

TIMP-1. As secondary outcome measures, the association between SPM levels with disease severity by admission GCS will be determined at 24 hours post-TBI, and the association between SPM levels and GCS and mortality will be determined at 14-days. We hypothesize that SPM levels will be positively associated with admission and 14-day GCS and will be independently associated with 14-day survival. **DISCUSSION/SIGNIFICANCE OF FINDINGS:** Using the SPM lipidome as a biomarker of disease is a novel tool for future translational research. It will inform a foundational mechanistic framework for TBI pathophysiology and attenuation of neuroinflammation post-TBI, providing rationale for pre-clinical and clinical research focused on novel therapeutics

77085

Impact of MYH6 Variants on Development and Clinical Course of Hypoplastic Left Heart Syndrome

Melissa Anfinson¹, Sara Creighton², MD, Jeanne James^{1,2}, MD, Peter Frommelt^{1,2}, MD, Mary Goetsch¹, MS, Pippa Simpson¹, PhD, Michael E Mitchell^{1,2}, MD and Aoy Tomita-Mitchell¹, PhD

¹Medical College of Wisconsin and ²Children's Wisconsin

ABSTRACT IMPACT: This work represents a novel way in which genetic information can be used to improve clinical decision making as it pertains to both treatment and management of congenital heart disease. **OBJECTIVES/GOALS:** Our lab found that MYH6 variants are both enriched in hypoplastic left heart syndrome (HLHS) and associated with decreased cardiac transplant-free survival. To elucidate the mechanisms of MYH6 variant pathogenicity, we are assessing their impact on atrial function during HLHS development and progression. **METHODS/STUDY POPULATION:** We are using 2D speckle-based tracking to retrospectively evaluate echocardiograms (echos) from 51 HLHS patients, 17 with MYH6 variants and 34 matched controls. Atrial function will be assessed by myocardial strain and strain rate at seven time points, beginning at the time of the patients' earliest prenatal echo, and ending with their last available echo before death or cardiac transplant. Early left atrial function will examine the role of MYH6 variants in the development of HLHS in vivo, while longitudinal right atrial function will be assessed in order to look for differences that could be contributing to the decreased transplant-free survival seen in MYH6 variant carriers. **RESULTS/ANTICIPATED RESULTS:** We hypothesize that MYH6 variants cause HLHS by impairing early left atrial (LA) contractility, resulting in altered left ventricular hemodynamics and consequent hypoplasia. We therefore expect to find diminished prenatal LA function in HLHS patients with MYH6 variants. We also hypothesize that MYH6 variants continue to impair right atrial (RA) function in surgically-reconstructed HLHS hearts, necessitating earlier transplantation. Accordingly, we expect variant carriers to exhibit lower RA function at birth versus controls. We expect differences between groups to persist over time, and possibly increase in magnitude. In HLHS patients with MYH6 variants, we anticipate declining RA function will precede right ventricular function and therefore be an early indicator of transplant need. **DISCUSSION/SIGNIFICANCE OF FINDINGS:** This study represents a novel way in which genetic information can inform clinical decision-making. Identifying MYH6 variants as an early cause of HLHS offers chances for intervention. Understanding long-term effects of MYH6 on right atrial function in HLHS may aid in cardiac transplant risk stratification, thus improving patient outcomes.

88462

Fluconazole distribution in CNS and gynecological tissues in HIV-related cryptococcal meningitis decedents

Melanie R Nicol¹, Fan Wang¹, Ambayo Richard², Olivie Carolyne Namuju², Katelyn A Pastick³, David R Boulware³, David B Meya² and Robert Lukande⁴

¹University of Minnesota College of Pharmacy, ²Makerere University Infectious Disease Institute, ³University of Minnesota Medical School and ⁴Makerere University

