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Technical Bulletin

Carisoprodol

Report Type: Pharmacogenetics

About: Carisoprodol is a centrally acting skeletal muscle relaxant that is prescribed to relieve discomfort associated with acute, painful musculoskeletal conditions in adults.[1] The mechanism of action of carisoprodol is not completely understood, but use of the drug can lead to adverse effects such as tachycardia and dizziness.[2] The CYP2C19 enzyme, a member of the cytochrome P450 family, metabolizes carisoprodol to the active metabolite meprobamate.[3,4,5]

Genetics: Variants of the CYP2C19 gene that affect enzyme function are associated with plasma concentrations of carisoprodol. Individuals can be classified based on their CYP2C19 enzyme activity into four metabolizer groups: Ultrarapid Metabolizer (UM, higher than normal enzyme activity), Extensive Metabolizer (EM, normal enzyme activity), Intermediate Metabolizer (IM, intermediate enzyme activity) and Poor Metabolizer (PM, low or no enzyme activity).[6]

The association between CYP2C19 variants and carisoprodol pharmacokinetics is supported by multiple studies. Some data suggest a gene dosing effect, where the number of active CYP2C19 alleles correlates with the ratio of carisoprodol to meprobamate.[4] Carisoprodol plasma clearance is four-fold lower in PMs than EMs, and plasma concentrations and elimination half-lives are higher in PMs and IMs compared to EMs.[3,5] Oral contraceptives containing ethinylestradiol, desogestrel, gestodene and 3-ketodesogestrel are believed to inhibit the CYP2C19 enzyme, which could explain why oral contraceptive use increases plasma concentrations of carisoprodol.[3]

Though carisoprodol is associated with fatal intoxication, an association between CYP2C19 metabolizer status and mortality risk of carisoprodol has not been found.[2]

Recommendations: NA

Possible Outcomes: Poor Metabolizer, Intermediate Metabolizer, Extensive Metabolizer, Ultrarapid Metabolizer

Markers Tested: CYP2C19 [CYP2C19 *2, CYP2C19 *3, CYP2C19 *4, CYP2C19 *5, CYP2C19 *6, CYP2C19 *7,CYP2C19 *8, CYP2C19 *17]

Ethnic Distribution of Tested Alleles

Allele	Enzyme activity	CYP2C19 marker	Caucasian	African	East Asian	Middle Eastern
*1	Normal	Wild-type	63%	68%	60%	87%
*2	None	rs4244285	15%	15%	29%	12%
*3	None	rs4986893	0.42%	0.52%	8.9%	1.1%
*4	None	rs28399504	0.25%	0.093%	0.049%	ND[a]
*5	Reduced	rs56337013	0.0073%	ND	0.062%	ND
*6	None	rs72552267	0.017%	0%	0%	ND
*7	None	rs72558186	ND	ND	0%	ND
*8	Reduced	rs41291556	0.35%	0%	0%	ND
*17	Increased	rs12248560	21%	16%	2.7%	ND

[a]Not Determined

Predicted CYP2C19 Metabolizer Status[6]

CYP2C19 Diplotype	Predicted Metabolizer Status
*2-*8/*2-*8	Poor Metabolizer
*1/*2-*8, *17/*2-*8	Intermediate Metabolizer
*1/*1	Extensive Metabolizer
*1/*17, *17/*17	Ultrarapid Metabolizer

*Limitations and Warnings: Many rare CYP2C19 variants have been identified, but are not part of this test. It is possible that the patient may have a variant that is not included in this test. CYP2C19 genotype and metabolizer status may also affect responses to other drugs.[7]

References

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Celecoxib

Report Type: Pharmacogenetics

About: Celecoxib is a nonsteroidal anti-inflammatory drug (NSAID) indicated for osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis in patients two years and older, ankylosing spondylitis, acute pain and primary dysmenorrhea. This drug and other NSAIDs can increase the risk of gastrointestinal adverse effects.[1] Celecoxib inhibits prostaglandin synthesis, a step in the inflammatory process, and is metabolized by the CYP2C9 enzyme, a member of the cytochrome P450 family.[2,3]

Genetics: Variants of the CYP2C9 gene that affect enzyme function are associated with the risk of celecoxib-induced gastrointestinal bleeding or cardiotoxicity. The frequency of CYP2C9 *3 and CYP2C9 *2 variants was higher in NSAID users with endoscopically documented NSAID-related gastroduodenal bleeding lesions compared to NSAID use-matched controls with no lesions at endoscopy.[4] Additionally, patients on NSAIDs demonstrated a gene dose effect that implies an increased risk of bleeding with greater numbers of CYP2C9 mutant alleles, particularly the CYP2C9 *2 allele.[5] Over a 3-year period, individuals on high doses (400 mg twice daily) of celecoxib with either CYP2C9 *2 or CYP2C9 *3 alleles were at increased risk of cardiovascular and thrombotic events believed to be caused by celecoxib treatment.[6]

Recommendations: The FDA-approved drug label recommends reducing the dose by half for CYP2C9 PMs.[1]

Possible Outcomes: Poor Metabolizer, Intermediate Metabolizer, Extensive Metabolizer

Markers or Alleles Tested: CYP2C9 [CYP2C9 *2, CYP2C9 *3, CYP2C9 *6]

Ethnic Distribution of Alleles[7]

Allele	CYP2C9 marker	African	Caucasian	Japanese	Chinese
*1	Wild-type	80.6%	77.9%	96.5%	95.8%
*2	rs1799853	1.2%	15.9%	0%	0.1%
*3	rs1057910	0%	5.7%	3.4%	4.1%
*6	rs9332131	1.2%	0%	0%	0%

Predicted CYP2C9 Metabolizer Status[8]

CYP2C9 Diplotype	Predicted Metabolizer Status
*2/*2, *2/*3, *2/*6, *3/*3, *3/*6, *6/*6	Poor Metabolizer
*1/*2, *1/*3, *1/*6	Intermediate Metabolizer
*1/*1	Extensive Metabolizer

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Limitations and Warnings: Many CYP2C9 variants have been identified but are not part of this test. The possibility that the patient may have a variant that is not included in this test cannot be ruled out.

