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# Chapter 5

## **Developmental changes in morphine clearance across the entire paediatric age range are best described by a bodyweight-dependent exponent model**

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## Abstract

*Introduction:* Morphine clearance has been successfully scaled from preterm neonates to 3-year-old children on the basis of a bodyweight-based exponential function and age younger or older than 10 days. The aim of current study is to characterize the developmental changes in morphine clearance across the entire paediatric age-range.

*Methods:* Morphine and morphine-3-glucuronide (M3G) concentration data from 358 (pre)term neonates, infants, children and adults, and morphine concentration data from 117 adolescents were analyzed using NONMEM 7.2. Based on available data, two models were developed: I. using morphine data; II. using morphine and M3G data.

*Results:* In model I, morphine clearance across the paediatric age range was very well described by a bodyweight-based exponential function in which the allometric exponent decreased in a sigmoidal manner with bodyweight (BDE model) from 1.47 to 0.88, with half the decrease in exponent reached at 4.01 kg. In model II, the exponent for the formation and elimination clearance of M3G was found to decrease from 1.56 to 0.89 and from 1.06 to 0.61, with half the decrease reached at 3.89 and 4.87 kg, respectively. Using the BDE model, there was no need to use additional measures for size or age.

*Conclusion:* The BDE model was able to scale both total morphine clearance and glucuronidation clearance through the M3G pathway across all age-ranges between (pre)term neonates and adults by allowing the allometric exponent to decrease across the paediatric age range from values higher than 1 for neonates to values lower than 1 for infants and children.

## 5.1. Introduction

The pharmacokinetics of morphine have been widely studied in the paediatric population using different approaches and modeling techniques [1]. In paediatric population pharmacokinetic models, bodyweight was reported the most significant covariate for morphine clearance [2-4]. While a variety of bodyweight-based functions has been used, i.e. exponential equations using a 0.75 fixed exponent or an estimated exponent of 1.44, in all models additional age-related variables were needed to adequately describe clearance across paediatric age-ranges [1-5]. This may be explained by the fact that single exponent functions based on body weight may not be expected to be suitable for the prediction of drug clearance in children of all ages [6, 7]. However, as bodyweight and age are correlated in a complex and highly nonlinear manner as part of a child's growth and development, the use of both bodyweight and age as covariates on a single parameter may harm the predictive performance of the resulting model [8, 9]. Additionally, many studies on morphine clearance in paediatrics are limited to small age-ranges [2-4, 10] and no study has proven adequate extrapolation potential outside the studied age-range. This highly limits the development of unambiguous continuous dosing guidelines for children.

Recently, a bodyweight dependent exponent (BDE) model was developed to scale clearance from preterm neonates to adults [11]. Using this function, clearance scales with bodyweight on the basis of an allometric function. However, because the allometric exponent is allowed to vary with bodyweight, the BDE function offers maximal flexibility to capture different maturation rates at varying stages of pediatric development [11]. Typically, this exponent  $k$  has a certain value  $k_0$  at a hypothetical bodyweight of 0 kg after which it decreases with bodyweight sigmoidally according to an Emax model [11]. More recently, also simplified decreasing functions on the basis of a power function have been proposed when a smaller weight range is concerned (i.e. lack of data of preterm neonates) [12]. In both analyses, the BDE function proved to optimally describe the changes in clearance between neonates and adults using bodyweight without of the need for a secondary age-related covariate [11, 12].

Therefore, in the current study, we analyzed morphine concentration – time profiles from 475 preterm and term neonates, infants, children, adolescents

and adults with the aim to characterize developmental changes in morphine clearance across the entire human lifespan. Given the strong evidence for a high maturation rate (exponent of 1.44) in children under the age of 3 years [4, 10] and the need to reach a plateau for the maturation rate at older age ranges with a lower value for the exponent, the recently developed BDE model was applied [11]. This analysis also allows us to study whether the changes in clearance of morphine and its metabolite can be described by the BDE function without subsequent need for additional age-related covariates.

## 5.2. Methods

### 5.2.1. Subjects

Morphine concentration – time data from a total of 475 subjects participating in eight different clinical studies [13-20] were included in the current analysis. Studies represented three age groups: neonates and young children (0-3y), older children and adolescents (6-15y), adults (18-36y) (Table 5-1). The studies were performed at different centers in different countries resulting in the administration of two different morphine salts. To compare the administered doses, the amount of administered morphine base was calculated for each individual in each study.

#### Neonates and Young children [13-18]

Morphine and morphine-3-glucuronide (M3G) metabolite concentrations in 338 pediatric patients (age 0.1-1070 days; bodyweight 0.57-16.8 kg) of six different studies [13-18] were included in our analysis. Detailed demographic and clinical information on the patients in the six studies can be found in original publications [13-18]. In Table 5-1, a summary of patient demographics is presented of these six studies.

#### Older children and Adolescents [19]

The study in older children and adolescents was a prospective, genotype blinded, clinical observational study to investigate the impact of race and genotype on morphine clearance [19]. Children of all races aged 6-15 years scheduled for elective adenotonsillectomy with American Society of Anesthesiologists (ASA) physiological status 1 or 2 were included. As African-American children

were found to have higher morphine clearance than Caucasian children [19], we excluded 29 African subjects out of the total of 146 subjects, leaving 117 patients aged between 6 – 15 years with a bodyweight between 17.9 – 79.5 kg) for our modeling analysis (Table 5-1).

**Table 5-1** Overview of the datasets used to develop the population PK model for parent morphine (Model I) and for parent morphine and M3G metabolite (Model II).

| Age group                      | Population  | N   | Weight (kg) | Age           | Samples                   | Reference |
|--------------------------------|---|-----|-------------|---------------|---------------------------|-----------|
| Neonates and young children    | Postoperative term neonates, infants and children       | 185 | 1.9–16.8    | 0.1–1070 days | Morphine: 618<br>M3G: 512 | [13]      |
|                                | Preterm and term neonates on artificial ventilation     | 63  | 0.56–3.87   | 0.1–6.7 days  | Morphine: 110<br>M3G: 132 | [14]      |
|                                | Preterm neonates on artificial ventilation              | 41  | 0.64–3.55   | 0.1–13 days   | Morphine: 88<br>M3G: 111  | [15]      |
|                                | Postoperative term neonates and infants                 | 28  | 1.7–9.3     | 0.1–294 days  | Morphine: 98<br>M3G: 122  | [16]      |
|                                | Postoperative term neonates and infants                 | 9   | 2.64–8.1    | 1–271 days    | Morphine: 16              | [17]      |
|                                | Term neonates and infants on artificial ventilation     | 12  | 2.2–8.7     | 3–354 days    | Morphine: 8<br>M3G: 12    | [18]      |
| Older children and adolescents | Older children and Adolescents after adenotonsillectomy | 117 | 17.9–79.5   | 6–15 years    | Morphine: 264             | [19]      |
| Adults                         | Healthy adults  | 20  | 56–85       | 20–36 years   | Morphine: 300<br>M3G: 300 | [20]      |

M; morphine; M3G: morphine-3-glucuronide

### Adults [20]

This prospective study compared the analgesic effects of a bolus and short infusion of morphine in healthy male and female volunteers [20]. Twenty healthy non-obese adults were given 0.1 mg/kg intravenous bolus of morphine followed by an infusion of  $0.03 \text{ mg} \times \text{kg}^{-1} \times \text{h}^{-1}$  for 1 hour after which 15 samples per individual were collected.

