DOI: 10.7860/JCDR/2016/21067.8914

Review Article

Pharmacology Section

The Impact of CYP1A2 and CYP2E1 Genes Polymorphism on Theophylline Response

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ABSTRACT

Theophylline is a medicine with narrow therapeutic index. This implies that a small change in dosage would cause side effects. Theophylline is metabolized by CYP1A2 and CYP2E1. The aim of this review is to know the impact of CYP1A2 and CYP2E1 genes polymorphism on theophylline response. The review was done by searching literature in Pubmed and Science Direct databases with keywords 'polymorphism', 'pharmacogenetic', 'CYP1A2', 'CYP2E1' and 'theophylline'. There were 5 research articles from Pubmed and 65 articles (21 research articles, 23 review articles and 21 book chapters) from Science Direct. The exclusion criteria were - articles discussing about polymorphism but not CYP1A2 or CYP2E1, the ones with a mention of theophylline but not about its metabolism, articles on CYP1A2 and/or 2E1 polymorphism but not on the effect on theophylline. Thus, 33 articles were reviewed due to their suitability. The review discusses the influence of polymorphism of CYP1A2 and CYP2E1 genes on theophylline response.

Keywords: Influence, Narrow therapeutic index, Theophylline

INTRODUCTION

Theophylline, a methylxanthine drug is indicated to treat asthma and other chronic lung disease (emphysema and chronic bronchitis) [1]. It dilates bronchial smooth muscle (bronchodilator) [2]. Theophyline has narrow therapeutic index, implying that a small dosage change would lead to side effects. The use of theophylline may require therapeutic drug monitoring [2,3]. The side effects of theophylline include: tachycardia, headache, nausea, vomitting and confusion [1].

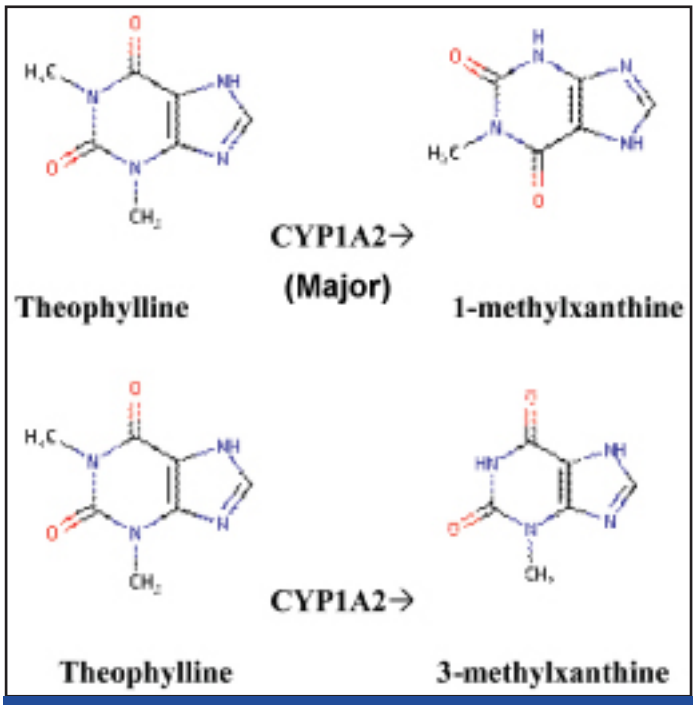
Several hypothesis were built on the mechanism of action of theophylline. First hypothesis states that theophylline dilates smooth muscle of bronchus and vascular system, reduces airway sensitivity to histamine, methacholine, adenosine and other allergens [1]. The other hypothesis states that theophylline binds to adenosine A2B receptors and blocks adenosine that causes broncho-constriction. Theophylline also inhibits phosphodiesterase (type III and type IV) competitively and activates histone deacetylase to prevent the inflammation [1].