References

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Codeine

Report Type: Pharmacogenetics

About: Codeine is an opioid analgesic used to relieve mild to moderately severe pain.[1] The hepatic CYP2D6 enzyme metabolizes inactive codeine to active morphine, which binds the mu-opioid receptor with an affinity 200-fold greater than codeine.[2] The exact mechanism of codeine's analgesic effect is unknown.[1]

Genetics: Variants of the CYP2D6 gene that affect enzyme function have been shown to be associated with codeine metabolism and analgesic effects.[3,4,5,6] Individuals can be classified based on their CYP2D6 enzyme activity into four metabolizer groups: Ultrarapid Metabolizer (UM, higher than normal enzyme activity), Extensive Metabolizer (EM, normal enzyme activity), Intermediate Metabolizer (IM, intermediate enzyme activity) and Poor Metabolizer (PM, low or no enzyme activity).

PMs may experience little to no pain relief from codeine.[5,6] Clinical studies show that PMs taking codeine have very low systemic exposure to morphine compared to EMs.[4,5] However, insufficient clinical evidence exists to recommend using higher codeine doses for PMs.[3] Additionally, standard doses of codeine may result in below average systemic exposure in IMs.[4,5]

In contrast, UMs are at high risk of severe toxicity and may experience adverse reactions, such as respiratory depression, respiratory arrest, shock and/or cardiac arrest.[3] Infants who are breastfed by mothers who are UMs and taking codeine are also at increased risk of morphine overdose, which can result in opioid toxicity. In UMs, standard doses of codeine may result in above average systemic exposure to morphine.[7]

CYP2D6 metabolizer status is also associated with urinary recovery of multiple codeine metabolites, including the active metabolites morphine and morphine-6-glucuronide (M6G). PMs are likely to have undetectable or very low urinary recovery of morphine and M6G, and IMs are likely to have decreased levels of these compounds in their urine compared to EMs.[4,8] In contrast, UMs are likely to have increased urinary recovery of morphine and M6G.[7,9]

Recommendations: The NIH Clinical Pharmacogenetics Implementation Consortium Guidelines recommend that PMs should not be treated with codeine due to increased risk of inefficacy, and alternative medications, such as morphine or a nonopioid, should be considered for PMs. The guidelines also recommend that IMs should be monitored for a suboptimal response and an alternative medication should be used, if necessary. According to the guidelines, UMs should also avoid codeine due to increased risk of overdose and alternative medications are recommended.[3,10,11] Tramadol is also a CYP2D6 substrate; it is not recommended as an alternative to codeine in PMs and UMs, and its use in IMs should be monitored for suboptimal response.[3]

In 2007, U.S. Food and Drug Administration (FDA) issued a warning regarding codeine use in nursing mothers. Breastfeeding infants may be at increased risk of morphine overdose if their mothers are UMs and taking codeine. There is

at least one reported instance of infant mortality due to morphine overdose in an infant whose mother was a confirmed UM.[12,13]

Concurrent use of codeine with CYP2D6 inhibitors may decrease morphine levels (see "Known CYP2D6 Inhibitors" table below).[14,15] Concurrent use of CYP3A4 inducers or inhibitors may also affect response to codeine;[1] lists of these compounds are available at various web sites.[16,17] CYP2D6 UMs, in particular, should avoid the concurrent use of codeine with CYP3A4 inhibitors.[10] CYP2D6 genotype and metabolizer status may also affect responses to other drugs (see "Known CYP2D6 Substrates" table below).

Possible Outcomes: Poor Metabolizer, Intermediate Metabolizer, Extensive Metabolizer, Ultrarapid Metabolizer

Markers or Alleles Tested: CYP2D6 alleles are classified as non-functional, reduced-function, normal-function and increased-function.

Non-functional alleles: *3, *4, *5, *6, *7, *8, *11, *12, *14A, *15, *36, *4xN, and *36xN
Reduced-function alleles: *9, *10, *17, *29, *41, *9xN, *10xN, *17xN, *41xN and *36-*10
Normal-function alleles: *1, *2 and *35
Increased-function alleles: *1xN, *2xN and *35xN

Predicted CYP2D6 Metabolizer Status

Metabolizer Status	CYP2D6 Genotype
Poor metabolizer	Two non-functional alleles
Intermediate metabolizer	One non-functional allele and one reduced-function allele OR Two reduced-function alleles
Extensive metabolizer	One or two normal-function copies of the CYP2D6 gene
Ultrarapid metabolizer	Three or more normal-function copies of the CYP2D6 gene

Ethnic distribution of CYP2D6 phenotypes[18,19,20]

Metabolizer Status	African American	Caucasian	East Asian	Hispanic
Poor Metabolizer	2-8%	5-10%	<2%	3-10%
Intermediate Metabolizer	~30%	10-17%	50-60%	No data
Extensive Metabolizer	60-70%	70-80%	40-50%	No data
Ultrarapid Metabolizer	~5%	3-10%	<1%	0-5%

Limitations and Warnings: Many rare CYP2D6 variants have been identified but are not part of this test. It is possible that the patient may have a variant that is not included in this test.

