CYP2D6: Amitriptyline

AMI: amitriptyline, Clor: oral clearance, Css: steady state plasma concentration, EM: extensive metabolizer, IM: intermediate metabolizer, MR: metabolic ratio, NS: not statistically significant, NOR: nortriptyline, PM: poor metabolizer, S: statistically significant, UM: ultrarapid metabolizer.

Reference	Level of evidence	Clinical relevance	Effect	Remarks
ref. 1 Koski A et al. CYP2D6 and CYP2C19 genotypes and amitriptyline metabolite ratios in a series of medicolegal autopsies. Forensic Sci Int 2006 ;158:177-83. PMID: 16024198	3	IM: A PM: A	195 postmortem toxicology cases. 13x PM, 60x IM, 108x EM, 14x UM. Concomitant use of CYP2D6 inhibitors varied. Compared to EM: IM: - MR AMI / (E)-10-hydroyAMI increased (S) - MR NOR / (E)-10-hydroxyAMI increased (S) - MR (E)-10-hydroxyNOR / (Z)-10-hydroxyNOR decreased (S) - MR (Z)-10-hydroxyAMI / (Z)-10-hydroxyNOR decreased (S) PM: - MR AMI / (E)-10-hydroyAMI increased (S) - MR NOR / (E)-10-hydroxyAMI increased (S) - MR (E)-10-hydroxyNOR / (Z)-10-hydroxyNOR decreased (S) - MR (Z)-10-hydroxyAMI / (Z)-10-hydroxyNOR decreased (S) - MR NOR / (E)-10-hydroxyNOR increased (S) - MR NOR / (Z)-10-hydroxyAMI	Conclusion authors: “Our study shows a concordance of AT metabolite patterns with CYP2D6 and CYP2C19 genotypes in the presence of confounding factors typical for postmortem material. This result demonstrates the feasibility of postmortem pharmacogenetic analysis and supports the dominant role of genes in drug metabolism.”

			increased (S) - MR (E)-10-hydroxyAMI / (Z) -10-hydroxyAMI decreased (S) - MR AMI / NOR decreased (S) The cause of death was a drug intoxication in 103 patients. In 63 cases AMI overdose was the primary cause of death of which 39 intentionally, 17 by accident and 7 unknown. The accidental intoxications were not associated with the PM-genotype (1x PM with low AMI plasma concentration, 9x IM, 6x EM, 1x UM). Covariate analyses for CYP2D6, CYP2C19, age, sex) revealed a dominant effect of CYP2D6 status on AMI-metabolism. Note: *41 was not genotyped	
ref. 2 Steimer W et al. Amitriptyline or not, that is the question: pharmacogenetic testing of CYP2D6 and CYP2C19 identifies patients with low or high risk for side effects in amitriptyline therapy. Clin Chem 2005;51:376-85. PMID: 15590749	3	IM: C	Prospective 'blinded' study with 50 patients, 32x EM, 17x IM, 1x UM. AMI 150 mg/day for 3 weeks. For 5 patients the AMI dose was adjusted during the study to 75 mg/day (n=1), 100 mg/day (n=3), 125 mg/day (n=1). Concomitant medication: 13x possibly a CYP2D6 inhibitor was prescribed. Compared to EM+UM: IM: - Percentage of patients with side-effects increased from 12.1% to 76.5% (S, 523%). This effect was	Conclusion authors: "Combined pharmacogenetic testing for CYP2D6 and CYP2C19 identifies patients with low risk for side effects in amitriptyline therapy and could possibly be used to individualize antidepressive regimens and reduce treatment cost. Identification of genotypes associated with slightly reduced intermediate metabolism may be more important than currently anticipated" Plasmaconcentration NOR

			also seen in patients without concomitant mediaction influencing CYP2D6 (4.2% to 69.2%) (S, 1548%) - Css NOR increased: - from 49.0 to 101.2 µg/l in CYP2C19 IM+PM (S, 107%) - from 65.0 to 108.4 µg/l for CYP2C19 EM (S, 67%) - Css (AMI + NOR) increased - from 154.8 to 202.0 µg/l for CYP2C19 IM+PM (S for trend, 30%) - from 134.7 to 201.9 µg/l for CYP2C19 EM (S for trend, 50%) - No difference in therapeutic response (NS) NOR but not AMI, concentrations correlated with side effects. Both NOR and AMI concentrations did not correlate with therapeutic response.	compared to EM: IM: 167-207% Plasmaconcentration AMI + NOR compared to EM: IM: 130-150%
ref. 3 Steimer W et al. Allele-specific change of concentration and functional gene dose for the prediction of steady-state serum concentrations of amitriptyline and nortriptyline in CYP2C19 and CYP2D6 extensive	3	IM: A	Identical to ref 2, but this paper reports the results of the pharmacokinetic analyses. - Significant differences in Css NOR[a] between different gene-dose groups (Null alleles=0, decreased functional allele=0.5, fully functional allele=1). Compared to EM: IM: - 0.5 vs. 1.5: from 37,6 to	Conclusion authors: “CYP2D6 but not CYP2C19 correlates with the sum of both concentrations used to guide AT therapy.” NOR plasma concentration: Compared to EM: IM: 178-265%