#### 5.2.2. Pharmacokinetic Modeling

The population pharmacokinetic analysis was performed with the non-linear mixed effects modeling software NONMEM version 7.2. (ICON Development Solutions, Ellicott City, MD, USA) using the first-order conditional estimation

method with the interaction option (FOCEI). The S-PLUS interface for NONMEM (LAP&P Consultants BV, Leiden, NL), S-Plus (version 8.1, Insightful Software, Seattle, WA, USA), PsN, Pirana and R (version 2.14.2) were used to visualize the output and evaluate the models.

### ***Structural model***

As morphine concentrations were available for all three age groups whereas M3G metabolite concentrations were only available in neonates and young children and adults (not in older children and adolescents), two different structural models were used in our pharmacokinetic analysis.

#### Parent morphine model (Model I)

A two-compartment structural model [4] was applied to the parent morphine concentration data for all three age groups depicted in Table 5-1.

#### Parent morphine and M3G metabolite model (Model II)

A two-compartment structural model for parent morphine and a one compartment structural model for M3G [4] was applied to parent morphine and M3G metabolite concentration data that were available in datasets of neonates and young children and the adult population (Table 5-1).

### ***Statistical model***

The inter-individual variability on morphine and M3G clearance and volumes of distribution was assumed to be log-normal distributed, and expressed as:

$$\theta_i = \theta_{TV} \times e^{\eta_i} \quad , \quad \eta_i \sim N(0, \omega^2) \quad (\text{eq. 1})$$

where  $\theta_i$  is the individual parameter value for i-th individual,  $\theta_{TV}$  is the population parameter value, and  $\eta_i$  is a random variable from a normal distribution with mean zero and variance  $\omega^2$ .

All concentration data were log-transformed in the analysis. An additive residual error model was applied on the log-transformed data, which corresponds to the proportional error on the linear scale, expressed as:

$$\log C_{ij} = \log C_{pred_{ij}} \times \varepsilon_{ij} \quad , \quad \varepsilon_{ij} \sim N(0, \sigma^2) \quad (\text{eq. 2})$$



where  $C_{ij}$  is the observed concentration of i-th individual at time j and  $C_{predij}$  is the corresponding predicted concentration.  $\varepsilon_{ij}$  is a random variable from a normal distribution with mean zero and variance  $\sigma^2$ .

### **Covariate model**

The BDE function, as shown in equation 3 [eq. 3], was applied to the total morphine clearance in Model I and the formation clearance of morphine-3-glucuronide and the elimination clearance of the morphine-3-glucuronide in Model II:

$$Cl_i = Cl_p \times \left( \frac{BW_i}{70} \right)^k, \quad k = k_0 - \frac{k_{max} \times BW_i^\gamma}{k_{50}^\gamma + BW_i^\gamma} \quad (\text{eq. 3})$$

in which  $Cl_i$  is clearance in the i-th individual with bodyweight  $BW_i$ ;  $Cl_p$  is the clearance in a standardized adult with a bodyweight of 70 kg;  $BW_i$  is bodyweight of an individual i;  $k$  is the exponent;  $k_0$  is the value of the exponent at a theoretical bodyweight of 0 kg;  $k_{max}$  is the maximum decrease of the exponent;  $k_{50}$  is the bodyweight at which a 50% decrease in the maximum decrease of exponent value is attained, and  $\gamma$  is the Hill coefficient determining the steepness of sigmoidal decline in the exponent.

Beside the BDE function for bodyweight that was tested on the different clearance parameters, bodyweight was tested in a linear or power function on other pharmacokinetic parameters, as shown in equation 4 [eq. 4]:

$$\theta_i = \theta_p \times \left( \frac{BW_i}{70} \right)^m \quad (\text{eq. 4})$$

In this equation,  $\theta_i$  is the parameter of i-th individual with bodyweight  $BW_i$ ;  $\theta_p$  is the parameter standardized adult with a bodyweight of 70kg;  $BW_i$  is bodyweight of an individual i. In case of a power function, m represents the exponent value, while for a linear relationship m is fixed to 1.

The covariate was included in the model if the decrease in objective function value (OFV) was greater than 7.88 points, which corresponds to  $p < 0.005$  in the Chi-square test. In addition, criteria as defined under Model Validation were considered.

### 5.2.3. Model Validation

The two models were validated internally using five criteria that were recently proposed for pediatric population model evaluation [5]. (i) It was checked whether the coefficient of variation (CV) of the parameter estimates either from the covariance step in NONMEM or from stratified bootstrap resampling results was less than 50%. (ii) The basic diagnostic plots and particularly the plots of the observed versus population predicted concentrations stratified for age, were visually assessed for bias. (iii) The  $\eta$ -shrinkage was calculated according to Karlsson and Savic was considered [21]. (iv) The individual and population predicted parameters were plotted against bodyweight to evaluate whether the individual predicted parameters were equally distributed around the population predicted parameters. (v) The simulation-based normalized prediction distribution error (NPDE) proposed by Brendel *et al.* [22], was calculated based on 2,000 simulations of the entire dataset and were evaluated visually for bias and precision.

## 5.3. Results

For the analysis, data of 475 subjects varying from preterm and term neonates to adults were available from eight different clinical studies (Table 5-1). Data of all 475 subjects were used in the model describing the time-course of the parent drug concentration (parent morphine model; Model I), whereas data of 358 individuals in which both morphine and M3G concentrations were available, were used to describe the time-course of both morphine and M3G concentration (parent morphine and M3G metabolite model; Model II). A summary of the available datasets is given in Table 5-1.

A BDE model in which the exponent decreased with bodyweight in a sigmoidal manner [eq. 3] very well described the developmental changes in total clearance of morphine (CLT) in the parent morphine model (Model I). Similarly, a BDE model well described changes in the formation clearance of M3G ( $CL_{M3G}$ ) and the elimination clearance of M3G ( $CL_{E_{M3G}}$ ) across all ages in the parent morphine and M3G metabolite model (Model II). Figure 5-1 (upper panels) shows the *post hoc* estimates of total morphine clearance, formation clearance of M3G and elimination clearance of M3G *versus* bodyweight ( $\eta$ -shrinkage values being

