CYP2D6: Codeine

AUC: 'area under the concentration-time curve', Clor: oral clearance, Css: steady state plasma concentration, EM: extensive metabolizer, IM: intermediate metabolizer, M3G: morphine-3-glucuronide, M6G: morphine-6-glucuronide, MR: metabolic ratio, NS: not statistically significant, PCA: patient-controlled-analgesia, PM: poor metabolizer, S: statistically significant, t1/2: half life, UM: ultrarapid metabolizer.

Reference	Level of evidence	Clinical relevance	Effect	Remarks
ref. 1 Madadi P et al. Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: a casecontrol study. Clin Pharmacol Ther 2009;85:31-5. PMID: 18719619	3	UM: C	72 mother–child pairs, 17 (24%) breastfed infants were reported to exhibit CNS depression while their mothers used codeine. - Prevalence of UMs was 11.8% in cases and 1.8 in controls (NS, 600%). Moreover, the single asymptomatic case of a CYP2D6 UM mother was a 6 months baby that was also receiving formula and solid foods. - Of the 2 UM cases, 1 was described previously (Koren 2006). The 2nd case was a mother who used 120 mg/day codeine for severe muscle pain after childbirth. She reported feeling sedated, nauseous, dizzy, and weak during the period she was taking codeine. Her breastfed infant was described as extremely drowsy and feeding poorly. She began supplementing breast milk with formula after delivery because of personal exhaustion and due to her infant's feeding difficulties. The family doctor was contacted with concerns about the infant's condition. By 7 days after delivery, the mother had switched completely to formula feeding, and she noted complete reversal of the infant's symptoms in the following days. Both cases are CYP2D6 UM and UGT2B7*2/*2.	Conclusion authors: 'Breastfed infants of mothers who are CYP2D6 UMs combined with the UGT2B7*2/*2 are at increased risk of potentially life-threatening CNS depression.'
ref. 2 Kirchheiner J et al. Pharmacokinetics of	3	PM: A (UM+EM):	26 healthy subjects. 3x PM (1x *3/*3, 2x *4/*4), 11x EM (4x *1/*1, 3x *1/*2, 1x *1/*9, 1x *1/*10, 1x *2/*41, 1x *35/*41), 12x UM + EM (1x *1/*35, 1x *1x2/*9, 1x	Conclusion authors: 'No severe adverse effects were seen in the UMs in our study most

codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. Pharmacogenomics J 2007;7:257-65. PMID:16819548		A	*1x2/*10, 1x *1x2/*41, 1x *2x2/*41, 1x *35x2/*1, 2x 2x2/*35, *1x 1x2/*35, 2x *2x2/*1, 1x *1x2/*1). Codeine 30 mg single dose. No concomitant medication. <u>Pharmacokinetic endpoints:</u> Compared to EM: PM: - AUC decreased from 191 to 180 µg.hour/l (NS, by 6%), - AUC morphine decreased from 11 to 0.5 µg.hour/l (S, by 2100%). - t½ codeine= 4.8 hour - t½ morphine=17 hour UM + EM: - No effect on AUC codeine - AUC morphine increased from 11 to 16 µg.hour/l (S, by 45%). - t½ codeine= 3.7 hour - t½ morphine= 14 hour The proportion of variability in morphine AUC explained by CYP2D6 genotype was 60%-63%. <u>Clinical endpoints:</u> Compared to EM: PM: - Pupil diameter (surrogate endpoint for effect on mu-opiod receptors) was larger (NS) - 66% reported side effects. An increase of 57% compared to EM (NS, by 57%) UM + EM: - No significant effect on pupil diameter (NS) - Side effects increased from 42% to 100% - 91% of the UMs reports sedation vs. 50% of the EMs (NS, by 82%).	likely because we used for safety reasons a low dose of only 30 mg.' AUC morphine compared to EM: PM: 5% UM + EM: 145% AUC codeine compared t. EM: PM: 94% UM + EM: 100%

