

Newsletter



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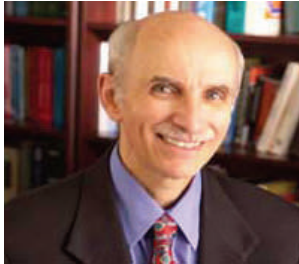
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CRI Therapeutic Areas:

- Obesity & Nutritional Disorders
- Infectious Disease
- HIV
- Pediatrics
- Neurology
- Geriatrics/Dementia
- Women's Health
- General Psychiatry
- Addiction Medicine

Message from the President



Previous issues have outlined the various activities and capabilities of CRI beyond its clinical trials. This issue highlights one of these activities: Working with sponsors to publicize the results of their trials through presentations and publications.

So far this year, CRI has published the results of two studies and is scheduled to present at eight national or international meetings. See page 4.

Page 2 summarizes the results of two studies published in the *Journal of Clinical Psychopharmacology*, the leading journal in its area. These studies compared the relative effects of three widely used antidepressants on the drug metabolizing enzyme, cytochrome P450 (CYP) 2D6 using metoprolol as the model substrate: the first compared duloxetine versus sertraline and the second escitalopram versus sertraline.

These two studies illustrate several CRI capabilities: protocol development, study execution, data analysis, report preparation, and the value of its special population databases. CRI designed both studies, developed the protocols, executed the studies, prepared the reports, and presented the results as posters and as journal publications. CRI worked with its collaborators at Tufts University and the University of Indiana to have both the drug assays and pharmacokinetic analyses done.

In terms of CRI special population databases, these two studies were conducted in healthy volunteers including being normal in terms of CYP 2D6 drug metabolism. The gene for CYP 2D6 is polymorphic such that approximately 5-10% of Caucasians are genetically deficient in functional CYP 2D6 and hence are termed CYP 2D6 "poor" metabolizers (PMs). Since the goal of these two studies was to compare the relative effects of the three antidepressants on CYP 2D6 activity, CYP 2D6 PM status was a study exclusion criterion. The CRI genetic database was thus important to the timely execution of this study.

The study highlighted on page 3 involved the converse. Here the goal was to examine the effects of CYP 2D6 on the metabolism of the marketed antidepressant, venlafaxine, and the investigational antidepressant, desvenlafaxine. Venlafaxine is known to be metabolized by CYP 2D6 but desvenlafaxine is not based on preclinical data. This study extended that preclinical data into man by studying pharmacokinetics of both antidepressants in two groups of genetically defined volunteers: CYP 2D6 extensive metabolizers (EMs) and CYP 2D6 PMs. The CRI genetic database was again important to this study's timely execution.

Future issues of this newsletter will report on the results of other studies which CRI is working with sponsors to prepare for presentation and/or publication. These studies will highlight other special CRI populations and capabilities.

We look forward to discussing how CRI resources and capabilities can assist you from study design through presentation/publication. In all of these regards, the goal of CRI is the timely and high quality completion of your studies to further your drug development goals.

Sheldon Preskorn, M.D., President & CEO

Comparison of Duloxetine, Escitalopram and Sertraline Effects on Cytochrome P450 (CYP) 2D6 Function in Healthy Volunteers

Preskorn SH, Greenblatt DJ, Flockhart DA, Luo Y, Perloff ES, Harmatz JS et al.. *Journal of Clinical Psychopharmacology*. 27(1):28-34, February 2007.

This study was the first to directly compare the relative effects of duloxetine, escitalopram, and sertraline on the functional activity of the drug-metabolizing cytochrome P450 (CYP) 2D6 enzyme as assessed by changes in the pharmacokinetics of the CYP 2D6 model substrate-drug, metoprolol. Single-dose pharmacokinetics of metoprolol were measured before and after 17 days of treatment with escitalopram 20 mg/day, duloxetine 60 mg/day or sertraline 100 mg/day in young healthy male and female participants. The outcome measures were changes in metoprolol peak plasma levels (C_{max}), area under the plasma concentration-time curve (AUC) and clearance. The results were tested using paired t-tests and independent t-tests. The addition of each drug produced statistically significant changes in metoprolol pharmacokinetics when baseline values were compared to on drug values. Duloxetine, compared to sertraline, produced statistically significantly larger changes in metoprolol pharmacokinetic parameters. The changes produced by escitalopram and sertraline were not statistically different.

