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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

Di Wu
Thomas Jefferson University

Walter K. Kraft
Thomas Jefferson University, walter.kraft@jefferson.edu

Michelle E. Ehrlick
Thomas Jefferson University

Jeffrey S. Barnett
University of Pennsylvania, barrettj@email.chop.edu

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ABSTRACT

Background: About 55 to 84% 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 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 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—56.6% in newborn patients as compared to 0.165—1.4% in adult patients. BUP-to-NBUP ratio (0.7—19.19) is higher than adult s (0.165—1.4). 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 CYP3A, 2C, 2C9, 2C18 and 2C19.

CONCLUSIONS

The higher BUP-to-NBUP ratio (0.7—19.19) than adults (0.165—1.4) has been observed in newborn patients studied. BUP-to-NBUP ratio (0.7—19.19) than adult s (0.165—1.4). 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 CYP3A, 2C, 2C9, 2C18 and 2C19.

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