May 13th, 12:30 PM - 12:45 PM

Variability in Naltrexone Biotransformation

Stephani L. Stancil
Children's Mercy Kansas City, slstancil@cmh.edu

Variability in Naltrexone Biotransformation

Submitting/Presenting Author (must be a trainee): Stephani Stancil, PhD, APRN
Primary Email Address: slstancil@cmh.edu

☐ **Resident/Psychology Intern (≤ 1 month of dedicated research time)**
☐ **Resident/Ph.D/post graduate (> 1 month of dedicated research time)**
X Fellow

Primary Mentor (one name only): Steve Leeder
Other authors/contributors involved in project: Whitney Nolte, Robin Pearce

IRB Number: non-human subjects

Describe role of Submitting/Presenting Trainee in this project (limit 150 words):

Dr. Stancil designed and carried out the experiments and analyzed the data under the mentorship of Drs. Leeder, Pearce and Nolte.

Background, Objectives/Goal, Methods/Design, Results, Conclusions limited to 500 words

Background: Naltrexone (NTX), an opioid antagonist metabolized by AKR1C4, is used in pediatrics to treat numerous conditions involving compulsiveness (e.g., autism spectrum, Prader-Willi, eating disorders, non-suicidal self-injury). Pharmacokinetic variability is apparent in adults, but no data are present in children.

Objectives/Goal: The purpose of this study was to determine the impact of age and other variables on naltrexone biotransformation.

Methods/Design: Human liver cytosol samples (n=164) isolated from pediatric and adult donors were treated with therapeutically relevant concentrations of NTX (0.1, 1 μM). NTX biotransformation was determined by UPLC-MS/MS quantification of primary metabolite, 6-beta-naltrexol (6bn), and 6bn formation rate (pmol/mg protein/min) was calculated. Transcript expression of AKR1C1/2/4 was detected by RNA-seq (n=52). The presence of non-synonymous AKR1C4 coding region single nucleotide variants (SNPs) was determined by Taq-Man genotype assays (n=164). Other factors assessed included donor age and sex. Regression analysis was employed.

Results: Human liver donors (n=164), age range 0-79 y (mean 16.0±18.2 y), 37% (n=60) female, 20% (n=33) heterozygous and 1.2% (n=2) homozygous for co-occurring AKR1C4 variants (S145C/L311V) demonstrated >200-fold range in 6bn formation (0.37-76.5 pmol/mg protein/min at NTX 1 μM). Activity increased steadily from birth reaching a peak in middle childhood (6-11 years) followed by a decline through adulthood to 54% of the peak activity in those aged 22-50 years. AKR1C4 expression explained 31% of the variability in 6bn formation ($p<0.01$). A multiple regression model including AKR1C4 expression, S145C/L311V, age, ethnicity, and cytosol protein per

gram liver-CPPGL explained 65% of variability in 6bn formation ($p<0.001$). Sex did not have a significant impact on 6bn formation.

Conclusions: NTX biotransformation is highly variable in pediatric and adult liver samples and able to be explained by individual factors, most of which are feasible to obtain (e.g., genotype, age and ethnicity). This data may inform a precision therapeutics approach (e.g., exposure optimization) to further study NTX responsiveness in children.