4-24-2009

Prediction of Sublingual Bioavailability of Buprenorphine in Newborns with Neonatal Abstinence Syndrome—a case study on physiological and developmental changes using NONMEM and SIMCYP

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Prediction of Sublingual Bioavailability of Buprenorphine in Newborns with Neonatal Abstinence Syndrome— a case study on physiological and developmental changes using NONMEM and SIMCYP

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ABSTRACT

Background: **About 55 to 94% of infants born to opioid dependent mothers have neonatal abstinence syndrome (NAS). Buprenorphine (BUP) is used clinically as an analgesic and a detoxification agent and a maintenance treatment for opioid dependence. No data, however, has been reported about the use of sublingual administration of BUP below the age of 4 year, especially for term infants with NAS.**

Objectives: **Characterize pharmacokinetics (PK) of BUP in newborn patients; Evaluate the developmental changes in newborns in order to assist dosing optimization in ongoing clinical studies.**

Methods: In silico **prediction of PK behavior and physiological development in newborn patients were evaluated using SIMCYP. Intravenous clearance was predicted through physiologically based simulation method in SIMCYP. Based on sublingual clearance obtained from a one compartmental model developed previously using NONMEM, individual changes of sublingual bioavailability were evaluated with physiological development in the first one and half month during the newborn period.**

Results: **Intrinsic clearance of BUP in newborns were incorporated into enzyme kinetic data obtained from literature. Change of sublingual bioavailability for newborns was evaluated with bioavailability-postmenstrual age profiles. Sublingual bioavailability of BUP was estimated as 8.9–56.6% in newborn patients studied during the first one and half postnatal month.**

Conclusion: **Developmental considerations for the PK of BUP in newborns are important for the characterization of the dose-exposure relationship. We have evaluated this from "bottom-up" and "top-down" approaches with SIMCYP and NONMEM respectively and found these approaches to be complementary and valuable for clinical trial design and routine clinical care. Presumably they would facilitate rational decision making in pediatric drug development as well.**

OBJECTIVES

1. **To characterize PK and sublingual bioavailability of buprenorphine (BUP) in target population during newborn period.**
2. **To evaluate the developmental changes in newborns in order to assist dosing optimization in ongoing clinical studies.**

INTRODUCTION

- **BUP is a semi-synthetic opioid derived from thebaine and used in clinics as an analgesic and as a detoxification and maintenance treatment for opioid dependence.**
- **BUP is administered via intravenous and sublingual routes, since BUP has very low oral bioavailability due to extensive first-pass metabolism.**
- **BUP has large volume of distribution and is extensively metabolized to norbuprenorphine (NBUP) by N-dealkylation mediated mainly by CYP3A4 (65%) and CYP2C8 (30%).**
- **BUP is metabolized in other metabolic pathways to a minor extent by CYP 2C9, 2C18, and 2C19 and to a major extent by CYP 3A.**
- **Both BUP and NBUP undergo glucuronidation by UGT1A3, 1A8, and 2B7.**
- **NAS occurs in 55 to 94% of infants who are born to opioid-dependent mothers.**
- **No data has been reported about the use of sublingual administration below the age of 4 year, especially for term infants with NAS. Therefore, there is a great need to determine the PK characteristics to optimize pediatric therapy.**

MODEL DEVELOPMENT

- **Nonlinear mixed-effect modeling was employed to characterize the pharmacokinetics of BUP and NBUP based on data from a pilot clinical trial in 12 newborn patients with NAS (*Pediatrics*, 2008, 122, e601-607).**
- **Population PK analysis was performed using non-linear mixed-effects modeling with the NONMEM software, Version VI, Level 1.1.**
- **One compartment model with first order absorption, metabolism, and elimination was developed in describing the PK of BUP and NBUP.**

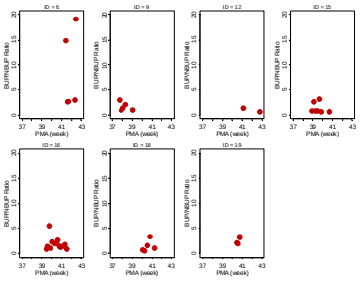
MODEL DESCRIPTION

Table 1 Summary of demographic characteristics for neonates (N = 12) at baseline

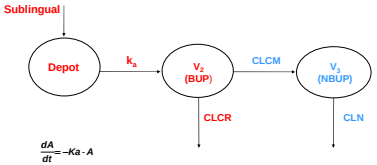
Covariate	Statistic	Summary
Gestational Age (weeks)	Mean (SD) Median (min, max)	39.28 (1.06) 39.31 (37, 41)
Postnatal Age (days)	Mean (SD) Median (min, max)	22 (11) 17 (11, 47)
Postmenstrual Age (PMA) (weeks)	Mean (SD) Median (min, max)	41.9 (1.22) 42.15 (39.6, 43.55)
Weight (kg)	Mean (SD) Median (min, max)	3.002 (0.347) 3.060 (2.39, 3.459)
Gender		
Male	Number (%)	10 (83.3%)
Female	Number (%)	2 (16.7%)
Race		
White	Number (%)	10 (83.3%)
Hispanic / Latino	Number (%)	2 (16.7%)

Table 2 Treatment information

Subject	Treatment starting date from birth (days)	Treatment duration (days)	Co-medication with phenobarbital
AN06	1	14	No
AN09	4	15	No
AN12	4	17	No
AN13	3	30	Yes (started at 143.29 hr & stopped at 287.29 hr)
AN15	1	15	No
AN16	3	16	No
AN18	4	11	No
AN19	2	24	No
AN22	2	47	Yes (started at 222.62 hr & stopped at 381.5 hr)
AN25	1	26	No
AN27	2	39	Yes (started at 121.09 hr & stopped at 409.09 hr)
AN28	2	15	No