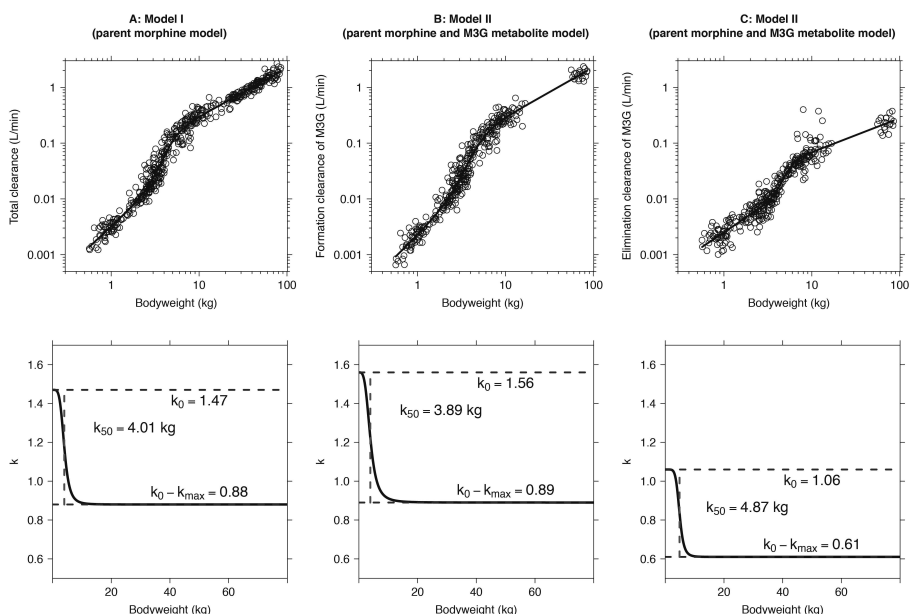
24.9%, 18.9% and 20.4%, respectively). The lower panels in Figure 5-1 show how the bodyweight-dependent exponent ( $k$ ) of total morphine clearance, formation clearance of M3G and elimination clearance of M3G was found to change with bodyweight. For the parent morphine model (Model I), the value of  $k$  for CLT dropped from 1.47 ( $k_0$ ) at the theoretical bodyweight of zero kilogram to 0.88 ( $k_0 - k_{max}$ ) and reached half this decrease at 4.01 kilogram ( $k_{50}$ ) (see Table 5-2 for estimated parameters for the exponent  $k$ ). For parent morphine and M3G metabolite model (Model II), the value of  $k$  for  $CLM_{M3G}$  dropped from 1.56 ( $k_0$ ) at the theoretical bodyweight of zero kilogram to 0.89 ( $k_0 - k_{max}$ ) and reached half this decrease at 3.89 kilogram ( $k_{50}$ ), while the  $k$ -value for  $CLE_{M3G}$  dropped from 1.06 ( $k_0$ ) to 0.61 ( $k_0 - k_{max}$ ) and reached half this decrease at 4.87 kilogram ( $k_{50}$ ) (see Table 5-3 for estimated parameters for the exponent  $k$ ).

**Table 5-2** Parameter estimates of the parent morphine model (Model I).

| Parameter                           | Estimated value   | Bootstrap <sup>§</sup> |
|-------------------------------------|---|------------------------|
| <b>Fixed Effect</b>                 |   |                        |
| CLT (L/min)                         | CLT = TVCLT $\times$ (BW/70) $k$                                  |                        |
| TVCLT (L/min $\cdot$ 70kg)          | 1.62 (5.3%)   | 1.63 (6.1%)            |
| $k$                                 | $k = k_0 - k_{max} \cdot BW^\gamma / (k_{50}^\gamma + BW^\gamma)$ |                        |
| $k_0$                               | 1.47 (3.7%)   | 1.47 (5.8%)            |
| $k_{max}$                           | 0.59 (4.7%)   | 0.59 (9.3%)            |
| $k_{50}$ (kg)                       | 4.01 (3.9%)   | 4 (4.1%)               |
| $\gamma$                            | 4.62 (9.5%)   | 6.4 (88.5%)            |
| -----                               |   |                        |
| Q (L/min)                           | Q = TVQ $\times$ (BW/70)  |                        |
| TVQ (L/min $\cdot$ 70kg)            |   |                        |
| Pop $\neq$ 2                        | 1.9 (9.6%)  | 1.95 (11.9%)           |
| Pop = 2                             | 0.5 (19%)   | 0.49 (16.1%)           |
| -----                               |   |                        |
| Vc (L)                              | Vc = TVVc $\times$ (BW/70)  |                        |
| TVVc (L/70kg)                       |   |                        |
| Pop $\neq$ 2                        | 81.2 (7.8%)   | 79.16 (6.4%)           |
| Pop = 2                             | 46 (5.1%)   | 45.44 (3.8%)           |
| -----                               |   |                        |
| Vp (L)                              | Vp = TVVp $\times$ (BW/70)  |                        |
| TVVp (L/70kg)                       | 128 (8%)  | 129.91 (7.2%)          |
| <b>Inter-individual variability</b> |   |                        |
| $\omega^2$ (CLT)                    | 0.16 (6.9%)   | 0.156 (12.9%)          |
| $\omega^2$ (Vc)                     | 0.25 (27.5%)  | 0.24 (43.6%)           |
| <b>Residual error</b>               |   |                        |
| $\sigma^2$                          | 0.19 (8.7%)   | 0.19 (7.7%)            |
| $\sigma^2$ for time>1900min         | 0.46 (113.2%)   | 0.79 (76.9%)           |

CLT: total morphine clearance; TVCLT: CLT normalized to bodyweight value of 70kg; BW: bodyweight in kilogram;  $k$ : bodyweight dependent exponent (BDE) on BW for total clearance;  $k_0$ : BDE at the theoretical bodyweight of zero;  $k_{max}$ : maximum decrease of the exponent;  $k_{50}$ : the bodyweight at which a 50% decrease in the maximum decrease of exponent is attained;  $\gamma$  is the Hill coefficient determining the steepness of sigmoidal decline in the exponent;  $Q$ : inter-compartmental clearance; TVQ:  $Q$  normalized to bodyweight value of 70kg  $V_c$ : volume of distribution of the central compartment of morphine; TVVc:  $V_c$  normalized to bodyweight value of 70kg; Pop=2: population of older children and adolescents; Pop  $\neq$  2: population of neonates and young children or adults;  $V_p$ : the volume of distribution of the peripheral compartment of morphine; TVVp:  $V_p$  normalized to bodyweight value of 70kg;  $\omega^2$  variance of the normal distribution that quantifies the inter-individual variability on the designated parameter according to equation 1;  $\sigma^2$ : variance of the normal distribution that quantifies the residual error of the morphine observations according to equation 2;  $\sigma^2$  for time>1900min: variance of the normal distribution that quantifies the residual error of extra additive error for concentrations of morphine when the time after dose is beyond 1900 minutes [4]