Figure 1. Plasma levels of metoprolol before (Day -7) and after coadministration (Day 17) of escitalopram (A) and sertraline (B)

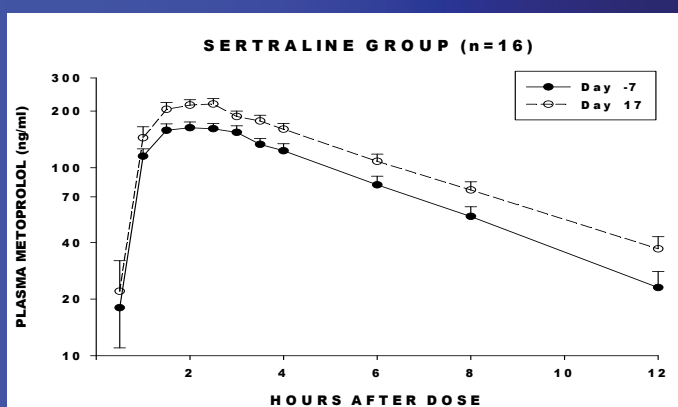
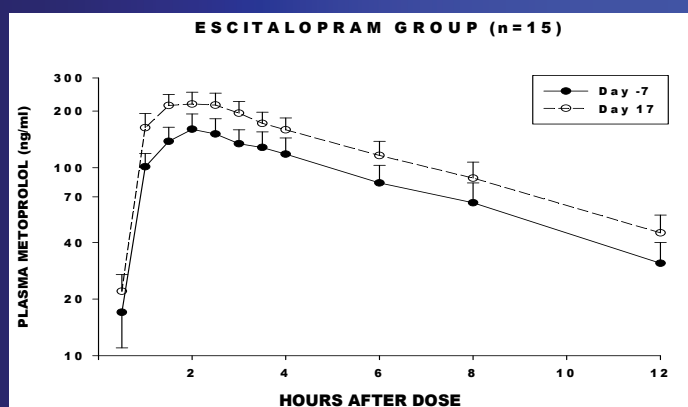
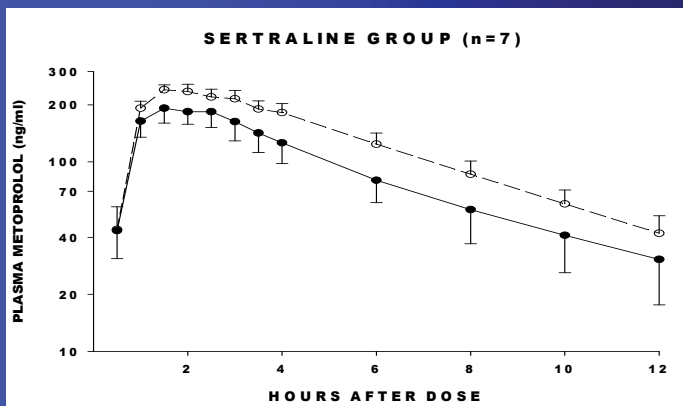
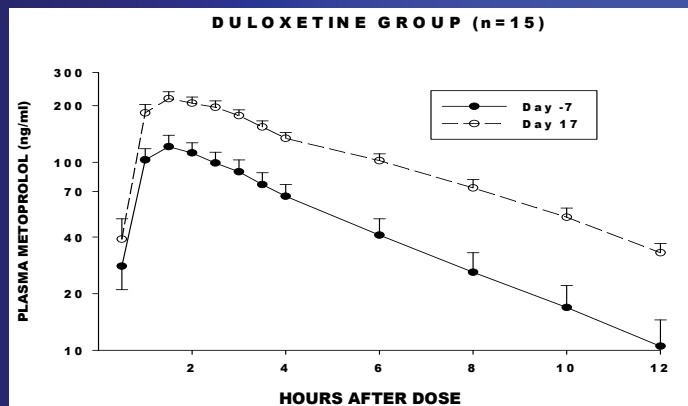


Figure 2. Plasma levels of metoprolol before (Day -7) and after coadministration (Day 17) of duloxetine (A) and sertraline (B)



The Pharmacokinetics of Venlafaxine Extended Release and Desvenlafaxine Succinate in Healthy Subjects who are Extensive and Poor Metabolizers via Cytochrome P450 (CYP) 2D6

Sheldon Preskorn, MD¹; Albena Patroneva, MD²; Alice Nichols, PhD²; Heather Silman²; Ron Pedersen, MS²; Jeff Paul, PhD²; Saeed Ahmed, MD²

¹Clinical Research Institute, Wichita, KS; ²Wyeth Research, Collegeville, PA.

Objective:

The study evaluated the pharmacokinetics (PK) of single doses of VEN extended release (VEN ER) and DVS in healthy adults who are extensive or poor metabolizers (EMs or PMs, respectively) via CYP2D6.

Methods:

This open-label, randomized, crossover, single-dose study enrolled subjects aged 19 to 36 years. Either VEN ER 75 mg or DVS 100 mg was administered. CYP2D6 genotyping was determined by analyzing whole blood samples. There were 14-allele designations identified by the genotyping process. Plasma drug levels were measured using validated liquid chromatography/tandem mass spectrometry (LC/MS/MS). Genotypes comparisons were calculated with ANOVA using logarithms of AUC and C_{max} . The least squares geometric mean and 90% CI for AUC and C_{max} were calculated.

