for midazolam, alfa-hydroxymidazolam (1OH-M) and alfa-hydroxymidazolamglucuronide (1OH-MG) in terminally ill adult patients

## Background

- Midazolam is commonly used as a sedative in terminally ill patients and is the drug of choice for palliative sedation
- In other populations it has been shown that midazolam has large interpatient variability in pharmacokinetics
- In the case of refractory symptoms it is of great clinical importance to achieve adequate sedation as soon as possible. It would therefore be preferential if an individualised dose could be determined beforehand

## Conclusion

- The pharmacokinetics of midazolam, 1OH-midazolam and 1OH-midazolam glucuronide in terminally ill patients could be accurately described with a one-compartment model for midazolam, 1OH-M and 1OH-MG
- Low albumin levels resulted in decreased midazolam clearance. A decrease in albumin from 35 g/L to 20 g/L would result in a 44% decrease in midazolam clearance (from 11.8 L/h to 6.7 L/h)
- Low eGFR levels were associated with lower 1OH-MG clearance. A decrease in eGFR from 90 ml/min to 50 ml/min would decrease the 1OH-MG clearance with 26% (from 4.9 L/h to 3.6 L/h) and a decrease of eGFR to 30 ml/min would reduce the clearance of 1OH-MG with 44% (to 2.8 L/h)

## Methods



192 Blood samples were collected randomly from 43 terminally ill patients who received morphine (orally or subcutaneously) and concentrations of midazolam, 1-OH-M and 1-OH-MG were determined using LC-MS/MS

Data were log-transformed and one- two- and three-compartment models were tested for midazolam and both metabolites using NONMEM 7.2<sup>®</sup> with the ADVAN7 subroutine and FOCE+I

Between-subject variability was assessed using an exponential and additive model. Covariates (blood chemistry patient and disease characteristics) were analysed using forward inclusion (p<0.05) backward elimination (P<0.01)

Model evaluation was based on minimum objective function values, parameter precision, error estimates, shrinkage values and goodness of fit plots. To obtain 95% confidence intervals a bootstrap was performed and the final model was evaluated with an NPDE analysis

Monte Carlo simulations were performed to illustrate the effect of the significant covariates (eGFR and plasma albumin) on midazolam and metabolite concentrations.

## Results

- The final structural model was a one-compartment model for midazolam, 1OH-M and 1OH-MG (figure 1)
- Two significant associations were found: albumin levels with midazolam clearance, and estimated GFR with 1OH-MG clearance (equation 1a,b)
- GOF plots and NPDE analysis demonstrate the adequacy and validity of the model (NPDE global adjusted p-values of 1.0, 0.41 and 0.30 for midazolam, 1OH-M and 1-OHMG) (figure 2)

$$Cl_i \text{ midazolam} = Cl_{pop} \times \frac{ALB^{1.03}}{25} \times e^{\eta_i}$$

$$Cl_i \text{ 1OH MG} = Cl_{pop} \times \frac{eGFR^{0.52}}{104} \times e^{\eta_i}$$

**Equations 1a,b** Cl<sub>i</sub>: individual clearance, Cl<sub>pop</sub>: population clearance, ALB: albumin level (g/L), eGFR: estimated glomerular filtration rate (calculated using the standard 4-item MDRD equation)

**Figure 1. Structural model**

F: bioavailability of oral midazolam, Cl<sub>1</sub>: clearance of midazolam to 1OH-M, Cl<sub>2</sub>: clearance of 1OH-M to 1OH-MG, Cl<sub>3</sub>: (renal) elimination of 1OH-MG

