CYP2C19: Imipramine

AUC: Area under the concentration-time curve, BID: twice a day, Clor: oral clearance, Css: steady state plasma concentrations, DES: desimipramine, EM: extensive metabolizer (*1/*1, *1/*17), IM: intermediate metabolizer (*1/*2, *1/*3, *17/*2, *17/*3), IMI: imipramine, MR: metabolic ratio, NS: not statistically significant, PM: poor metabolizer (*2/*2, *2/*3), Rs: correlationcoefficient, S: statistically significant, UM: ultrarapid metabolizer (*17/*17).

Reference	Level of evidence	Clinical relevance	Effect	Remarks
ref. 1 Morinobu S et al. Effects of genetic defects in the CYP2C19 gene on the N- demethylation of imipramine, and clinical outcome of imipramine therapy. Psychiatry Clin Neurosci 1997;51:253- 7. PMID: 9316174	3	PM: A	10 patients (5x EM; 5x PM (2x *2/*2, 3x *2/*3). IMI 0.745-2.174 mg/kg BID for 4 weeks. No statistically significant differences in IMI dose between the EM and PM group. Concomitant medication with flunitrazepam was allowed. Compared to EM: PM: - Css IMI[a] increased from 0.0084 to 0.0194 ng/ml per mg/kg (S, by 131%) - Css IMI[a] decreased from 0.0091 to 0.0052 ng/ml per m/kg (NS, by 43%) - Css hydroxyimipramine[a] increased from 0.0024 to 0.0076 ng/ml per mg/kg (S, by 217%) - MR DES / IMI decreased from 1.220 to 0.270 ng/ml per mg/kg (S, by 78%) - MR hydroxydesipramine / hydroxyimipramine decreased from 2.098 to 0.279 ng/ml (S, by 78%) - Improvement rate increased from 51.0% to 56.1% (NS, by 10%) - Autonomic UKU score (score for side-effects) decreased from 2.40 to 1.40 (NS, by 42%).	Conclusion authors: “The results of this study suggest that determination of mutations in the CYP2C19 gene may not be of clinical importance in predicting the therapeutic response to or the side effects of imipramine. However, previous studies demonstrated that levels of imipramine positively correlated with the therapeutic response and severity of side effects.” IMI + DES plasmaconcentrations compared to EM: PM: 141%
ref. 2 Madsen H et al. Imipramine demethylation in vivo: impact of CYP1A2,	3	IM: A PM: A	32 healthy subjects. IMI 25 mg single dose. Urine was collected for 24 hours and metabolites were quantitated. All subjects were CYP2C19 EM[*] and CYP2D6 PM (n=31) or slow EM[*] (n=1). Concomitant medication allowed.	Conclusion authors: “CYP2C19 seemed to be responsible for the N-demethylation of imipramine (19%) and 2-hydroxyimipramine (30%) but from

CYP2C19, and CYP3A4. Clin Pharmacol Ther 1997;61:319-24. PMID: 9084457			- There was a negative correlation between the MR mephenytoin S/R ratio and the 2 N-demethylation ratios (DES / IMI and 2- hydroxydesipramine / 2-hydroxyimipramine) (S). - CYP2C19 activity expressed by the mephenytoin S/R ratio accounted for 19% of the N-demethylation of imipramine to desipramine and 29% of the N-demethylation of 2-hydroxyimipramine to 2-hydroxydesipramine in vivo. Note: genotype not reported	this in vivo study we found no sign of CYP1A2 or CYP3A4 to be involved in the N-demethylation of imipramine or 2-hydroxyimipramine."
ref. 3 Koyama E et al. Steady-state plasma concentrations of imipramine and desipramine in relation to S-mephenytoin 4'-hydroxylation status in Japanese depressive patients. J Clin Psychopharmacol 1996;16:286-93. PMID: 8835703	3	PM: A IM: A	28 patients, (23x EM* and 5x PM; all CYP2D6 EM*). IMI 25-57 mg/day (0.39-1.39 mg/kg/day) for 2 weeks. Benzodiazepines taken on occasion when indicated for anxiety and/or insomnia throughout the study period had no effect on the IMI steady-state kinetic variables in the EM. Compared to EM+IM: PM: - Css IMI[a] increased from 0.0041 to 0.0193 ng/ml per mg/kg (S, by 371%) - Css IMI+ DES[a] increased from 0.0132 to 0.0244 ng/ml per m/kg (S, by 85%) - Mean N-demethylation index (MR of DES/IMI) decreased from 0.705 to 0.271 (S, by 62%) - Css DES[a] not decreased from 0.0052 to 0.0051 ng/ml per m/kg (NS, by 2%) Negative correlations of CYP2C19 activity (expressed as S-mephenytoin metabolism): - Css IMI[a] (S) - Css IMI + DES[a] (S) Positive correlations of CYP2C19 activity (expressed as S-mephenytoin metabolism):	Conclusion authors: "By taking into account that the incidence of the PMs of CYP2C19 is much greater (18-23%) than that of CYP2D6 (<1%) in Japanese population, the individually Predetermined assessment of the CYP2C19-mediated metabolic capacity of imipramine would be more valuable than that of the CYP2D6-mediated capacity for forecasting the steady-state concentrations of imipramine and desipramine in Japanese depressive patients." IMI + DES plasmaconcentrations compared to EM + IM: PM: 185%

