Mechanistic Population Pharmacokinetics of Morphine in Neonates with Abstinence Syndrome after Oral Administration of Diluted Tincture of Opium

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Introduction

Neonatal Abstinence Syndrome (NAS) is a clinical syndrome of opiate withdrawal in neonates exposed to drugs prenatally via chronic maternal opiate use. Morphine is the standard first line pharmacotherapy in NAS. However, the pharmacokinetic (PK) characteristics of morphine after oral administration in neonates is still unknown.

Objective

The aim of this analysis is to develop a morphine population pharmacokinetics (PopPK) model using data collected during a randomized control trial[1] in infants with NAS.

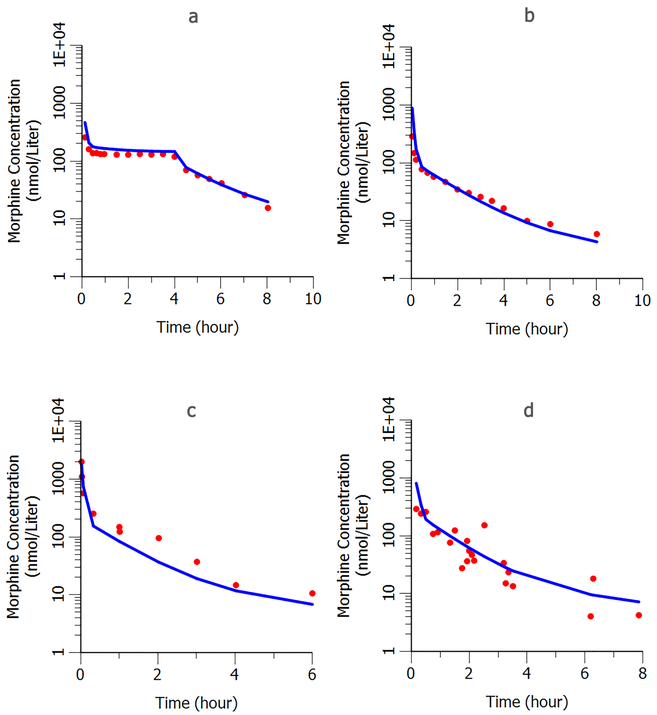

Figure 1 External evaluation of morphine structural model after IV administration of morphine a) healthy adults with mean age 24.6 years and mean body weight 74.2kg b) healthy volunteers with mean body weight 71.4kg and mean age 25.8 years c) children undergoing elective surgery with mean age 21 months and mean body weight 9.2 kg d) children with leukemia undergoing therapeutic lumbar puncture (median age 5.5 years and median weight 20.0 kg)

Methods

The development of the PK model involved two major steps: 1) a structural model after intravenous administration in adults was extrapolated to pediatrics using the allometric scaling approach with maturation of PK parameters based on age; and 2) a population PK model after oral administration of diluted tincture of opium (DTO) was built based on this structural model and plasma data collected from the current clinical trial.

PopPK model analysis was performed using Phoenix NLME 1.3 (Pharsight, Cary, North Carolina). The first order conditional estimation method with interaction (FOCE-I) was used in the modeling process .

Results

A three compartment structural model based on adult PK[2] along with physiologic models for body weight and maturation was employed to analyze the sparse data from neonates. The maturation effect on clearance was modeled as a function of PMA[3] and on volume as a function of PNA[4]. In external evaluation of the structural IV model, the predictions are in good agreement with the observed PK profile in both adults and pediatrics[5-8] (Figure 1).

88 plasma samples were collected from 34 neonates with abstinence syndrome after oral administration of DTO, in which morphine is the active ingredient. By fixing the PK parameters in the structural PK model after IV administration, the estimated first-order absorption rate constant was 0.751 hour^{-1} and the bioavailability was 48.5% in neonates with abstinence syndrome (Table 1). Bayesian individual concentration time profiles during the entire study were simulated based on post hoc PK parameter estimates in four representative subjects (Figure 2).

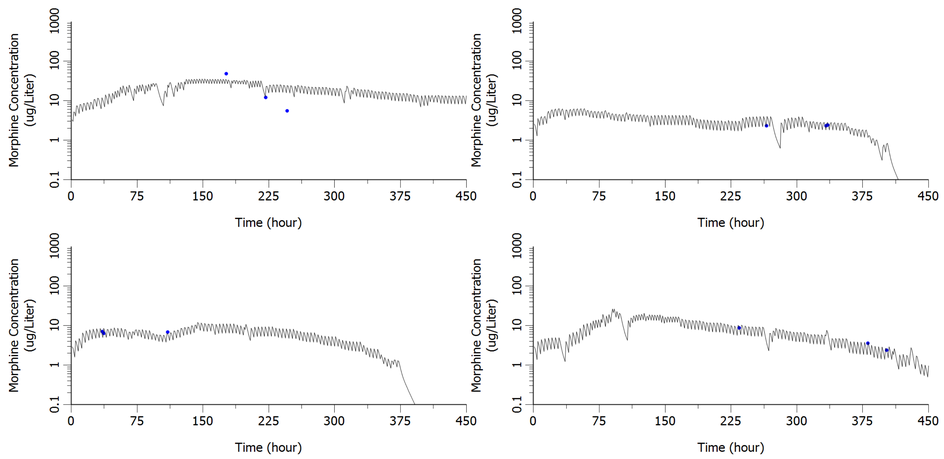

Figure 2 Comparison of post hoc PK profiles with observed concentration in representative neonate

Results

Table 1: Final Parameters Estimates

Parameter	Units	FOCE-I Point Estimate 95% Confidence Interval	Bootstrap (n=200) Median 95% Percentile Interval
Ka	1/hour	0.751 (0.196, 1.31)	0.732 (0.562, 0.908)
F	%	48.5 (38.9, 58.2)	45.5 (37.9, 53.7)
Vstd*	Liter	17.8	17.8
CLstd*#	Liter/hour	75.3	75.3
V2std*	Liter	87.3	87.3
Q2std*	Liter/hour	136	136
V3std*	Liter	199	199
Q3std*	Liter/hour	19.5	19.5
CLmat50*	weeks	58.3	58.3
HillCL*		3.6	3.6
Tvol*	weeks	9.65	9.65
βvol*		0.614	0.614
Proportional Error		44.9% (35.3%, 54.6%)	47.9% (38.1%, 62.8%)

*Parameters were fixed to the estimates in structural IV model
#Between Subject Variability on clearance: FOCE-I: 58.3% (38.9%, 67.2%) Bootstrap:48.1% (33.1%, 66.0%)

Conclusion

The population PK model of morphine after oral administration of DTO is reasonable and acceptable, and can be used to guide future studies by simulating exposure under different dosing regimens among various infants with NAS.

Reference

1. Agthe, a. G. et al. Pediatrics 123, e849–e856 (2009).
2. Lötsch, J., et al. Clin. Pharmacol. Ther. 72, 151–162 (2002).
3. Holford, N. H. G., et al. Paediatr. Anaesth. 22, 209–22 (2012).
4. William E. Evans, et al. Lippincott Williams & Wilkins, 1992.
5. Stuart-Harris, et al. Br. J. Clin. Pharmacol. 49, 207–214 (2000).
6. Lötsch, J., et al. Clin. Pharmacol. Ther. 63, 629–639 (1998).
7. Hain, R. D., et al. Br. J. Clin. Pharmacol. 48, (1999).
8. Lundeberg, S., et al. Acta Anaesthesiol. Scand. 40, 445–51 (1996).