Get to know a gene: CES1A1

Summary: CES1A1 is the primary enzyme responsible for the metabolism of methylphenidate (MPH).[1] The Gly143Glu polymorphism reduces enzyme activity, which could result in elevated plasma concentrations of some parent compounds that are substrates of CES1A1.[2-7,9-17] Therefore, lower doses of MPH may be necessary for patients with the CES1A1 Gly/Glu variation.

What is CES1A1?

The CES1A1 gene encodes carboxylesterase 1, an enzyme involved in the metabolism of several therapeutic medications and some illicit drugs.[2] One of the more studied polymorphisms of the CES1A1 gene is a G>A substitution at codon 143. This substitution results in a glycine to glutamate amino acid change (Gly143Glu).[2] The CES1A1 Gly143Glu polymorphism is associated with reduced enzyme activity.[2-17] Therefore, since CES1A1 is the primary enzyme responsible for the metabolism of methylphenidate (MPH)[1], individuals with the Gly143Glu variant may experience reduced metabolism of this medication.

What do the studies say about the effect of CES1A1 variation on the metabolism of MPH?

This section reviews the studies investigating the effect of the CES1A1 Gly143Glu polymorphism on the metabolism of MPH. This analysis helps determine whether variation in CES1A1 may have a clinically significant impact on MPH metabolism.

Table 1 describes seven studies evaluating the effect of the Gly143Glu variant on MPH metabolism, all of which found the variant to decrease metabolism. This variant was originally discovered in a patient who displayed significant elevations in Cmax (i.e., peak serum concentration) of MPH. The patient was subsequently found to be heterozygous (i.e., having one normal and one variant version of the gene) for the Gly143Glu polymorphism (Gly/Glu).[2] This finding prompted further investigation of the effect of this polymorphism on MPH metabolism. One *in vivo* study (n=122) found that Gly/Glu heterozygotes who responded to MPH (n=5) required significantly lower doses of MPH for ADHD symptom reduction.[3] Additionally, three other *in vivo* studies have concluded that the Gly143Glu polymorphism decreases metabolism of MPH.[4-6] One study found that in patients that were heterozygous for the allele, plasma levels of MPH were significantly higher compared to individuals without the variant.[4] The other two *in vivo* studies completed further pharmacokinetic and covariate analyses on similar populations, and both found that the Gly143Glu allele reduced metabolism of MPH.[5,6] Two *in vitro* experiments also found that the Gly143Glu polymorphism impaired CES1A1 catalytic activity, resulting in a substantial decrease in the metabolism of MPH.[2,7]

Table 1: Studies Evaluating the Effect of the Gly143Glu Variation on MPH Metabolism

Medication	# of Studies	Study Type	Result
Methylphenidate	5	*in vivo*	decreased metabolism[2,3,4-6]
Methylphenidate	2	*in vitro*	decreased metabolism[2,7]

What do the studies say about the effect of CES1A1 variation on the metabolism of other CES1A1 substrates?

This section reviews the studies investigating the effect of the CES1A1 Gly143Glu polymorphism on the metabolism of other medications that are substrates of CES1A1. Since the metabolism of CES1A1 substrates may be affected by the Gly143Glu polymorphism, studies involving this polymorphism and other substrates (besides MPH) can be used to help understand the general effect of the Gly143Glu polymorphism.

Since there is evidence that CES1A1 is substrate specific,[8] it is important to investigate the data for individual medications. Table 2 describes eleven studies, six *in vitro* and five *in vivo*, that have investigated the effect of the Gly143Glu variant on the metabolism of other CES1A1 substrates. All *in vitro* studies concluded that Gly143Glu led to decreased metabolism of the respective prodrugs, which may indicate lower levels of the biologically active compound. One *in vitro* study found that the Gly143Glu variant resulted in decreased metabolism of the prodrug trandolapril.[9] Similarly, other *in vitro* studies showed that the Gly143Glu variation led to decreased activation of the prodrugs oseltamivir, sacubitril, enalapril, and dabigatran.[10,11,12,13] CES1A1 also plays a role in metabolizing clopidogrel, as well as its active metabolite, into inactive metabolites. One *in vitro* study found that the Gly143Glu variation resulted in increased levels of clopidogrel and its active metabolite.[7]

Preliminary evidence for oseltamivir was confirmed by an *in vivo* study (n=22) which showed that those with the heterozygous genotype (Gly/Glu) had an 18% increase in the mean AUC of oseltamivir compared to non-carriers. The metabolism of oseltamivir was even more impaired in the one subject with the Glu/Glu genotype, whose mean AUC value was approximately 290% and 360% greater than those with the Gly/Glu or Gly/Gly genotypes, respectively.[14] Furthermore, *in vivo* data supports the previous findings regarding clopidogrel; two studies (n=528) found that individuals with the Gly/Glu genotype had significantly higher levels of clopidogrel active metabolite.[15,16] Subsequent *in vivo* studies with enalapril provided mixed results. One study (n=22) found that the Gly143Glu allele resulted in significantly reduced activation of enalapril,[17] while another (n=44) found no significant differences between carriers and noncarriers.[8] Quinapril has also been studied *in vivo* (n=22), and the Gly143Glu allele had no observable effect on hydrolytic activation.[17]

Table 2: Studies Evaluating the Effect of the Gly143Glu Variation on Metabolism of Other CES1A1 Substrates

Medication	# of Studies	Study Type	Result
Trandolapril	1	*in vitro*	decreased metabolism[9]
Oseltamivir	1	*in vitro*	decreased metabolism[10]
Oseltamivir	1	*in vivo*	decreased metabolism[14]
Clopidogrel	1	*in vitro*	decreased metabolism[7]
Clopidogrel	2	*in vivo*	decreased metabolism[15,16]
Dabigatran	1	*in vitro*	decreased metabolism[13]
Sacubitril	1	*in vitro*	decreased metabolism[11]
Enalapril	1	*in vitro*	decreased metabolism[12]
Enalapril	2	*in vivo*	mixed results[8,17]
Quinapril	1	*in vivo*	no change[17]

Methodology: The search was conducted within the PubMed database. Results were limited to studies written in English, performed in vitro or on human subjects, and focused on the CES1A1 Gly143Glu polymorphism and medication metabolism. After irrelevant studies were eliminated, a total of 10 in vivo studies and 8 in vitro studies entered the metabolism review.

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