Table S2: Modeling Details

Holford model:

The Holford model was chosen as the default model in the EHR embedded NeoRelief decision support application. The Holford model corresponds with the SIZEMAT2 model in the original publication. The structural model is a two-compartment model with theoretical allometric exponents for scaling of elimination and intercompartmental clearances (¾) and central and peripheral volumes (1) as described by Holford (2012).[1]

$$CL_i = CLst_d \times \left(\frac{BW}{70}\right)^{0.75} \times \frac{PMA^{Hill}}{TM_{50}{}^{Hill} + PMA^{Hill}} \times FDEVCL$$

$$V1_i = V1_{std} \times \left(\frac{BW}{70}\right) \times \left(1 - \beta Vol \times exp(-PNA \times \ln(2) / TVOL)\right) \times FDEVV$$

$$Q_i = Qs_{td} \times \left(\frac{BW}{70}\right)^{0.75}$$

$$V2_i = V2_{std} \times \left(\frac{BW}{70}\right) \times \left(1 - \beta Vol \times exp(-PNA \times \ln(2) / TVOL)\right) \times FDEVV$$

The elimination clearance (CL) is modulated by 3 components: size, maturation and ventilation. The size factor is determined by allometric scaling of body weight using a theoretical fixed exponent of 0.75. The maturation factor is established using a sigmoidal equation driven by the post menstrual age (P_{ma}). The rate of maturation is determined by the time of half-maximal maturation TM50. And finally, a correction factor (FVENT) is applied in case of ventilated neonates in order to correct for a 50% lower clearance due to mechanical ventilation. The distribution clearance (Q) is only modulated by allometric scaling of body weight using an exponent of 0.75.

The volumes of distribution (V1 and V2) are also modulated by 3 components: size, maturation and term state. The size factor is determined by allometric scaling of body weight using a theoretical fixed exponent of 1.0. The maturation factor is established using an exponential equation driven by the post-natal age (Pna). The rate of maturation is determined by the maturation half-life TVOL. And finally, a correction factor (FDEVV) is applied in case of pre-terms.

PK model parameters in the NeoRelief model are listed below (Units for CL and Q in L/h per 70kg; and volumes in L/70 kg).

Holford		
2012		
Parm(4)	**Value**	**±SD**
CLstd	86.4	41.2
V1std	46.8	26.6
V2std	203	127
Qstd	68.6	7.61
TM50	58.1	
HILL	3.58	
BVOL	0.252	
TVOL	20.3	
FVENT	0.497	
FDEVV	0.696	
CLexp	0.75	
Vexp	1	
Assay	**Value**	
Sd0	1.7	
Sd1	0.07	

Holford-Meta Extension

The morphine metabolism model of Bouwmeester (2004)[2] is plugged-in to the Holford model by applying a fixed fraction metabolized (f_m) for M3G (f_m=0.90) and M6G (f_m=0.05) to the morphine clearances reported by Holford. So, the formation clearances used by Bouwmeester were not used.

$$CLM3G=[CLM3G_{std}\times(Wt/70)^{0.75}]\times\{1-\beta rf\times EXP[-PNA\text{ in days}\times Ln(2)/Trf]\}$$
$$CLM6G=[CLM6G_{std}\times(Wt/70)^{0.75}]\times\{1-\beta rf\times EXP[-PNA\text{ in days}\times Ln(2)/Trf]\}$$

$$V=[V_{std}\times(Wt/70)]\times\{1+\beta vol\times EXP[-PNA\text{ in days}\times Ln(2)/Tvol]\}$$

The elimination clearance of morphine metabolites (M3G and M6G) is modulated by size and maturation components. The size factor is determined by allometric scaling using a theoretical fixed exponent of 0.75. The maturation factor is established using an exponential equation driven by the post-natal age (Pna). The rate of maturation is determined by the maturation half-life T_{rf}.

The volume of distribution of morphine metabolites is also modulated by size and maturation components. The size factor is determined by allometric scaling of body weight using a theoretical fixed exponent of 1.0. The maturation factor is established using an exponential equation driven by the post-natal age (PNA). The rate of maturation is determined by the maturation half-life T_{vol}.

Anand

The Anand model corresponds with the SIZEMAT1 model (a one-compartment model based on Anand 2010 as described by Holford[1]). In turn this model is equivalent with a previous model (Anand 2008)[3] after re-estimation using corrected conversion of morphine doses from morphine sulfate to morphine hydrochloride to morphine base. The equations are identical to the Holford model equations without parameters for the 2nd compartment.

$$CL_i = CLst_d \times \left(\frac{BW}{70}\right)^{0.75} \times \frac{PMA^{Hill}}{TM_{50}{}^{Hill} + PMA^{Hill}} \times FDEVCL$$
$$V1_i = V1_{std} \times \left(\frac{BW}{70}\right) \times \left(1 - \beta Vol \times exp(-PNA \times \ln(2) / TVOL)\right) \times FDEVV$$

Knibbe

Knibbe (2009)[4] described an empirical allometric model with an estimated exponent for clearance to characterize morphine pharmacokinetics in neonates. The Holford and Anand models are mechanistic models because they include different parameter modulating components, each driven by a physiological parameter. Empiric models, like the Knibbe model (2009), do not decompose parameter variability into different mechanistic causes. Typically, a single physiological parameter (like body weight) is correlated to a parameter using an empirical exponential equation.

$$CL_i = CLst_d \times BW^{1.44}$$
$$V1_i = V1_{std} \times BW$$
$$Q_i = Qs_{td}$$
$$V2_i = V2_{std} \times BW$$

Clearance and volumes of distribution are correlated to body weight. In the clearance equation an exponent of 1.44 is used whereas in the volume equations and exponent of 1.0 is used. The intercompartment clearance is assumed to be constant.

Wang

The Wang models (2013)[5] are bodyweight dependent exponent (BDE) empiric models. These are a special type of models because the bodyweight appears both in the base and in the exponent of the power function.

$$CL_i = CLst_d \times \left(\frac{BW}{70}\right)^k$$
$$k = k_0 - \frac{K_{max} \times BW^{4.62}}{K_{50}{}^{4.62} + BW^{4.62}}$$
$$V1_i = V1_{std} \times \left(\frac{BW}{70}\right)$$
$$Q_i = Qst_d \times \left(\frac{BW}{70}\right)$$
$$V2_i = V2_{std} \times \left(\frac{BW}{70}\right)$$

With the calculation of the individual clearance, the scaling of bodyweight is not using a fixed exponent of 0.75 (as with the Holford and Anand models), but a variable value k, which in turn is also a function of bodyweight.

The Wang1 model does not include metabolite formation. It discriminates between two age groups (A = between 6-12 years, B = all other ages), each having a different value for the standard parameter values (CL, Q, V1 and V2).

The Wang2 model includes M3G metabolite formation (not M6G). The BDE equation is both applied to the M3G formation clearance (BDE parameter set 1) and the M3G elimination clearance (BDE parameter set 2).

Knosgaard

Knosgaard (2016)[6] performed a meta-analysis of the models listed so far (except for the Holford model). For morphine concentration prediction, the Anand 1-compartment model (2008) was found to be superior. For M3G and M6G metabolite level predictions the model of Bouwmeester (2004) was used, for describing the effect of maturation on M3G and M6G clearance. We refer to the Holford-Meta model for the equations used.

Note: The Holford model is the most complex model in terms of covariate usage and number of compartments.

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