Determination of CYP2D6 Phenotyping for Metoprolol using the *CYP2D6* Genotype-derived Activity Score: Results from a Prospective, Clinical Trial

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Background

- *CYP2D6* genotype-derived activity score (AS) is assigned to describe an individual's CYP2D6 phenotype:

AS	Genotype Description	Phenotype
0	2 no-function alleles	PM
0.5	1 no-function and 1 decreased function allele	IM
1	Equivalent of 1 normal function allele	IM or NM*
1.5	1 normal function and 1 decreased function allele	NM
2	2 normal function alleles	NM

PM, Poor metabolizer; IM, Intermediate metabolizer; NM, normal metabolizer
*IM per Dutch Pharmacogenetic Working Group (*Clin Pharmacol Ther*. 2011;89:662-73); NM per Clinical Pharmacogenetics Implementation Consortium (*Clin Pharmacol Ther*. 2014;95:376-82)

- rs133333, a novel *CYP2D6* regulatory polymorphism, increases CYP2D6 expression and is often inherited with the decreased function **2, *17, *29*, and **41* alleles. (*Human Mol Genet*. 2014;23:268-78)
- Metoprolol, a model CYP2D6 substrate, is well suited to address the phenotype assignment for a *CYP2D6* AS = 1

Objective

Evaluate the pharmacokinetics (PK) of metoprolol succinate across *CYP2D6* AS of 1 – 2 to define CYP2D6 phenotypes for metoprolol.

Methods

- Open-labeled PK study of metoprolol succinate extended-release (ER) (NCT02417246).
- Of 57 enrolled hypertensive patients, 43 received brand name metoprolol ER 50-150 mg/day for ≥5 days followed by 24-hr serial blood collection, and 36 were included in this analysis.
- Metoprolol concentrations were determined by LC-MS/MS.
- Genotyping was done via PCR and pyrosequencing for the *CYP2D6 *2-*6, *10, *17, *29, *40*, **41,* and rs133333 alleles and by pyrosequencing allele quantification and TaqMan Copy Number Assay for copy number variation.
- AS was assigned per number of functional alleles and use of CYP2D6 inhibitors.

Methods Continued: Data Analysis

- Apparent oral clearance (CLo) calculated as:

$$CLo\ (mL/min) = \frac{Metoprolol\ Dose\ (mg)}{Area\ Under\ the\ Curve_{\ o\_t}\ (min * mg/mL)}$$

- Regression analysis with Dunnett's test for multiple comparisons was used to compare CLo by *CYP2D6* AS. AS, age, gender, BMI, and race were included as covariates and were held constant during analysis for each individual predictor. Significant p-values are reported here.

Results

Baseline Demographics and Metoprolol ER Doses for PK Study

Demographics	Pharmacokinetic Study (n = 36)
Age (years) – mean (SD)	53 (12)
Males – n (%)	16 (44)
Race – n (%)	
White	23 (64)
African American (AA)	12 (33)
Asian	1 (3)
BMI (kg/m^2) – mean (SD)	30 (5)
Metoprolol ER dose – n (%)	
50 mg	28 (78)
100 mg	6 (17)
150 mg	2 (5)

Diplotypes with AS Change After Including Enhancer SNP

Diplotype	Race	AS (-) Enhancer	rs133333: Genotype at Enhancer SNP locus	AS (+) Enhancer
**17/*29* (n = 1)	AA	1	C/T	0.5
**2/*4x2* (n = 1)	White	1	T/T	0.5
**2/*41* (n = 1)	White	1.5	T/T	1
**2/*2* (n = 1)	AA	2	T/T	1
**2/*2* (n = 1)	AA	2	C/T	1.5
**1/*2* (n = 1)	AA	2	T/T	1.5

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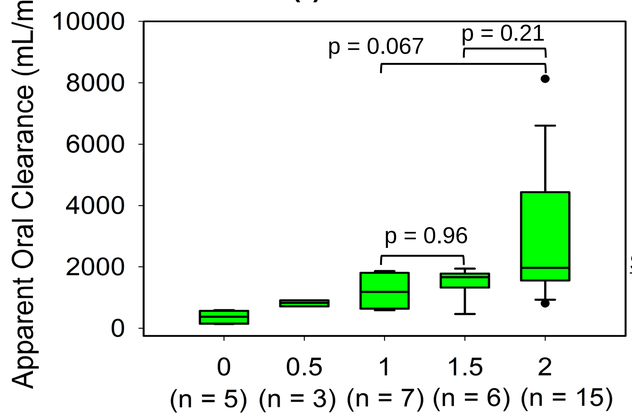
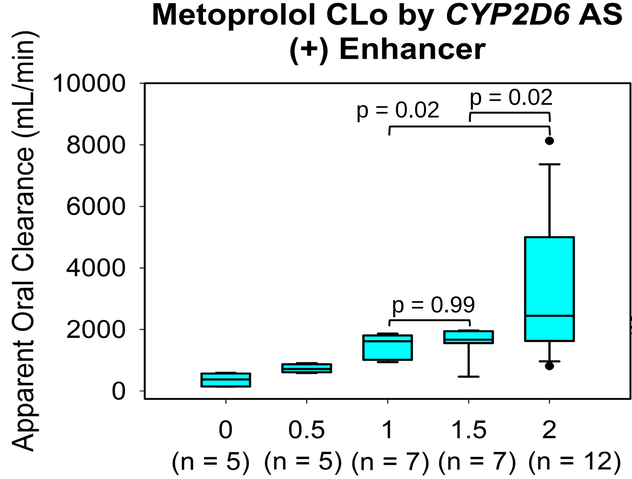
Results

Metoprolol CLo by *CYP2D6* AS (-) Enhancer



Significant p-values
CYP2D6 AS;
Adjusted p = 0.02

Metoprolol CLo by *CYP2D6* AS (+) Enhancer



Significant p-values
CYP2D6 AS;
Adjusted p = 0.002

Summary and Conclusion

- Metoprolol ER CLo differed significantly between AS of 1 and 2, when the enhancer SNP was considered.
- The enhancer SNP changed the AS for AAs (33%) more often vs. Whites (9%). Further assessment of the effects in AAs is warranted.
- Future directions include a pharmacodynamic assessment of metoprolol response across *CYP2D6* AS of 1 – 2.