Cytochrome P450 2C9 Polymorphism in Puerto Rican Alzheimer's Disease Patients and its role in the Pharmacokinetics of IGC-AD1, an Investigational Drug

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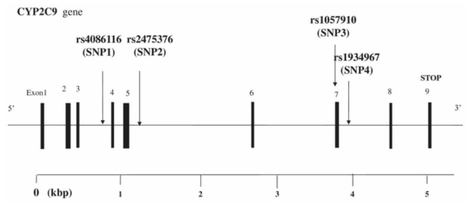
Takeaway message: Polymorphisms of CYP2C9 affect the PK of THC and is a factor in determining dosing in patients with AD.

Introduction

- Alzheimer's disease (AD) is a complex and chronic neurodegenerative illness. Patients with AD are on many medications to manage their symptoms and their comorbidities.
- Cytochromes P450 (CYPs) are a superfamily of enzymes (1, 2, and 3 types) that play a key role in the metabolism of a wide range of substances, including endogenous molecules and clinical drugs. The most common CYPs-mediated pathways include CYP3A4/5, CYP2C9, CYP2D6, and CYP2C19, which are accounted for approximately 79% of the drugs' oxidation. In particular, cytochrome 2C9 (CYP2C9) is highly expressed in the liver, contributing to >25 % of the metabolism of most clinical drugs.[1] In addition, it is responsible for the metabolic clearance of several clinically used drugs with a narrow therapeutic index.
- Four polymorphism sites have been identified on the CYP2C9 gene (**Figure 1**), which lead to inter-individual variability in the phenotype of CYP2C9 protein expression. CYP2C9 variability may impact the efficacy and safety of drug treatment.[1-2]
- In this study different metabolizing phenotypes of CYP2C9 were considered, such as poor (PM), intermediate (IM), normal (NM), and ultra-rapid (UM)[3] (**Table 1 and Figure 2**).

Figure-1. Polymorphism sites that have been identified on CYP2C9 gene.



- IGC-AD1 is an oral formulation of tetrahydrocannabinol (THC) and Melatonin. CYP2C9 is the main enzyme involved in the metabolism of THC, converting THC into the active metabolite 11-hydroxy-delta-9-THC metabolite.[2] In contrast, melatonin is primarily metabolized by CYP1A2 and CYP2C19 enzymes, with CYP2C9 being found to be less important[3].
- In this study, the CYP2C9 polymorphism in AD patients was examined and its influence on the pharmacokinetics of THC was determined.

Figure-2. Effect of CYP450 Polymorphism on Drug Metabolism

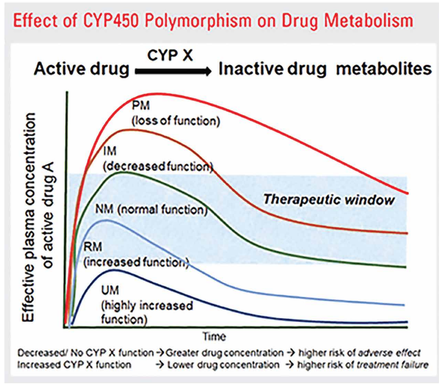
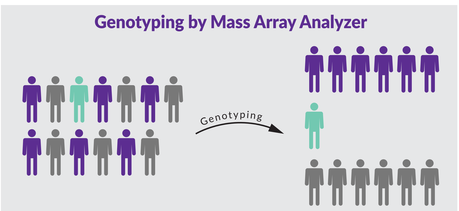


Table 1. Genotypes of CYP2C9 and Phenotypes

Genotype	Phenotype	Function
CYP2C9*1/*1	Normal Metabolizer	Homozygous for wild type
CYP2C9*1/*2	Intermediate Metabolizer	Heterozygous for reduced function
CYP2C9*1/*3	Intermediate Metabolizer	Heterozygous for no function
CYP2C9*2/*2	Intermediate Metabolizer	Homozygous for wild type
CYP2C9*2/*3	Poor Metabolizer	Heterozygous for reduced and no function
CYP2C9*3/*3	Poor Metabolizer	Homozygous for no function

Methods:

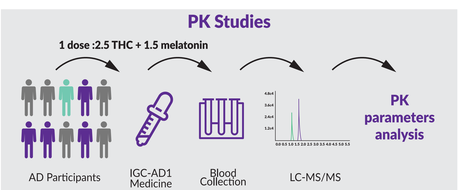
- The Phase-1 trial (n = 13) was conducted in Puerto Rican population to assess the CYP2C9 polymorphisms and their impact on THC pharmacokinetics in AD patients.
- CYP2C9 polymorphisms (alleles: *2, *3, *4, *5, *6, *8, *11, *13, *15) were determined using the Mass Array Analyzer 4 instrument (Invitae Inc., MAA4, Agena, San Diego, CA).
- Pharmacokinetics (PK) were analyzed using LC-MS/MS method at the Northeast Biolabs, Hamden, CT, USA.



