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PHARMACOKINETICS AND TOLERABILITY OF ATOMOXETINE IN ADULTS OF KNOWN CYP2D6 PHENOTYPE. J. Witcher, PhD, A. Long, BS, J. M. Sauer, PhD, B. Smith, PhD, H. Read, MD, PhD, Eli Lilly and Company, Indianapolis, IN.

BACKGROUND/AIMS: This study was designed to evaluate atomoxetine pharmacokinetics, dose proportionality, and safety in CYP2D6 extensive metabolizer (EM) and poor metabolizer (PM) subjects after single dose and at steady state.

METHODS: Part A: single-blind, placebo-controlled, single-dose escalation design from 10 to 120 mg. Part B: single-blind, placebo-controlled, multiple-dose design of 40 mg BID for 7 days. The pharmacokinetics of atomoxetine, 4-hydroxyatomoxetine, and *N*-desmethylatomoxetine were evaluated using noncompartmental analysis. Safety assessments included adverse events, heart rate (HR), blood pressure (BP), and orthostatic measures.

RESULTS: Dose proportionality and linearity were shown in both EM and PM. PM had a 10-fold lower clearance and a longer $t_{1/2}$ than EM subjects (5.23 hr vs. 24.4 hr). HR increases were similar for EM and PM in Part A, while PMs had a maximum HR about 10 bpm higher than EMs in Part B.

CONCLUSIONS: Atomoxetine pharmacokinetics were influenced by the CYP2D6 polymorphism. Orthostatic changes in systolic BP and HR were not clinically significant. The hemodynamic response to atomoxetine was similar across subjects, despite marked differences in exposure due to CYP2D6 polymorphism. EM and PM subjects had similar drug-related adverse event profiles, therefore no dose adjustment is necessary.

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HEMODYNAMIC EFFECTS OF DULOXETINE AT SUPRATHERAPEUTIC DOSAGES. M. Derby, L. Zhang, C. Gonzales, J. Chappell, R. Lucas, J. T. Callaghan, Eli Lilly, Indianapolis, IN.

BACKGROUND/AIMS: Hemodynamic effects of duloxetine, a potent dual inhibitor of serotonin and norepinephrine uptake, were evaluated in a study designed to definitively establish the absence of QT prolongation at supratherapeutic exposures.

METHODS: Vital signs were collected in a multicenter, double-blind, randomized, placebo-controlled, crossover study that enrolled 117 healthy women aged 19–74 years. Duloxetine dosages escalated from 60 mg BID to 200 mg BID. Supine and postural vital signs were monitored at baseline, prior to morning dosing, and at steady state.

RESULTS: Initiation of duloxetine at 60 mg BID caused a 5–7 mmHg increase in supine systolic and diastolic blood pressures that remained stable despite continued dose-escalation. Supine heart rate also increased upon dosing with duloxetine 60 mg BID, but the increase was more gradual and dose-dependent, reaching 10–12 bpm above baseline levels by the end of the 200-mg BID dosing period. Dose-dependent postural changes occurred with duloxetine, which increased throughout dose escalation. Of 11 subjects who met predefined criteria for outliers, only 5 had associated symptoms. All vital signs returned to normal by 1–2 days after stopping the drug.

CONCLUSIONS: Supratherapeutic duloxetine exposures produce minor and generally asymptomatic changes in supine and postural vital signs. Some prehypertensive subjects may become hypertensive upon initial dosing with duloxetine, but this can be predicted from predose values.

PI-73

FEASIBILITY OF ASSESSING DIFFERENTIAL PHARMACODYNAMIC (PD)/ADVERSE EVENTS (AE) PROFILES ON CNS AGENTS. A. Moton, PharmD, D. Ouellet, PhD, R. Morlock, PhD, J. Nyberg, MS, D. Feltner, MD, Pfizer, Ann Arbor, MI.

BACKGROUND: The AE profile of psychotropics is an important opportunity for differentiation of new drugs in development relative to marketed competitors. This study was designed to assess the feasibility of using different subjective scales as biomarkers of PD response using 4 model CNS drugs.

METHODS: 20 healthy subjects were randomized in a double-blind, single dose, 5 way crossover study in a Phase 1 clinic. Treatments were atomoxetine (A, 80 mg), olanzapine (O, 10 mg), lorazepam (L, 2 mg), paroxetine (P, 40 mg) and placebo (PCB). PD responses were measured up to 24 hrs post-dose using Visual Analogue Scale (VAS, 6 items), and Likert scales (7-point ordered categorical, 70 items) to assess items like somnolence, dizziness, nausea, restlessness, etc. ANCOVA analyses were conducted on peak change and time-average area under the curve vs. PCB.

RESULTS: Different PD profiles (Likert and VAS) and time course of PD response were noted for the 4 model drugs. For L and O, CNS depressant activities such as sleepy, confused, poor balance, dizzy, and difficulty concentrating, were different from PCB. Decreases in DSST were also significant (L, O). A different pattern of PD effects (e.g., dry mouth, sweating, hot or flushed, excited, nervous, gastrointestinal (GI) effects were observed with A. Only GI effects were significant with P.

CONCLUSIONS: Different PD/AE profiles can be detected in a small Phase 1 study; and may be used as biomarkers to compare potency and tolerability of new drugs relative to marketed compounds.

PI-74

A RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED 3-WAY CROSSOVER STUDY INVESTIGATING PSYCHOMOTOR AND COGNITIVE RESIDUAL EFFECTS OF A NEW ZOLPIDEM MODIFIED-RELEASE FORMULATION IN HEALTHY VOLUNTEERS. O. Blin, PhD, J. Micallef-Rolle, E. Legangeux, I. Zobouyan, Centre de Pharmacologie Clinique et d'Evaluations Therapeutiques (CPCET), Hopital de la Timone, Sanofi-Synthelabo Research, Marseille, France.

AIMS/BACKGROUND: To assess the residual psychomotor and cognitive effects and safety of a new zolpidem modified-release (MR) formulation 8 h after a single dose.

METHODS: A randomized, double-blind, placebo- and reference-controlled, 3-period crossover study in 18 healthy volunteers (22 to 38 years old, 10 male) comparing zolpidem MR 12.5 mg or flurazepam 30 mg to placebo. Cognitive and psychomotor tests were performed 8 h postdose: Critical Flicker Fusion (CFF), Choice Reaction Time (CRT), Compensatory Tracking Time (CTT), Immediate and Delayed Word Recall (WR_i, WR_d), and Digit Symbol Substitution Test (DSST). Subjective sleep quality was evaluated using the Leeds Sleep Evaluation Questionnaire. Clinical laboratory parameters, vital signs, and adverse event recording evaluated safety.

RESULTS: Pairwise comparisons between zolpidem MR and placebo demonstrated no significant difference in performance in CFF, CRT, WR_i, WR_d and DSST, 8 h postdose. A significant increase in CTT time reaction was half that observed with flurazepam. Flurazepam significantly impaired performance in all tests except DSST compared to placebo.

CONCLUSION: This study demonstrates that unlike flurazepam (positive control), zolpidem MR 12.5 mg has no residual effects on CNS integrative capacity, sensorimotor or psychomotor performance, immediate and delayed memory recall except for CTT time reaction compared to placebo. Zolpidem MR is well tolerated and exhibits a comparable safety profile to placebo.