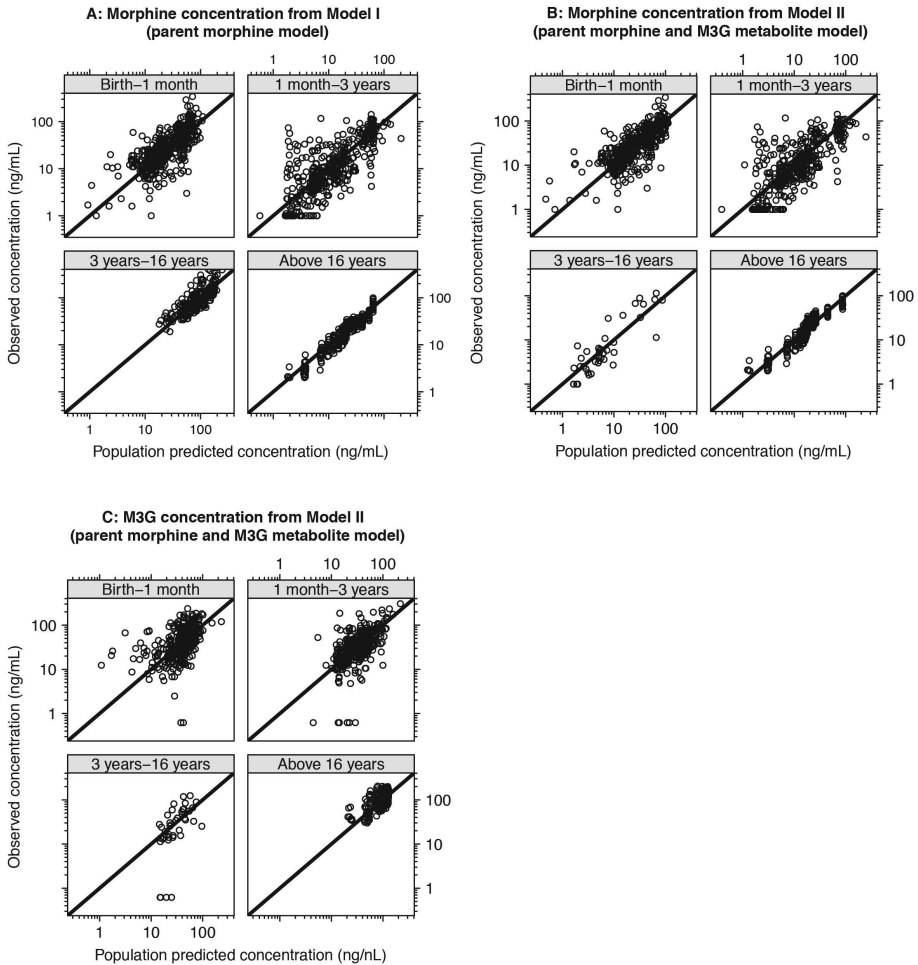
§ Bootstrap mean and CV percentage



**Figure 5-1** Post hoc clearance values of total clearance, formation clearance of M3G, and elimination clearance of M3G and values of the corresponding bodyweight dependent exponent ( $k$ ) versus bodyweight from Model I (parent morphine model) and Model II (parent morphine and M3G metabolite model).

Upper panels: open circles are post hoc values of total clearance (A), formation clearance of M3G (B), or elimination clearance of M3G (C); solid curves are corresponding model predicted values.

Lower panels:  $k$  is the bodyweight dependent allometric exponent (eq.3) of total clearance (A), formation clearance of M3G (B), or elimination clearance of M3G (C);  $k_0$  is the value of the exponent at a theoretical bodyweight of 0 kg;  $k_{max}$  is the maximum decrease of the exponent;  $k_{50}$  is the bodyweight at which a 50% decrease in the maximum decrease of exponent is attained; upper blue dash line is the reference line of  $k_0$ ; lower blue dash line is the reference line of  $k_0 - k_{max}$ ; red vertical dash line is the reference line of  $k_{50}$ .



**Figure 5-2** Age-stratified observed versus population predicted log-transformed concentrations of morphine from Model I (parent morphine model) and of parent morphine and M3G metabolite from Model II (parent morphine and M3G metabolite model)

For CLT of the parent morphine model (Model I) and  $CLM_{M3G}$  and  $CLE_{M3G}$  of the parent morphine and M3G metabolite model (Model II), no additional covariates could be identified based on visual inspection of the corresponding inter-individual variability against covariate plot and given the criteria as defined under Methods (Covariate Model and Model Validation). In the parent morphine model (Model I), bodyweight was identified as a covariate in a linear equation for volume of distribution of the central compartment of morphine ( $V_c$ ), volume of distribution of the peripheral compartments of morphine

(Vp), and inter-compartmental clearance (Q) (Table 5-2). In addition, lower bodyweight normalized population values of Q and Vc were identified for the older children and adolescents (0.071 L/kg/min and 0.66 L/kg) compared to children younger than 3 years and adults (0.027 L/kg/min and 1.16 L/kg) (Table 5-2). In the parent morphine and M3G metabolite model (Model II), bodyweight was identified as a covariate in a linear equation for clearance of morphine through other routes than M3G ( $CL_o$ ), volume of distribution of the central compartment of morphine (Vc), volume of distribution of the peripheral compartments of morphine (Vp), and inter-compartmental clearance (Q) (Table 5-3). For the volume of distribution of M3G ( $V_{M3G}$ ), a population value of 20L was estimated, which proved in accordance with literature [23] and which was later on fixed to this value in order to achieve successful minimization with a covariance step.  $V_{M3G}$  was found to vary with bodyweight, which was best described by a power function with an estimated exponent value of 0.71. In both the parent and the parent and metabolite model (Model I and Model II respectively), no other covariates were identified on any of the other parameters based on the criteria as described in section Methods (Covariate Model and Model Validation).

Figure 5-2 shows that both the parent morphine model (Model I) and the parent morphine and M3G metabolite model (Model II) described the morphine and M3G concentration data in all different age groups well. The NPDE analysis as a simulation based validation method, shows that morphine and M3G concentrations in the models were normally distributed around the median prediction and that there was no trend in the NPDE versus TIME and versus the log-transformed individual predicted concentrations (Figure 5-3). All parameter estimates and results of the bootstrap validation of the parent morphine model (Model I) and the parent morphine and M3G metabolite model (Model II) are listed in Table 5-2 and Table 5-3, respectively.

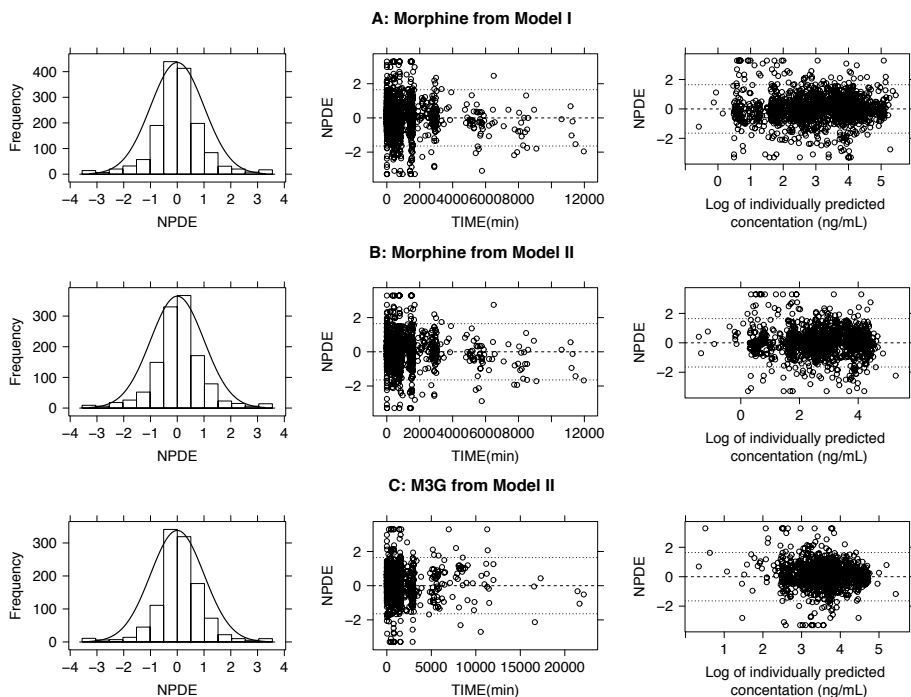
Figure 5-4 illustrates that postnatal age (PNA) younger or older than 10 days, which was reported as a covariate for morphine glucuronidation clearance in a previous study in children younger than 3 years of age [4], was not a covariate for clearance in the final model of the current study.

