Pharmacokinetic-pharmacodynamic model of fentanyl sedation in children with severe acute bronchiolits

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PAGE Ljubljana, 30 June - 1 July 2022

Background

Children with severe acute bronchiolitis often require mechanical ventilation with sedation to decrease anxiety and discomfort of the intubation. Opioid agonist fentanyl is used as a first-line treatment, mostly in combination with midazolam [1, 2]. Drug dosing in this patient group is challenging due to complex pharmacokinetics (PKs) and pharmacodynamics (PDs) changing rapidly during the first year of life. Furthermore, long-term treatment with fentanyl is associated with tolerance development.

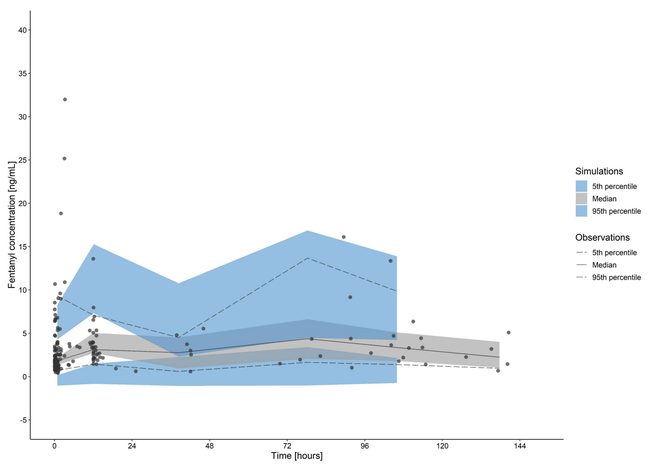
Objectives

We aimed to develop a population PK-PD model of fentanyl sedation in critically ill children younger than 2 years to optimise the long-term treatment. Additionally, we aimed to explore the influence of common polymorphisms of the catechol-O-methyltransferase, opioid receptor μ_1, and *ABCB1* genes.

Model

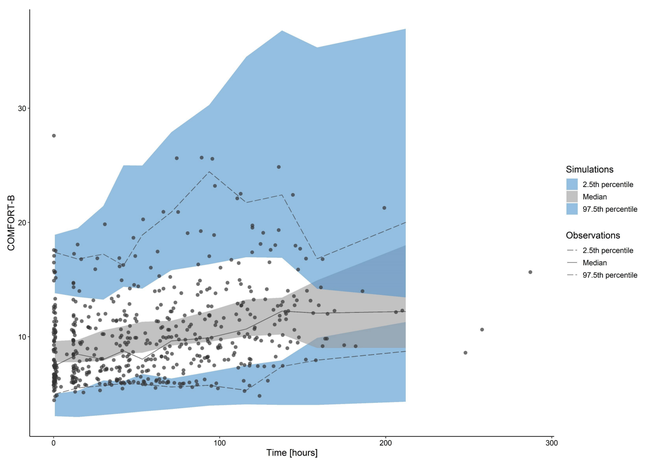
Pharmacokinetics

Parameter	Estimate [RSE%]	IIV [RSE%]
CL (L/h/70 kg)	**36.6** [33]	**49.5** [42]
PMA_{50} (week)	**43.5** [24]	
s	**2.68** [99]	
V_1 (L/70 kg)	**109** [26]	**93.9** [73]
V_2 (L/70 kg)	**39.9** [16]	
Q (L/h/70 kg)	**87.1** [31]	
$\sigma_{additive}$ (ng/mL)	**0.579** [47]	
$\sigma_{proportional}$ (%)	**46.4** [14]	



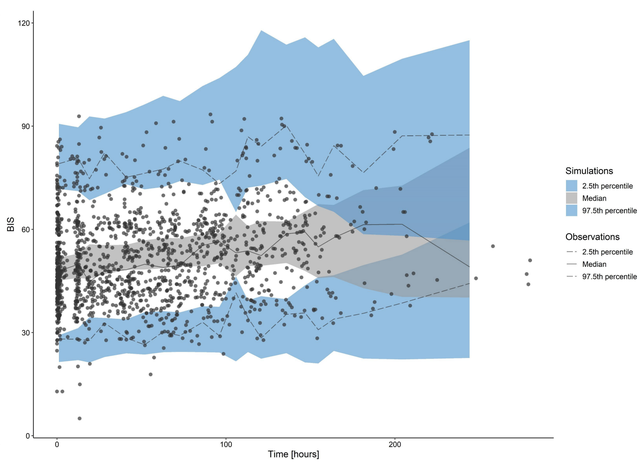
COMFORT-B

Parameter	Estimate	IIV
E0	**15.1**	
E_{max}	**6.97**	**39.8**
EC_{50} (ng/mL)	**1.26**	
PMA on EC_{50}	**0.0382**	
COMT on EC_{50}	**-0.789**	
γ	**1 FIX**	
k_{t0} (h-1)	**1E-8**	
I_{max}	**7.20**	**63.3**
IC_{50} (ng/mL)	**5.61E-7**	
$\sigma_{proportional}$ (%)	**23.3**	



BIS

Parameter	Estimate	IIV
E0	**73.2**	
E_{max}	**44.0**	**16.5**
PMA on E_{max}	**0.434**	
ABCB1 on E_{max}	**+0.148**	
EC_{50} (ng/mL)	**0.0785**	**200**
PMA on EC_{50}	**2.71**	
γ	**1 FIX**	
k_{t0} (h-1)	**1E-8**	
I_{max}	**46.9**	**14.2**
IC_{50} (ng/mL)	**4.84E-7**	
$\sigma_{additive}$ (%)	**5.17**	
$\sigma_{proportional}$ (%)	**17.2**	



References

[1] Vet NJ et al. Sedation in Critically Ill Children with Respiratory Failure. Front Pediatr 2016, 24 (4): 89.
[2] Lamas A, Lopez – Herce J. Monitoring sedation in the critically ill child. Anaesth 2010, 65: 516–524.
[3] Porchet HC, Benowitz NL, Sheiner LB. Pharmacodynamic Model of Tolerance: Application to Nicotine. J Pharmacol Exp Ther 1988, 244 (1), 231-236.