Results:

The ratio of VEN:desvenlafaxine following VEN ER administration was statistically greater in PMs compared with EMs, indicating greater VEN exposure and lower desvenlafaxine exposure. Desvenlafaxine exposure following DVS administration was not statistically different between PMs and EMs. Common treatment emergent adverse events (TEAEs) included nausea (36%) and headache (21%).

Conclusions:

Unlike the PK following the administration of VEN, the exposure to desvenlafaxine following DVS administration is not significantly affected by CYP2D6 polymorphisms. This lack of effect may reduce variability in drug tolerance and efficacy.

Geometric Means of the Area Under the Plasma Concentration — Time Curve (AUC) of venlafaxine in individuals who are genetically either extensive metabolizers (EM) or poor metabolizers (PM) via the Cytochrome P450 (CYP) enzyme 2D6 given 75mg of venlafaxine extended release (VEN ER) or 100mg desvenlafaxine succinate sustained release (DVS SR)

Figure 1. Ven ER 75mg: VEN PK
P Value < 0.001

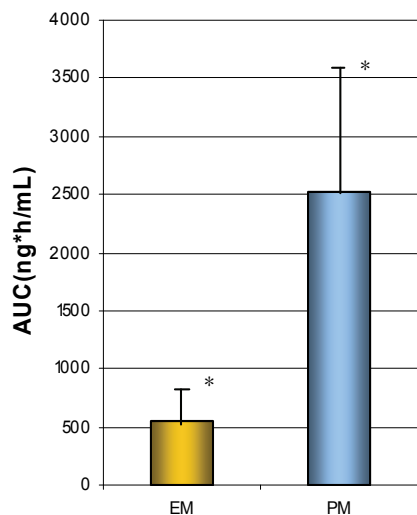


Figure 2. Ven ER 75mg: ODV PK
P Value < 0.001

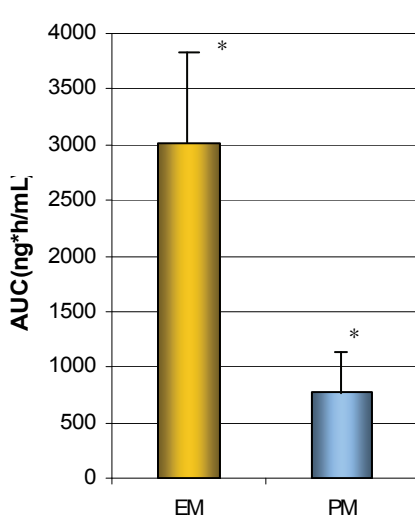
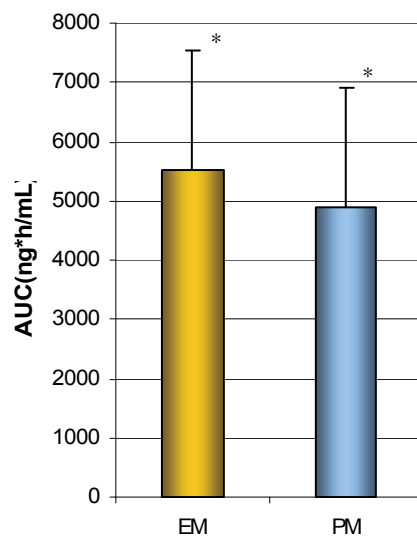


Figure 3. DVS SR 100mg: ODV PK



* 90% Confidence Interval

This poster will be presented at the NCDEU Annual Meeting, June 11-14, 2007 in Boca Raton, Florida.



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Recent and Upcoming CRI Publications and Presentations

In addition to the publication highlighted on page 2, CRI from December 2006 to December 2007 has either presented or has submitted for presentation at the following national and international meetings:

- American Psychiatric Association¹
- American Society for Clinical Pharmacology and Therapeutics²
- American College of Neuropsychopharmacology¹
- European Congress of Psychiatry¹
- International Congress of Schizophrenia Research¹
- New Clinical Drug Evaluation Unit³
- Canadian Psychiatric Association³
- European College of Neuropsychopharmacology³

These presentations cover a range of studies including: effect of food on drug absorption, effects of various drugs on hemodynamics, QTc, cognitive function, and clinical depression.

The participants in these studies include: healthy volunteers, participants with mild probable Alzheimer’s disease, residual schizophrenia, and treatment resistant depression.

For further details about the presentations, please contact Becky Soeganto at 293-1833.

¹ presentation scheduled, ² presentation done, ³ application pending

How to Reach Us

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