P22 ADME PROPERTIES OF VAMOROLONE, A FIRST-IN-CLASS DISSOCIATIVE STEROIDAL ANTI-INFLAMMATORY DRUG

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Background Vamorolone is a first-in-class dissociative steroidal drug currently in Phase 2b/3 clinical trials in four to seven-year old boys with Duchenne muscular dystrophy (DMD). Recent published findings from a Phase 2a study in DMD boys have demonstrated that vamorolone is well-tolerated through the highest dose tested (6 mg/kg/day; two-weeks treatment) and shows a similar pharmacokinetic profile to prednisolone.[1] The objective of the current study was to assess the ADME (absorption, distribution, metabolism, excretion) properties of vamorolone using *in vivo* quantitative whole-body autoradiography (QWBA) and mass balance experimentation in rats.

Methods For the QWBA study, Long Evans (LE) rats were dosed with ^{14}C-labeled vamorolone and sacrificed after a defined time interval (6 groups with n=5 rats per time interval). Each frozen rat carcass was embedded in a carboxymethylcellulose matrix and cyrosectioned. Autoradiography images were acquired, analyzed, and the radioactivity in each tissue was quantified. For the mass balance study, LE rats (n=6) were dosed with ^{14}C-labeled vamorolone. Urine and feces were collected from each animal at defined time intervals.

Results The QWBA study demonstrated a widespread distribution of vamorolone amongst body organs with a peak absorption between 2–6 hours for most structures. In gastrointestinal tract organs, the peak absorption fell between the 6 and 24-hour time points. The mass balance study revealed that vamorolone was eliminated to low steady state levels by 5 days post administration in urine and 7 days post administration in feces.

Conclusions This study provides crucial information regarding the ADME properties of vamorolone. The results will help guide the design of a human mass balance study scheduled to take place in late 2019 or early 2020.

REFERENCE

1. Conklin LS, Damsker JM, Hoffman EP, *et al*. Phase IIa trial in Duchenne muscular dystrophy shows vamorolone is a first-in-class dissociative steroidal anti-inflammatory drug. *Pharma Res*. 2018; **136**: 140–150.

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P23 EVALUATION OF EXPOSURE TO VANCOMYCIN IN NEONATES WITH CURRENT DOSING APPROACHES

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Background Several neonatal dosing recommendations for vancomycin are found in the literature, variably based on age, renal function and body weight. Still there is no consensus regarding optimal initial dosing in term or preterm neonates. Our objective was to evaluate and compare how current dosing approaches perform with respect to target plasma concentration attainment, using a comprehensive population PK model of vancomycin developed in a large cohort of neonates.

Methods A single-compartment, linear elimination population pharmacokinetic model incorporating postmenstrual age, kidney function and body weight as covariates was elaborated using NONMEM®, based on 1848 vancomycin concentration values measured in 405 neonates during routine TDM. The model was then used to simulate the distribution of vancomycin concentrations resulting from 20 dosing guidelines identified in the literature. Proportions of patients within and above target exposure were used as a performance measure of each dosing regimen, defining target as AUC_{24}/MIC ratio of 400–700 h and trough concentration of 10–20 mg/L, both on days 1 and 7 of treatment.

Results Only 2 out of 20 current dosing recommendations (Neonatal Formulary 7 and Neofax® meningitis regimens) ensured target attainment in about 60% of neonates on both days 1 and 7. Most other guidelines produced below-target exposure in a large fraction of patients (22–97%), except two that frequently produced overexposure (55–66%).

Conclusion A majority of currently used vancomycin dosing regimens proposed in the literature failed to ensure target attainment in at least 60% of neonates. It is important that concentration exposure associated with best chances of therapeutic success is promptly reached, in particular in neonatal units having a high prevalence of coagulase negative Staphylococci. We recommend electing an effective dosage regimen, with a loading dose, to ensure early target attainment in a majority of patients. Subsequent therapeutic concentration monitoring remains warranted to further individualize vancomycin dosage and optimize exposure in all patients.

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P24 CAFFEINE IN PRETERM NEONATES: IMPACT ON SLEEP WAKE REGULATION

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Background Sleep wake regulation undergoes distinctive maturational changes. Ultradian sleep wake rhythm predominates at preterm age and is mainly driven by the internal clock. Increased perinatal morbidity in preterm neonates often appears with breathing disorders, among which apnea of prematurity (AOP) is the most frequently observed. Pharmacological support with caffeine has been successfully employed in the treatment of AOP. Nowadays, caffeine citrate is administered to all preterm neonates suffering from AOP. Objective of our study was a quantitative investigation of whether caffeine citrate treatment for reduction of apnea and bradycardia of prematurity affects sleep-wake behavior in preterm neonates.