**Table 5-3** Parameter estimates of the parent morphine and M3G metabolite model (Model II (based on morphine and M3G concentrations)).

| Parameter                           | Estimated value   | Bootstrap <sup>s</sup> |
|-------------------------------------|---|------------------------|
| <b>Fixed Effect</b>                 |   |                        |
| $CLM_{M3G}$ (L/min)                 | $CLM_{M3G} = TVCLM_{M3G} \times (BW/70)^k$                        |                        |
| $TVCLM_{M3G}$ (L/min•70kg)          | 1.67  | 1.66 (5.2%)            |
| $k$ of $CLM_{M3G}$                  | $k = k_0 - k_{max} \cdot BW^\gamma / (k_{50}^\gamma + BW^\gamma)$ |                        |
| $k_0$ of $CLM_{M3G}$                | 1.56  | 1.56 (4.1%)            |
| $k_{max}$ of $CLM_{M3G}$            | 0.67  | 0.67 (6.8%)            |
| $k_{50}$ of $CLM_{M3G}$ (kg)        | 3.89  | 3.91 (3.8%)            |
| $\gamma$ of $CLM_{M3G}$             | 3.61  | 3.94 (21%)             |
| <hr/>                               |   |                        |
| $CLE_{M3G}$ (L/min)                 | $CLE_{M3G} = TVCLE_{M3G} \times (BW/70)^k$                        |                        |
| $TVCLE_{M3G}$ (L/min•70kg)          | 0.23  | 0.22 (7.1%)            |
| $k$ of $CLE_{M3G}$                  | $k = k_0 - k_{max} \cdot BW^\gamma / (k_{50}^\gamma + BW^\gamma)$ |                        |
| $k_0$ of $CLE_{M3G}$                | 1.06  | 1.07 (9%)              |
| $k_{max}$ of $CLE_{M3G}$            | 0.45  | 0.45 (11.8%)           |
| $k_{50}$ of $CLE_{M3G}$ (kg)        | 4.87  | 4.68 (6.4%)            |
| $\gamma$ of $CLE_{M3G}$             | 6.84  | 9.49 (78.3%)           |
| <hr/>                               |   |                        |
| $CL_0$ (L/min)                      | $CL_0 = TVCL_0 \times (BW/70)$                                    |                        |
| $TVCL_0$ (L/min•70kg)               | 0.06  | 0.06 (40.3%)           |
| $Q$ (L/min)                         | $Q = TVQ \times (BW/70)$  |                        |
| $TVQ$ (L/min•70kg)                  | 4.2   | 4.12 (4.9%)            |
| $V_c$ (L)                           | $V_c = TVV_c \times (BW/70)$                                      |                        |
| $TVV_c$ (L/70kg)                    | 29.3  | 27.67 (13.5%)          |
| $V_p$ (L)                           | $V_p = TVV_p \times (BW/70)$                                      |                        |
| $TVV_p$ (L/70kg)                    | 155   | 155.29 (7.1%)          |
| $V_{M3G}$ (L)                       | $V_{M3G} = TVV_{M3G} \times (BW/70)^p$                            |                        |
| $V_{M3G}$ (L/70kg)                  | 20 FIX  | 20 FIX                 |
| $p$                                 | 0.71  | 0.71 (6.2%)            |
| <hr/>                               |   |                        |
| <b>Inter-individual variability</b> |   |                        |
| $\omega^2 CLM_{M3G}$                | 0.20  | 0.20 (15%)             |
| $\omega^2 CLE_{M3G}$                | 0.19  | 0.18 (20.5%)           |
| $\omega^2 CL_0$                     | 0.07  | 0.26 (173.3%)          |
| $\omega^2 V_c$                      | 0.51  | 0.47 (26.4%)           |
| $\omega^2 V_p$                      | 0.31  | 0.31 (43.6%)           |
| $\omega^2 V_{M3G}$                  | 0.37  | 0.39 (37.7%)           |
| <hr/>                               |   |                        |
| <b>Residual error</b>               |   |                        |
| $\sigma^2$ additive morphine        | 0.20  | 0.19 (8.1%)            |
| $\sigma^2$ additive M3G             | 0.14  | 0.13 (10.1%)           |
| $\sigma^2$ for time>1900min         | 1.85  | 1.92 (32.5%)           |

CLM<sub>M3G</sub>: formation clearance of morphine-3-glucuronide; TVCLM<sub>M3G</sub>: CLM<sub>M3G</sub> normalized to bodyweight value of 70kg; BW: bodyweight in kilogram; CLE<sub>M3G</sub>: elimination clearance of morphine-3-glucuronide; TVCLE<sub>M3G</sub>: CLE<sub>M3G</sub> normalized to bodyweight value of 70kg; k: bodyweight dependent exponent (BDE) of BW CLM<sub>M3G</sub> or CLE<sub>M3G</sub>; k<sub>0</sub>: BDE at the theoretical bodyweight of zero; k<sub>max</sub>: maximum decrease of the exponent; k<sub>50</sub>: the bodyweight at which a 50% decrease in the maximum decrease of exponent is attained;  $\gamma$  is the Hill coefficient determining the steepness of sigmoidal decline in the exponent; CL<sub>0</sub>: clearance of morphine via other elimination routes; TVCL<sub>0</sub>: CL<sub>0</sub> normalized to bodyweight value of 70kg; Q: inter-compartmental clearance; TVQ: Q normalized to bodyweight value of 70kg; Vc: the volume of distribution of the central compartment of morphine; TVVc: Vc normalized to bodyweight value of 70kg; Vp: the volume of distribution of the peripheral compartment of morphine; TVVp: Vp normalized to bodyweight value of 70kg; V<sub>M3G</sub>: volume of distribution of the morphine-3-glucuronide; TVV<sub>M3G</sub>: V<sub>M3G</sub> normalized to bodyweight value of 70kg; p: exponent value of the power function of BW for V<sub>M3G</sub>;  $\omega^2$  variance of the normal distribution that quantifies the inter-individual variability on the designated parameter according to equation 1;  $\sigma^2$ : variance of the normal distribution that quantifies the residual error of the morphine or morphine-3-glucuronide observation according to equation 2;  $\sigma^2$  for time>1900min: variance of the normal distribution that quantifies the residual error of extra additive error for concentrations of morphine or morphine-3-glucuronide when the time after dose is beyond 1900 minutes [4]

§ Bootstrap mean and CV percentage



**Figure 5-3** NPDE results of morphine concentrations from Model I (parent morphine model) and parent morphine and M3G metabolite concentrations from Model II (parent morphine and M3G metabolite model).