			Note: 1 EM is heterozygous for the μ-opioïd receptor gene	
ref. 3 Koren G et al. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. Lancet 2006;368:704. PMID: 16920476	2	UM: F[§]	Breastfed neonate showed intermittent periods of difficulty in breastfeeding and lethargy starting on day 7. Mother was prescribed codeine 120 mg/day. Reduced to 60 mg/day from day 2. On day 11 the baby had regained his birthweight. On day 12, however, he had grey skin and his milk intake had fallen. He was found dead on day 13. Postmortem blood concentration of morphine was 70 ng/mL (normal range: 0-2.2 ng/ml. The morphine concentration in the milk on day 10 was 87 ng/ml (normal range 1.9-20.5 ng/ml at doses of 60 mg/6hr). The mother was UM (duplication *2: 2x*2).	Conclusion authors: 'This case shows that polymorphism of CYP2D6 can be life threatening for some breastfed babies.'
ref. 4 Gasche Y et al. Codeine intoxication associated with ultrarapid CYP2D6 metabolism. N Engl J Med 2004 30;351:2827-31. PMID: 15625333	2	UM: D	Patient with renal failure and pneumonia is prescribed antibiotics and codeine 25 mg three times a day to relieve the cough. Concomitant medication: CYP3A4 inhibitors. Signs of opioid intoxication. On hospital day 4, the patient's level of consciousness rapidly deteriorated, and he became unresponsive. Intravenous administration of naloxone resulted in a dramatic improvement in the patient's level of consciousness. CYP2D6 genotyping showed three or more functional alleles (UM, MR dextromethorphan<< 0.0005). Morphine plasma concentration was 80 μg/l (expected range, 1 to 4 μg/l). M3G and M6G concentrations were also increased.	
ref. 5 Williams DG et al. Pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability. Br J Anaesth 2002;89:839-45.	3	IM: A PM: AA	96 children hildren undergoing adenotonsillectomy of which 48x received codeine. 2x PM (2 non-functional alleles), 9x IM/PM (1 non-functional allele and 1 reduced activity allele), 17x IM (2 reduced activity alleles), 19x EM (2 functional alleles or 1 functional allele and 1 reduced activity allele), Genotyping for *1- *5, *9, *10 and *17. Codeine 1.5 mg/kg single dose. Concomitant diclofenac. Blood was collected 1 hour after injection of the study drug.	Conclusion authors: 'Codeine analgesia is less reliable than morphine, but was not well correlated with either phenotype or plasma morphine in this study.'

PMID: 12453926			Compared to EM: IM + IM/PM: - Morphine concentration decreased (S) PM: Morphine concentration below limit of detection Neither phenotype nor morphine concentration was correlated with either pain score or the need for rescue analgesia.	
ref. 6 Poulsen L et al. Codeine in postoperative pain. Study of the influence of sparteine phenotype and serum concentrations of morphine and morphine-6-glucuronide. Eur J Clin Pharmacol 1998;54:451-4. PMID: 9776433	3	PM: A	81 patients with postoperative pain. 74x phenotyped with sparteine. 8x PM and 66x EM. Codeine 100 mg single dose. No concomitant CYP2D6 inhibitors. Blood was collected 1 hour after medication. PM: - Morphine and M6G were below the limit of detection. - The sum of differences between pre- and post-operative pain ratings did not differ between the two phenotypes. - Patients with serum concentrations of morphine+M6G below 10 nmol/l had a marginally significant lower decrease in pain level than the patients with higher levels of these substances. - There was no correlation between the serum concentration of morphine+M6G and pain reduction. Note: - Escape medication was allowed - Genotype not reported	Conclusion authors: 'With the overall low efficacy of codeine …it is very difficult to detect subgroup differences in effect. …Together with the fact that the number of PM was small, it is not surprising that there was no statistically significant difference in analgesic effect between PM and EM.'
ref. 7 Eckhardt K et al. Same incidence of adverse drug events after codeine administration irrespective of the genetically	3	PM: B	18 healthy subjects. 9x PM (6x *4/*4, 1x *3/*5, 1x *4/*5) and 9x EM (2x *1/*1, 4x *1/*2, 1x *1/*10, 1x *1/*5, 1x *2/*3). Codeine 170 mg single dose. No concomitant medication. Endpoints assessed at t=25 hour. <u>Pharmacokinetic endpoints:</u> Compared to EM:	Conclusion authors: 'Suggesting that PMs showing no analgesic effects from codeine doses up to 170 mg implicates that 7-10% of the Caucasian population will have no analgesic benefit after codeine administration but may suffer side effects caused by