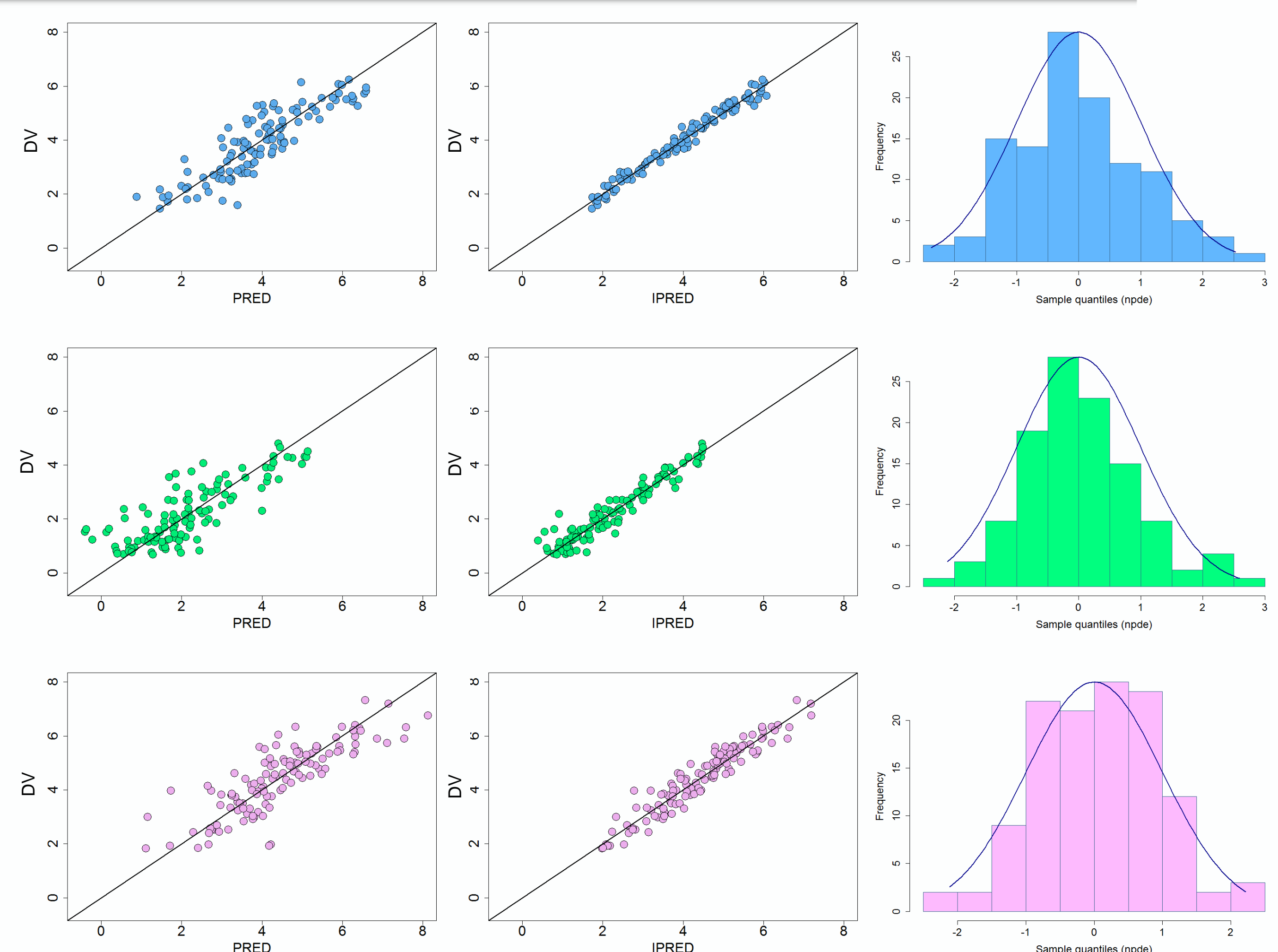