and intermediate metabolizers. Clin Chem 2004;50:1623-33. PMID: 15205367			66,8 µg/l per kg/mg (S, 78%) - 0.5 vs. 2.0: from 25.2 to 66.8 µg/l per kg/mg (S, 165%) - 1.0 vs. 2.0: from 25.2 to 48.2 µg/l per kg/mg (S, 91%) Low EM vs. High EM: - 1.5 vs. 2.0: from 25.2 to 37,6 µg/l per kg/mg (S, 49%) - AMI + NOR Css is mainly influenced by change in NOR concentrations due to CYP2D6 polymorphisms. Css AMI + NOR[a] is: - Gene dose 0.5: 101.6 µg/l per kg/mg - Gene dose 1.0: 89.9 µg/l per kg/mg - Gene dose 1.5: 75.1 µg/l per kg/mg - Gene dose 2.0: 59.8 µg/l per kg/mg Note: Mean Css AMI + NOR and NOR for the whole population displayed the exact mean concentration obtained for the individuals with a *CYP2D6* gene dose of 1.5, and not a gene dose of 2.0.	AMI+NOR plasma concentration compared to EM: IM: 120-170%
ref. 4 Grasmader K et al. Impact of polymorphisms of	3	UM: AA	136 patients, 3 with AMI, dose not reported. 1 UM, 2 IM or EM. Mean dose corrected Css AMI+NOR was 0.61 ng/ml per mg AMI. Dose	AMI + NOR plasma concentration compared to EM + IM: UM: 106%

cytochrome-P450 isoenzymes 2C9, 2C19 and 2D6 on plasma concentrations and clinical effects of antidepressants in a naturalistic clinical setting. Eur J Clin Pharmacol 2004;60:329-36. PMID: 15168101			corrected Css in UMs was 6% increased compared to the mean.	
ref. 5 Shimoda K et al. The impact of CYP2C19 and CYP2D6 genotypes on metabolism of amitriptyline in Japanese psychiatric patients. J Clin Psychopharmacol 2002;22:371-8. PMID: 12172336	3	IM: A	50 patients. 25-225 mg/day AMI (0.46-5.18 mg/kg/day) for 2 weeks. 8x 0 mutant alleles (EM genotype 1-1), 32x 1 mutant allele (29x EM (genotype 1-0.5) and 3x IM (genotype 1-0)), 10x 2 mutant alleles (all IM, genotype 0,5-0,5 (n=8) of 0,5-0 (n=2)). Compared to EM: IM: - MR NOR / (E)-10-hydroxyNOR increased from 0.73 to 1.31 (NS, 79%) The combined effect of sex and the number of mutant CYP2D6 alleles explained 17.7% of the observed variability in log (NOR / (E)-10-hydroxyNOR) Note: gene duplications were not assessed.	
ref. 6	3	IM: A	11 healthy nonsmokers. 50 mg	Conclusion authors:

