The Effects of the Genetic Absence and Inhibition of CYP2D6 on the Metabolism of Codeine and Its Derivatives, Hydrocodone and Oxycodone

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Approximately 7% of Caucasians, 3% of Blacks, and 1% of Asians are poor metabolizers (PMs) of CYP2D6, an enzyme of the hepatic P450 microsomal enzyme system. These individuals produce no CYP2D6 or undetectable levels of it, thus preventing them from metabolizing drugs that are substrates of this enzyme. The remainder of individuals in these populations produce functional levels of CYP2D6 and are labeled extensive metabolizers (EMs).[1-8] To date, over 30 drugs, including antiarrhythmics, antidepressants, neuroleptics, beta receptor antagonists, codeine, and the derivatives of codeine, hydrocodone and oxycodone, are known to be metabolized by CYP2D6[2-4] (Table 1). Given that codeine, hydrocodone, and oxycodone are all prodrugs (inactive drugs that must be metabolized to active drugs within the body) people who are PMs of CYP2D6 will experience little to no analgesia from these medications since they lack the enzyme to metabolize these drugs (Table 2). Likewise, a patient who takes codeine or its derivatives in combination with a high-affinity substrate or potent inhibitor of CYP2D6 will experience attenuated analgesia, whether this person is a PM or an EM.[4,5]

PMs of CYP2D6 are homozygous for the 29B autosomal recessive mutation of the CYP2D6 gene located on chromosome 22.[1,4,6] The resultant genotype (29B/29B) leads to no immunodetectable levels of hepatic CYP2D6 enzyme production.[4] In individuals without the homozygous mutation of this gene, codeine is successfully *O*-demethylated by CYP2D6 to morphine, the active metabolite of codeine that exerts analgesia.[1,4,6] Without CYP2D6, codeine provides little to no analgesia.[7] The same holds true for hydrocodone and oxycodone: only through their bioconversion to their active metabolites (hydromorphone and oxymorphone, respectively) do they induce analgesia.[2,4,6]

Certain probe drugs may be used to clinically distinguish the EM phenotype from the PM phenotype. These drugs include sparteine, debrisoquine, and dextromethorphan.[1,3,5,7-10] In an 8–12-hr urine sample, individuals with PM phenotypes have a metabolic ratio (amount of parent drug/amount of its metabolite) of >20 for sparteine, >12.6 for debrisoquine, or >0.3 for dextromethorphan.[10] It is useful to know a patient's CYP2D6 phenotype in advance of treatment in order to avoid prescribing an analgesic to a patient to whom it would be ineffective.[9]

Evidence supporting the role of CYP2D6 in the mediation of codeine-related analgesia is provided in a study by Sindrup et al (1991). In this study, Sindrup observes that codeine significantly increases pain thresholds to nocioceptive laser stimuli in EMs but not in PMs. Sindrup also observes that urine collected from PMs had undetectable levels of morphine after a dose of codeine was administered. By contrast, when the same dose was given to EMs in the same study, measurable levels of morphine were detectable in their urine. The failure of PMs to bioconvert codeine to its active metabolite has also been demonstrated for hydrocodone and oxycodone. For example, following administration of a 10-mg oral dose of hydrocodone, hydromorphone levels in EMs were found to be approximately 5–10 times greater than hydromorphone levels in PMs, further illustrating the failure of PMs to bioconvert these prodrugs.[6]

Beside PMs, who demonstrate absent production of CYP2D6, patients taking potent inhibitors or high-affinity substrates of CYP2D6 are unable to metabolize codeine, hydrocodone, and oxycodone into their active metabolites.[4,5,8] Examples of potent inhibitors of

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Table 1. Drugs Metabolized by the Hepatic p450 Microsomal Enzyme CYP2D6

Substrates	*Inhibitors*
Opioids	Fluoxetine
Codeine	Norfluoxetine
Amitriptyline	Paroxetine
Desipramine	Sertraline
Dextromethorphan	Quinidine
Doxepin	Cimetidine
Encainide	Haloperidol
Flecainide	Methadone
Fluoxetine	Moclobemide
Haloperidol (mostly CYP1A2)	Perphenazine
Imipramine	Thioridazine
Maprotiline	
Metoprolol	
Nortriptyline	
Paroxetine	
Perphenazine	
Propafenone	
Propranolol	
Risperidone	
Thioridazine	
Timolol	
Tramadol	
Trazodone	
Trimipramine	
Venlafaxine	

