[10:00 – 10:30]

Influence of *CYP2D6* genotype on the metabolic properties of metoprolol in Korean

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Abstract

Variation in genotype for drug-metabolizing enzymes, drug receptors, and drug transporters is associated with individual and ethnic variation in drug response. Cytochrome P450(CYP) 2D6 is the most extensively characterized polymorphic drug-metabolizing enzyme. The variability in metabolism is associated with inter-individual variation in drug pharmacokinetics. Metoprolol, among the β-blockers, is most extensively metabolized by CYP2D6, with this enzyme accounting for 70% to 80% of metoprolol metabolism. In this study, 107 subjects of healthy Korean were genotyped for the CYP2D6*10 allele. Of them, subjects were classified into following 3 groups (*1/*1, n=8; *1/*10, n=7; *10/*10, n=6) and metoprolol tartrate 100mg (Betaloc® tablet) was once administered orally. Then the pharmacokinetic parameters of metoprolol and α-hydroxymetoprolol were determined. As results, AUC, Cmax and T1/2 of metoprolol and α-hydroxymetoprolol were significantly different among the *1/*1, *1/*10 and *10/*10 ($p<0.05$), but Tmax was not. And metabolic ratio was

significant different among 3 groups ($p<0.05$). These results suggest that CYP2D6*10 allele may alter the pharmacological properties of metoprolol.

Subject: The 107 healthy Koreans participated in the determination of CYP2D6*10 genotyping study. All volunteers were included after obtaining the informed consent. They are categorized into three groups (CYP2D6*1/*1, *1/*10, and *10/*10). Of them, twenty-one volunteers (16 males, 5 females, Age 21~30 years) were selected for the pharmacokinetic study of metoprolol and α-hydroxymetoprolol. Metoprolol 100mg were administered to them orally.

CYP2D6 genotyping: Genomic DNA was isolated by phenol-chloroform extraction methods. DNA samples were processed with allele-specific primer by polymerase chain reaction for detection of the CYP2D6 alleles *1 and *10.

Quanitification of metoprolol and α-hydroxymetoprolol: Plasma samples were extracted by t-butylmethyl ether. Metoprolol and α-hydroxymetoprolol were analyzed using HPLC. HPLC conditions were as follows ;

Column : Capcell Pak UG120 (4.6mm x 150mm)

Detector : FS (Ex. 225nm, Em. 310nm)

Mobile Phase : 0.02M phosphate buffer(pH 3.0)•Acetonitril (875:125)

Flow rate : 1.0ml/min

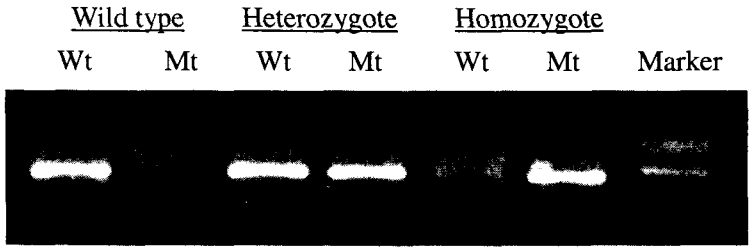
Inj. Vol. : 10μl

Pharmacokinetic study: After fasting overnight, each subject was given a single dose of 100mg metoprolol tratrate tablet (Betaloc®). Blood samples were drawn at 0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hours after administration. Plasma concentration of metoprolol and α-hydroxymetoprolol were determined as mentioned above. AUC, T1/2, Cmax, and Tmax were calculated using WinNonlin program.

Statistical Analysis: A one-way ANOVA was used for the comparison among 3 groups

Results:

1. CYP2D6*10 Genotypes



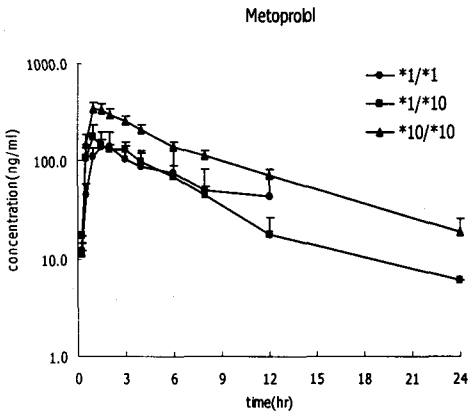
Detection of C188T mutation in CYP2D6 gene

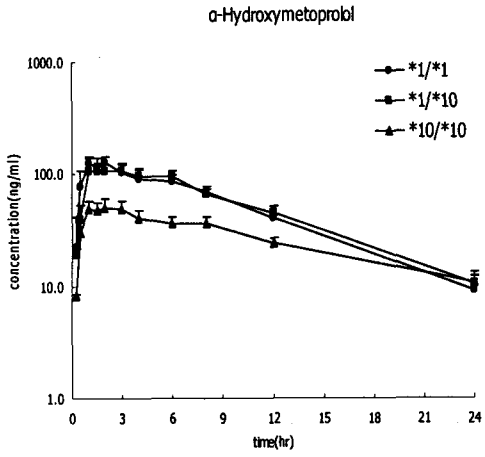
2. Allele frequencies of CYP2D6 in Korean

No. of subject	Genotype Frequency (%)			Allele Frequency	
	CC	CT	TT	C	T

107	33 (30.9)	47 (43.9)	27 (25.2)	0.53	0.47

3. Pharmacokinetic Profiles





4. Data Analysis

	parameter	*1/*1	*1/*10	*10/*10	P
Metoprolol	AUC0→∞	953.66±1069.73	995.59±288.55	2534.85±565.89[b),c)]	0.002*
	Cmax	164.64±104.22	218.41±70.85	359.08±107.97[b)]	0.007*
	Tmax	1.31±0.46	1.57±1.01	1.33±0.41	0.978
	T1/2	3.20±1.19	3.21±1.34	5.30±1.19[c)]	0.03*
α-Hydroxy metoprolol	AUC0→∞	1311.63±383.36	1348.17±288.55	804.43±201.35[b),c)]	0.009*
	Cmax	152.50±50.47	139.63±38.31	55.17±17.25[b),c)]	<0.001*
	Tmax	2.06±1.66	2.29±1.22	2.00±0.63	0.653
	T1/2	5.68±1.49	5.99±1.41	10.09±3.96[b),c)]	0.007*

Metabolic ratio (at Tmax of Metoprolol)	1.34±1.06	3.75±5.37	7.18±1.55[b)]	0.003*

*, a P value less than 0.05 was considered to be statistically significant. ;

b), statistical significance ($p<0.05$) between *1/*1 and *10/*10 ;

c), statistical significance ($p<0.05$) between *1/*10 and *10/*10

Conclusion;

In this study, the frequencies of CYP2D6*1/1, *1/*10 and *10/*10 were 30.9 %, 43.9 % and 25.2 %, respectively. And AUC, Cmax, and Tmax of metoprolol were significant different among *1/*1, *1/*10, and *10/*10 groups ($p<0.05$). And those of α-hydroxymetoprolol were significant among three groups ($p<0.05$). Metabolic ratio was significant different among *1/*1, *1/*10, and *10/*10 groups ($p<0.05$). These results suggest that CYP2D6*10 genotype has an impact on the pharmacokinetics of metoprolol in Korean.