			- MR DES/IMI (S) Note: genotype not reported	
ref. 4 Madsen H et al. Imipramine metabolism in relation to the sparteine and mephenytoin oxidation polymorphisms—a population study. Br J Clin harmacol 1995;39:433-9. PMID: 7640151	3	IM: A PM: A	327 healthy volunteers (324x EM*, 3x PM). IMI 25 mg single dose. Urine was collected for 24 hours and metabolites were quantitated. No concomitant medication. - Small negative correlation between MR mephenytoin S/R and the 2 demethylation ratios (DES / IMI and and 2-hydroxy-DES and 2-hydroxy-IMI) (S) - Demethylation ratios were higher in 80 smokers than in 245 non-smokers suggesting that CYP1A2 catalyzes the N-demethylation of imipramine. Note: genotype not reported	
ref. 5 Koyama E et al. Metabolic disposition of imipramine in oriental subjects: relation to metoprolol alpha-hydroxylation and S-mephenytoin 4'-hydroxylation phenotypes. J Pharmacol Exp Ther 1994;271:860-7. PMID: 7965806	3	PM: A IM: A	16 healthy subjects. 7x EM* and 5x PM; all CYP2D6 EM*. No concomitant medication. Smoking status not reported. Compared to EM+IM: PM: - AUC_8 IMI increased from 215 to 375 ng.hr/ml (S, by 74%) - AUC DES decreased from 111.8 to 68.2 ng.hr/ml (S, by 39%) - AUC IMI + DES increased from 362.8 to 443.2 ng.hr/ml (calculated by DPWG from presented data, by 36%) - Ration DES/IMI decreased from 0.52 to 0.18 (S, by 65%) - Clor IMI decreased from 30.1 to 15.6 ml/min per kg (S, by 48%) Positive correlations of CYP2C19 activity (expressed as 4'-hydroxymephenytoin secretion in urine): - AUC DES (S)	Conclusion authors: “The results suggest that the 2-hydroxylation and the N-demethylation of imipramine metabolism are under a pharmacogenetic control of debrisoquin- and mephenytoin-type oxidation, respectively, in Oriental subjects.” AUC IMI + DES compared to EM+IM: PM: 136%

			- Ratio AUC DES/IMI (S) No significant correlation with AUC (DES+IMI). The metabolic disposition data obtained from urine and plasma samples were in good agreement. Note: genotype not reported	
ref. 6 Skjelbo E et al. The N-demethylation of imipramine correlates with the oxidation of S-mephenytoin (S/R-ratio). A population study. Br J Clin Pharmacol 1993;35:331-4. PMID: 8471415	3	PM: A IM: A	106 healthy subjects, 104x EM*, 2x PM; all CYP2D6 EM). IMI 25 mg single dose. - The DES/IMI and the 2-OH-DES/2-OH-IMI ratio in plasma, reflecting the demethylation of imipramine and 2-OH-imipramine, respectively, showed significant negative correlations with the mephenytoin S/R ratio (S). Note: genotype not reported	Conclusion authors: "These findings confirm those of an earlier panel study showing that the demethylation of imipramine and 2-OHimipramine cosegregates in part with the mephenytoin oxidation polymorphism."
ref. 7 Skjelbo E et al. The mephenytoin oxidation polymorphism is partially responsible for the N-demethylation of imipramine. Clin Pharmacol Ther 1991;49:18-23. PMID: 1988236	3	PM: A	22 healthy subjects, 16x EM*, 6x PM; all CYP2D6 EM. IMI 100 mg (n=20) or 50 mg (n=1; PM for CYP2D6 and CYP2C19) single dose. All subjects experienced mild side effects (sedation, dry mouth, dizziness). The CYP2D6 and CYP2C19 PM had the lowest Clor: 0.66 l/min. Compared to EM+IM: PM: - IMI demethylation clearance decreased from 1.43 to 0.74 l/min (S, 48%). - Clor decreased from 2.48 to 1.83 l/min (S, 26%) - MR DES/IMI decreased from 1.26 to 0.39 (S, 69%) Note: genotype not reported	Conclusion authors: "This and an earlier study show that the oxidation of imipramine is mediated by means of two different polymorphic P450 isozymes, 2-hydroxylation by way of the sparteine oxygenase (P450IID6) and demethylation by way of the mephenytoin oxygenase (P450IIC8)."