determined differences in morphine formation. Pain 1998;76:27-33. PMID: 9696456			PM: - AUC morphine decreased from 173 to 10 nM.hour (S, by 94%) - Morphine t½= 5.0 hour. - AUC codeine increased from 4014 to 5140 nM.hour (NS, by 28%) - Codeine t½ = 3.8 hour <u>Clinical endpoints:</u> PM: No difference in adverse events compared to EM (NS). Pain tolerance not different from placebo (NS) EM: Pain tolerance is increased by 1293% compared to placebo (S).	codeine itself.' AUC morphine compared to EM: PM: 6% AUC codeine compared to EM: PM: 128%
ref. 8 Dalen P et al. Quick onset of severe abdominal pain after codeine in an ultrarapid metabolizer of debrisoquine. Ther Drug Monit 1997;19:543-4. PMID: 9357099	2	UM: B	Patients received 1000 mg paracetamol and 60 mg codeine following a tooth extraction. Within 30 minutes, she experienced euphoria, dizziness, and difficulty recognizing the details in a television program she was watching. Simultaneously, she experienced very severe pain in the epigastrium. The pain was constant but peaked at regular intervals. The pain was more severe than during delivery of her three children. The euphoria and pain lasted for approximately 3 to 4 hours and then vanished. A rechallenge with codeine 30 mg resulted in the same symptoms, although they were less pronounced. Patient was found to be an UM (MR-debrisoquine was 0.1, duplication of *2)	
ref. 9 Mikus G et al. Effect of codeine on gastrointestinal motility in relation to CYP2D6 phenotype. Clin Pharmacol Ther	3	PM: A	10 healthy subjects. 5x PM (3x *4/*4, 1x *3/*34, 1x *5/*5), 5x EM (2x *1/*1, 3x *1/*4), Codeine 60 mg single dose. No concomitant medication. <u>Pharmacokinetic endpoints:</u> Compared to EM: PM:	AUC morphine compared to EM: PM: 7% AUC codeine compared to EM: PM: 93%

1997;61:459-66. PMID: 9129563			- AUC codeine decreased from 1440 to 1338 pmol/ml.hour (NS, by 7%) - t½ codeine= 2.3 hour - AUC morphine decreased from 27.8 to 1.9 pmol/ml.hour (S, by 93%) - t½ morphine=4.8 hour <u>Clinical endpoints:</u> PM: - Oro-caecal transit time was not significantly prolonged compared to placebo (NS) EM: - Oro-caecal transit time was significantly prolonged in compared to placebo (S)	
ref. 10 Hasselstrom J et al. The effect of codeine on gastrointestinal transit in extensive and poor metabolisers of debrisoquine. Eur J Clin Pharmacol 1997;53:145-8. PMID: 9403287	3	PM: AA	24 healthy subjects, 12x PM and 12x EM (MR debrisoquine < 1). Codeine 50mg single dose. No concomitant medication. Oro-caecal transit time was not significantly different for EM compared to PM.	
ref. 11 Tseng CY et al. Formation of morphine from codeine in Chinese subjects of different CYP2D6 genotypes. Clin Pharmacol Ther 1996;60:177-82. PMID: 8823235	3	IM: AA	32 healthy subjects. 12x *10/*10, 12x *1/*10, 8x *1/*1. Codeine 30 mg single dose. No concomitant medication. Compared to *1/*1: *10/*10: - AUC codeine increased from 938 to 998 nM.hr (NS, by 6%) - t½= 2.3 hour *1/*10: AUC codeine increased from 938 to 966 nM.hr t (NS, by	

			3%) - t½= 2.5 hour	
ref. 12 Poulsen L et al. Codeine and morphine in extensive and poor metabolizers of sparteine: pharmacokinetics, analgesic effect and side effects. Eur J Clin Pharmacol 1996;51:289-95. PMID: 9010701	3	PM: B	28 healthy subjects. 14x PM and 14x EM (phenotyped with sparteine), Codeine 75-100 mg single dose. No concomitant medication. Pain tests performed before and 1, 2, 3, and 4 h after medication included the cold pressor test and pain thresholds for heat and pressure stimulation. <u>Pharmacokinetic endpoints:</u> Compared to EM: PM: - $AUC_{0\text{-}4.5hr}$ codeine increased from 1427 to 1569 nM.hr (NS, by 10%) - For 13 of the 14 PM's morphine and M6G concentrations were below the limit of detection. <u>Clinical endpoints:</u> PM: There was no difference in any of the 3 pain tests or adverse effects compared to placebo. EM: -The number of adverse events increased compared to placebo (S) - The response to the cold pressor test was different.	
ref. 13 Persson K et al. Patient-controlled analgesia (PCA) with codeine for postoperative pain relief in ten extensive metabolisers and one poor metaboliser of dextromethorphan. Br J Clin Pharmacol	3	PM: AA	11 postoperative patients undergoing hysterectomy. 1x PM, 10x EM (phenotyped with dextromethorphan). Codeine 10 mg IV per PCA, Concomitant medication during the surgery. 2 patients did not experience sufficient effect of codeine, 1x PM, 1x EM with severe hip damage.	