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In addition to the genetic variants included in this test, other genetic and nongenetic factors can influence the effective dose of codeine, including variants in other genes, other medications and liver and kidney conditions.[1]

Known CYP2D6 Inhibitors and Substrates Tables

Known CYP2D6 Inhibitors[16,17,21]		
amiodarone	escitalopram	paroxetine
bupropion	flecainide acetate	perphenazine
celecoxib	fluoxetine	primaquine phosphate
chloroquine phosphate	fluphenazine	propafenone
chlorpheniramine	fluvoxamine maleate	propoxyphene
chlorpromazine	halofantrine	quinacrine
cimetidine	haloperidol	quinidine
cinacalcet	histamine H1 receptor antagonists	ranitidine
citalopram	hydroxychloroquine	reduced haloperidol
clemastine	hydroxyzine	ritonavir
clomipramine	labetalol	sertraline
cocaine	levomepromazine	terbinafine
codeine	lomustine	thioridazine
darifenacin hydrobromide	lumefantrine	ticlopidine
delavirdine mesylate	methadone	tripelennamine
desipramine	metoclopramide	valdecoxib
diphenhydramine	mibefradil	vinblastine sulfate
doxepin	midodrine	vincristine sulfate
doxorubicin	moclobemide	vinorelbine tartrate
dronedarone	norfluoxetine	yohimbine
duloxetine		

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Known CYP2D6 Substrates[16,17,22]		
alprenolol	fenfluramine	oxycodone
amitriptyline	fentanyl	paliperidone
amoxapine	flecainide	paroxetine
amphetamine	fluoxetine	penbutolol sulfate
aripiprazole	fluphenazine	pentazocine lactate
atomoxetine	fluvoxamine	perhexiline
betaxolol	formoterol	perphenazine
bisoprolol	galantamine	phenacetin
bufuralol	haloperidol	phenformin
captopril	hydrocodone	pindolol
carvedilol	hydrocortisone	promethazine
cevimeline	hydroxyamphetamine hydrobromide	propafenone
chlorpheniramine	iloperidone	propoxyphene
chlorpromazine	imipramine	propranolol
chlorpropamide	labetalol	protriptyline
cinacalcet	lidocaine	quetiapine
clomipramine	loratadine	ranolazine
clonidine	maprotiline	risperidone
clozapine	meperidine	ropivacaine
codeine	methadone	selegiline
cyclobenzaprine	methamphetamine	S-metoprolol
cyclophosphamide	methoxyamphetamine	sparteine
darifenacin hydrobromide	metoclopramide	tamoxifen
debrisoquine	metoprolol	tamsulosin
delavirdine mesylate	mexiletine	thioridazine
desipramine	minaprine	tiagabine
dexfenfluramine	mirtazapine	timolol
dextromethorphan	molindone	tolterodine
diphenhydramine	morphine	tramadol
dolasetron	nebivolol	trazodone
donepezil	nortriptyline	trimipramine maleate
doxazosin mesylate	olanzapine	venlafaxine
doxepin	ondansetron	yohimbine
duloxetine	orphenadrine citrate	zuclopenthixol
encainide		

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22. CYP2D6-substrates. MedSort web site. http://drugs.medsort.com/Drugs/ClassProfile.aspx?ClassID=49. Accessed September 20, 2012.

Diclofenac

Report Type: Pharmacogenetics

About: Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) approved for clinical use in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.[1] Diclofenac is also used to treat painful menstrual periods, and diclofenac solution is used to treat migraine headaches in adults. The FDA-approved drug label states that diclofenac treatment may lead to increased risks of cardiovascular and gastrointestinal adverse events. Diclofenac, like other NSAIDs, functions by inhibiting the synthesis of prostaglandin that is involved in mediating inflammation, pain, fever and swelling.[2,3] The CYP2C9 enzyme is involved in converting diclofenac into its major metabolite, 4'-hydroxydiclofenac.[4,5] Concomitant use of CYP2C9 inhibitors with diclofenac may result in an increased risk of diclofenac-associated toxicity; therefore, the total daily dose of diclofenac should not exceed the lowest recommended dose.

Genetics: Variants of the CYP2C9 gene have been associated with altered diclofenac metabolism. Individuals with one or more CYP2C9*2 or CYP2C9*3 allele (*1/*2, *2/*2, *1/*3, *2/*3, *3/*3) have increased plasma concentrations of diclofenac compared to those with the CYP2C9*1 wild-type allele (*1/*1) (PMID 23959274 and PMID 12734606). The effects were most pronounced in CYP2C9*3 carriers. Individuals can be classified into three metabolizer groups based on their CYP2C9 enzyme activity: extensive metabolizer (EM, normal enzyme activity), intermediate metabolizer (IM, intermediate enzyme activity) and poor metabolizer (PM, low or no enzyme activity).

Recommendations: Patients who are CYP2C9 poor metabolizers should take diclofenac with caution as they may have abnormally high plasma concentrations of diclofenac due to reduced metabolic clearance. There are no specific dosing recommendations based on CYP2C9 metabolizer status due to insufficient clinical evidence.

Possible Outcomes: Poor Metabolizer, Intermediate Metabolizer, Extensive Metabolizer

Markers or Alleles Tested: CYP2C9 [CYP2C9 *2, CYP2C9 *3, CYP2C9 *6]

Ethnic Distribution of Alleles[6]

Allele	CYP2C9 marker	African	Caucasian	Japanese	Chinese
*1	Wild-type	80.6%	77.9%	96.5%	95.8%
*2	rs1799853	1.2%	15.9%	0%	0.1%
*3	rs1057910	0%	5.7%	3.4%	4.1%
*6	rs9332131	1.2%	0%	0%	0%

Predicted CYP2C9 Metabolizer Status[7]

CYP2C9 Diplotype	Predicted Metabolizer Status
*2/*2, *2/*3, *2/*6, *3/*3, *3/*6, *6/*6	Poor Metabolizer
*1/*2, *1/*3, *1/*6	Intermediate Metabolizer
*1/*1	Extensive Metabolizer

Limitations and Warnings: Many CYP2C9 variants have been identified but are not part of this test. The possibility that the patient may have a variant that is not included in this test cannot be ruled out.