The volume distribution of theophylline is 0.3 to 0.7L/kg with 40% bound to albumin [1]. Most of theophylline (90%) is metabolized in liver [4]. Theophylline is metabolized by CYP1A2 (major) and CYP2E1 (minor) genes [5]. CYP1A2 catalyzes the demethylation and hydroxylation of theophylline, while CYP2E1 catalyzes its hydroxylation [6-8].

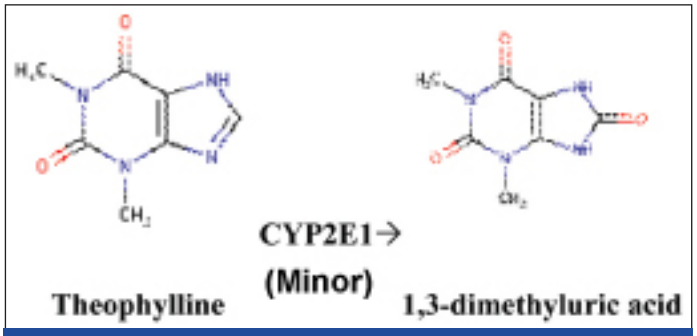
The metabolism of theophylline by CYP1A2 results in metabolite 1 methylxanthin (3-N-demethylation and 3-methyl xantin (1-N-demethylation reaction) [Table/Fig-1].

Theophylline is also metabolized (minor) by CYP2E1 enzyme into 1,3-dimethyluric acid (8-hydroxylation reaction) [Table/Fig-2].

The $t^{1/2}$ (half life) of theophylline is 8 hours and its clearance is about 1.7mL/kg/min in children (1-4 years); 0.65mL/kg/min in adults (16-60 years) and 0.41mL/kg/min in elderly (>60 years) [1].



[Table/Fig-1]: The metabolism of theophylline by CYP1A2 enzyme [1].



[Table/Fig-2]: The metabolism of theophylline by CYP2E1 [1].

Polymorphism

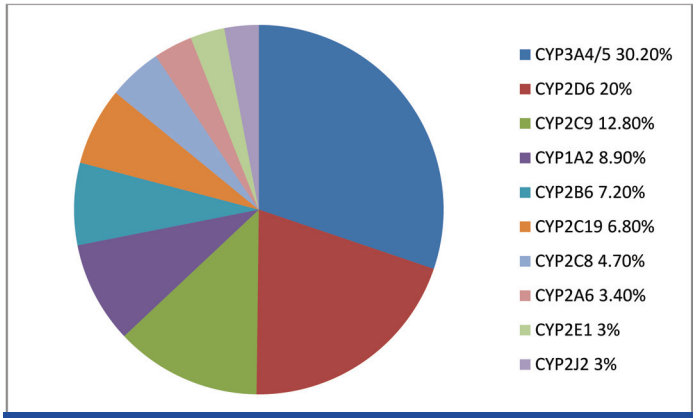
The treatment response is influenced by many factors. Genetic variation is one of the factors that may affect treatment response. Polymorphism is defined as a genetic variation in DNA sequences occurring with frequency of at least 1% in a population. In relation with drug response, polymorphism may occur in some places, such as: polymorphism of the gene encoding the enzymes that metabolize drugs, drug transporter genes and polymorphism in drug target genes [9].

The most common polymorphism is genetic polymorphism of drug metabolizing enzyme. Most polymorphism in phase 1 metabolism occurs by polymorphism at CYP, while in phase II metabolism, the polymorphism occurs by the enzyme N-acetyltransferase, thiopurine S-methyltransferase, and glutathione transferase [9].

Cytochrome P450 (CYP)

Cytochrome P450 (CYP) is an enzyme involved in the metabolism of most drugs. CYP plays an important role in the occurrence of variations in drug response between individuals. There are 57 human CYPs identified, which are classified into 18 families and 43 sub families [10]. Many drugs, xenobiotics and endogenous molecules were metabolized by CYP families 1, 2 or 3 [11]. One CYP can metabolize several drugs and instead, one drug is often metabolized by several CYPs. Several drugs can induce or inhibit activity of CYP [12].