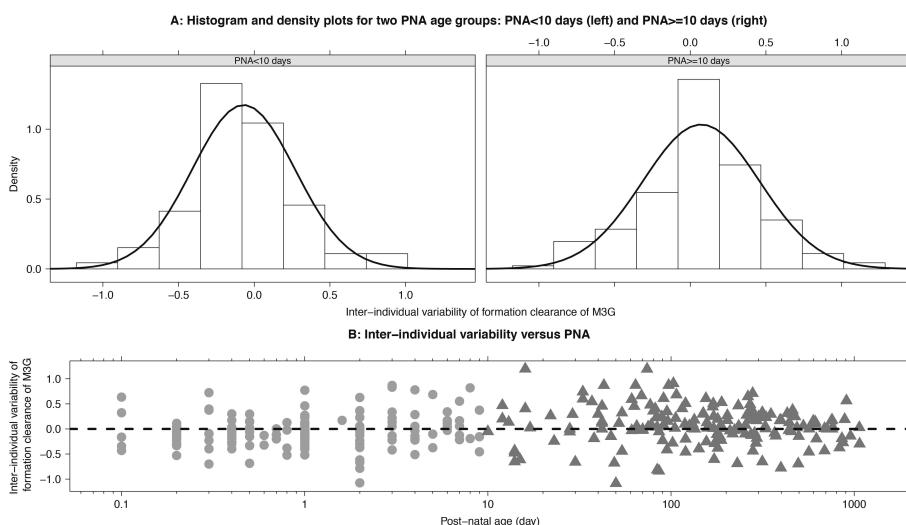


## 5.4. Discussion

Morphine is metabolized mainly through glucuronidation mediated by the enzyme UDP-glucuronosyltransferase 2B7 (UGT2B7), which was reported to be expressed at very low levels in early life [24-26]. In the past, several models have been developed to describe the changes in glucuronidation clearance of morphine and to predict its clearance in children for the purpose of dosing guidance [2-4]. Among those models, a model was developed for pediatric patients aged less than 3 years including preterm and term neonates [4], in which an allometric exponent value of 1.44 for morphine clearance was identified. Additional extensive investigations confirmed this finding using external data [10] and data from another UGT2B7 substrate [27]. Upon these studies, the allometric exponent of 1.44 for UGT2B7-mediated glucuronidation in children under the age of 3 years was proposed to be a system-specific parameter reflecting the maturation of the UGT2B7 enzyme in humans [27, 28]. The current study confirms not only the validity of the exponent value as high as 1.44 in neonates and young infants given the estimated exponent at a hypothetical bodyweight of 0 kg of 1.56 in this study, but also provides a basis for extrapolation to older age-ranges by the quantification of the maturation of glucuronidation across the entire pediatric age-range with the estimation of a lower exponent for higher bodyweight ranges.

In this study, we successfully scaled morphine clearance from preterm and term neonates to infants, children, adolescents and adults using an allometric function, in which the exponent ( $k$ ) was allowed to vary with bodyweight in a bodyweight-dependent exponent (BDE) function (eq.3). In both Model I and Model II of our study, the BDE function was able to capture the changes in the clearance parameters (total morphine clearance, formation of M3G, and elimination of M3G), such despite the fact that they were highly nonlinear in nature (**Figure 5-1, upper panels**). According to Karlsson and Savic [21], diagnostics based on the empirical Bayes estimates (EBE) should be assessed in combination with corresponding  $\eta$ -shrinkages as they may distort covariate relationships. Based on a simulation study, it was reported that EBE-based diagnostics generally lose their power with false indications starting to appear at a level of 20-30% [29]. In our study, the  $\eta$ -shrinkages of total clearance, formation clearance of M3G and elimination clearance of M3G were all below

25%, which is on the border of what is acceptable. In addition, both the age-stratified goodness-of-fit diagnostic plots (Figure 5-2) and simulation based NPDE diagnostics (Figure 5-3) demonstrate good population and individual prediction performance of the final bodyweight-dependent exponent (BDE) models for concentrations of morphine and its M3G metabolite. Based on these results, it is concluded that the bodyweight-dependent exponent (BDE) model allows for the description of maturational changes in morphine glucuronidation clearance using a single continuous function, which has not been possible in previous attempts based on the use of allometric equations with single exponents [2-5].



**Figure 5-4** Inter-individual variability of formation clearance of M3G from Model II (parent morphine and M3G metabolite model) stratified by postnatal age (PNA) of 10 days

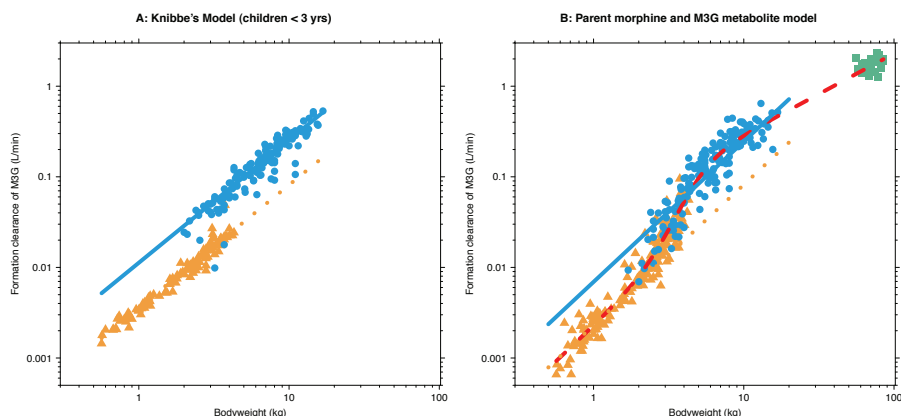
filled circle: individuals PNA < 10 days; triangle: individuals PNA >= 10 days

The parameter values of the bodyweight-dependent exponent (BDE) function, i.e.  $k_0$ ,  $k_{\max}$ ,  $k_{50}$  and  $\gamma$ , were found to be similar for total morphine clearance (parent morphine model; Model I) and formation clearance of M3G (parent morphine and M3G metabolite model; Model II). This result can in our opinion be explained by the fact that morphine-3-glucuronide is the major metabolite of morphine and glucuronidation of morphine is the rate-limiting step in the clearance of morphine. On the contrary, these sigmoidal equations describing the changes in the exponent  $k$  differed between the formation and elimination

of M3G (Figure 5-1, lower panel A and B *versus* C). In our view, these results can be explained by differences in maturation of the glucuronidation of morphine *versus* the renal elimination of M3G. Even though we do not intend to enforce any physiological meaning on the parameters in the BDE function, as the aim of this analysis was primarily to most optimally describe the observations from preterm neonates to adults, this limitation does in our opinion not preclude studies in which the parameters of the BDE function reported for morphine glucuronidation in this study are explored for the prediction of maturational changes in clearance of morphine or other drugs that are glucuronidated. In a similar manner, the parameters of the BDE function for the renal excretion of the M3G metabolite can be explored for its predictive value for the maturation in excretion of other renally excreted compounds as this approach may largely accelerate paediatric data analysis [27, 28].

