CYP2C19: Citalopram / Escitalopram

Clor: oral clearance, BID: twice a day, CT: citalopram, eCT: escitalopram, EM: extensive metabolizer (*1/*1, sometimes referred to as homozygous EM or homEM, *1/*17), IM: intermediate metabolizer (*1/*2, *1/*3, sometimes referred to as heterozygous EM or hetEM), MR: metabolic ratio, NS: not statistically significant, PM: poor metabolizer (*2/*2, *2/*3, *3/*3), S: statistically significant, UM: ultrarapid metabolizer (*17/*17).

Reference	Level of evidence	Clinical relevance	Effect	Remarks
ref. 1 - escitalopram Ohlsson Rosenborg S et al. Kinetics of omeprazole and escitalopram in relation to the CYP2C19*17 allele in healthy subjects. Eur J Clin Pharmacol 2008 Jul 25. (Epub ahead of print) PMID: 18654768	4	*17/*17: AA	16 healthy subjects, 11x *1/*1, 5x *17/*17. eCT 5mg BID for 6 days. No relevant concomitant medication. Compared to *1/*1: *17/*17: - Mean AUC0-12 eCT decreased by 21% (NS) - Decreased intraindividual variation in AUC (variation coefficient decreased from 41 to 19) - Decreased number of adverse events (NS). The authors conclude that a decrease of eCT AUC by 21% is not clinically relevant and therefore no dose adjustment is required.	Conclusion authors: 'Concluding from this and previous studies, the CYP2C19*17/*17 genotype may be associated with higher than average clearance of CYP2C19 substrates, but the clinical importance seems limited.' AUC0-12 eCT vs. EM: UM: 79%
ref. 2 - citalopram Peters EJ et al. Pharmacokinetic genes do not influence response or tolerance to citalopram in the STAR*D sample. PLoS ONE 2008;3:e1872.	3		Case control study examining associations between CYP2C19 polymorphisms and citalopram response and tolerance. Significant associations were validated in a second stage and cohort. Non-responders were compared to responders (≥50% reduction in symptoms), patients in remission (almost complete reduction in symptoms), and specific responders (persistent response during the entire study period. This response type was defined to attempt to	Conclusion authors: 'Thus, at least for citalopram, it may be premature to advocate pharmacokinetic gene analysis for dose adjustment or clinical decision making.'

PMID: 18382661			separate placebo response from true drug response). In an additional analysis patients tolerant for CT were compared with intolerant patients. Comparisons were made within the Caucasian and African-American subgroup. The number of patients per group varied from 51-544 for the Caucasian sample and 9-89 for the African-American sample. Patients received CT 20-60 mg/day for 12 weeks. The average CT dose at study exit was 45.5 mg. Relevant concomitant medication allowed. Compared to no *2: *2: - In the first stage of the study a significant difference in frequency between the tolerant and intolerant patients was reported. This was not confirmed in the second stage of the study. Compared to no *3: *3: - No significant differences. Compared to no *17: *17: - No significant differences. Compared to EM+IM+UM: PM: - No effect on response or tolerance. - No significant effect on CT dose at study exit. - No significant effect on the ability to remain in the trial	
		IM + PM: AA *1/*17 + *2/*17 + *3/*17 + *17/*17: AA PM: AA		
ref. 3 - escitalopram Rudberg I et al. Impact of the ultrarapid CYP2C19*17 allele	4		166 patients, 60x *1/*1, 43x *1/*17, 7x *17/*17, 6x *2/*17 or *3/*17, 34x IM, 6x PM. All eCT. No relevant concomitant medication. Compared to *1/*1:	Conclusion authors: 'Although the impact of CYP2C19*17 on serum concentration of escitalopram was less pronounced than defective

on serum concentration of escitalopram in psychiatric patients. Clin Pharmacol Ther 2008;83:322-7. PMID:17625515		*17/*17: A *1/*17: AA *2/*17 + *3/*17: AA PM: A IM: A	*17/*17: - Concentration[a] decreased from 2.72 to 1.59 nM/mg per day (S, by 42%). *1/*17: - No significant effect *2/*17 + *3/*17: - No significant effect PM: - Concentration[a] increased from 2.72 to 15.5 nM/mg per day (S, by 470%) IM: - Concentration[a] increased from 2.72 to 5.10 nM/mg per day (S, by 88%)	CYP2C19 alleles, CYP2C19*17 might be associated with increased risk of therapeutic failure of escitalopram treatment.' Concentration[a] escitalopram Compared to EM: UM: 58%
ref. 4 - citalopram Yin OQ et al. Phenotype- genotype relationship and clinical effects of citalopram in Chinese patients. J Clin Psychopharmacol 2006;26:367-72. PMID: 16855453	4	IM: A PM: A	53 Chinese patients, 21x EM, 25x IM (24x *1/*2, 1x *1/*3), 7x PM (3x *2/*2, 2x *2/*3, 2x *3/*3). CT 10-60 mg/day for ≥2 weeks. Concomitant use of CYPC19 inhibitors or inducers was excluded. Use of concomitant CYP2C19 substrates was allowed. - No significant effect on the Toronto Side Effects Scale (TSES) score with a score of 89.2:93.3:100.1 for EM, IM, and PM respectively (NS). - Significant relationship between adverse effect (TSES score) and citalopram Clor (based on population pharmacokinetic model) was observed.	
ref. 5 – citalopram + escitalopram Rudberg I et al. Heterozygous mutation in CYP2C19 significantly increases the	4		89 patients, 50x EM en 33x IM (*1/*2). CT ((23x EM 35 mg/day, 17x IM 34 mg/day) or eCT (27x EM 20 mg/day, 16x IM 22 mg/day). Concomitant CYP2C19 inhibitors or inducers excluded. <u>CT:</u> Compared to EM:	Conclusion authors: 'Citalopram and S-citalopram are well-tolerated drugs, but it cannot be ruled out that the approximately 2-fold increase in C/D ratio among HEMs is of possible therapeutic importance. However, the use of