References

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Fentanyl

Report Type: Pharmacogenetics

About: Fentanyl is an opioid analgesic used to relieve pain in cancer patients and as a surgical anesthetic. This drug acts primarily as a mu-opioid receptor agonist and is metabolized to an inactive metabolite by the CYP3A4 enzyme. The exact mechanism of fentanyl's analgesic effect is unknown.[1]

*Genetics: Variants of the OPRM1 gene, which encodes the mu-opioid receptor, have been shown to be associated with the analgesic efficacy of fentanyl. The OPRM1A>G allele leads to reduced OPRM1 expression in the brain and decreased opioid receptor signaling efficiency in the pain-relevant brain region.[2]

Most of the studies that demonstrate an association between the G allele of the rs1799971 marker and postoperative requirements for fentanyl were conducted in Asian patients. In studies of Japanese and Han Chinese patients, individuals were treated with fentanyl after undergoing abdominal surgery (hysterectomy, myomectomy, laparoscopic surgery) or orofacial surgery. Patients who are homozygous for the G allele of rs1799971 had decreased analgesic efficacy or increased postoperative requirements for fentanyl compared to patients who were homozygous for the A allele.[3,4,5,6,7,8] The association of the G allele with fentanyl efficacy or increased postoperative requirements for fentanyl was not confirmed when used for labor analgesia or cancer pain in Caucasian women.[4,9,10] One study that consisted primarily of Caucasian women reported that patients who were homozygous for the A allele required more intrathecal fentanyl for labor analgesia than women carrying the G allele.[9] Thus, the association between the G allele and fentanyl efficacy is has been demonstrated only for patients of Japanese or Han Chinese descent.

Individuals who are heterozygous for the OPRM1A>G allele receive an outcome of "Inconclusive" because there is insufficient evidence to support an association between the heterozygous genotype and decreased analgesic effect.

Recommendations: NA

Possible Outcomes: Decreased Analgesic Efficacy, Typical Analgesic Efficacy, Inconclusive

Markers or Alleles Tested: OPRM1 [rs1799971]

Ethnic Distribution of Tested Alleles

The G allele of the rs1799971 marker has an allelic frequency of 0.8% in Sub-Saharans, 8.2-17% in Caucasians and 48.9% in Asians.[2]

Limitations and Warnings: The results of this test are based on studies of Japanese or Han Chinese patients treated with fentanyl after abdominal or orofacial surgery and may not apply to patients of other ethnic groups or patients being treated for other conditions.

References

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 OmeCare

Flurbiprofen

Report Type: Pharmacogenetics

About: Flurbiprofen is a nonsteroidal anti-inflammatory drug (NSAID) approved for the treatment of osteoarthritis and rheumatoid arthritis. Flurbiprofen is also used to treat ankylosing spondylitis. The FDA-approved drug label states that flurbiprofen treatment may lead to increased risks of cardiovascular and gastrointestinal adverse events. Flurbiprofen, like other NSAIDs, functions by inhibiting the synthesis of prostaglandin that is involved in mediating inflammation, pain, fever and swelling.[1,2] Approximately 45% of the flurbiprofen dose is cleared by the CYP2C9 enzyme, converting fluriprofen into its major metabolite 4'-hydroxyflurbiprofen, which has little anti-inflammatory activity.[3]

Genetics: Variants of the CYP2C9 gene have been associated with altered flurbiprofen metabolism and accounted for approximately 59% of the variability in systemic flurbiprofen exposure.[3] Individuals with one or more CYP2C9*2 or CYP2C9*3 allele (*1/*2, *2/*2, *1/*3, *2/*3, *3/*3) have increased plasma concentrations of flurbiprofen compared to those with the CYP2C9*1 wild-type alleles (*1/*1).[4,5] The effects were most pronounced in CYP2C9*3 carriers. Individuals can be classified into three metabolizer groups based on their CYP2C9 enzyme activity: extensive metabolizer (EM, normal enzyme activity), intermediate metabolizer (IM, intermediate enzyme activity) and poor metabolizer (PM, low or no enzyme activity).

Recommendations: The FDA-approved drug label recommends patients who are CYP2C9 poor metabolizers take flurbiprofen with caution as they may have abnormally high plasma concentrations of flurbiprofen due to decreased metabolic clearance. There are no specific dosing recommendations based on CYP2C9 metabolizer status due to insufficient clinical evidence.

Possible Outcomes: Poor Metabolizer, Intermediate Metabolizer, Extensive Metabolizer

Markers or Alleles Tested: CYP2C9 [CYP2C9 *2, CYP2C9 *3, CYP2C9 *6]

Ethnic Distribution of Alleles[6]

Allele	CYP2C9 marker	African	Caucasian	Japanese	Chinese
*1	Wild-type	80.6%	77.9%	96.5%	95.8%
*2	rs1799853	1.2%	15.9%	0%	0.1%
*3	rs1057910	0%	5.7%	3.4%	4.1%
*6	rs9332131	1.2%	0%	0%	0%

Predicted CYP2C9 Metabolizer Status[7]

CYP2C9 Diplotype	Predicted Metabolizer Status
*2/*2, *2/*3, *2/*6, *3/*3, *3/*6, *6/*6	Poor Metabolizer
*1/*2, *1/*3, *1/*6	Intermediate Metabolizer
*1/*1	Extensive Metabolizer

Limitations and Warnings: Many CYP2C9 variants have been identified but are not part of this test. The possibility that the patient may have a variant that is not included in this test cannot be ruled out.

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1. Smyth EM, Grosser T, Wang M, Yu Y, FitzGerald GA. Prostanoids in health and disease. *Journal of lipid research.* 2009;50 Suppl:S423-8.
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Hydrocodone

Report Type: Pharmacogenetics

About: Hydrocodone is an opioid analgesic used to relieve moderate to moderately severe pain. The CYP2D6 enzyme is responsible for 95% of the conversion of hydrocodone to hydromorphone in liver microsomes.[1] Hydromorphone has greater affinity to mu-opioid receptors than hydrocodone.[2,3,4]

Genetics: Variants of the CYP2D6 gene that affect enzyme function have been shown to be associated with hydrocodone metabolism.[5] Individuals can be classified based on their CYP2D6 enzyme activity into four metabolizer groups: Ultrarapid Metabolizer (UM, higher than normal enzyme activity), Extensive Metabolizer (EM, normal enzyme activity), Intermediate Metabolizer (IM, intermediate enzyme activity) and Poor Metabolizer (PM, low or no enzyme activity).