Previously, for children younger than 3 years of age, postnatal age (PNA) of less than 10 days was identified as a separate covariate for formation clearance of M3G, M6G and their corresponding elimination clearances in addition to the allometric scaling function with an exponent of 1.44 [4]. While it has been suggested before that single allometric exponent functions would not be suitable for the prediction of drug clearance in children of different age-groups [6], different publications have confirmed this conclusion by reporting that an additional covariate function on the basis of an age-related covariate was needed when using single exponent functions [2-4]. In our study, we found an exponent that changed with bodyweight from an initial value at a hypothetical bodyweight of 0 kg of 1.47 and 1.56 for total clearance and formation clearance of M3G, respectively. While the initial value is in good agreement with the previously obtained value of 1.44, in the current analysis, no additional age or weight related covariates could be identified after inclusion of the (BDE) covariate model. From these results, it seems that the changes that were accounted for by the inclusion of the additional covariate relationship based on PNA [4] are now captured by the BDE function, in which the exponent was allowed to change with bodyweight being of specific relevance in the youngest age ranges (Figure 5-4). In this respect, Figure 5-5 illustrates these findings with a graphical comparison of *post hoc* values for glucuronidation clearance of morphine to M3G *versus* bodyweight between the previous model in children younger than 3 years [4] and Model II. In the figure, two parallel lines are placed

with different intercepts for subjects with  $PNA < 10$  days and  $PNA \geq 10$  days at the lower end of the bodyweight range from our study (Figure 5-5 B), which were found to be quite similar to the patterns described by the previous model (Figure 5-5 A). The two simulated lines in Figure 5-5 B have slope values of 1.56, which corresponds with  $k_0$  in the BDE function for  $CL_{m3g}$ , and can roughly describe the changes in M3G formation clearance in children in two subgroups ( $PNA > 10$  days and  $PNA < 10$  days) up to a bodyweight of 10 kg. From this figure, it seems that applying an allometric function in which the exponent is allowed to vary with bodyweight itself results in an optimal description of the varying rates of maturation of glucuronidation clearance of morphine across all age ranges without the need for additional age-based covariates.



**Figure 5-5** Comparison of formation clearance of M3G versus bodyweight in log-log scale between current Model II (parent morphine and M3G metabolite model) that included all age ranges except for older children and adolescents (B) and a previously published population model for morphine in children younger than 3 years by Knibbe *et al.* [4] (A). **PNA=postnatal age.**

(A): Orange filled triangle: children with  $PNA < 10$  days; Blue filled circle: children with  $PNA \geq 10$  days; Orange dotted line: Knibbe's model [4] predicted clearance curve for  $PNA < 10$  days ( $CL \text{ (mL/min)} = 3.48 * BW^{1.44}$ ); Blue solid line: Knibbe's model [4] predicted clearance curve for  $PNA \geq 10$  days ( $CL \text{ (mL/min)} = 8.62 * BW^{1.44}$ ) (B): Orange filled triangle = children with  $PNA < 10$  days; Blue filled circle: children with  $PNA \geq 10$  days; Green filled square: adults; Orange dotted line: simulated population clearance curve for  $PNA < 10$  days ( $CL \text{ (L/min)} = 0.0023 * BW^{1.56}$ ); Blue solid line: simulated population clearance curve for  $PNA \geq 10$  days ( $CL \text{ (L/min)} = 0.0069 * BW^{1.56}$ ); Red dash line: the BDE model predicted clearance curve of Model II in which,  $CL_i = 1.67 * \left(\frac{BW_i}{70}\right)^k$ ,  $k = 1.56 - \frac{0.67 * BW_i^{3.61}}{3.89^{3.61} + BW_i^{3.61}}$

The development of the bodyweight dependent exponent model was triggered by the reports that single exponent functions are not suitable for the prediction of

drug clearance in children of all age ranges [6] and the idea of using a continuous function describing clearance across a large age-span without the need for an additional age based function [11]. Beside application to propofol [11], this BDE model has been successfully applied to busulfan [12] and midazolam [30], albeit in a simplified power equation (). However, in the current analysis on morphine glucuronidation clearance between preterm neonates and adults, the full sigmoidal BDE model was more appropriate. This was the result of the S-shape in the double log plot of clearance versus bodyweight (Figure 5-1), which can be captured by the Emax function with Hill factor of the full BDE model [11], but not by the simplified function that consists of a power function [12, 30]. From these results it seems that the choice for a full BDE model which was applied in this study and for propofol, or for a simplified BDE model as applied for busulfan and midazolam is related to both the age range studied and the properties of the drug. Further study of the BDE model on datasets of other drugs across the entire paediatric age range will demonstrate in which cases the simplified or full BDE model is applicable. In any case, the choice for the final model should depend on the observed data in this data-driven approach whereby the model with the lowest number of parameters should be chosen (the principle of parsimony).

## 5.5. Conclusion

In this study, developmental changes in total morphine clearance were described in 475 preterm and term neonates, infants, children, adolescents and adults using an allometric function, in which the exponent decreased with bodyweight in a sigmoidal manner from 1.47 for preterm neonates to 0.88 in adults, with no need to use other body size or age-based measures. Similarly, we identified values for the exponent for formation clearance of M3G to vary from 1.56 to 0.89 while these values varied from 1.06 to 0.61 for elimination of M3G. From these results, it can be concluded that an allometric function with a bodyweight-dependent exponent (BDE) may be of great value when scaling clearance of drugs across the entire pediatric age-range.

## 5.6. Acknowledgements

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## Appendix: NONMEM codes

### Model I: Parent morphine model

```

$SUBROUTINES ADVAN5
;-----
$MODEL NCOMPARTMENTS=2
COMP (CENTRAL, DEFDOSE) ;MORPHINE CENTRAL
COMP =(2) ;PERIPHERAL COM OF MORHINE
;-----
$PK
KDEC = THETA(1) ; DECREASE OF EXPONENT FOR CLM1
KMAX = THETA(2)+KDEC ; MAXIMUM EXPONENT OF CLM1
KHAL = THETA(3) ; K50 OF CLM1
GAMMA = THETA(4) ; GAMMA OF CLM1
KBDE = KMAX-KDEC*(BW**GAMMA)/(KHAL**GAMMA+BW**GAMMA)
;-----
TVCL = THETA(5)*(BW/70)**KBDE ; POPULATION CLEARANCE OF MORPHINE
CL = TVCL*EXP(ETA(1)) ; INDIVIDUAL ...
TVQ2 = THETA(6)*(BW/70) ; POPULATION INTERCOMPARTMENTAL
CLEARANCE OF MORHPINE
IF (POP.EQ.2) TVQ2= THETA(10)
Q2 = TVQ2*EXP(ETA(2)) ; INDIVIDUAL ...
;-----
TVV1 = THETA(7)*(BW/70) ; POPULATION VOLUME OF MORPHINE CENTRAL
COMPARTMENT
IF (POP.EQ.2) TVV1=THETA(11)*(BW/70);
V1 = TVV1 * EXP(ETA(3)) ; INDIVIDUAL ...
TVV2 = THETA(8)*(BW/70) ; POPULATION VOLUME OF MORPHINE PEREPHERAL
COMPARTMENT
V2 = TVV2*EXP(ETA(4)) ; INDIVIDUAL ...
;-----
S1=V1
;-----
K10 = CL/V1
K12 = Q2/V1