concentrations/dose ratio of racemic citalopram and escitalopram (S-citalopram). Ther Drug Monitor 2006;28:102-5. PMID: 16418702		IM: A IM: A	IM: - Concentration[a] CT increased from 4.9 to 8.0 (S, by 63%) - MR[a] increased by 81% (S) eCT: Compared to EM: IM: - Concentration[a] eCT increased from 2.6 to 5.3 (S, by 63%) - MR[a] increased by 100% (S)	equal daily doses in the EM and HEM groups for both drugs suggests that the dose reductions compensating for the reduced metabolism among HEMs are not performed in clinical practice.' CT: Concentration compared to EM: IM: 163% eCT: Concentration compared to EM: IM: 204%
ref. 6 - citalopram Herrlin K et al. Metabolism of citalopram enantiomers in CYP2C19/CYP2D6 phenotyped panels of healthy Swedes. Br J Clin Pharmacol 2003;56:415-21. PMID:12968986	4	PM: A	19 healthy subjects, 7x PM (CYP2C19 status assessed with mephenytoin, CYP2D6 status assessed with debrisoquine). CT 20 mg/day (1 subject 2C19 PM and 2D6 PM: 10 mg/day) for 7 days. No relevant concomitant medication. 2C19 PM: - AUC CT increased from 1398 to 1669 nM/h (NS, by 19%) - AUC eCT increased from 530 to 830 nM/h (S, by 57%). - AUC R-CT not significantly different. - AUC S-desmethyl-CT decreased from 208 to 182 nM/h (NS, by 13%) - AUC R-desmethyl- CT decreased from 233 to 172 nM/h (NS, by 26%) The 1 subject who was 2C19 PM and 2D6 PM stopped taking CT after five days due to severe adverse effects (possibly a serotonin syndrome). This subject had a very long CT half-life of 95 hours.	AUC compared to EM: PM: 119%

ref. 7 – citalopram Yu BN et al. Pharmacokinetics of citalopram in relation to genetic polymorphism of CYP2C19. Drug Metab Dispos 2003;31:1255-9. PMID: 12975335	3	PM: A IM: A	13 healthy Chinese subjects, 4x EM (*1/*1), 4x IM (*1/*2), 5x PM (*2/*2 or *2/*3). CT 40 mg single dose. No relevant concomitant medication. Significant effect on the N-demethylation of CT. Compared to EM: PM: - AUC CT increased from 1638.0 to 2132.5 µg.h/l (S, by 30%) - Clor CT decreased from 0.39 to 0.31 l/h/kg (S, by 21%) - t½ CT increased from 35.6 to 39.1 h (S, by 10%) - AUC N-desmethyl-CT decreased from 855.4 to 516.7 µg.h/l (S, by 40%) IM: - No significant effect on any of the pharmacokinetic parameters for CT en N-desmethyl-CT Note: experiment was performed in presence or absence of a dose of 250 mg troleandomycin (a CYP3A4 inhibitor). For EM's addition of a CYP3A4 inhibitor had no effect. For PM's addition of a CYP3A4 inhibitor resulted in significantly increased AUCs of CT and N-desmethyl-CT	Compared to EM: PM: - AUC: 130% - Clor: 79%
ref. 8 - citalopram Baumann P et al. A double-blind, placebo-controlled study of citalopram with and without lithium in the treatment of therapyresistant depressive patients: a clinical, pharmacokinetic, and	4	PM: A	69 patients, 6x CYP2C19 PM, 3x CYP2D6 PM (CYP2C19 status assessed with mephenytoin, CYP2D6 status assessed with debrisoquine). All CT 40-60 mg/day for 4 weeks. No relevant concomitant medication. 45 responders and 24 non-responders at t=4 weeks. Of the 6 CYP2C19 PMs, 3 were responders and 3 non-responders. Compared to EM: PM: - Plasmaconcentration[a] CT increased from 2.22 to 3.64	Conclusion authors: 'The fact that the metabolism of citalopram and N-desmethylcitalopram is affected in patients with a genetic deficiency of CYP2D6 or CYP2C19 does not seem to be an important factor for adverse effects. Concentration compared to EM: PM: 164%