BUP/NBP Ratio: Concentration Ratio of BUP/NBUP at the Same Time Point
PMA: Postmenstrual Age

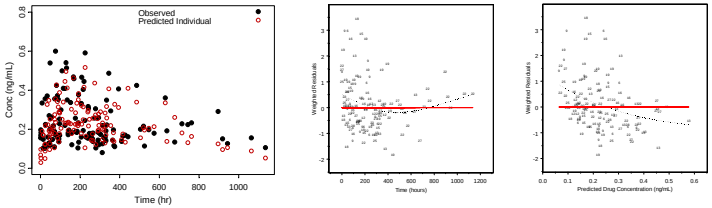


$$\frac{dA}{dt} = -Ka \cdot A$$

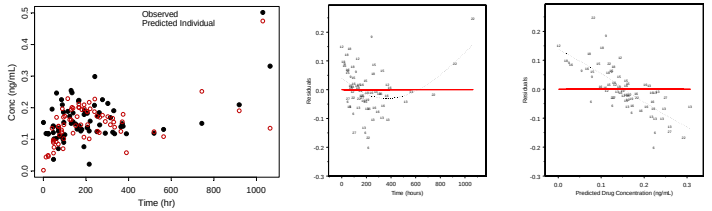
$$V_2 \frac{dC}{dt} = Ka \cdot A - CLCR \cdot C - CLCM \cdot C$$

$$V_3 \frac{dC_m}{dt} = CLCM \cdot C - CLN \cdot C_m$$

BUP



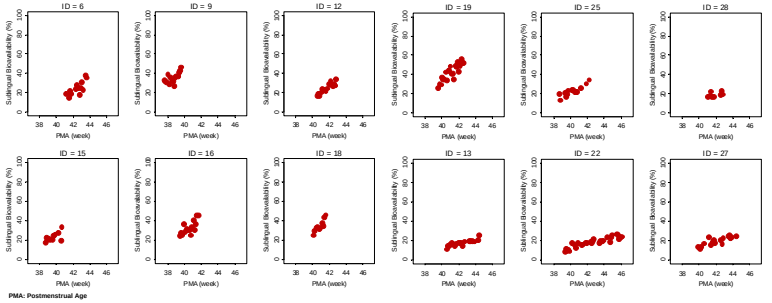
NBUP



SIMULATION with SIMCYP

- **The population pharmacokinetic model is based on data from 12 newborn patients with NAS. Three newborn patients (ID13, 22, & 27) were co-treated with phenobarbital during certain period of treatment.**
- **Simulation of intravenous clearance of BUP was conducted in 12 newborn patients with NAS.**
- ***In vitro*** **enzyme kinetic data was incorporated into SIMCYP to simulate intravenous clearance in newborn patients.**
  - *** molecular weight, pKa, log P**
  - *** unbound fraction in plasma (f_u)**
  - *** average renal clearance in adult**
  - *** V_{max} and K_m values derived using human liver microsomes /recombinant CYPs**
  - *** unbound fraction in human liver microsomes /recombinant CYPs (f_{uMic})**
  - ***dose**
  - ***dose interval**
  - ***blood to plasma ratio**
- **Sublingual bioavailability was estimated by comparing intravenous clearance (CL_{iv}) obtained from SIMCYP simulation to sublingual clearance (CL_{sub}) generated using non-linear mixed effect modeling with NONMEM.**
- **Sublingual bioavailability—PMA profiles were drawn from the time they were born till BUP treatment completed for each of the 12 newborn patients.**

RESULTS



PMA: Postmenstrual Age

CONCLUSIONS

- **The higher BUP-to-NBUP ratio (0.7—19.19) than adults (0.165—1.4) has been observed in newborn patients studied. It might be due to immature hepatic function in newborns and compliance to BUP sublingual administration.**
- **ID 6 showed the two highest BUP/NBUP ratio among 12 newborns examined. It might be due to large percentage of BUP dose not being administrated (medical record errors) and/or analytical measurement errors.**
- **Large individual variability has been observed in sublingual bioavailability . Higher values of bioavailability observed might be due to underestimated CL_{sub} and/or overestimated CL_{iv}.**
- **Sublingual bioavailability was estimated from 13.5% to 56.6% in the 9 neonates treated exclusively with BUP during the first postnatal month. The bioavailability of these 9 neonates except ID 28 was increased gradually by 13% at least during this period. Linear increase trend is observed when plotting sublingual bioavailability versus PMA for each of the 9 neonates studied.**
- **Sublingual bioavailability of ID 13, 22, and 27 showed less linear increase with PMA, compared with that of all other patients. It might be due to enzyme induction of CYP 3A, CYP 2C, and UGTs caused by phenobarbital.**
- **Growth factors such as age, body weight can be important covariates to BUP exposure levels in newborns, given the fact of the significant changes of body fat content and enzyme levels of CYP 3A, 2C8, 2C9, 2C18 and 2C19.**
- **Dose adjustment is needed for BUP therapy in newborns based on lower sublingual bioavailability estimated in newborn patients, compared to 50% of BUP sublingual bioavailability observed in adults, and drug-drug interaction induced by phenobarbital. A larger, double-blind, properly powered clinical trial on BUP in young infants will enhance and validate this model and simulation.**

ACKNOWLEDGMENT

We cordially thank Dr. Masoud Jamei and Mr. Steve Marciniak in Simcyp Limited for their technical assistance to operation and installation of SIMCYP software.