Mellstrom B et al. Amitriptyline metabolism: association with debrisoquin hydroxylation in nonsmokers. Clin Pharmacol Ther 1986;39:369-71. PMID: 3956053		PM: A	AMI single dose. Clor was negatively correlated with urinary MR debrisoquine/4-hydroxy-desibroquine. Note: genotype not reported	"Our data suggest that there may be a common regulation of the hydroxylation of debrisoquin and the oxidative metabolism of amitriptyline in nonsmokers."
ref. 7 Bertilsson L et al. Extremely rapid hydroxylation of debrisoquine: a case report with implication for treatment with nortriptyline and other tricyclic antidepressants. Ther Drug Monit 1985;7:478-80. PMID: 4082245	2	UM: C	Patient receive AMI 150 mg/day. Plasma concentrations were 33 and 28 µg/l and 13 and <19 µg/l for AMI and NOR, respectively at t=3 and t=5 weeks after first AMI prescription. After an initial short improvement of the depression during AMI treatment, the patient became depressed again. The patient had previously been treated with NOR (300-500 mg/day) and was found to have an MR NORT / 10-hydroxyNORT of 0.13 indicating ultrarapid metabolism. No severe anticholinergic side effects were reported. Note: genotype not reported	Conclusion authors: "Our patient developed low plasma levels of both AT and NT when she was treated with AT. There seem to be difficulties in optimizing the treatment of extremely rapid hydroxylators with all tricyclic antidepressants. In such cases it may be warranted to try a nontricyclic antidepressant, which is not metabolized by the debrisoquine hydroxylase."
ref. 8 Baumann P et al. Amitriptyline pharmacokinetics and clinical response: II. Metabolic	3	IM: A PM: A UM: A	16 patients, 12x EM*, 4x PM. AMI 75 mg/day for 2 days, followed by AMI 150 mg/day for 19 days. Compared to IM+EM+UM:	

polymorphism assessed by hydroxylation of debrisoquine and mephenytoin. Int Clin Psychopharmacol 1986;1:102-12. PMID: 3571939			PM: - MR (hydroxyAMI + hydroxyNOR) / (AMI + NOR) decreased. - 2 PM had the highest (AMI + NOR) concentration - PMs reported no excessive side effects. - Clinical response could not be predicted from hydroxylation status or plasma concentrations of the active components. Correlation between MR of desibroquine / hydroxy desibroquine in urine and AMI + metabolites in plasma: - positive: AMI (S) and AMI + Nor (S) - Negative: hydroxyAMI / AMI (S), hydroxyNOR/NOR (S), (hydroxyAMI + hydroxyNOR) / (AMI+NOR) (S), (hydroxyAMI + hydroxyNOR) / AMI (S) Note: genotype not reported	

* IM, EM and UM phenotypes are not separated by phenotyping. EM* therefore consists of IM+EM+UM.
[a] adjusted for dose and bodyweight

Groups at risk	Concomitant use of a CYP2D6 inhibitor

Remarks
Date literature search: 22 June 2007

Both studies with genotyping and phenotyping were considered. If only phenotyping was used this is indicated by the line "Note: genotype not reported"

	Phenotype	Code	Gene-Drug Interaction	Action Required	Date
Decision DPWG	PM	3A	Yes	Yes	19 September 2007
	IM	3C	Yes	Yes	
	UM	3C	Yes	Yes	

Action Pharmacy Technician	First prescription: Consult pharmacist Subsequent prescription: Dispense. If genotype was not previously known, consult pharmacist.
Action Pharmacist, Physician	PM: Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g., citalopram, sertraline) or monitor amitriptyline and nortriptyline plasma concentration
	IM: Reduce dose to 75% of the recommended dose and monitor plasma concentration or select alternative drug (e.g., citalopram, sertraline)
	UM: Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g., citalopram, sertraline) or monitor (E-10-hydroxy)amitriptyline plasma concentration. Be alert to reduced efficacy due to decreased amitriptyline plasma concentration. Be alert to increased concentrations of the active hydroxymetabolites. These are possibly cardiotoxic.

Considerations

PM: There are insufficient data for PM. Theoretically a similar but enlarged effect of the effect reported for IMs can be anticipated. Selection of an alternative drug is recommended.

IM: One of the studies reports an increase in the number of side effects for IMs. Therefore a dose reduction or selection of an alternative drug is recommended. The population size-weighted mean of the dose adjustments calculated for the individual papers is 71% of the recommended dose (based on AMI + NOR Css data). For clinical applicability this is translated to a reduction to 75% of the recommended dose.

UM: There is a case report about failure of therapy with amitriptyline in an UM. There are insufficient data for UM to calculate a dose adjustment. Selection of an alternative drug is recommended.

Mechanism

Amitriptyline is metabolized to nortriptyline by CYP2C19 (N-demethylation). Both amitriptyline and nortriptyline are metabolized to their 10-hydroxy derivatives by CYP2D6. (mainly E-10-hydroxy derivatives). E-10-OH-amitriptyline has approximately 30% of the potency of amitriptyline. E-10-OH-nortriptyline has approximately 50% of the potency of nortriptyline. Amitriptyline is also metabolized by N-oxidation and N-glucurunodiation. Nortiptyline is metabolized by CYP2D6 and CYP2C19 to the inactive metabolite didesmethylamitriptyline (desmethylnortriptyline).