Most drugs are metabolized by CYP3A4/5. The Percentage of drugs metabolized by CYP can be seen in [Table/Fig-3] [13].



[Table/Fig-3]: The frequency of drugs which were metabolized by CYP [13].

Polymorphism of CYP1A2 gene

The human CYP1A2 gene is located on chromosome 15q24.1. This gene contains 7 exons and 6 introns with molecular weight 58,294 Da [14]. The structural characteristics of this enzyme are aromatic, polyaromatic, heterocyclic amide and amine. The substrates of this enzyme are : caffeine, clomipramine, clozapine, phenacetin, propanolol, theophylline, tizanidine [13,14]. Several drugs are known as inhibitor of this enzyme: cimetidine, ciprofloxacin, disulfiram, mexiletine, tolfenamic acid and oral contraceptives. Some drugs act as potent inducer of CYP1A2. They are: antipyrine, carbamazepine, nelfinavir, omeprazole, phenobarbital, phenytoin, primaquine, rifampicin, ritonavir, sulfinpyrazone [13].

The research conducted by Uslu et al., (2010) on Turkish people found that theophylline is metabolized by CYP1A2. There are several polymorphism genes of CYP1A2, among others: CYP1A2*1C, CYP1A2*1D, CYP1A2*1E and CYP1A2*1F polymorphisms [15]. There are several variant types of CYP1A2 in Japanese population: CYP1A2*1F allele (-163C>A (with a 0.628 frequency, while CYP1A2*15 allele (125C>G), CYP1A2*16 allele (1130G>A) and CYP1A2 *8 allele (1367G>A) with frequencies of 0.002, 0.002 and 0.004, respectively [16]. Wang et al., 2013 stated that there were four polymorphisms of CYP1A2 among Chinese population: CYP1A2*1C (G-3860A), G-3113A, CYP1A2*1F (C-163A) and CYP1A2*1B (C-5347T). The CYP1A2*1F polymorphism increases CYP1A2 activity in subjects with -3860G/-3113G/5347C homozygote (0.66 ± 0.24 versus 0.46 ± 0.05, p = 0.034). The activity of CYP1A2 on people with the -3113 AA genotype was lower than people with the -3113 AG genotype (0.35 ± 0.04 versus 0.48 ± 0.07, p = 0.016) or the -3113 GG genotype (0.35 ± 0.04 versus 0.58 ± 0.22, p = 0.037) [17]. Research by Yoon et al., 2006 stated that the 1,3-dimethyluric acid/theophylline plasma was affected by CYP1A2 -2964G>A gene polymorphism [18].

Polymorphism CYP2E1 Gene

CYP2E1 gene is located on chromosome 10q26.3. This gene encodes enzyme involved in metabolism of theophylline. Almost 7% of total CYPs are CYP2E1 [19]. This enzyme is characterized by being small, hydrophilic and planar. The substrates of this enzyme are: aniline, arachidonic acid, halothane, salicylic acid. Many drugs may inhibit CYP2E1 enzymes: clomethiazole, disulfiram, orphenadrine. However, acetone, ethanol, isoniazid and pyrazole induce this enzyme [13].

There were 11 polymorphisms of CYP2E1 gene in Korean people: Ins(96), -1566 T>A, -1515 T>G, -1414 C>T, -1295 G>C, -1055 C>T, -1027 T>C, -930 A>G, -807 T>C, -352 A>G, and -333 T>A [18]. The frequency of CYP2E1 *1A/*1A in non-white and white among Brazilian population were 96.0% and 87.4%, while CYP2E1 *1A/*5B 2.7% and 11.3%. The frequency of CYP2E1 *5B/*5B, CYP2E1 *1A/*6 and CYP2E1 *6/*6 were 1.3; 1.3; 12.0; 15.2; 1.3 and 0.7 % respectively [20].

