

Morphine, morphine-3-glucuronide and morphine-6-glucuronide pharmacokinetics in terminally ill patients

Linda Franken¹: I.franken@erasmusmc.nl

A.D. Masman², B.C.M de Winter¹, B.C.P. Koch¹ F.P.M. Baar³, D. Tibboel², T. van Gelder¹ and R.A.A. Mathot⁴

Aim

Developing a population pharmacokinetic model for morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) in terminally ill adult patients

Background

- Morphine is widely used in terminally ill patients to treat pain and dyspnoea
- Dosing can be challenging due to the heterogeneous nature of the population and because pain assessment can be complicated by delirium or palliative sedation

Conclusions

- The pharmacokinetics of morphine, M3G and M6G in terminally ill patients could be accurately described with a two-compartment model for morphine and two one-compartment models for M3G and M6G
- Morphine clearance reduces when patients were closer to death, falling by more than 10 l/h (26%) in the last week before death
- Estimated GFR together with albumin levels explained 61.1% and 56.6% of the between-subject variability in M3G and M6G clearance

Methods

Blood samples were collected randomly from 47 terminally ill patients who received morphine (orally or subcutaneously)

Data were log-transformed and one- two- and three-compartment models were tested for morphine, M3G and M6G using the ADVAN5 subroutine and FOCE with interaction

Between-subject variability was assessed using an exponential and additive model

Covariates were evaluated using a forward inclusion and backward elimination method

The final model was evaluated using a bootstrap and a normalised prediction distribution error (NPDE) analysis

- Results**
- The final structural model was a two-compartment model for morphine with two one-compartment models for M3G and M6G (figure 1)
 - The covariate analysis resulted in three significant covariates: time to death (TTD) on morphine clearance, and estimated (eGFR) and serum albumin (ALB) on M3G and M6G clearance
 - Bootstrap of the final model showed good model stability
 - NPDE analysis showed good model predictability (figure 2)

Parameter	Base model	Final model	Shrinkage %	Bootstrap of final model		
				Estimate	95% CI (lower)	95% CI (upper)
Morphine						
F	0.27	0.30	-	0.31	0.18	0.53
Cl _t (L/h)	37.3	47.5	-	49.9	39.1	75.6
V1 (L)	232	190	-	190	116	369
Q (L/h)	14.6	76.1	-	65.1	9.95	146
V2 (L)	258	243	-	248	121	377
M3G						
Fm1	0.55*	0.55*	-	0.55*	0.55*	0.55*
Cl (L/h)	1.46	1.44	-	1.44	1.30	1.59
V1 (L)	7.83	8.02	-	7.75	3.62	14.9
M6G						
Fm2	0.1*	0.1*	-	0.1*	0.1*	0.1*
Cl (L/h)	1.77	1.78	-	1.79	1.56	2.05
V1 (L)	9.14	8.24	-	7.97	3.77	14.0
Covariate effect on M3G and M6G clearance						
eGFR	-	0.673	-	0.67	0.50	1.03
Albumin	-	1.1	-	1.06	0.332	1.56
Covariate effect on morphine clearance						
TTD (Δ)	-	17.6	-	19.2	9.48	46.6
TTD (rate)	-	0.13	-	0.12	0.05	0.31
Between subject variability (%)						
F	48.8	37.8	9.5	38.7	1.7	58.0
Cl morphine	52.0	53.4	13.3	50.0	31.7	71.8
Cl M3G	75.4	29.3	5.5	29.3	20.4	41.7
Cl M6G	79.1	34.3	5.5	34.1	23.8	48.4
V1 M3G	159	152	6.1	148	80.3	203
V1 M6G	160	143	6.1	142	76.8	194
Residual variability						
Morphine	0.445	0.432	10	0.425	0.335	0.510
M3G	0.268	0.246	10	0.239	0.194	0.282
M6G	0.274	0.265	10	0.254	0.218	0.294