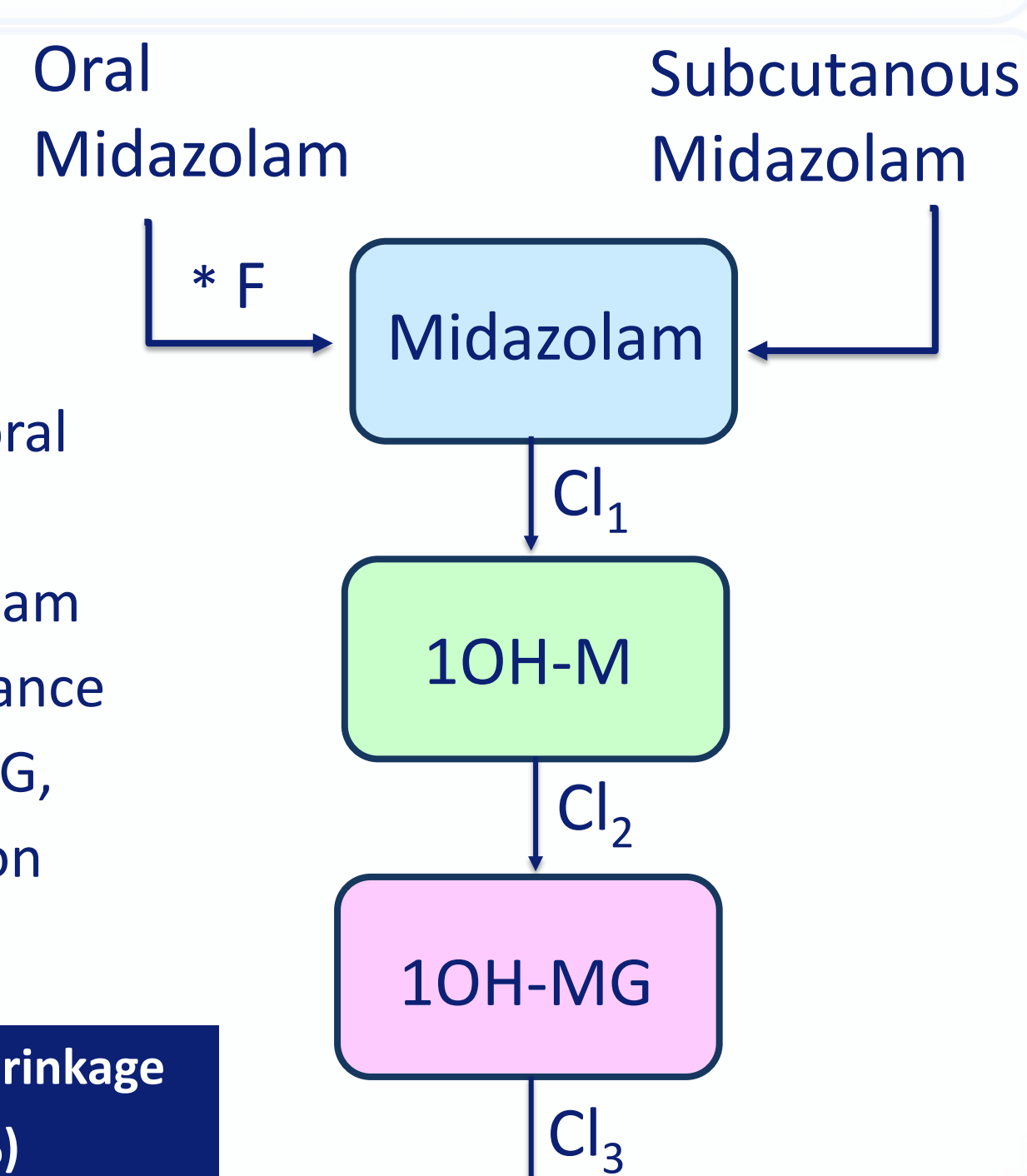