The Polymorphism of CYP1A2 and CYP2E1 Genes and Theophylline Response

Previous studies identified that there were varying expressions of CYP1A2 and CYP2E1 genes, at inter-individual level impacting metabolism of several drugs including theophylline [21-25].

The impact of polymorphism of CYP1A2 and CYP2E1 can be seen in [Table/Fig-4] [5,18,26,27].

From [Table/Fig-4] it can be seen that the polymorphism of CYP1A2 -3860G>A point mutation with an A mutant allele genotype (GA+AA) on Korean people have higher theophylline clearance than GG type [5]. Obase et al., (2003), found that there was a significant increase in the theophylline clearance in people with A mutant alleles in contrast with wild type (29.11 ± 0.91mL/kg/h vs.

Polymorphism	Type of Polymorphism	Impact on theophylline response	Ref.
CYP1A2	3860AG>A	Higher clearance of theophylline on GA&AA allele than GG allele	[5]
	3113G>A (CYP1A2*1F)	Decrease of CYP1A2 activity→decrease of theophylline metabolism	[26]
	163C>A (CYP1A2*1F)	Increase of CYP1A2 activity→Increase of theophylline metabolism	[27]
CYP2E1	-1055C>T	Decrease CYP2E1 enzyme activity and decrease 1.3-DMU/theophylline ratio	[18]
	-1027C>T		
	-807T>C		
	-1566T>A		
	-1295G>C		

[Table/Fig-4]: The impact of polymorphism of CYP1A2 & CYP2E1 on theophylline effect.

26.12 ± 0.80 mL/kg/h, p = 0.014). The metabolism of theophylline is lower among asthma people with A allele at -3860G>A [28], while research by Yim showed that no association of theophylline clearance in six SNPs in CYP1A2 (p > 0.05) including -3598G>T [5]. The CYP1A2 polymorphisms (T allele at -2467 del T and the C allele at -163 C >A) increase the risk of chronic obstructive pulmonary disease [15]. Chen et al., (2005) conducted a research on Chinese people and found that the G-3113A polymorphism (CYP1A2*1F) is associated with the decrease of CYP1A2 activity [26], while the *1F allele (CYP1A2*1F (-163C>A) allele) increase of enzyme activity resulting in increased metabolism of theophylline [27].

A significantly higher activity was observed in CYP1A2*1C, CYP1A2*1K, CYP1A2*3, CYP1A2*4, CYP1A2*6, CYP1A2*7, CYP1A2*8, CYP1A2*11, CYP1A2*15, and CYP1A2*16 variants [29-33].

Yoon et al., (2006) found that five polymorphisms of CYP2E1 influenced 1,3-dimethyluric acid (DMU)/theophylline ratio on

Korean people. The five SNPs were –1055 C>T; –1027 T>C; –807 T>C; –1566 T>A and –1295 G>C. They reduced CYP2E1 enzyme activity. The 1,3-DMU/ theophylline ratio of each types were as follows: genotypes of CC on 1055 C>T is 0.0533±0.0343 (CT= 0.0368±0.0171); TT on –1027 T>C is 0.0533±0.0343 (TC=0.0368±0.0171); TT on –807 T>C is 0.0533±0.0343 (TC=0.0368±0.0171); TT on –1566 T>A is 0.0533±0.0343(TA=0.0368±0.0171); GG on –1295 G>C is 0.0533±0.0343 (GC=0.0368±0.0171) respectively [18].

CONCLUSION

Polymorphism of CYP1A2*1F allele (CYP1A2*1F (-163C>A) allele) increases CYP1A2 enzyme activity. The five SNPs of CYP2E1 namely –1055 C>T; –1027 T>C; –807 T>C; –1566 T>A and –1295 G>C reduce CYP2E1 enzyme activity and 1,3-DMU/ theophylline ratio.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **May 02, 2016**
Date of Peer Review: **May 28, 2016**
Date of Acceptance: **Aug 30, 2016**
Date of Publishing: **Nov 01, 2016**