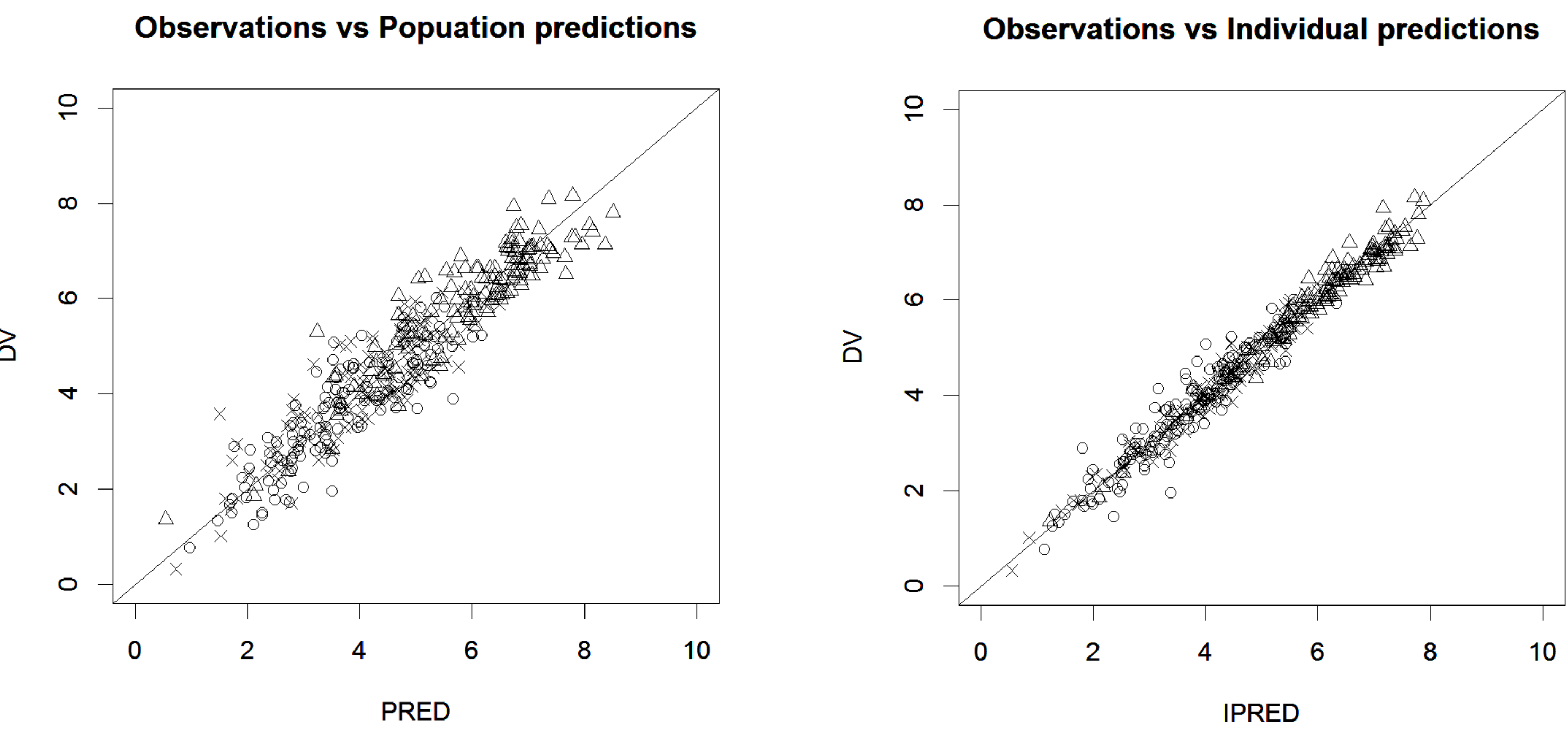