Conclusion

In the developed PK-PD models bodyweight, PMA, *COMT* and *ABCB1* gene polymorphisms influenced the levels of sedation achieved by continuous infusion of fentanyl. The model can be used for fentanyl dosing regimen design to optimize sedation in critically ill children with acute bronchiolitis.

Results

The final PK model of fentanyl was a two compartment model with the estimated volume of central compartment 109 L/70 kg, volume of peripheral compartment 39.9 L/70 kg, clearance 36.6 L/h/70 kg, and distribution clearance 87.1 L/h/70 kg. Theoretical allometric relationship of PK parameters with body weight was used. Maturation of clearance with postmenstrual age (PMA) was assessed with a sigmoidal maturation function. The estimated value of PMA_{50} was 43.5 weeks. PK-PD relationships with COMFORT-B and BIS were adequately described by a direct-link E_{max} model and tolerance was modelled as an interaction with partial agonist. *COMT* genotype was associated with the fentanyl effect on COMFORT-B. The potency of fentanyl was higher (80% lower EC_{50}) in carriers of variant allele compared to patients who were homozygous wild-type. Additionally, EC_{50} increased with PMA. In the model for BIS, efficacy of fentanyl was higher in patients homozygous for variant *ABCB1* allele (15% higher E_{max}), while older children had higher EC_{50} and E_{max}.

Covariates on COMFORT-B

$$EC_{50} = 1.26 \cdot \left(1 + 0.0382 \cdot (PMA[week] - 49)\right) \cdot (1 - 0.789 \cdot COMT_d)$$

$COMT_d$ = 1, if homozygous for the variant allele, 0 otherwise.

Covariates on BIS

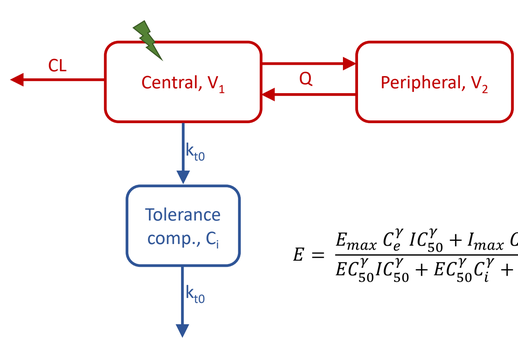
$$E_{max} = 44 \cdot \left(\frac{PMA[week]}{49}\right)^{0.434} \cdot (1 + 0.148 \cdot ABCB1_r)$$

$ABCB1_r$ = 1, if carrier of the variant allele, 0 otherwise.

$$EC_{50} = 0.0785 \cdot \left(\frac{PMA[week]}{49}\right)^{2.71}$$

Methods

- 49 children, median age 9.7 weeks (1 day – 130 weeks), median body weight 5.3 kg (2.8 – 13.5 kg), median PMA 49 weeks (34 – 170 weeks).
- Continuous infusion of fentanyl (0.27 – 13 μg/kg/h) for 3 – 12 days, occasional bolus doses, if necessary.
- 5 blood samples per patient, at 5, 15, 60 min and 12 h after the start of infusion and before stopping the infusion.
- Monitoring sedation and anaesthesia with bispectral index score (BIS) before the infusion, at every blood draw, then at least two measurements per day. Assessment of pain and distress using COMFORT-B at the same time points.
- Genotyping *COMT* Val158Met (catechol-O-methyltransferase), *ABCB1* C3435T (ABCB1 transporter), and *OPRM1* A118G (opioid receptor μ_1).
- Sequential PK-PD analysis in NONMEM.
- PK: 2-compartment model, allometric scaling for body weight, maturation of clearance with PMA using a sigmoidal maturation function.
- PD: direct link E_{max} model.
- Tolerance development was modelled using the approach proposed by Porchet et al [3]. Net pharmacological effect of the interaction of fentanyl and accumulation of the hypothetical inhibitor in its effect compartment. Various types of interaction derived from receptor theory were tested (reverse agonist, competitive agonist, non-competitive agonist and partial agonist). Partial agonist model best fitted the observed BIS and COMFORT-B data.



$$CL_i = \theta_{CL}\left(\frac{WT_i}{70}\right)^{0.75} \frac{PMA_i{}^s}{PMA_i{}^s + PMA_{50}{}^s} \qquad Q_i = \theta_Q\left(\frac{WT_i}{70}\right)^{0.75}$$

$$V_{1i} = \theta_{V1}\left(\frac{WT_i}{70}\right)^{1} \qquad V_{2i} = \theta_{V2}\left(\frac{WT_i}{70}\right)^{1}$$

$$E = \frac{E_{max}\, C_e^{\gamma}\, IC_{50}^{\gamma} + I_{max}\, C_i^{\gamma}\, EC_{50}^{\gamma}}{EC_{50}^{\gamma} IC_{50}^{\gamma} + EC_{50}^{\gamma} C_i^{\gamma} + IC_{50}^{\gamma} C_e^{\gamma}}$$