ABSTRACT IMPACT: Plasma and CSF are not reliable estimates of drug exposure in tissue compartments relevant for treatment and prevention of infectious diseases. **OBJECTIVES/GOALS:** Globally, high dose fluconazole is widely used in the management of cryptococcal meningitis. While it is known to readily penetrate into cerebrospinal (CSF), less is known about drug concentrations in brain parenchymal tissues. Similarly, distribution of fluconazole into gynecological tissues has not been robustly characterized. **METHODS/STUDY POPULATION:** With informed consent from next-of-kin, we conducted autopsies within 24h of death for hospitalized Ugandans receiving fluconazole for treatment or secondary prophylaxis of cryptococcal meningitis. Dosing history was abstracted from medical chart and caregiver interviews. Fluconazole concentrations were determined using high-performance liquid chromatography- tandem mass spectrometry (LC-MS/MS) in plasma, CSF, 10 brain compartments (frontal, parietal, and occipital lobes, corpus callosum, globus pallidus, hippocampus, midbrain, medulla oblongata, spinal cord, and choroid plexus) and 4 female genital compartments (cervix, vagina, ovary, and uterus), depending on tissue availability. Descriptive statistics of tissue to plasma ratios were used to describe concentrations relative to plasma. **RESULTS/ANTICIPATED RESULTS:** Fluconazole concentrations were measured in available tissues of 21 individuals with detectable fluconazole in plasma. Daily doses of fluconazole were 200 mg (n=4), 400 mg (n=1), 800 mg (n=4), 1200 mg (n=9) or unknown (n=3). CSF concentrations (n=10) ranged from 93-1380% (median 100%) of plasma while brain concentrations (n=3) across all 10 compartments ranged from 45% to 89% (median 69%) of plasma. In the female genital tract, cervical concentrations (n=10) were 9-78% (median 65%) of plasma and in the 2 individuals with available tissue, concentrations in vaginal, ovarian, and uterine tissues were similar to cervix, ranging from 63-105% of plasma. **DISCUSSION/SIGNIFICANCE OF FINDINGS:** Measuring drug concentrations directly in tissues, the presumed site of action, improves estimates of drug efficacy. While fluconazole concentrations in CSF were similar to plasma, actual brain tissues were consistently lower. Concentrations were similar between upper and lower female genital tracts, but were consistently lower than plasma.

Regulatory Science/Team Science

10122

Development of an In Vitro in Vivo Correlation of Itraconazole Spray-Dried Dispersion Tablets

Ana Luisa Coutinho, Asmita Adhikari, and James Polli
University of Maryland Baltimore

ABSTRACT IMPACT: As the number of poorly water-soluble drugs in development increases, our research will expand on the science behind improving drug solubility and absorption and ensuring that promising poorly-water solubility drugs do not fail drug

development. OBJECTIVES/GOALS: Spray-dried dispersion (SDD) tablet formulation is an approach to increase oral drug solubility and absorption. Methods to predict SDD performance in humans are poorly developed. We aim to develop an in vivo in vitro correlation (IVIVC) between in vitro dissolution and in vivo absorption of itraconazole SDD tablets. METHODS/STUDY POPULATION: This research project involves tablet manufacturing, in vitro dissolution experiments, and a clinical study. We manufactured fast-, medium-, and slow-release SDD tablets containing amorphous solid dispersion of itraconazole (100 mg) and different grades of the polymer hypromellose acetate succinate (HPMC-AS). Tablets differed in slug pressure, tablet compression force, and formulation composition. Dissolution studies were performed using the United States Pharmacopeia (USP) type II apparatus. The clinical study is an ongoing randomized, cross-over, open-label, fasted, single-dose trial in healthy participants (n=12). An IVIVC will be created by comparing the rank order of drug in vitro dissolution with in vivo absorption. RESULTS/ANTICIPATED RESULTS: Tablet manufacturing was successful, and the tablets displayed the same dissolution rate ranking order as anticipated. Fast-release tablets showed the highest percentage of drug dissolved by 10 min (74%) compared to medium- (62%) and slow-release (1.2%) tablets. Percentage drug dissolved differs by at least 10% at all time points among the different release-rate tablets. The clinical study is currently ongoing, and we expect that the pharmacokinetic (PK) profiles differ among the different tablets. We predict that the rank order of tablet absorption in humans will agree with the order of drug dissolved observed in the dissolution experiments. DISCUSSION/SIGNIFICANCE OF FINDINGS: Spray-dried dispersions are a formulation method to try to improve drug solubility and oral drug absorption. This research will elucidate manufacturing parameters that can impact tablet performance and expand on the ability of in vitro dissolution to predict human PK and streamline drug development of poorly soluble drug candidates.

