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# Population Pharmacokinetic and Pharmacodynamic Analysis of Buprenorphine for the Treatment of Neonatal Abstinence Syndrome

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## Introduction

Neonatal abstinence syndrome (NAS) is a condition affecting newborns exposed to an opioid *in utero*. Symptoms of NAS include excessive crying, poor feeding, and disordered autonomic control. Up to 2/3 of infants will require pharmacologic therapies to reach symptom control. Opioids including morphine and methadone are the current first-line treatments. Buprenorphine is being investigated as a treatment of NAS. The purpose of this analysis was to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of BUP in infants with NAS.

## Methods

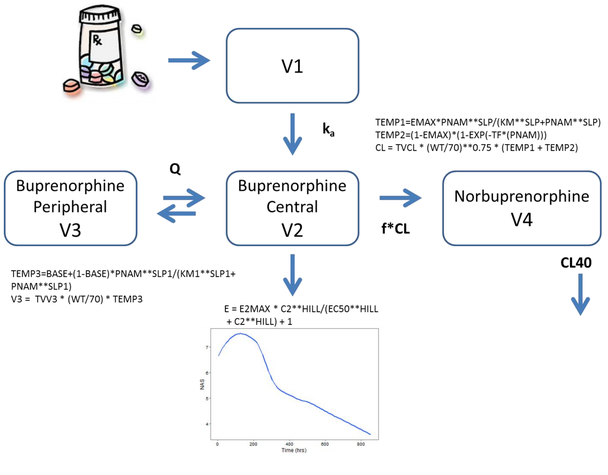
The Blinded Buprenorphine OR Neonatal morphine solution (BBORN) trial (NCT01452789) was a double-blind, double-dummy, randomized, controlled trial that assessed the efficacy of buprenorphine and morphine in NAS. Blood was analyzed from patients who received buprenorphine. All infants were monitored using the MOTHER NAS Scale, a modified Finnegan scoring instrument.

Term infants were treated for NAS if they had 3 scores ≥24 or a single score ≥12. The neonates allocated to the buprenorphine group were treated with sublingual buprenorphine 5.3 µg/kg every eight hours. Doses were up-titrated by 25% for inadequate symptom control up to a maximal dose of 20 µg/kg.

When the infant was stabilized, the dose was tapered at a rate of 10% daily until within 10% of the starting dose. Blood for PK analysis was drawn in all study patients using a sparse sampling regimen. Buprenorphine and norbuprenorphine concentrations were analyzed using liquid chromatography/mass spectrometry. The limit of quantification was 0.1 ng/mL for both buprenorphine and norbuprenorphine.

The data were used to validate and adapt an existing model of buprenorphine PK in neonates *(Ng CM,. Pharmacotherapy. 2015 Jul;35(7):670-80. PMID 26172282).* This reference model utilized a 2-compartment model with PK parameters scaled allometrically by weight and maturation functions on clearance and peripheral volume of distribution. The model was then extended to norbuprenorphine. Norbuprenorphine formation was modeled as a fraction of previously established clearance of buprenorphine given the potential for buprenorphine to be metabolized by multiple pathways. The metabolite PK parameters were also scaled by weight allometrically. The buprenorphine/norbuprenorphine data were analyzed against the NAS scores to identify potential PD relationships. The knowledge of the relationship was used to link the PK to a PD model of NAS.

**Figure 1. PK and PD Model Schematic**




## Results

**Patient Demographics**

| Demographic Factors | Mean (SD) |
|---|---|
| N | 28 |
| Female | 39% |
| Birth Weight (kg) | 3.10 (0.43) |
| Age at Last Dose (days) | 21 (11.6) |

172 buprenorphine/norbuprenorphine serum concentrations and 4373 NAS scores were collected from 28 full term infants. The reference model from a Phase 1 trial was shown to reasonably predict the new data with mean squared error of 0.062 and root mean squared error of 0.251.

**PK and PD Model Parameters**

| Parameters | Estimate | RSE% |
|---|---|---|
| **Parent Model** | | |
| Ka (hr-1) | 0.416 | FIX |
| CL (L/hr) | 203 | 12 |
| V2 (L) | 142 | 142 |
| Q (L/hr) | 1010 | 96 |
| V3 (L) | 6350 | 61 |
| KM (days) | 2.18 | 29 |
| SLP | 5 | FIX |
| EMAX | 0.477 | FIX |
| TF | 0.104 | 32 |
| KM1 (days) | 4.79 | 24 |
| SLP1 | 5 | FIX |
| BASE | 0.0268 | FIX |
| Proportional Error | 0.58 | 6 |
| CL-ISV (%) | 49.9 | 17 |
| V2-ISV (%) | 363 | 53 |
| V3-ISV (%) | 74.1 | 12 |
| **Metabolite Model** | | |
| V4 (L) | 2930 | 30 |
| CL40 (L/hr) | 187 | 12 |
| KM2 (days) | 6.99 | 17 |
| SLP2 | 5 | FIX |
| Additive Error | 0.101 | 10 |
| Proportional Error | 0.28 | 48 |
| V4-ISV | 74.8 | 28 |
| CL40-ISV | 50.9 | 13 |
| **NAS Model** | | |
| KNAS | 0.652 | 30 |
| EMAX | 0.656 | 110 |
| HILL | 1.23 | 57 |
| EC50 | 0.305 | 147 |
| NASKM | 0.166 | 102 |
| NASHILL | 0.263 | 25 |
| Additive Error | 2.32 | 3 |
| KNAS-ISV | 79.2 | 49 |
| NASKM-ISV | 52.1 | 28 |