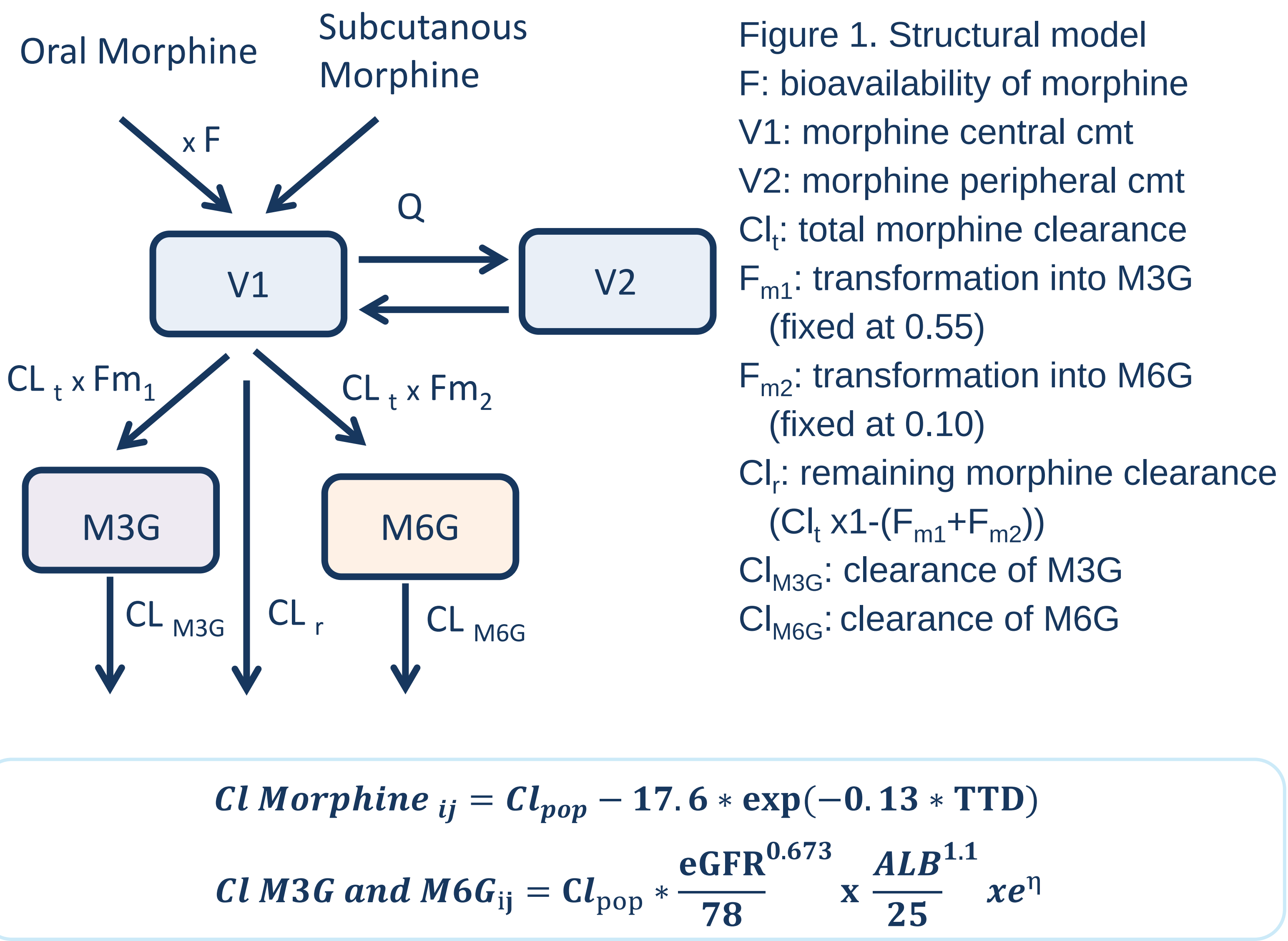