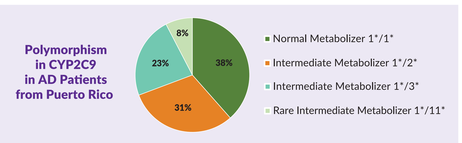
IGC-AD1 PK Studies

Table 2. PK Blood draws over Cohort 1 and Cohort 2

Cohort 1: IGC-AD1 (2.5mg THC & 1.5mg melatonin) Administered at or about T=8:00 p.m. (after dinner, time is for illustration)								
Draws (the next day) (hrs.)	T+12 (8:00 am)	T + 14	T + 16	T + 24				
Cohort 2: IGC-AD1 (2.5mg THC & 1.5mg melatonin) Administered at or about T=8:00 a.m. (after breakfast, time is for illustration)								
Draws same day (hrs.)	T-15 minutes	T + 1	T + 2	T + 2.5	T + 3	T + 3.5	T + 4	T + 5



Results:



Effects of polymorphism of CYP2C9 on PK of THC Metabolism

THC	Mean over All	Mean over *1/*1	Mean over *1/*2	Mean over *1/*3
No. Patients	N=10	Normal (n=4)	Intermediate (n=4)	Intermediate (n=2)
T1/2(h)	3.60	1.73	3.75	7.10
Tmax(h)	2.15	2.38	2.13	1.75
Cmax(ng/ml)	2.01	2.60	1.46	1.93
AUClast (h*ng/ml)	5.58	6.72	4.20	6.06
AUCinf (h*ng/ml)	8.92	9.04	7.24	11.22

Effects of polymorphism of CYP2C9 on PK of OH-THC Metabolism

OH-THC	Mean over	Mean over *1/*1	Mean over *1/*2	Mean over *1/*3
No. Patients	N=10	Normal (n=4)	Intermediate (n=4)	Intermediate (n=2)
T1/2 (h)	3.30	2.98	3.35	3.84
Tmax(h)	1.90	1.75	2.00	2.00
Cmax(ng/ml)	4.30	3.53	3.35	7.73
AUClast (h*ng/ml)	17.03	12.30	12.51	35.53
AUCinf (h*ng/ml)	21.60	16.40	17.73	39.75

- Puerto Rican AD patients had 62% CYP2C9 polymorphism; 54% were intermediate metabolizers (*1/*3 and *1/*2) and 38% were normal metabolizers.
- Intermediate metabolizers (*1/*3 and *1/*2) had altered THC metabolism leading to longer THC half-lives compared with normal metabolizers (*1/*1).

Conclusion:

Puerto Rican population have high incidence of intermediate metabolizers compared to normal metabolizers.

Polymorphisms in CYP2C9 can lead to accumulation of THC and its' active metabolite as well as prolonging its' elimination.

There is a need for future studies to explore the presence of CYP2C9 polymorphisms in diverse populations. And to explore further impact on the pharmacokinetics.

Disclosure of Funding:

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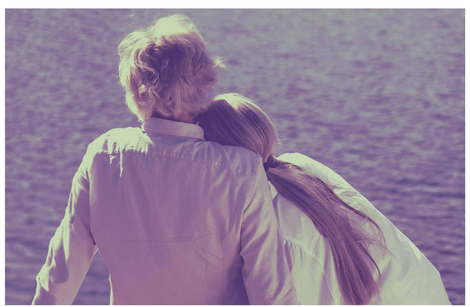

References:

1. J. Pers. Med. 2018, 8(1), 1.
2. Lipids in Health and Disease. 2014. 13(1):143
3. J. Med. ToxicolDec;12(4):396-40.
4. US Pharm. 2021;54(3):23-30.

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