In a small study, EMs and PMs were administered a single oral dose of 10 mg hydrocodone bitartrate. The average maximum concentration of hydromorphone in plasma was over five times greater in EMs than in PMs.[5] In a case study of a 40-year old Caucasian UM (*2xN/*1), the patient reported feeling very light-headed and out of control after taking a single dose of 5 mg hydrocodone.[6]

Urinary recovery of hydrocodone in healthy patients is higher in PMs than EMs, whereas urinary recovery of hydromorphone is lower in PMs compared to EMs.[5]

Recommendations: NA

Possible Outcomes: Poor Metabolizer, Intermediate Metabolizer, Extensive Metabolizer, Ultrarapid Metabolizer

Markers or Alleles Tested: CYP2D6 alleles are classified as non-functional, reduced-function, normal-function and increased-function.

Non-functional alleles: *3, *4, *5, *6, *7, *8, *11, *12, *14A, *15, *36, *4xN, and *36xN
Reduced-function alleles: *9, *10, *17, *29, *41, *9xN, *10xN, *17xN, *41xN and *36-*10
Normal-function alleles: *1, *2 and *35
Increased-function alleles: *1xN, *2xN and *35xN

Predicted CYP2D6 Metabolizer Status

Metabolizer Status	CYP2D6 Genotype
Poor metabolizer	Two non-functional alleles
Intermediate metabolizer	One non-functional allele and one reduced-function allele OR Two reduced-function alleles
Extensive metabolizer	One or two normal-function copies of the CYP2D6 gene
Ultrarapid metabolizer	Three or more normal-function copies of the CYP2D6 gene

Ethnic distribution of CYP2D6 phenotypes[7,8,9]

Metabolizer Status	African American	Caucasian	East Asian	Hispanic
Poor Metabolizer	2-8%	5-10%	<2%	3-10%
Intermediate Metabolizer	~30%	10-17%	50-60%	No data
Extensive Metabolizer	60-70%	70-80%	40-50%	No data
Ultrarapid Metabolizer	~5%	3-10%	<1%	0-5%

Limitations and Warnings: Many rare CYP2D6 variants have been identified but are not part of this test. It is possible that the patient may have a variant that is not included in this test.

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Ibuprofen

Report Type: Pharmacogenetics

About: Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) indicated to temporarily relieve minor aches and pains due to headache, muscular aches, menstrual cramps, the common cold, backache, toothache, minor pain of arthritis and to temporarily reduce fever (FDA-approved drug label). Ibuprofen may be used for prolonged treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and other chronic conditions at prescription level dosage (1800--2400 mg/day).[1] The FDA-approved drug label states that ibuprofen treatment may lead to increased risks of cardiovascular and gastrointestinal adverse events. Ibuprofen, like other NSAIDs, functions by inhibiting the synthesis of prostaglandin that is involved in mediating inflammation, pain, fever and swelling.[2,3] The CYP2C9 enzyme is the major cytochrome P450 enzyme responsible for the metabolism of ibuprofen, converting ibuprofen to 3-hydroxyibuprofen.

Genetics: Variants of the CYP2C9 gene have been associated with altered ibuprofen metabolism. Individuals with one or more CYP2C9*2 or CYP2C9*3 allele (*1/*2, *2/*2, *1/*3, *2/*3, *3/*3) have significantly slower ibuprofen clearance compared to those with the CYP2C9*1 wild-type alleles (*1/*1).[4,5] The effects were most pronounced in CYP2C9*3 carriers. Individuals can be classified into three metabolizer groups based on their CYP2C9 enzyme activity: extensive metabolizer (EM, normal enzyme activity), intermediate metabolizer (IM, intermediate enzyme activity) and poor metabolizer (PM, low or no enzyme activity).

Recommendations: Patients who are CYP2C9 poor metabolizers should take ibuprofen with caution as they may have elevated plasma concentrations of ibuprofen due to decreased metabolic clearance. There are no specific dosing recommendations based on CYP2C9 metabolizer status due to insufficient clinical evidence.

Possible Outcomes: Poor Metabolizer, Intermediate Metabolizer, Extensive Metabolizer

Markers or Alleles Tested: CYP2C9 [CYP2C9 *2, CYP2C9 *3, CYP2C9 *6]

Ethnic Distribution of Alleles[6]

Allele	CYP2C9 marker	African	Caucasian	Japanese	Chinese
*1	Wild-type	80.6%	77.9%	96.5%	95.8%
*2	rs1799853	1.2%	15.9%	0%	0.1%
*3	rs1057910	0%	5.7%	3.4%	4.1%
*6	rs9332131	1.2%	0%	0%	0%

Predicted CYP2C9 Metabolizer Status[7]

CYP2C9 Diplotype	Predicted Metabolizer Status
*2/*2, *2/*3, *2/*6, *3/*3, *3/*6, *6/*6	Poor Metabolizer
*1/*2, *1/*3, *1/*6	Intermediate Metabolizer
*1/*1	Extensive Metabolizer

Limitations and Warnings: Many CYP2C9 variants have been identified but are not part of this test. The possibility that the patient may have a variant that is not included in this test cannot be ruled out.

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5. García-Martín E, Martínez C, Tabarés B, Frías J, Agúndez JA. Interindividual variability in ibuprofen pharmacokinetics is related to interaction of cytochrome P450 2C8 and 2C9 amino acid polymorphisms. *Clinical pharmacology and therapeutics.* 2004;76:119-27.
6. Man M, Farmen M, Dumaual C, et al. Genetic variation in metabolizing enzyme and transporter genes: comprehensive assessment in 3 major East Asian subpopulations with comparison to Caucasians and Africans. *Journal of clinical pharmacology.* 2010;50:929-40.
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Meloxicam