Figure 2 observations (DV) versus predictions (PRED) and individual predictions (IPRED) and NPDE results for midazolam (blue) 1-OH-M (green) and 1-OH-MG (purple)

Parameter	Base Model	Final model	95% CI		Shrinkage (%)
	OFV: -83.0	OFV: -115.9	Lower	Upper	
<b>Midazolam</b>					
F	0.21	0.27	0.221	0.866	
Cl <sub>1</sub> (L/h)	7.78	8.37	0.691	10.0	
Vd (L)	119	114	84.6	153.7	
<b>1OH-midazolam</b>					
Cl <sub>2</sub> (L/h)	42.8	44.1	35.7	57.0	
<b>1OH-midazolam glucuronide</b>					
Cl <sub>3</sub> (L/h)	3.94	5.29	4.34	6.44	
Vd (L)	1.62	1.37	0.64	1.72	
<b>Covariate effect</b>					
Albumin	-	1.03	0.4	1.58	
eGFR	-	0.523	0.296	0.753	
<b>Between subject variability (%)</b>					
F	51.6	51.5	34.7	66.8	13
Cl <sub>1</sub>	61.3	49.8	34.2	65.8	13
Vd midazolam	81.7	80.2	51.7	99.3	13
Cl <sub>2</sub>	54.8	57.3	33.6	77.0	14
Cl <sub>3</sub>	68.3	45.6	25.9	65.0	24
<b>Residual variability</b>					
Midazolam	0.246	0.247	0.202	0.285	21
1OH-M	0.397	0.399	0.234	0.551	17
1OH-MG	0.463	0.441	0.346	0.518	15

Figure 3 simulated concentration time profiles of midazolam and the total effective concentrations ([midazolam] + 0.8\*[1-OH-M] + 0.1\*[1-OH-MG]) for different albumin levels after a 10 mg midazolam loading dose followed by 5mg 6 times daily via subcutaneous bolus injection

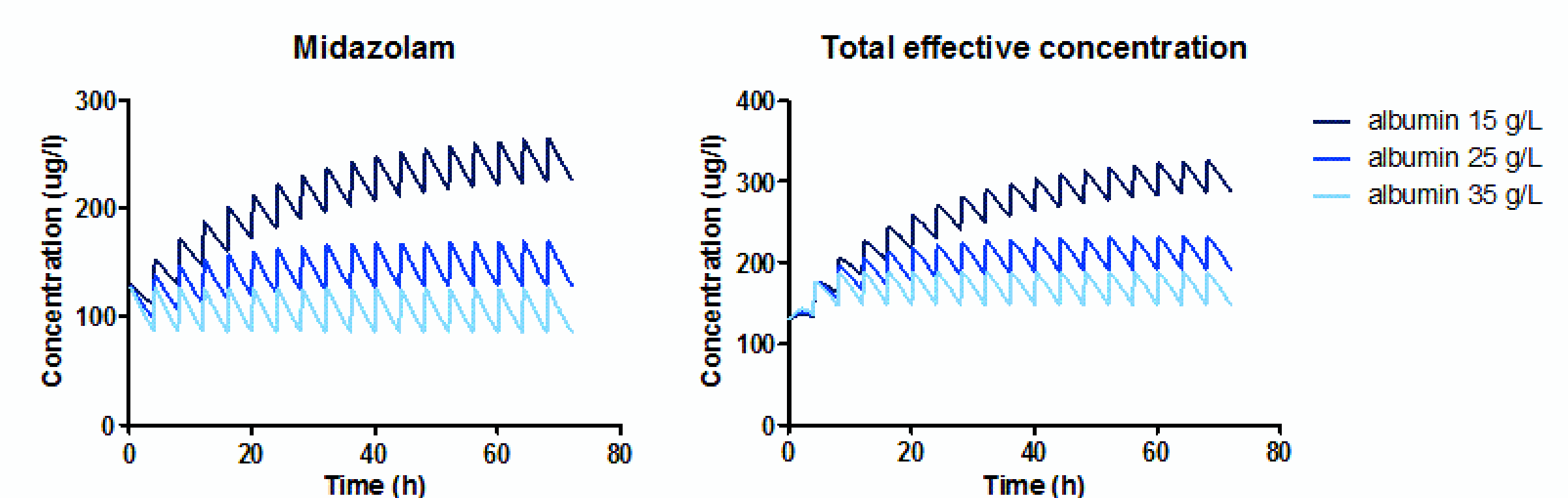


Figure 4 simulated concentration time profiles of 1OH-MG and total effective concentrations for different eGFR values after a 10 mg midazolam loading dose followed by 5mg 6 times daily via subcutaneous bolus injection

