FENTANYL PHARMACOKINETIC AND PHARMACODYNAMIC (PK/PD) ESTIMATION IN NEONATES AND INFANTS USING ALLOMETRIC AND ONTOGENY METHODS

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BACKGROUND

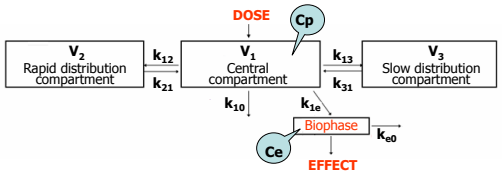
Off-label use of fentanyl i.v. for prolonged sedation during mechanical ventilation in neonates and infants has become increasingly widespread. An important issue remains in that dose schedules are usually extrapolated from adults, based on body weight (BW). However, this is questionable because important age-related changes on PK/PD, not simply proportional to BW, take place after birth. In fact, fentanyl is remarkably influenced by the degree of maturation, as it is highly bound to plasma α_1-acid glycoprotein (α_1AG) and primarily eliminated by CYP 3A4 metabolism.

PURPOSE

The aim of the present study was to develop and validate a predictive PK/PD model of fentanyl for sedation in neonates and infants, based on the integration of knowledge of the drug behaviour in adults and physiological changes during ontogenic development in human. The model will also be applied to estimate whether the target concentration and, consequently, the optimum degree of sedation are reached after a particular dose schedule of fentanyl.

METHODS

A three compartment PK model previously described for adults [1,2] was used as a reference, also accounting for a possible accumulation of fentanyl in tissues.



$CLd_{1\text{-}2} = k_{12} * V_1$

$CLd_{1\text{-}3} = k_{13} * V_1$

$Vss = V_1 + V_2 + V_3$

Two approaches were used for estimation of PK parameters:

A) Allometric approach in combination with maturation of clearance

Equations based on body weight were used for all volumes of distribution (V) and intercompartmental clearances (CLd). Systemic clearance (CLs) was modelled using a general hyperbolic maturation equation described for CYP 3A4.[4]

B) Physiologically based ontogeny:

B.1. ESTIMATION OF CLs

$$CLs \sim CL_H\ ^{[5]} = \frac{Cl_{int} \times MPPGL \times LW \times fu \times Q_H}{Cl_{int} \times MPPGL \times LW \times fu + Q_H}$$

CL_H: Hepatic clearance (L/min)
Cl_{int}: intrinsic clearance (L/min/mg prot)
MPPGL: mg microsomal protein/g liver
LW: liver weight (g)
fu: unbound fraction of fentanyl
Q_H: Hepatic blood flow (L/min)

$$fu_{ped}\ ^{[5,6]} = \frac{1}{1 + \frac{(1 - fu_{adult}) \times [P]_{ped}}{[P]_{adult} \times fu_{adult}}}$$

$$\alpha_1AG\ (g/L)\ ^{[6]} = \frac{0.887 \times Age^{0.38}}{8.89^{0.38} + Age^{0.38}}$$

$$Cl_{int\ adult}\ (L/min) = CL_H \frac{Q_H}{fu \times (Q_H - CL_H)}$$

$CL_{H\ adult} \sim CLs = 0.57$ L/min

÷ (liver weight (g)* MPPGL) → Cl_{int} (L/min/mg prot) × F → $Cl_{int\ ped}$ (L/min/mg prot)

F = CYP3A4 enzyme activity (expressed as fraction of adult values) [5]

Neonates	Infants				Children
(0-27 day)	1 month	3 months	6 months	1 year	10 years
0.24	0.5	0.7	1.1	1.3	1

B.2. ESTIMATION OF VOLUMES, INTERCOMPARTMENTAL CLEARANCES and EFFECT COMPARTMENT EQUILIBRIUM RATE CONSTANT (k_{e0})

Assumption: proportions are maintained at all ages.

$V_1 \sim$ Extracelular water (ECW)
$V_2 \sim$ Total body water (TBW)
$V_{ss} = (V1 + V2)/0.15$
$V_3 = Vss \times 0.85$

$CLd_{1\text{-}2} \sim$ 70% of cardiac output (CO)
$CLd_{1\text{-}3} \sim$ 30% of cardiac output (CO)
$k_{e0} \sim$ brain blood flow (Q_B)/ CO

LW, Q_H, MPPGL, ECW, TBW, CO and Q_B are tabulated as a function of age in the literature [7]

B.3. MODEL VALIDATION AND SIMULATION

- Validation: estimated parameters were statistically compared to literature values [8].
- Based on the estimated PK parameters and their variabilities, Cp-time profiles for (N=150) neonates after a dosing protocol of fentanyl (10.5 µg/kg/h x 1 h followed by 1,5 µg/kg/h x 48 h) [9] were simulated in NONMEM, and compared to those profiles described in the literature [9].
- Simulations of the effect (sedation %)-time profiles were performed by semi-parametric implementation, in WINNOLIN, of an effect-compartment link model that affords to relate Cp and Ce by means of the k_{e0} equilibration rate constant *(see scheme above)*. The effect (E) *vs.* time data were finally generated through a sigmoid PD model. The values of the parameters used in simulation were: EC_{50} target for sedation (3 ng/mL), gamma (2) and k_{e0} (estimated; B.2.)

RESULTS

Both approaches A and B are applicable for all the age ranges (neonates and infants). However, solely the results obtained for the neonatal subpopulation are shown, due to the larger amount of information available in the literature regarding sedation protocols, compared to infants.

