CYP2D6: Zuclopenthixol

AUC: 'area under the concentration-time curve', Clor: oral clearance, Css: steady state concentration, EM: extensive metabolizer, IM: intermediate metabolizer, NS: not statistically significant, PM: poor metabolizer, S: statistically significant, UM: ultrarapid metabolizer.

Reference	Level of evidence	Clinical relevance	Effect	Remarks
ref. 1 Van Berlo-van de Laar et al. Dosering aanpassen aan eliminatiesnelheid. Pharm Weekblad 2004;139:740-43. (article in Dutch) PMID: NA	4	PM: AA IM: A	23 patients, 2x PM (2 mutant alleles, *3, *4 or *5), 11x IM (*1/*3, *1/*4 or *1/*5), 10x EM (*1/*1). Zuclopenthixol decanoate dose was titrated to clinical response (dose varied from 3.6-50 mg/day). No concomitant CYP2D6 inhibitors. Compared to EM: PM: - Large interpatient variability. Comparison with EM not possible. PMs show a similar trend as IMs IM: - Daily dose decreased from 24.5 to 15 mg/day (S, by 39%) - Cmax[a] increased from 0.77 to 1.35 mg/day (S, by 75%) - At t=14 days the mean concentration[a] increased from 0.47 to 0.64 mg/day (NS, by 36%) - Number of dose adjustments increased with 3.9 vs. 1.5 respectively (S) - Similar history of anticholinergic drug use.	Conclusion authors: 'Slow metabolizers appear to have increased Zuclopenthixol concentrations at t=5 days and to a lesser extent at t=14 days.' The authors recommend the following initial dose for IM: 200 mg / 2 weeks EM: 300 mg / 2 weeks Cmax[a] compared to EM: IM: 175%
ref. 2 Jaanson P et al. Maintenance therapy with zuclopentixol decanoate: associations between plasma	4	PM: A IM: A	52 patients, 35x EM (*1/*1), 13x IM (*1/*4), 4x PM (*3/*4). Zuclopenthixol decanoate 100-400 mg per 4 weeks. No concomitant CYP2D6 inhibitors. Compared to EM: PM:	Css compared to EM: PM: 166% IM: 131%

concentrations, neurological side effects and CYP2D6 genotype. Psychopharmacology 2002;162:67-73. PMID: 12107620			- Css[a] increased from 0.029 to 0.048 nM/mg (S, by 66%) IM: - Css[a] increased from 0.029 to 0.038 nM/mg (S, by 31%) CYP2D6*3 and *4 alleles tended to occur more frequently in patients with extrapyramidal side effects and tardive dyskinesia (NS)	
ref. 3 Linnet K et al. Influence of Cyp2D6 genetic polymorphism on ratios of steady state serum concentration to dose of the neuroleptic zuclopentixol. Ther Drug Monit 1996;18:629-34. PMID: 8946657	4	PM: A	108 patients, 12x PM (*4/*4), 107x EM + IM (64x wt/wt, 2x *1/*3, 40x *1/*4). Zuclopenthixol 2-32 mg/day. 58 EMs + IMs use no concomitant drug that affect CYP2D6 phenotype. Compared to EM+IM without concomitant medication: PM: - Css[a] zuclopenthixol increased from 1.25 to 2.0 nM/mg (S, by 60%).	Css[a] compared to EM + IM: PM: 160%
ref. 4 Jerling M et al. The CYP2D6 genotype predicts the oral clearance of the neuroleptic agents perphenazine and zuclopentixol. Clin Pharmacol Ther 1996;59:423-8. PMID: 8612387	3	PM: A IM: A	36 patients, 20 receive zuclopenthixol, 3x PM (*3/*3, *3/*4 of *4/*4), 9x IM (*wt/*3 of *wt/*4), 8x EM (*wt/*wt). Zuclopenthixol 23 (1-125) mg/day. 1 PM is prescribed the concomitant CYP2D6 inhibitor levomepromazine. Compared to EM: PM: - Clor decreased from 95 to 42 l/hr (S, by 56%). IM: - Clor decreased from 95 to 65 l/hr (S, by 32%) Note: unknown if reported results are adjusted for the dose.	Clor compared to EM: PM: 44% IM: 68%
ref. 5	3	PM: A	12 healthy subjects, 6x PM, 6x EM[#] (phenotyped with	AUC[a] compared to EM + IM:

Dahl ML et al. Disposition of the neuroleptic zuclopentixol cosegregates with the polymorphic hydroxylation of debrisoquine in humans. Acta Psychiatr Scand 1991;84:99-102. PMID: 1927573			debrisoquine). Zuclopenthixol 6-10 mg single dose, no concomitant medication. Compared to EM: PM: - AUC[a] increased from 145 to 269 nM.hr (S, 86%) - Clor decreased from 2.12 to 0.78 l/hr/kg (S, 63%) - t½ increased from 17.6 to 29.9 hr Note: IM and EM phenotypes are not separated by phenotyping. EM[#] therefore consists of IM+EM.	PM: 186%

[a] adjusted for dose

Groups at risk	IMs prescribed a concomitant CYP2D6 inhibitor

Remarks

Date literature search: 17 February 2009

	Phenotype	**Code**	**Gene-Drug Interaction**	**Action Required**	**Date**
Decision DPWG	PM	4 A	Yes	Yes	26 May 2009
	IM	4 A	Yes	Yes	
	UM	--	Yes	Yes	

Action Pharmacy Technician	PM: The metabolism of venlafaxine by CYP2D6 is decreased due to a genetic polymorphism. Consult pharmacist
	IM: The metabolism of venlafaxine by CYP2D6 is decreased due to a genetic polymorphism. Consult pharmacist
	UM: The metabolism of venlafaxine by CYP2D6 is increased due to a genetic polymorphism. Consult pharmacist

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 zuclopenthixol concentrations. Reduce dose by 50% or select alternative drug (e.g. flupenthixol, quetiapine, olanzapine, clozapine)
	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 zuclopenthixol concentrations. Reduce dose by 25% or select alternative drug (e.g. flupenthixol, quetiapine, olanzapine, clozapine)
	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 zuclopenthixol concentrations. There are insufficient data for UM to calculate a dose adjustment. Be alert to low zuclopenthixol plasma concentrations and titrate dose in response of clinical effect. If not possible, select an alternative drug that is less metabolized by CYP2D6 e.g. flupenthixol, quetiapine, olanzapine, clozapine.

Considerations

PM: The population size-weighted mean of the dose adjustments calculated for the individual papers is 54% of the recommended dose (44%-66%). For clinical applicability this is translated to a reduction to 50% of the recommended dose. If not possible, select an alternative drug that is less metabolized by CYP2D6 e.g. flupenthixol, quetiapine, olanzapine, clozapine.

IM: The population size-weighted mean of the dose adjustments calculated for the individual papers is 68% of the recommended dose (57%-76%). For clinical applicability this is translated to a reduction to 75% of the recommended dose. If not possible, select an alternative drug that is less metabolized by CYP2D6 e.g. flupenthixol, quetiapine, olanzapine, clozapine.

UM: There are insufficient data for UM to calculate a dose adjustment. Be alert to low zuclopenthixol plasma concentrations and titrate dose in response of clinical effect. If not possible, select an alternative drug that is less metabolized by CYP2D6 e.g. flupenthixol, quetiapine, olanzapine, clozapine.

Mechanism

Zuclopenthixol is mainly metabolized by CYP2D6 to inactive metabolites. 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 altered zuclopenthixol plasma concentrations.