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. However, no data, however, has been reported about the sublingual administration of BUP below the age of 4 years, 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 of 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: Intravenous 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 8.9–56.8% 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.

CONCLUSIONS

• 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.

• 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, "dose" average renal clearance in adult "Blood to plasma ratio" "dose interval" Vm, and Km values derived using human liver microsomes (recombinant CYPs).

• Sublingual bioavailability was estimated using intravenous clearance (CLv) obtained from SIMCYP simulation to sublingual clearance (CLsub) 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.