1995;39:182-6. PMID: 7742159				
ref. 14 Yue QY et al. Pharmacokinetics of codeine and its metabolites in Caucasian healthy volunteers: comparisons between extensive and poor hydroxylators of debrisoquine. Br J Clin Pharmacol 1991;31:635-42. PMID:1867957	4	PM: A	20 healthy subjects. 9x PM, 11x EM (phenotyped with debrisoquine). 6 PMs and 8 EMs receive codeine 50 mg single dose. 3 PM and 3 EM receive 50 mg codeine every 6 hour for 54 hours. No concomitant medication. <u>Single dose:</u> PM: - AUC codeine unchanged - t½= 2.9 hours - Morphine concentration was above the level of detection in only 1 PM - AUC M6G decreased from 117 to 5.2 nM·hr compared to EM (S, by 96%). - The AUC of M3G and normorfine were also decreased (S) EM: - AUC codeine= 1010 nM.hour - t½= 2.43 hour - AUC M6G= 117 nM.hour Multiple dosing produces similar results. Note: Genotype not reported	
ref. 15 Desmeules J et al. Impact of environmental and genetic factors on codeine analgesia. Eur J Clin Pharmacol 1991;41:23-6. PMID: 1782973	3	PM: B	8 healthy subjects, 1x PM, 7x EM (phenotyped with dextromethorphan). Codeine 100 mg single dose. Concomitant medication not reported. <u>Pharmacokinetic endpoints:</u> PM: - AUC morphine below limit of detection <u>Clinical endpoint:</u>	Conclusion authors: 'In PM of genetic origin, or due to environmental alteration of the phenotypic expression (i.e. drug interaction), codeine is not activated into morphine and is an inefficient analgesic.'

			- Subjective (VAS) and objective (R-III reflex) pain thresholds in response to selective transcutaneous nerve stimulation PM: - Both subjective and objective pain thresholds are unaffected by codeine compared to placebo. EM: Until 2 hours after codeine administration both the subjective and objective pain thresholds are increased by codeine compared to placebo (S). Note: genotype not reported	
ref. 16 Sindrup SH et al. Codeine increases pain thresholds to copper vapor laser stimuli in extensive but not poor metabolizers of sparteine. Clin Pharmacol Ther 1990;48:686-93. PMID: 2249379	3	PM: B	24 healthy subjects, 12x PM, 12x EM (phenotyped with sparteine). 75 mg codeine single dose. No concomitant medication. <u>Pharmacokinetic endpoints:</u> PM: - Codeine concentration decreased compared to EM (NS). - Morphine concentration is below the limit of detection <u>Clinical endpoint:</u> Laser stimulation and determination of pain thresholds before and at t=90, 150 and 210 min after drug administration) PM: - Pain threshold does not significantly change at t=90, 150 and 210 min. compared to before administration (NS) EM: - Pain threshold is significantly increased at t=90 and t=150 min after codeine administration (S)	Conclusion authors: 'This study showed that codeine increased pain thresholds to laser stimuli in extensive metabolizers but not in poor metabolizers. Thus in poor metabolizers the analgesic activity to codeine is either absent or at least much weaker than in extensive metabolizers.'

			- Significant correlation between the increase in pain threshold and plasma concentration of morphine (S) Note: genotype not reported	

§ effect on neonate, mother is UM and uses codeine.

Groups at risk	IMs prescribed a concomitant CYP2D6 inhibitor

Remarks
Date literature search: 10 July 2009

- Studies that only reported urinary concentrations have not been included in the review.
- Studies published after 2007 that reported only metabolic ratios and not concentrations or AUC's of the drug or it's metabolites and studies that did not provide enough detail to separate PM, IM, EM, and UM (e.g. studies with a gene-dose ≤ 1.5) were also excluded.
- Gasche, 2004: Intoxication is probably the result of the CYP2D6 UM phenotype combined with 2 CYP3A4-inhibitors and decreased renal function. Note that the codeine concentration was also increased.