In neonates, methodologies A and B provided similar values for some PK parameters. Nevertheless, the physiologically based ontogenic model was able to describe the general disposition processes of the drug, accounting both for PK and PD, as a function of age-related changes. Estimated parameters for neonates by means of approach B and corresponding adult references are shown on the tables:

Physiological variables tabulated in the literature for neonates and adults [7]

AGE	LW (g)	Q_H (L/min)	MPPGL (mg/g liver)	BW (kg)	ECW (% BW)	TBW (% BW)	CO (L/min)	Q_B (L/min)
Adult (ref.)	1800	1.72	35	70	0.18	0.61	6.79	0.78
Neonate	120	0.22	26	3.5	0.36	0.75	0.58	0.18

Physiological variables and PK/PD parameters estimated for neonates with base on the adult references adapted from the literature

AGE	α_1AG (g/L)	fu	Cl_{int} (L/min/mg prot)	CLs (L/min)	V_1 (L)	V_2 (L)	V_3 (L)	V_{ss} (L)	$CLd_{1\text{-}2}$ (L/min)	$CLd_{1\text{-}3}$ (L/min)	k_{e0} (min^{-1})	$t_{1/2\ ke0}$ (min)
Adult (ref.)	0.6	0.156	0.00009	0.57	12.6	42.70	313.37	368.67	4.80	2.30	0.11	6.3
Neonate	0.10	0.53	0.00002	0.03	1.26	2.63	22.02	25.90	0.44	0.21	0.31	2.24

There are considerable differences in physiological variables and PK parameters between neonates and adults, not simply proportional to body weight. The validation showed that physiologically based model was a good predictor of fentanyl PK behaviour, as calculated parameter values show an acceptable bias when compared to public domain observations [8] (statistically not different from zero).

Results from simulation after the mentioned dosing protocol [9] are shown in figures 1, 2 and 3. Cp-time profiles resulted to be similar to those described in the literature [9], thus confirming the predictive capacity of the present model.

Taking the variability into account (fig. 1), not all the neonates (41%) would reach the target Cp (3 ng/mL for sedation) in the steady state (ss). (Note that Ce = Cp at ss).

Fig 1. Simulation Cp vs. time (n=150)

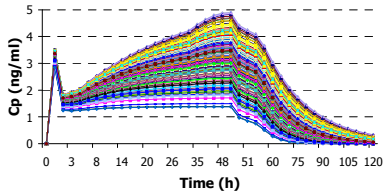


Fig. 2 is a schematic representation of fig. 1, solely considering the mean, upper and lower IDs, which were used to simulate E *vs.* time through the described PD model.

Fig 2. Cp vs. Time (mean, upper, lower)

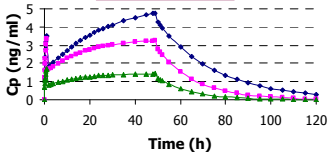
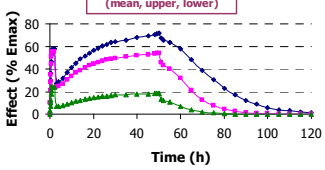


Fig 3. Effect vs. Time (mean, upper, lower)



PK/PD integration (fig. 3) suggests that neonates could not reach the optimum degree of sedation early within this protocol and under fentanyl alone. Delay to maximum sedation is independent of dose, although in clinical practice comedication is used to achieve the effect faster.

CONCLUSION

The developed physiological-based model satisfactorily predicts fentanyl PK/PD in neonates and could be applied to design dosing regimens that optimize the time to sedation at minimal exposures. Lacking in this work and overall is the quantification of synergy at the effect as coadministration of other opiates for sedation is common. This combined effect is not taken into consideration in the simulations shown here.

The present model integrates physiology (growth and development), thus allowing identification of potential sources of the interindividual variability observed in certain clinical situations. However, given the important variability that characterizes this subpopulation, monitoring of plasma levels in addition to the usual effect monitoring is highly recommended. In this sense, the present model could also aid in optimizing the sampling protocol. A collaborative study is ongoing with the neonatal unit at Cruces Hospital (Bizkaia, Spain).

ACKNOWLEDGMENTS

• Supported by a predoctoral scholarship from the Research Staff Training Program. Department of Education, Universities and Research. Government of the Basque Country.
• To Nuria Rivas, for data analysis.
• INNPACTO Project: DynaPUMP NEO. MICINN. 2010-2012.

REFERENCES

[1] Ebling WF et al., Anesthesiology. 1990 Apr; 72(4):650-8
[2] Hughes MA et al., Anesthesiology. 1992 Mar; 76(3):334-41
[3] Verotta D, et al., Am J Physiol. 1989 Apr; 256(4 Pt 2): R1005-10.
[4] Bouillon-Pichault M et al., J Pharmacokinet Pharmacodyn. 2011 Feb;38(1):25-40
[5] Bouzom F, et al., Fundam Clin Pharmacol. 2008 Dec;22(6):579–87
[6] Johnson TN et al., Clin Pharmacokinet. 2006; 45(9):931-56
[7] ICRP Publication 89. Pergamon Press, Oxford, 2003.
[8] Gauntlett IS et al., Anesthesiology. 1988 Nov; 69(5):683-7
[9] Saarenma E et al., J Pediatr. 2000 Jun;136(6):767-70