Report Type: Pharmacogenetics

About: Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) indicated to treat pain, tenderness, swelling and stiffness caused by osteoarthritis, rheumatoid arthritis and juvenile rheumatoid arthritis in patients two years or older (FDA-approved drug label). It is sometimes used to treat ankylosing spondylitis. The FDA-approved drug label states that meloxicam treatment may lead to increased risks of cardiovascular and gastrointestinal adverse events. Meloxicam functions by inhibiting the synthesis of prostaglandin that is involved in mediating inflammation, pain, fever and swelling.[1,2] Meloxicam is primary metabolized by the CYP2C9 enzyme, whereas CYP3A4 enzyme plays a minor role in meloxicam metabolism.[3]

Genetics: Variants of the CYP2C9 gene have been associated with altered meloxicam metabolism. Individuals with two copies of the CYP2C9*3 alleles (*3/*3) have a nine-fold slower clearance of oral meloxicam compared to those with the CYP2C9*1 wild-type alleles (*1/*1).[4] Individuals can be classified into three metabolizer groups based on their CYP2C9 enzyme activity: extensive metabolizer (EM, normal enzyme activity), intermediate metabolizer (IM, intermediate enzyme activity) and poor metabolizer (PM, low or no enzyme activity).

Recommendations: Patients who are CYP2C9 poor metabolizers should take meloxicam with caution as they may have elevated plasma concentrations of meloxicam due to reduced metabolic clearance. There are no specific dosing recommendations based on CYP2C9 metabolizer status due to insufficient clinical evidence.

Possible Outcomes: Poor Metabolizer, Intermediate Metabolizer, Extensive Metabolizer

Markers or Alleles Tested: CYP2C9 [CYP2C9 *2, CYP2C9 *3, CYP2C9 *6]

Ethnic Distribution of Alleles[5]

Allele	CYP2C9 marker	African	Caucasian	Japanese	Chinese
*1	Wild-type	80.6%	77.9%	96.5%	95.8%
*2	rs1799853	1.2%	15.9%	0%	0.1%
*3	rs1057910	0%	5.7%	3.4%	4.1%
*6	rs9332131	1.2%	0%	0%	0%

Predicted CYP2C9 Metabolizer Status[6]

CYP2C9 Diplotype	Predicted Metabolizer Status
*2/*2, *2/*3, *2/*6, *3/*3, *3/*6, *6/*6	Poor Metabolizer
*1/*2, *1/*3, *1/*6	Intermediate Metabolizer
*1/*1	Extensive Metabolizer

Limitations and Warnings: Many CYP2C9 variants have been identified but are not part of this test. The possibility that the patient may have a variant that is not included in this test cannot be ruled out.

References

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Methadone

Report Type: Pharmacogenetics

About: Methadone is an opioid analgesic used to relieve moderate to severe pain. It is also used for maintenance treatment of opioid addiction. Methadone is a mu-opioid receptor agonist that is usually administered as a racemic mixture. The (S)-enantiomer is associated with cardiotoxicity, whereas the (R)-enantiomer binds the mu-opioid receptor more strongly and is primarily responsible for the methadone's therapeutic effect.[1,2] The primary pathway of methadone metabolization involves N-demethylation by the CYP2B6 and CYP3A4 enzymes and results in formation of inactive metabolites.[3] CYP2B6 preferentially demethylates (S)-methadone.[4,5]

Genetics: Variants of the CYP2B6 gene have been shown to be associated with methadone metabolism and QTc interval prolongation.[2,6,7,8,9] Individuals can be classified based on their CYP2B6 enzyme activity into three metabolizer groups: Extensive Metabolizer (normal enzyme activity), Intermediate Metabolizer (intermediate enzyme activity) and Poor Metabolizer (low or no enzyme activity).

Studies show an association between the CYP2B6 *6 allele, which indicates a poor metabolizer status, and increased plasma concentrations of cardiotoxic (S)-methadone. Individuals who are homozygous for CYP2B6 *6 have increased risk of prolonged QT interval,[9] which is associated with heart palpitations, seizures or cardiac arrest.[10] Prolonged QT may be caused by the blockage of hERG channels by (S)-methadone.

Recommendations: If methadone is taken with other medicines or supplements, toxic accumulation of methadone may occur.[11] Concurrent use of methadone with drugs that prolong the heart QT interval, blockers of the hERG channel or CYP3A4 inhibitors may put CYP2B6 *6 PMs at increased risk of adverse effects. Some antipsychotics, antidepressants, antibiotic drugs and central nervous system depressants may increase QT interval and the rate of arrhythmia.[1,12,13,14]

Possible Outcomes: Poor Metabolizer, Intermediate Metabolizer, Extensive Metabolizer

Markers or Alleles Tested: CYP2B6 [CYP2B6 *2, CYP2B6 *4, CYP2B6 *5, CYP2B6 *6, CYP2B6 *9, CYP2B6 *18]

Ethnic distribution of CYP2B6 phenotypes[15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30]

Allele	Marker(s)	Enzyme Activity	Caucasian	African American	Asian	Hispanic
*2	rs8192709	Normal	3.0-5.3%	3.0-4.3%	3.4-13.2%	0-3.0%
*4	rs2279343	Increased	2.0-6.2%	0-2.0%	4.0-11.8%	3.0-14.3%
*5	rs3211371	Normal	3.0-12.2%	5.0-8.3%	0-4.0%	5.0-11.4%
*6	rs2279343, rs3745274	Reduced	20.0-28.1%	32.8-34.8%	12.0-27.0%	21.4-30.0%
*9	rs3745274	Reduced	0-1.4%	0-1.8%	0-1.8%	1.4-5.0%
*18	rs28399499	Reduced	0%	2.9-7.5%	0%	0%

The *1 allele is the wild type allele.