	Phenotype	**Code**	**Gene-Drug Interaction**	**Action Required**	**Date**
Decision DPWG	PM	4 B	Yes	Yes	12 November 2009
	IM	3 A	Yes	Yes	
	UM	3 F	Yes	Yes	

Action Pharmacy Technician	PM: First prescription: - Cough: Dispense - Analgesia: Consult pharmacist. Advise the patient to contact the prescriber in case of

	insufficient pain relief. Subsequent prescription: - Cough: Dispense - Analgesia: Advise the patient to contact the prescriber in case of insufficient pain relief.
	IM: First prescription: - Cough: Dispense - Analgesia: Consult pharmacist. Advise the patient to contact the prescriber in case of insufficient pain relief. Subsequent prescription: - Cough: Dispense - Analgesia: Advise the patient to contact the prescriber in case of insufficient pain relief.
	UM: First prescription: - Cough: Consult pharmacist - Analgesia: Consult pharmacist. Advise the patient to contact the prescriber in case of adverse events (e.g. lethargy, sedation, seizures, constipation, nausea, vomiting, respiratory depression, urinary retention). Subsequent prescription: - Cough: Dispense - Analgesia: Advise the patient to contact the prescriber in case of insufficient pain relief.
Action Pharmacist, Physician	PM: As a result of a genetic polymorphism in the gene coding for CYP2D6, the metabolic capacity of this enzyme is decreased. This might result in increased codeine plasma concentrations and decreased plasma concentrations of the active metabolites morphine and morphine-6-glucuronide. Cough: No dose adjustment is required. Analgesia: Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g.,

	acetaminophen, NSAID, morphine—not tramadol or oxycodone as these are metabolized by CYP2D6). If this is not possible, be alert to symptoms of insufficient pain relief.
	IM: As a result of a genetic polymorphism in the gene coding for CYP2D6, the metabolic capacity of this enzyme is decreased. This might result in increased codeine plasma concentrations and decreased plasma concentrations of the active metabolites morphine and morphine-6-glucuronide. Cough: No dose adjustment is required. Analgesia: Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g., acetaminophen, NSAID, morphine—not tramadol or oxycodone as these are metabolized by CYP2D6). If this is not possible, be alert to symptoms of insufficient pain relief.
	UM: As a result of a genetic polymorphism in the gene coding for CYP2D6, the metabolic capacity of this enzyme is increased. This might result in decreased codeine plasma concentrations and increased plasma concentrations of the active metabolites morphine and morphine-6-glucuronide. Cough: Insufficient data on the effect on cough in the UM phenotype. Be extra alert to ADEs (e.g. lethargy, sedation, seizures, constipation, nausea, vomiting, respiratory depression, urinary retention) due to increased morphine plasma concentrations. Analgesia: Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g., acetaminophen, NSAID, morphine—not tramadol or oxycodone as these are metabolized by CYP2D6). If this is not possible, be extra alert to ADEs (e.g. lethargy, sedation, seizures, constipation, nausea, vomiting, respiratory depression, urinary retention) due to increased morphine plasma concentrations.

Considerations

The analgesic effects of codeine are primarily dependent on its biotransformation into morphine and morphine-6-glucuronide.

- If codeine is prescribed for analgesia, the selection of an alternative drug is recommended. Tramadol and oxycodone are no suitable alternatives because they are also metabolized by CYP2D6. There are insufficient data to allow calculation of a codeine dose adjustment. Be extra alert to be alert to symptoms of insufficient pain relief in PMs and IMs if codeine is prescribed. UMs have an increased risk morphine related adverse events due to increased morphine plasma concentrations. Both codeine and morphine have an antitussive effect through suppression of the cough center in the medulla oblongata. The antitussive potency of codeine is about 3 times larger than the antitussive effect of morphine (Nattermann: Klinisches sachverständigen-gutachten zu Bronchicum Mono Codein Tropfen april 2006).
- If codeine is prescribed for cough, there is insufficient evidence that therapy adjustment is required. There are no data on the effect of CYP2D6 genotype or phenotype on the antitussive effect of codeine. The population size-weighted mean of the dose adjustments calculated for the individual papers (based on codeine AUC data) is 89% of the recommended dose. Such a small decrease might not be clinically relevant. Be extra alert to ADEs (e.g. lethargy, sedation, seizures, constipation, nausea, vomiting, respiratory depression, urinary retention) in UMs, due to increased morphine plasma concentrations.

Mechanism

Codeine is mainly metabolized by CYP2D6, CYP3A4, and glucuronidation. O-demethylation to the active metabolite morphine is catalyzed by CYP2D6. The affinity of morphine for the μ-receptor is 200x larger than the affinity of codeine for this receptor. Morphine is metabolized to morphine-3-glucuronide and the active morphine-6-glucuronide. A genetic polymorphism in CYP2D6 can result in altered concentrations of codeine, morphine, and morphine-6-glucuronide .