Team Science

35156

Sensory mechanisms of atypical motor variability and regularity in autism spectrum disorder*

Robin L Shafer¹, Zheng Wang², James Bartolotti¹ and Matthew W Mosconi¹

¹University of Kansas and ²University of Florida

ABSTRACT IMPACT: This project aims to better understand mechanisms of sensory and motor deficits in individuals with ASD with the goal of informing diagnosis and treatment development. OBJECTIVES/GOALS: Over-reliance on both visual and proprioceptive feedback have both been observed during motor behavior in persons with Autism Spectrum Disorders (ASD), suggesting that separate sensory feedback processes may be selectively altered during different behaviors. The objective of this study is to clarify sensory mechanisms of fine motor control in ASD. METHODS/STUDY POPULATION: Participants with ASD (N=43) and controls (N=23) matched on age (10-20 yrs) and non-verbal IQ completed tests of precision gripping. Participants were instructed to press on force sensors with their index finger and thumb so that a moving bar corresponding to their force output reached and stayed as stable as possible at the level of a stationary target bar. Visual feedback was manipulated by changing the visual gain of the force bar (low, medium and high). The force bar moved more per change in force

output at higher gains. Proprioceptive feedback was manipulated by applying 80 Hz tendon vibration at the wrist to induce an illusion of muscle contraction. This was compared to a condition with the tendon vibrator turned off. Force variability (standard deviation) and regularity (sample entropy) were examined. RESULTS/ANTICIPATED RESULTS: Controls showed increased force variability with the tendon vibration on compared to off ($t = -3.372$, $p < 0.001$); however, the ASD group showed no difference in force variability between the tendon vibration conditions ($t = -0.960$, $p = 0.338$). Individuals with ASD had stronger age-associated reductions in force variability relative to controls across tendon vibrator and gain conditions (Group x Age: $t = -4.05$, $p < .001$). The ASD group also had greater age-associated increases in force regularity relative to controls, especially at higher gain levels (Group x Gain Level x Age: $t = -3.22$, $p = 0.001$). Unlike the ASD group for whom regularity increased with age in both tendon vibration conditions, controls only showed these age-related gains when the tendon vibrator was off (Group x Vibration Frequency x Age: $t = 2.46$, $p = .014$). DISCUSSION/SIGNIFICANCE OF FINDINGS: Our findings indicate that while controls integrate proprioceptive and visual feedback online to accurately adjust fine motor behavior, persons with ASD rely mostly on visual feedback. Our results suggest delayed development of sensory integration and reduced reliance on multisensory feedback during online fine motor control in persons with ASD.

Translational Science, Policy, & Health Outcomes Science

13623

Daily relationship between social connectedness and health behaviors among dementia family caregivers

Kylie Meyer, Sara Masoud, Ashlie Glassner, Kevin Hamilton, Ariel Chinae, Darpan Patel, Jing Wang and Carole White
University of Texas Health Sciences at San Antonio

ABSTRACT IMPACT: Knowledge of which aspects of social connectedness most strongly associate with caregiver health and health behaviors can inform intervention targets to improve caregiver health. OBJECTIVES/GOALS: Stressed dementia caregivers are at risk of poor health. Social connectedness may reduce adverse health effects, yet it is unknown about which aspects relate most strongly to health. This is a barrier to intervention development. Our study identifies aspects of social connectedness most strongly associate with caregivers' daily health behaviors. METHODS/STUDY POPULATION: Data. Enrolled spousal caregivers completed 14 consecutive days of online surveys. Measures. We examined multiple health behaviors each day, which included: 1) number of occurrences of 3 potential binge-eating behaviors (range 0 to 30), 2) whether participants engaged in at least 30 minutes of physical activity, and 3) perceived sleep quality, rated 1 (very bad) to 5 (very good). We also examined a count of health symptoms caregivers experienced (e.g., backache; range: 0 to 7). Measures of social connectedness included: spousal emotional support, perceived spousal appreciation, emotional support from any source, and loneliness. Analysis. We applied bivariate multi-level mixed effects models to examine the association between each aspect of social connectedness and health behaviors day-to-day. RESULTS/ANTICIPATED RESULTS: Since November 2020, 5 of N=40 participants were enrolled, of whom 3 had completed all diary surveys. Participants were women ages 59 to 73, and included 4 non-Hispanic white and 1 Hispanic caregivers. Data included 51 days of surveys (93% adherence). No