Figure 2. Observations vs individual and population predictions for morphine (○), M3G (Δ) and M6G (x)

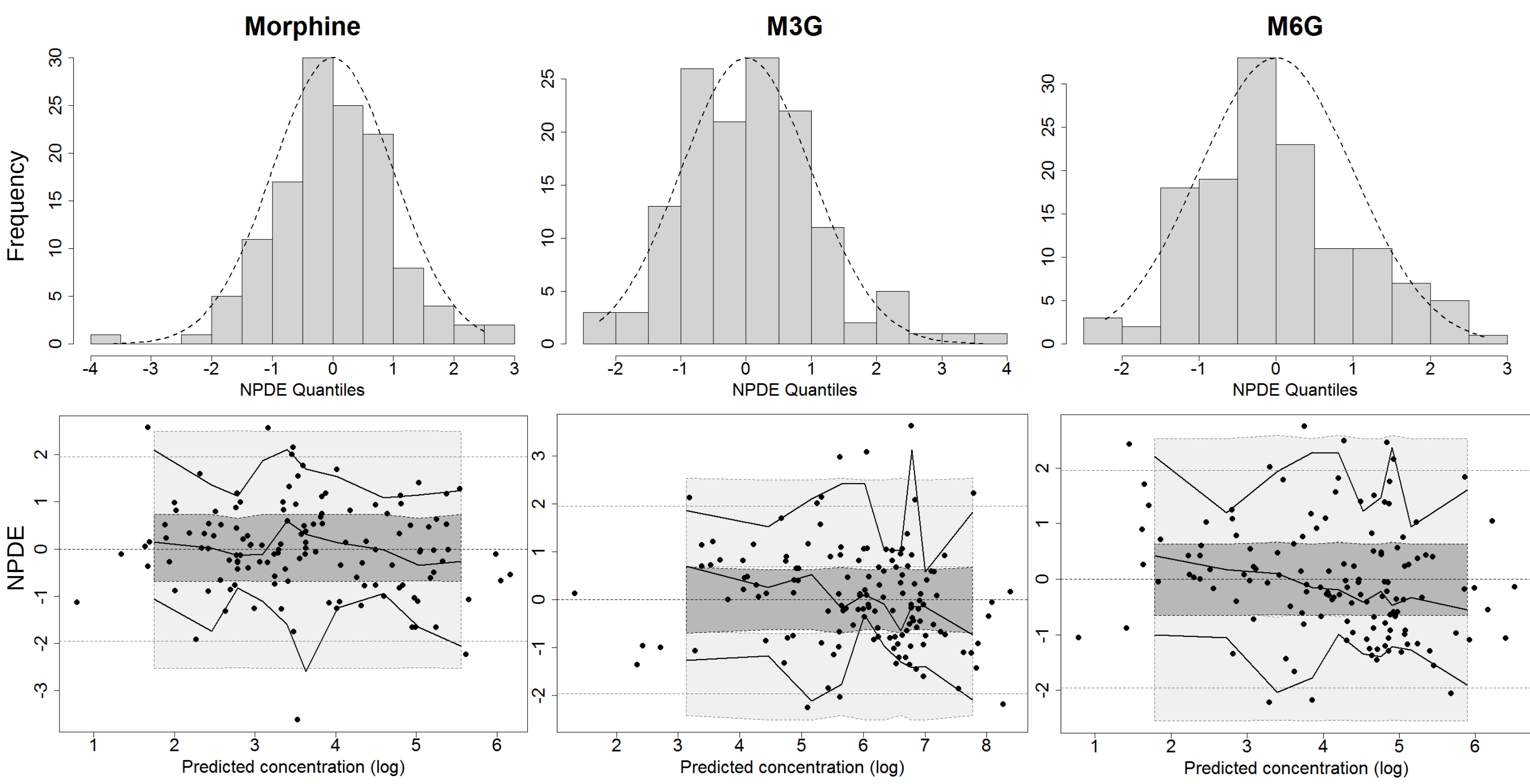


Figure 3. NPDE analysis with global adjusted p-values of 0.839 (morphine), 0.093 (M3G), and 0.191 (M6G)

(1) Department of hospital pharmacy, Erasmus Medical Centre, Rotterdam, the Netherlands, (2) Pain expertise Centre, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands, (3) Palliative Care Centre, Laurens Cadenza, Rotterdam, the Netherlands, (4) Hospital Pharmacy – Clinical Pharmacology, Academic Medical Centre, Amsterdam, the Netherlands