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Carboxylesterases and Drug Interactions

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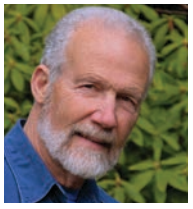

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Carboxylesterase Enzymes

The cytochrome P450 family of enzymes is responsible for the metabolism of numerous drugs and is involved in many drug interactions. Carboxylesterases (CEs) are another family of related enzymes that promote the hydrolysis of endogenous and exogenous compounds. CE1 is the primary CE in hepatic microsomes, with a smaller amount of CE2 present. CE2 is the only CE found in human intestinal microsomes. As with other metabolizing enzymes, CE hydrolysis produces a more hydrophilic metabolite that is more susceptible to renal elimination. In addition, several drugs are formulated as prodrugs to enhance their gastrointestinal absorption. The prodrugs are then metabolized by CE to an active moiety.[1]

Clopidogrel and Carboxylesterase Activity

Clopidogrel is an antiplatelet drug that is often cited for its potential to interact with various CYP450 enzymes that are required to convert the parent compound to an active metabolite. However, 85% of the parent compound, which is inactive, is metabolized to inactive metabolites by CE1. Further, the active metabolite of clopidogrel is inactivated by CE1. The administration of drugs that inhibit CE1 would be expected to increase the response to clopidogrel. This could result in a further reduction in platelet activity and increased risk for bleeding. Ethanol, an inhibitor of CE1, has been noted to slow the metabolism of clopidogrel to its inactive metabolite. This effect could enable more clopidogrel to be converted by CYP450s to the active metabolite.[2]

The related antiplatelet agent prasugrel is a substrate for CE2 in the intestine (Online Table). CE2 converts prasugrel into an inactive metabolite that is then converted into the active moiety by CYP450 enzymes. The effect of reduced CE2 activity on prasugrel active metabolite concentrations and antiplatelet efficacy is not known. Note that aspirin, commonly administered with clopidogrel and prasugrel, is converted by CE2 to an inactive (antiplatelet activity) metabolite, salicylic acid.

> Carboxylesterases are a family of enzymes that promote the hydrolysis of endogenous and exogenous compounds.

Modification of Carboxylesterase Activity

Clopidogrel is known to be an inhibitor of CE1. It has been reported to reduce CE1-mediated hydrolysis of oseltamivir to its active metabolite and decrease the antiviral effect of oseltamivir.[3] Other CE1 inhibitors might reduce the efficacy of oseltamivir in a similar manner. Orlistat has been shown in vitro to be a potent inhibitor of CE2, but the clinical significance of this remains to be determined with in vivo trials.[4]

In addition, like several CYP450 enzymes, CE activity is genetically determined. It has been demonstrated that patients who have a loss of CE1 function due to genetic mutation produce more active clopidogrel metabolite (~60%) and have a greater reduction in platelet aggregation (29% vs 43% of baseline) compared with patients with functional CE1. Associated with this increased magnitude of antiplatelet activity is an increased risk of bleeding.[5] Genetic polymorphisms in CE1 activity have been demonstrated for several other substrates, including oseltamivir and methylphenidate. Genetic alteration in CE activity is likely to result in altered substrate pharmacokinetics and, perhaps, altered drug response.

Summary

Much more research needs to be done to identify substrates for CE1 and CE2. The effect of genetic polymorphism and the coadministration of inhibitors and inducers of CE enzyme agents need to be evaluated. It is certainly possible that some of the variation in therapeutic response observed with known CE substrates may be caused by interacting drugs or genetic alterations. Pharmacists should be aware of the potential interactions involving CE1 and CE2. n

Drs. Horn and Hansten are both professors of pharmacy at the University of Washington School of Pharmacy. For an electronic version of this article, including references, if any, visit www.hanstenandhorn.com.