Determination of CYP2D6 phenotyping for metoprolol using the genotype-derived activity score

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Introduction

- Metoprolol succinate, at therapeutic doses, is a selective β_1-blocker metabolized by cytochrome P450 (CYP) 2D6
- Genetic polymorphisms in *CYP2D6* leads to variation in enzymatic activity (phenotype)
- Activity score (AS), determined by genotype and drug interactions, is used to phenotype CYP2D6 for clinical recommendations
- Based on pharmacokinetic (PK) data specific for dextromethorphan and codeine, a *CYP2D6* genotype-derived AS of 0 to >2 is assigned to describe a person's CYP2D6 phenotype
- There is inconsistent phenotyping among expert opinion groups for an AS = 1
- The Clinical Pharmacogenetics Implementation Consortium (CPIC), classifies an AS = 1 as the normal metabolizer (NM) phenotype
- The Dutch Pharmacogenetics Working Group (DPWG) classifies an AS = 1 as the intermediate metabolizer (IM) phenotype
- It is unknown which phenotyping most accurately describes the CYP2D6 substrate, metoprolol

Research Question

- How do metoprolol PK compare across CYP2D6-derived activity scores?

Study Design

- Open-labeled pharmacokinetic and pharmacodynamic (PK-PD) study of metoprolol succinate in hypertensive patients

Methods

- Twenty-nine (29) hypertensive patients were treated with metoprolol 50-150mg/day for ≥ 5 days, to obtain steady state before PK sampling
- PK samples were collected at 12 time points over a 24-hr period, and were immediately centrifuged with the plasma separated, frozen, and stored at -20ºC or -80 ºC until analysis
- Metoprolol plasma concentrations were analyzed by liquid chromatography tandem mass spectrometry (LC-MS)
- Genotyping for *CYP2D6* *2-*6, *10, *17, and *41 alleles was done via polymerase chain reaction (PCR) and pyrosequencing, including deletions
- Copy number variation was estimated by the TaqMan Copy Number Assay (Life Technologies) and a pyrosequencing-based method
- AS of 0-2.5 was assigned based on the number of functional alleles
- For 25 patients taking metoprolol 50 mg/day, exercise induced tachycardia (EIT) was recorded as the percent increase in heart rate (HR) during an exercise test (Bruce Protocol)
- For 20 patients initiating a beta-blocker (no beta-blocker therapy before study participation) and taking metoprolol 50 mg/day, resting HR was measured at baseline, before starting metoprolol, then again at steady state on 50mg/day, and expressed as change in HR (bpm)
- PK and PD metrics were grouped and reported by CYP2D6 AS

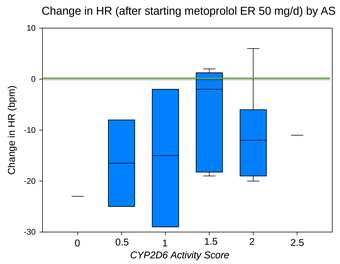
Results

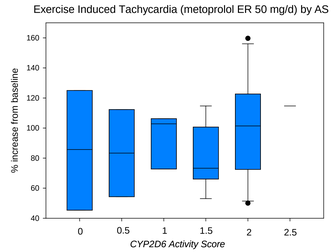
	PK		PD	
CYP2D6 AS (n=29)	AUC/dose (ng x hr/mL/mg)	C_{max}/dose (ng/mL/mg)	EIT[α] (%)	Change in HR[β] (bpm)
0 (n=5)	18.9 (15.2-56.2)	0.99 (0.79-2.9)	85.3 (39.9)	-23 (0)
0.5 (n=4)	12.1 (10.7-13.3)	0.79 (0.6-1.04)	83.3 (41)	-16.5 (12)
1 (n=3)	5.6 (4.4-10.1)	0.3 (0.25-0.68)	93.9 (18.4)	-15.3 (13.5)
1.5 (n=6)	5.7 (5.2-9.1)	0.34 (0.29-0.46)	80.1 (21.8)	-6.3 (9.6)
2 (n=10)	6.3 (4.4-8)	0.36 (0.28-0.47)	100.7 (32.5)	-10.1 (8.9)
2.5 (n=1)	2	0.12	114.7 (0)	-11 (0)

[α]metoprolol 50 mg/day; n=25
[β]new start beta-blocker and metoprolol 50 mg/day; n=20

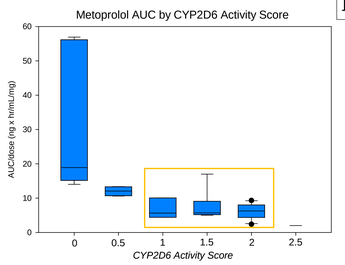
- Mean (SD) HR and EIT did not appear to show difference between AS groups
- Median (IQR) AUC and Cmax were similar across AS of 1, 1.5, and 2; therefore, these groups were combined (AS 1-2) for further analysis
- Median (IQR) AUC and Cmax for AS of 1-2 appear lower than with an AS of 0 and 0.5, and higher than with an AS of 2.5

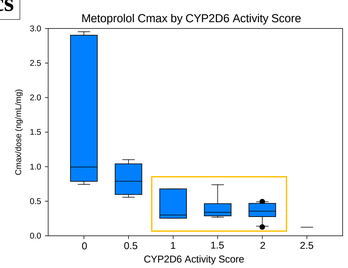
PD Metrics

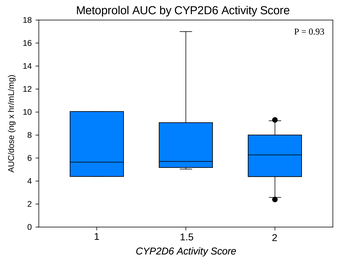


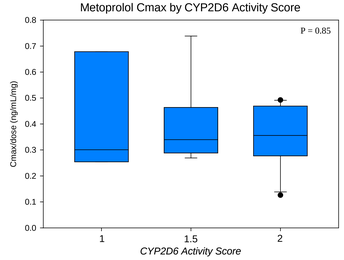


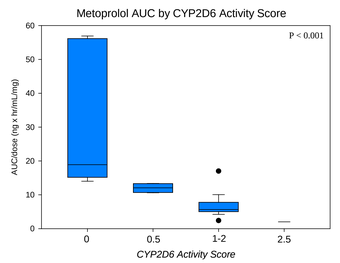
PK Metrics

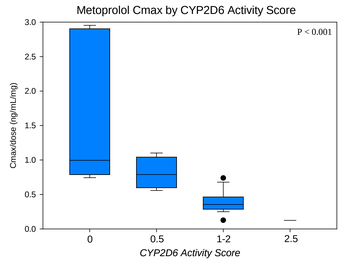












Conclusion

- These data suggest that metoprolol PK are similar between patients with an AS of 1-2 reflecting the CYP2D6 NM phenotype which differs significantly from an AS of 0, 0.5, and 2.5
- For the CYP2D6 substrate, metoprolol succinate, AS = 1 is more reflective of the NM phenotype
- Change in resting HR and EIT did not reveal any clear differences between CYP2D6 AS groups in the current sample size
- The complete data set with statistical analysis will include 38 patients

Acknowledgement

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