* IM and EM phenotypes are not separated by phenotyping. EM* therefore consists of EM+IM.

[a] adjusted for dose and bodyweight

Groups at risk	CYP2D6 PM, CYP2D6-inhibitors, CYP2C19-inhibitors

Remarks

- IMI efficacy and side effects are associated with the sum of the IMI+DES plasma concentrations (Glassman AH et al. Clinical implications of imipramine plasma levels for depressive illness. Arch Gen Psychiatry 1977;34:197-204; Reisby N et al. Imipramine: clinical effects and pharmacokinetic variability. Psychopharmacology 1977;54:363-72; Rudorfer MV et al. Pharmacokinetics of antidepressants. Psychopharmacology: The Third Generation Progress, ed. by HY Meltzer, pp. 1353-63. Raven Press, New York, 1987; Sallee FR et al. Clinical pharmacokinetics of imipramine and desipramine. Clin. Pharmacokinet 1990;18:346-64.).
- Both studies with genotyping and phenotyping were considered If only phenotyping was used this is indicated by the line "Note: genotype not reported"

Date literature search: 05 July 2007.

	Phenotype	**Code**	**Gene-Drug Interaction**	**Action Required**	**Date**
Decision DPWG	PM	3 A	Yes	Yes	19 September 2007
	IM	3 A	Yes	Yes	
	UM	--	Yes	No	

Action Pharmacy Technician	PM + IM: First prescription: Consult pharmacist. Subsequent prescription: Dispense. As a result of a genetic polymorphism the metabolism of imipramine by the enzyme CYP2C19 is decreased.
	UM: --
Action Pharmacist, Physician	PM: Due to a genetic polymorphism the metabolic capacity of CYP2C19 is decreased. As a result imipramine plasmaconcentration increase. Reduce dose to 70% of the recommended dose and titrate dose in response of imipramine + desipramine plasma concentrations. If not possible, or select alternative drug (e.g., fluvoxamine, mirtazapine)

	IM: Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g., fluvoxamine, mirtazapine). On theoretical ground the effect in IM will be smaller than in PM (for which a reduction to 70% of the recommended dose is advised).
	UM: --

Considerations

PM: No statistically significant associations of CYP2C19 polymorphisms with IMI efficacy or side effects were reported. An increased IMI + DES AUC and Css were reported for CYP2C19 PMs. Because IMI efficacy and side effects are associated with the sum of the IMI+DES plasma concentrations a dose reduction or selection of an alternative drug is warranted. The population size-weighted mean of the dose adjustments calculated for the individual papers is 65% of the recommended dose (median 71%). For clinical applicability this is translated to a reduction by 30% of the recommended dose. Monitor plasma concentrations after dose adjustment.

IM: Only the qualitative effect of CYP2C19 polymorphims on IMI pharmacokinetics has been reported and no quantitative data exist. On theoretical ground the effect in IM will be smaller than in PM. In line with the recommendation for PM it is recommended to select an alternative drug.

Mechanism

Imipramine main routes of metabolism are N-methylation by CYP2C19 to the active metabolite desipramine, and hydroxylation by CYP2D6 to 2-hydroxyimipramine. Desipramine is metabolized to 2-hydroxydesimipramine. Imipramine efficacy and side effects are associated with the sum of the imipramine and desipramine plasma concentrations. A genetic polymorphism in CYP2C19 can result in increased plasma concentrations of imipramine and decreased plasma concentrations of desipramine. Two studies reported an increased imipramine + desipramine plasma concentration that was associated with decreased CYP2C19 activity. This may result in an increased number of side effects.