**Figure 2. Buprenorphine GOF**

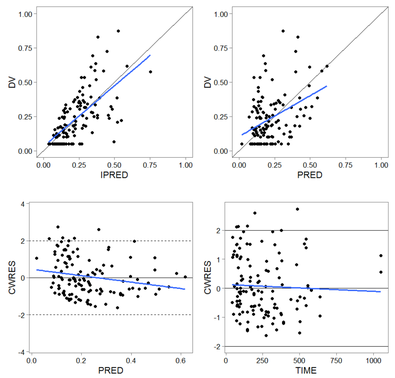



**Figure 3. Norbuprenorphine GOF**

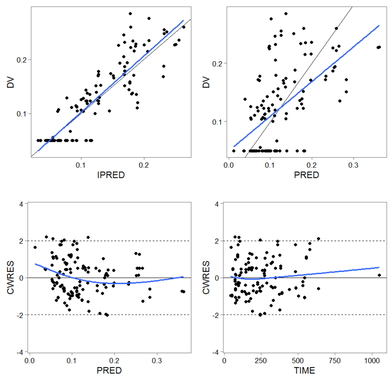
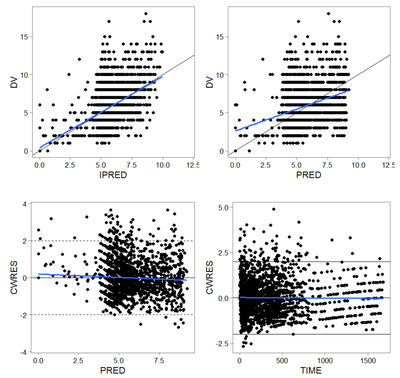



**Figure 4. NAS Score GOF**




The goodness-of-fit (GOF) plots demonstrate that the model was generally able to describe the data well.

**Figure 5. Relationship Between Clearance of Buprenorphine and Time to Stabilization**

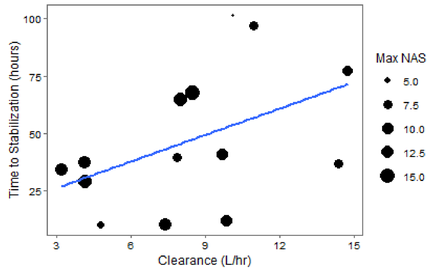



**Figure 6. NAS Severity Influenced Required Buprenorphine Exposure**

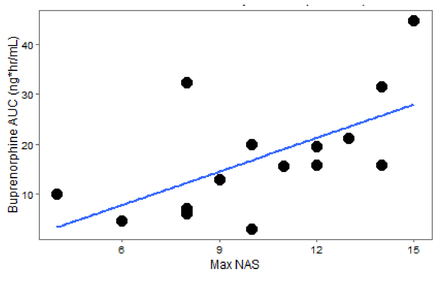
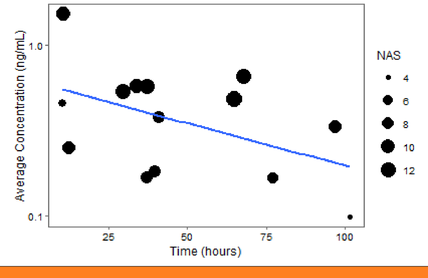
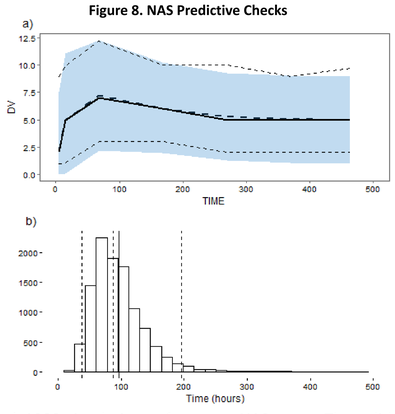



**Figure 7. Relationship Between Average Concentration of Buprenorphine and Time to Stabilization**




Exposure to buprenorphine drives clinical efficacy in NAS. The graphs show that time to stabilization of NAS was linked to the initial severity of NAS and the total exposure to buprenorphine. In Figure 5, neonates with higher clearances were exposed to less study agent and had higher times to stabilization. Figure 6 shows that more severe NAS generally required a higher AUC of buprenorphine to stabilize. Figure 7 demonstrates that higher average concentrations of buprenorphine were correlated with faster time to stabilization.

**Figure 8. NAS Predictive Checks**




a) 1000 simulations of average NAS score. The solid line and blue shaded area represent the median and 95% CI of the simulation, and the dashed lines represent the median and 95% CI of the observed data.

b) Histogram of 1000 simulated times to stabilization with the dotted lines as the median and 95% CI of the simulation. Black line is median of the observed data.

These graphs further demonstrate that the PD model was effective in the description of the course of NAS and the time to stabilization.

## Conclusions

- The findings confirm an existing PK model of buprenorphine in neonates and extend the model to describe the PK of norbuprenorphine and the PD of buprenorphine in NAS.
- This is the first PD model of a drug effect in NAS. It appeared to well describe relevant features of the NAS disease course.
- Exposure to buprenorphine was linked to stabilization of NAS. Clearance as the inverse of exposure appeared to be the primary driver of clinical efficacy.

## Future Directions

- This PK-PD model can be used to simulate dose regimens which may facilitate quicker stabilization or less frequent dosing.

## Acknowledgements

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Jefferson
HEALTH IS ALL WE DO