Predicted CYP2B6 Metabolizer Status[15,31,32,33,34]

CYP2B6 Diplotype	Predicted Metabolizer Status
*6/*6, *6/*9, *6/*18, *9/*9, *9/*18, *18/*18	Poor Metabolizer
*1/*6, *1/*9, *1/*18, *4/*6, *4/*18, *5/*6, *5/*9, *5/*18	Intermediate Metabolizer
*1/*1, *1/*4, *1/*5, *4/*4, *4/*5, *5/*5	Extensive Metabolizer

Limitations and Warnings: Many rare CYP2B6 variants have been identified but are not part of this test. It is possible, but unlikely, that the patient may have a variant that is not included in this test.[15]

CYP2B6 variants may affect plasma levels of (S)-methadone; however, they are unlikely to affect a patient's therapeutic response to methadone due to (R)-methadone being responsible for the drug's opioid effect.[35]

In addition to the genetic variants included in this test, other genetic and nongenetic factors can influence methadone metabolism, including variants in other genes, other medications, health status, age and gender.[2,6]

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Methotrexate toxicity

Report Type: Pharmacogenetics

About: Methotrexate (MTX) is a chemotherapeutic agent used in the treatment of lymphoma and leukemia, as well as uterine, breast, skin, ovarian and other cancers. MTX is also used to treat very severe and disabling psoriasis or in hematopoetic stem cell transplantation to prevent graft-versus-host disease. Some patients taking MTX may experience many and/or severe side effects, which are often referred to as MTX toxicity.[1]

Genetics: The T allele of the rs1801133 marker (C677T variant) in the MTHFR (5,10-methylenetetrahydrofolate reductase) gene, which is important for folate metabolism, was shown to be associated with MTX toxicity in patients with rheumatoid arthritis. The T allele results in an amino acid change that leads to reduced enzyme activity. Homozygotes for the T allele have approximately 30% of the expected MTHFR enzyme activity, and heterozygotes have approximately 65% activity, compared to the most common genotype, C allele homozygotes. Reduced MTHFR enzyme activity may result in reduced elimination of MTX, thus resulting in higher than expected MTX plasma concentrations and increasing the likelihood of MTX toxicity.[2]

While other MTHFR mutations are associated with MTHFR deficiency, only the C677T variant has shown significant association with methotrexate toxicity. In a meta-analysis of eight small studies, individuals with a T allele were shown to have a 1.7-fold increased risk for MTX-induced side effects.[3] These studies included patients from India, Japan, South Korea, Israel and the Netherlands. Additionally, a meta-analysis of 14 studies demonstrated that the T allele was associated with an increased risk of MTX-induced toxicity (liver toxicity, myelosuppression, oral mucositis, gastrointestinal toxicity and skin toxicity) in patients with acute lymphoblastic leukemia (ALL).[4]

Most studies with statistically significant data indicate an association between the T allele with MTX-induced side effects in patients with rheumatoid arthritis and ALL. It should be noted, however, that a 2011 meta-analysis did not identify a significant association between the C677T variant and MTX toxicity in patients with rheumatoid arthritis.[5] Association of the T allele with MTX toxicity has also been observed in patients undergoing hematopoetic cell transplantation and in patients with high-grade non-Hodgkin's lymphoma, acute leukemia, ovarian cancer, breast cancer, or juvenile idiopathic arthritis.[2] However, these studies are relatively small and controversial. In addition to MTX toxicity, the T allele has been associated with lowered efficacy of MTX, such as reduced anti-tumor activity or reduced survival in some studies but not others. The T allele has also been shown to be associated with therapeutic response to a different chemotherapy, fluorouracil (5-FU), in some studies but not others.[6,7,8,9]

Recommendations: Varying the MTX dose or supplementing with folic or folinic acid (leucovorin) has been shown to reduce the risk of toxicity-related discontinuation of MTX treatment in patients with and without the T allele.[10,11,12]

Please also see the related tests: MTHFR deficiency and Genetic risk for decreased folate.

Possible Outcomes: Increased Risk, Typical Risk

Markers or Alleles Tested: MTHFR [rs1801133]

Ethnic Distribution of Tested Alleles: The minor allele frequency was approximately 29.4% to 33.5% in Caucasians.[5]

Limitations and Warnings: Some variants not reported in the test also result in altered MTHFR activity. Therefore, a negative result for the reported MTHFR variant does not rule out the presence of additional variants that can cause altered MTHFR activity related adverse effects upon MTX treatment.

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Oxycodone

Report Type: Pharmacogenetics

About: Oxycodone is an opioid analgesic used to relieve moderate to moderately severe pain.[1] In one of oxycodone's two major metabolic pathways, the hepatic CYP2D6 enzyme metabolizes it to oxymorphone, which binds the mu-opioid receptors with a 40-fold greater affinity than oxycodone.[2] The CYP3A enzymes mediate the other major metabolic pathway that converts oxycodone to noroxycodone, which has a weaker affinity for mu-opioid receptors than either oxycodone or oxymorphone.[2]

Genetics: ariants of the CYP2D6 gene that affect enzyme function have been shown to be associated with oxycodone metabolism.[2,3,4,5] Individuals can be classified based on their CYP2D6 enzyme activity into four metabolizer groups: Ultrarapid Metabolizer (UM, higher than normal enzyme activity), Extensive Metabolizer (EM, normal enzyme activity), Intermediate Metabolizer (IM, intermediate enzyme activity) and Poor Metabolizer (PM, low or no enzyme activity).

CYP2D6 metabolizer status affects plasma levels of oxymorphone. Compared to EMs, exposure to oxymorphone is low in PMs.[2,3,4,5] Though pharmacokinetic data are strong, it is less clear if the changes in oxymorphone exposure affect analgesic or adverse effects in patients with different levels of CYP2D6 activity. Patients treated with oxycodone for post-operative pain and cancer pain were unaffected by CYP2D6 genotype.[4,5] This result may be explained by oxycodone's high affinity for kappa-opioid receptors, which suggests that unmetabolized oxycodone may exert analgesic effects by binding those receptors. However, experimental pain model studies showed decreased efficacy of oxycodone in CYP2D6 PMs and increased analgesic effects and risk of side effects in UMs.[3,6]

Recommendations: Concurrent use of oxycodone with CYP2D6 inhibitors can decrease plasma levels of oxymorphone in IMs, EMs and UMs.[2] Inducers of CYP3A enzymes, when used concurrently with oxycodone, are expected to lower the levels of oxycodone and oxymorphone, which may reduce the analgesic effects.[7,8,9] Similarly, CYP3A inhibitors may enhance analgesic effects and toxicity by increasing oxycodone exposure.[10,11] Lists of CYP2D6 inhibitors,[12,13,14] CYP3A inducers and CYP3A inhibitors[12,14] are available at various web sites.