Data from Manzey and Guthrie (1996)

CYP2D6 include quinidine (a Class IA antiarrhythmic) and the selective serotonin reuptake inhibitors (SSRIs), paroxetine (Paxil) and fluoxetine (Prozac). Another SSRI, sertraline (Zoloft), is also metabolized by CYP2D6. However, because of its lower affinity for CYP2D6 than paroxetine or fluoxetine, sertraline is not as potent an inhibitor as these other SSRIs. Consequently, sertraline may not render codeine or its derivatives completely ineffective, as is the case with paroxetine and fluoxetine. This difference may be explained by the higher affinity of paroxetine and fluoxetine for CYP2D6 than either codeine or sertraline.[5] Sertraline's lower affinity may allow some codeine to be metabolized so that partial, although not full, analgesia may be experienced.

As previously mentioned, several other drugs are also metabolized by CYP2D6 (Table 1). However, quinidine, paroxetine, and fluoxetine are currently believed to be the most potent inhibitors of CYP2D6.[4,5,8] Of the two SSRIs, paroxetine has been found to be the greater inhibitor of CYP2D6 *in vitro,* although both render codeine completely ineffective when taken in combination.[5]

The extent to which a drug inhibits the CYP2D6 enzyme depends on that drug's relative affinity for the enzyme and its concentration at the active site of the enzyme. Quinidine, paroxetine, and fluoxetine have a higher affinity for CYP2D6 than codeine has.[4,5,8] For this reason, these medications are competitive inhibitors of CYP2D6 in the presence of codeine.[5] Although reversible, this inhibition may last up to 1 wk after these drugs have been discontinued as a result of their relatively long half-lives.[4,5] In situations in which codeine and another drug have relatively equal affinities for CYP2D6, one may expect compromised pain relief rather than total absence of pain relief, as may be the case with sertraline. Finally, under circumstances in which codeine has a greater affinity for CYP2D6 than other drugs metabolized by this enzyme, codeine will potentially inhibit their metabolism, possibly resulting in their toxicity.[5]

Table 2. The Metabolism of Codeine, Hydrocodone, and Oxycodone into their Active Metabolites

Prodrug	*Active Metabolite*
Codeine	Morphine
Hydrocodone (Vicodin)	Hydromorphone (Dilaudid)
Oxycodone (Percodan)	Oxymorphone

Although CYP2D6 is responsible for metabolizing the majority of codeine that is introduced into the body, codeine is also metabolized to lesser degrees by other pathways involving other P450 microsomal enzymes.[7] However, it appears that these additional metabolic routes do not process codeine to levels great enough for either EM or PM patients to experience meaningful analgesia.[5] Although codeine may be slightly metabolized via these other enzymes in a PM patient, often many of these enzymes are also inhibited by the same drug that is inhibiting CYP2D6.[4,5,7] Such a scenario occurs with the use of fluoxetine, a drug that, in addition to inhibiting CYP2D6, also inhibits CYP2D9/10, CYP2C19, and CYP3A3/4 so that very little, if any, codeine is metabolized.[5]

In conclusion, a small percentage of patients who are prescribed codeine and its derivatives, hydrocodone and oxycodone, will experience little to no analgesia for no other reason than because they are PMs of CYP2D6. Presumably, an even larger percentage of patients who are prescribed these analgesics will be taking drugs that are other substrates or potent inhibitors of CYP2D6, such as quinidine, paroxetine, or fluoxetine. These patients, too, will experience little to no pain relief upon administration of codeine, hydrocodone, or oxycodone. Under these circumstances, it is advisable to prescribe to the patient another analgesic, such as a nonsteroidal anti-inflammatory drug, propoxyphene (Darvocet), or a drug already in its active form, such as hydromorphone (Dilaudid). Knowledge of potential drug interactions and toxicities ahead of

time will only serve to better assist the care provider in rendering the safest and most effective treatment for patients.

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