OII-B-3

TOLTERODINE (TOL) PROLONGED RELEASE (PR) IN CHILDREN AGED 11-15 YEARS. D. L. Blowey, MD, S. Abdel-Rahman, W. S. Bundrick, R. Jayanthi, P. Reddy, D. Rivas, M. Borin, N. Borgstein, Children's Mercy Hospitals & Clinics, Pfizer Global Research & Development, Kansas City, MO.

Purpose: To evaluate the pharmacokinetics (PK), safety and clinical effect of TOL PR in children aged 11-15 years with overactive bladder.

Methods: 10 children (8F; 13.2±0.9y) received 2 mg and 21 children (11F; 12.7±1.3y) received 4 mg TOL PR once daily × 6-10 days. A voiding diary and residual urine were collected prior to and during treatment. Serial blood samples (0-25h) on the last day of treatment were assayed for TOL and active metabolite (5HM) levels, and noncompartmental PK analysis was performed.

Results: The mean±SD TOL AUC_{0-24}, Cmax, Tmax and T1/2 in CYP2D6 extensive metabolizers for 2-mg group (n=7) were 39±37 μg·h/L, 3.2±2.9 μg/L, 3.6±1.3 h and 14±4 h, and for 4-mg group (n=20) were 43±34 μg·h/L, 3.4±2.6 μg/L, 3.9±1.6 h and 17±13 h. Active moiety (unbound TOL + unbound 5HM) AUC_{0-24} was 16±5.6 nM·h (2-mg) and 30±11 nM·h (4-mg). Number of micturitions and incontinence episodes decreased from baseline in both dose groups. Residual urine volume was unchanged. The only drug-related adverse events were mild headache and nausea in one child (4-mg group).

Conclusion: Mean drug exposure after a 4-mg once-daily dose of TOL PR is similar to that observed in adults (AUC_{0-24}: TOL=41 μg·h/L, active moiety=26 nM·h). The PK profile of TOL PR is consistent with "flip-flop" kinetics, based on the prolonged apparent T1/2 relative to TOL Immediate release tablet (~2 h). TOL PR improved voiding symptoms in children with overactive bladder without significant adverse effects.

OII-B-4

PHARMACOKINETICS OF METHOTREXATE IN INFANTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA. P. Thompson, MD, Z. E. Dreyer, MD, S. Blaney, MD, S. Berg, MD, D. Murry, PharmD, L. Bomgaars, MD, Texas Children's Hospital, Houston, TX.

An understanding of methotrexate (MTX) pharmacokinetics (PK) is important to achieve drug dosing that optimizes efficacy and minimizes toxicity. Limited information is available on the PK behavior of MTX in infants.

Objectives: To determine the PK of MTX and 7-OH MTX in infants, and to compare the PK parameters of infants to those in older children.

Methods: A subset of patients enrolled on the POG 9407 infant leukemia study participated in this MTX PK study. MTX (4 mg/m^2) was administered i.v. over 24 h on week 4, day 22 of treatment. Sixteen patients, median age 7.8 months (range, 4-13 months) had blood samples collected for analysis of MTX concentrations at 1, 6, 12, and 23 h after the start of the infusion. MTX concentrations were also measured as part of standard clinical practice at the end of the infusion and every 24 h until the MTX level was < 0.18 μM. Model independent PK parameters (AUC, C_{max}) were determined for each patient. MTX PK data were also analyzed using a two-compartment/first order model (ADAPT).

Results:

	MTX	7-OH MTX
AUC (μM-hr)	1750 ± 400	255 ± 128
C_{max} (μM)	58 ± 17	9.3 ± 4.5
CL (ml/min/m^2)	116 ± 30	–
V_c (L/m^2)	14.6 ± 4.6	–
V_p (L/m^2)	6.9 ± 6.3	–
$t_{1/2}$ distribution (h)	1.4 ± 0.63	–
$t_{1/2}$ elimination (h)	7.7 ± 4.9	–

Conclusions: The estimated MTX CL for infants > 3 months of age was very similar to that reported for older children between 1-19 years of age (103-151 ml/min/m^2). Further study of MTX PK in infants <3 months is ongoing.

PDI-A-1

TESTING SINGLE DOSE MOXIFLOXACIN AND IBUTILIDE AS POSITIVE CONTROLS FOR DETECTING QTC PROLONGATION IN HEALTHY SUBJECTS. C. J. Harris, PharmD, A. C. Cyr, Eli Lilly and Company, Purdue University, Indianapolis, IN.