Possible Outcomes: Poor Metabolizer, Intermediate Metabolizer, Extensive Metabolizer, Ultrarapid Metabolizer

Markers or Alleles Tested: CYP2D6 alleles are classified as non-functional, reduced-function, normal-function and increased-function.

Non-functional alleles: *3, *4, *5, *6, *7, *8, *11, *12, *14A, *15, *36, *4xN, and *36xN
Reduced-function alleles: *9, *10, *17, *29, *41, *9xN, *10xN, *17xN, *41xN and *36-*10
Normal-function alleles: *1, *2 and *35
Increased-function alleles: *1xN, *2xN and *35xN

Predicted CYP2D6 Metabolizer Status

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Metabolizer Status	CYP2D6 Genotype
Poor metabolizer	Two non-functional alleles
Intermediate metabolizer	One non-functional allele and one reduced-function allele OR Two reduced-function alleles
Extensive metabolizer	One or two normal-function copies of the CYP2D6 gene
Ultrarapid metabolizer	Three or more normal-function copies of the CYP2D6 gene

Ethnic distribution of CYP2D6 phenotypes[15,16,17]

Metabolizer Status	African American	Caucasian	East Asian	Hispanic
Poor Metabolizer	2-8%	5-10%	<2%	3-10%
Intermediate Metabolizer	~30%	10-17%	50-60%	No data
Extensive Metabolizer	60-70%	70-80%	40-50%	No data
Ultrarapid Metabolizer	~5%	3-10%	<1%	0-5%

Limitations and Warnings: Many rare CYP2D6 variants have been identified but are not part of this test. It is possible that the patient has a variant that is not included in this test.

In addition to the genetic variants included in this test, other genetic and nongenetic factors can influence the metabolism, safety, and effectiveness of oxycodone, including variants in other genes, age, other medications and liver and kidney conditions.[7,18]

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Tramadol

Report Type: Pharmacogenetics

About: Tramadol is an opioid analgesic used to relieve moderate to severe pain.[1] It is administered as a racemic mixture of two enantiomers, (+)-tramadol and (-)-tramadol. The hepatic CYP2D6 enzyme metabolizes (+)-tramadol to (+)-O-desmethyltramadol, which binds the mu-opioid receptor with an affinity 700-fold greater than the parent drug. However, tramadol also contributes an analgesic effect, although through different monoaminergic pathways.[2]

Genetics: Variants of the CYP2D6 gene that affect enzyme function have been shown to be associated with tramadol metabolism[3,4,5] and analgesic effects.[4,6,7,8] Individuals can be classified based on their CYP2D6 enzyme activity into four metabolizer groups: Ultrarapid Metabolizer (UM, higher than normal enzyme activity), Extensive Metabolizer (EM, normal enzyme activity), Intermediate Metabolizer (IM, intermediate enzyme activity) and Poor Metabolizer (PM, low or no enzyme activity).

PMs may experience a poor analgesic effect if treated with tramadol.[4,6,7] This metabolizer status has been associated with decreased levels of (+)-O-desmethyltramadol.[3] Despite the potential to experience analgesia through alternative monoaminergic pathways, PMs have been shown to respond poorly to tramadol compared to most people. In contrast, UMs may be at increased risk of cardiotoxicity and other opioid-associated adverse effects.[7,9]

Recommendations: Concurrent use of tramadol with CYP2D6 inhibitors can decrease the plasma levels of (+)-O-desmethyltramadol in IMs, EMs and UMs.[4,10]

Concurrent use of tramadol with CYP2D6, CYP3A4, or CYP2B6 inhibitors may increase the risk of adverse effects, such as serotonin syndrome.[11,12] Concurrent use of tramadol with CYP3A4 or CYP2B6 inhibitors in CYP2D6 PMs is not recommended. Lists of CYP2D6,[13,14,15] CYP2B6[13] and CYP3A4 inhibitors[13,15] are available at various web sites.

Possible Outcomes: Poor Metabolizer, Intermediate Metabolizer, Extensive Metabolizer, Ultrarapid Metabolizer

Markers or Alleles Tested: CYP2D6 alleles are classified as non-functional, reduced-function, normal-function and increased-function.

Non-functional alleles: *3, *4, *5, *6, *7, *8, *11, *12, *14A, *15, *36, *4xN, and *36xN
Reduced-function alleles: *9, *10, *17, *29, *41, *9xN, *10xN, *17xN, *41xN and *36-*10
Normal-function alleles: *1, *2 and *35
Increased-function alleles: *1xN, *2xN and *35xN

Predicted CYP2D6 Metabolizer Status

OmeCare

Metabolizer Status	CYP2D6 Genotype
Poor metabolizer	Two non-functional alleles
Intermediate metabolizer	One non-functional allele and one reduced-function allele OR Two reduced-function alleles
Extensive metabolizer	One or two normal-function copies of the CYP2D6 gene
Ultrarapid metabolizer	Three or more normal-function copies of the CYP2D6 gene

Ethnic distribution of CYP2D6 phenotypes[16,17,18]

Metabolizer Status	African American	Caucasian	East Asian	Hispanic
Poor Metabolizer	2-8%	5-10%	<2%	3-10%
Intermediate Metabolizer	~30%	10-17%	50-60%	No data
Extensive Metabolizer	60-70%	70-80%	40-50%	No data
Ultrarapid Metabolizer	~5%	3-10%	<1%	0-5%

Limitations and Warnings: Many rare CYP2D6 variants that affect CYP2D6 activity have been identified. It is possible that the patient may have a variant that is not included in this test.

In addition to the genetic variants included in this test, other genetic and nongenetic factors can influence the metabolism, safety and effectiveness of tramadol, including variants in other genes, other medications and liver and kidney conditions.[2]

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