```

$K21 = Q2/V2$

$F1 = 1$

IF (POP.EQ.3)  $F1 = 0.88$

;------

\$ERROR

IPRED=LOG(0.000001)

IF (F.GT.0) IPRED = LOG(F)

$W = THETA(9)$

$IRES = IPRED - DV$

$IWRES = IRES/W$

TEH=0

IF (TIME.GT.1900.AND.NKOD.EQ.1) TEH = 1

IF (TIME.GT.1900.AND.NKOD.EQ.2) TEH = 1

$Y = IPRED + ERR(1)*W + TEH*ERR(2)$  ;MORPHINE

;------

\$THETA (0.1, 0.5, ) ;KDEC

(0.2, 0.9, ) ;KMAX-KDEC OR MINIMUM EXP (TH2)

(0.05, 4, 20) ;KHAL

(1, 5, ) ;GAMMA

(0.001, 1.5, ) ;CL

(0.01, 1.7, ) ;Q2

(0.1, 70, ) ;V1

(0.1, 100, ) ;V2

(0, 0.33, ) ;ERR1

(0.1, 1.1, ) ;Q2 ADO

(0.1, 50, ) ;V1 ADO

;------

\$OMEGA 0.15 ;CL

0 FIX ;Q2

0.1 ;V1

0 FIX ;V2

;------

\$SIGMA

1 FIX ;ERR1

2 ;ERR2 >1900min

;------

```

$EST NOABORT SIGDIG=3 PRINT=15 MAXEVAL=9999 METHOD=1 INTERACTION
POSTHOC
$COV COMP PRINT=E

```

### *Model II: Parent morphine and M3G metabolite model*

```

$SUBROUTINES ADVAN5
;-----
$MODEL
NCOMPARTMENTS=3
COMP (CENTRAL, DEFDOSE);MORPHINE CENTRAL
COMP=(2);M3G
COMP=(3);PERIPHERAL COM OF MORHINE
;-----
$PK
KDEC1 = THETA(1)           ; DECREASE OF EXPONENT FOR CLM1
KMAX1 = THETA(2)+KDEC1      ; MAXIMUM EXPONENT OF CLM1
KHAL1 = THETA(3)           ; K50 OF CLM1
GAMMA1 = THETA(4)          ; GAMMA OF CLM1
KBDE1 = KMAX1-KDEC1*(BW**GAMMA1)/(KHAL1**GAMMA1+BW**GAMMA1)

KDEC2 = THETA(5)           ; DECREASE OF EXPONENT FOR CLE2
KMAX2 = THETA(6)+KDEC2      ; MAXIMUM EXPONENT OF CLE2
KHAL2 = THETA(7)           ; K50 OF CLE2
GAMMA2 = THETA(8)          ; GAMMA OF CLE2
KBDE2 = KMAX2-KDEC2*(BW**GAMMA2)/(KHAL2**GAMMA2+BW**GAMMA2)

;-----
TVCLM1 = THETA(9)*(BW/70)**KBDE1      ; POPULATION METABOLISM OF
MORPHINE TO M3G
CLM1 = TVCLM1*EXP(ETA(1))      ; INDIVIDUAL ...
TVCLE1 = THETA(10)*(BW/70)      ; POPULATION EXCRETION OF MORPHINE +
METABOLISM TO M6G
CLE1 = TVCLE1*EXP(ETA(2))      ; INDIVIDUAL ...
TVCLE2 = THETA(11)*(BW/70)**KBDE2    ; POPULATION EXCRETION OF M3G

```

```

CLE2 = TVCLE2*EXP(ETA(3))      ; INDIVIDUAL ...
;-----
TVV1 = THETA(12)*(BW/70)      ; POPULATION VOLUME OF MORPHINE CENTRAL
COMPARTMENT
V1 = TVV1 * EXP(ETA(4))      ; INDIVIDUAL ...
TVV2 = THETA(13)*(BW/70)**THETA(18) ; POPULATION VOLUME OF M3G
V2 = TVV2 * EXP(ETA(5))      ; INDIVIDUAL ...
TVQ2 = THETA(14)*(BW/70)      ; POPULATION INTERCOMPARTMENTAL
CLEARANCE OF MORHPINE
Q2 = TVQ2*EXP(ETA(6))      ; INDIVIDUAL ...
TVV3 = THETA(15)*(BW/70)      ; POPULATION VOLUME OF MORPHINE
PEREPHERAL COMPARTMENT
V3 = TVV3*EXP(ETA(7))      ; INDIVIDUAL ...

F1 = 1
IF (POP.EQ.3) F1 = 0.88
;-----
S1=V1
S2=V2
;-----
K10 = CLE1/V1
K12 = CLM1/V1
K13 = Q2/V1
K20 = CLE2/V2
K31 = Q2/V3

;-----
$ERROR
COM1=0
IF (CMT.EQ.1) COM1=1
COM2=0
IF (CMT.EQ.2) COM2=1
;
IPRED=LOG(0.000001)
IF (F.GT.0) IPRED = LOG(F)
W1 = THETA(16)      ;ERR Morphine

```

W2 = THETA(17) ;ERR M3G

IRES = IPRED-DV

IWRES = IRES/(COM1\*W1+COM2\*W2)

TEH=0

IF (TIME.GT.1900.AND.NKOD.EQ.1) TEH = 1

IF (TIME.GT.1900.AND.NKOD.EQ.2) TEH = 1

Y1 = IPRED + ERR(1)\*W1 + TEH\*ERR(3) ; MORPHINE

Y2 = IPRED + ERR(2)\*W2 + TEH\*ERR(3) ; M3G

Y=COM1\*Y1+COM2\*Y2

;------

\$THETA

(0.1, 0.74, ) ;KDEC1

(0.4, 0.7, ) ;KMAX1-KDEC1 OR MINMUM EXP1 (TH2)

(0.05, 4, 20) ;KHAL1

(1, 3, ) ;GAMMA1

;------

(0.1, 0.47, ) ;KDEC2

(0.4, 0.6, ) ;KMAX2-KDEC2 OR MINMUM EXP2 (TH15)

(0.05, 5, 20) ;KHAL2

(1, 6, ) ;GAMMA2

;------

(0.001, 1.4, ) ;CLM1

(0.001, 0.1, ) ;CLE1

(0.001, 0.23, ) ;CLE2

(0.01, 30, ) ;V1

20 FIX ;V2

(0.001, 4, ) ;Q2

(0.01, 180, ) ;V4

(0, 0.435, ) ;ERR MORP

(0, 0.362, ) ;ERR M3G

(0.1, 0.7, ) ;EXP V2

;------

```
$OMEGA
0.2 ;CLM1
0.1 ;CLE1
0.19 ;CLE2
0.2 ;V1
0.2 ;V2
0 FIX ;Q2
0.3 ;V3
;-----
$SIGMA
1 FIX
1 FIX
2 ;ERR3
;-----
$EST NOABORT SIGDIG=3 PRINT=15 MAXEVAL=9999 METHOD=1 INTERACTION
POSTHOC
$COV COMP PRINT=E
```