The ability to detect drug-induced changes in the QTc interval has become critical in drug development. Inclusion of a positive control can assure a study's ability to detect this effect. At weekly intervals, in a single blind randomized, crossover study, we administered either moxifloxacin 400 mg orally, ibutilide 0.002 mg/kg IV over 10 min, or placebo (infusion and tablets) to 23 healthy male and female subjects. Thirty-eight 12-lead ECGs were obtained on each treatment day. Subjects tolerated the treatments well and no clinically significant arrhythmias were detected on telemetry. Initial data analysis has focused on the machine-measured QT intervals with the Fridericia correction for heart rate. Using a time-matched analysis, the mean QTc change (95% CI) 4-11 hours after the moxifloxacin dose was 5.9 msec (2.0, 9.8). The QTc interval was elevated from 7-30 min after the start of the ibutilide infusion with a mean QTc change (95% CI) of 11.3 msec (3.9, 18.7). Cardiac intervals were also hand-measured by a cardiologist, and these values will be compared to the machine-measured values. Our preliminary data analysis shows that single-dose active controls (ibutilide or moxifloxacin) are not associated with a substantial proarrhythmic risk (< 20 msec) and produce detectable (> 5 msec) prolongation of the QTc interval.

PDI-A-2

A DEFINITIVE STUDY OF THE EFFECTS OF PDE-5 INHIBITORS ON CARDIAC REPOLARIZATION IN MIDDLE-AGE MALES. Ilson BE*, Shaddinger BC*, Dabiri GA*, Patel BR*, Boyle DA*, Sethuraman V*, Montague T*, Morganroth J. [Univ of Pennsylvania and eResearch Technology] *=GSK Pharmaceuticals, King of Prussia, PA.

Patients with erectile dysfunction may use PDE5 inhibitors such as vardenafil (V) and sildenafil (S), which alter the hERG channel of transfected cells only at suprapharmacologic nonclinical concentrations. This study evaluated effects of therapeutic and supratherapeutic doses of V and S on QT/QTc duration. A placebo- and active-control (moxifloxacin, M, at therapeutic dose), period balanced, double blinded, 6 way crossover study evaluated single oral doses of V 10 mg, V 80 mg, S 50 mg, S 400 mg, M 400 mg and placebo in 58 healthy men (mean age 53) with doses separated by 3 days. Six replicate 12-lead digital ECGs were recorded at 3 time points prior to and 5 time points post dose to cover the full exposure of drugs and metabolites. An independent lab blindly analyzed the ECGs. PK blood samples were drawn at the same 5 time points post dose. For placebo, mean change in QTcF (Fridericia) duration from baseline at 1 hour post dose (approximate Tmax of V and S) was 0 msec (+/− 0.7 SD). QT and QTc variability was small across regimens, indicating statistically powerful results due to large sample size and number (17,000) of ECGs. M demonstrated an expected 8 msec mean change and was the only drug to prolong absolute QT. Placebo-corrected values of mean change from baseline at 1 hour post-dose for each regimen are shown below. QT corrected using linear and nonlinear methods and each individual's QT/HR data (QTci) yielded similar trends of drug effect on QTc. PK/PD modeling demonstrated a very shallow QTc-concentration relationship for V and S. Therapeutic and supratherapeutic doses of V and S produced no increase of absolute QT and similar small increases in QTc interval. We conclude that these findings, and the absence of postmarketing reports of torsades de pointes with S, indicate that small increases in QTc for V and S are clinically insignificant. This study design may serve as a guide for future definitive QT assessment.

Treatment	Treatment effect (Placebo–corrected, 90% CI)			
	HR (bpm)	Absolute QT (msec)	QTcF (msec)	QTci, linear correction (msec)
V 10 mg	5 (4,6)	−2 (−4,0)	8 (6,9)	4 (3,6)
V 80 mg	6 (5,7)	−2 (−4,0)	10 (8,11)	6 (4,7)
S 50 mg	4 (3,5)	−2 (−4,0)	6 (5,8)	4 (2,5)
S 400 mg	5 (4,6)	−1 (−3,1)	9 (8,11)	5 (4,7)
M 400 mg	2 (1,3)	3 (1,5)	8 (6,9)	7 (5,8)