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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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 years, especially for term infants with NAS. Objectives: Characterize pharmacokinetics (PK) of BUP in newborns; 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 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: Intrusive 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 0.9–56.6% in the 9 neonates treated exclusively with BUP during the newborn period. 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 thebane 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 CYP2D6 (35%).
• 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.
• 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 years, 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 nonlinear mixed-effects modeling with the NONMEM software, Version VI, Level 1.1.

• One compartmental model with first order absorption, metabolism, and elimination was developed in describing the PK of BUP and NBUP.

• The population pharmacokinetic model is based on data from 12 newborn patients with NAS. Three newborn patients (D13, 22, & 27) were co-treated with phenobarbital during certain period of treatment.

• 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.

• One compartmental model with first order absorption, metabolism, and elimination was developed in describing the PK of BUP and NBUP.