pharmacogenetic investigation. J Clin Psychopharmacol 1996;16:307-14. PMID: 8835706			µg/l.mg CT dose (S, by 64%) - N-desmethyl-CT decreased from 1.05 to 0.64 µg/l.mg CT dose (S, by 39%) - Didesmethyl-CT decreased from 0.19 to 0.11 µg/l.mg CT dose (S, by 42%)	
ref. 9 - citalopram Sindrup SH et al. Pharmacokinetics of citalopram in relation to the sparteine and the mephenytoin oxidation polymorphisms. Ther Drug Monit 1993;15:11-7. PMID:8451774	4	PM: A	24 healthy subjects, 18x EM (of which 6 CYP2D6 PM), 6x PM. All 40 mg CT for 10 days. Concomitant medication not reported. Compared to EM: PM: - AUC CT increased from 4.588 to 8.145 nM.hr (S, by 76%) - Clearance decreased from 27.3 to 15.2 l/h (S, by 44%) - t½ increased from 30 to 42 h (S, by 40%) - AUC N-desmethyl-CT decreased from 1.768 to 1.475 nM.hr (NS, by 17%) - AUC didesmethyl-CT decreased from 370 to 153 nM.hr (NS, by 59%) There was no difference in type or frequency of side effects between the genotypes. In CYP2D6 PMs the AUC and t½ of CT were increased but less than for CYP2C19 PMs	Compared to EM: PM: - AUC: increased to 176% - Cl: decreased to 56%
ref. 10 – escitalopram SPC Lexapro (escitalopram) 06-12-2006.		PM: AA IM: AA	For CYP2C19 PMs it is recommended to reduce the initial and maximum dose by 50%. eCT plasma concentrations of 200% compared to CYP2C19 EMs have been reported for PMs. No significant difference in eCT exposure was reported for CYP2D6 PMs compared to EMs. (SPC provides no reference or citation; possibly data from Rudberg, 2006 are used.	

Groups at risk	IMs prescribed a CYP2D6 inhibitor

Remarks
Date literature search: 23 September 2008.

	Phenotype	Code	Gene-Drug Interaction	Action Required	Date
Decision DPWG	PM	4 A	Yes	No	11 December 2008
	IM	4 A	Yes	No	
	UM	4 A	Yes	Yes	

Action Pharmacy Technician	PM: -
	IM: -
	UM: The metabolism of citalopram and escitalopram by the enzyme CYP2C19 is increased as a result of a genetic polymorphism. After consult with pharmacist: - Recommend physician to monitor plasma concentration and titrate dose to a maximum of 150% of the recommended dose in response to efficacy and ADE - If dose increase is not possible, consider an alternative drug that is less metabolized by CYP2C19 (i.e. fluoxetine or paroxetine).
Action Pharmacist, Physician	PM: -
	IM: -
	UM: As a result of a genetic polymorphism in the gene coding for CYP2C19, the metabolic capacity of this enzyme is increased. This might result in decreased (es)citalopram plasma concentrations. - Monitor plasma concentration and titrate dose to a maximum of 150% of the recommended dose in response to efficacy and ADE - If dose increase is not possible, consider an alternative drug that is less metabolized by CYP2C19 (i.e. fluoxetine or paroxetine).

Considerations

- Escitalopram is the S-enantiomer of citalopram and mainly responsible for the antidepressant and anxiolytic effects. his CYP2C19 is more important in the metabolism of S-citalopram than R-citalopram (Rudberg, 2006 en Herrlin, 2003). However, Carlsson B et al. Ther Drug Monit 2001;23:658-64 reported no difference in S-/R- ratio for both citalopram and N-desmethyl-citalopram between CYP2C19 *1/*1 and *1/*2.
- Rudberg et al, 2006 note "Because CYP2C19 is a low-affinity, high- capacity enzyme in citalopram N-demethylation it might be that the quantitative importance of CYP2C19 genetics is increasing with higher doses/concentrations".
- In a series of twenty-nine cases with citalopram toxic effects blood concentrations ranged from 0.21 to 7.5 mg/L with 20 minutes to 8 hours between suggested time of ingestion and blood sampling (Jimmink A et al. Ther Drug Monit 2008;30:365-71).

IM + PM: Due to the large therapeutic window of both citalopram and escitalopram, a dose adjustment is not considered necessary. The altered pharmacokinetics in PMs and IMs appears not to result in differences in type or frequency of side effects.

UM: Only 2 studies reported results for a total of 12 patients with the UM phenotype (Ohlsson Rosenborg, 2008 en Rudberg, 2008). None of these studies report significant effects of the UM phenotype on side effects or efficacy. As a precaution it is recommended to be alert to aberrant plasma concentrations and increase the dose if required. The population size-weighted mean of the dose adjustments calculated for the individual papers is 152% of the recommended dose (126% - 171%). For clinical applicability this is translated to an increase to 150% of the recommended dose. If this is not possible, select an alternative drug that is less metabolized by CYP2C19 (i.e. fluoxetine or paroxetine).

Mechanism

Citalopram is metabolized primarily by CYP2C19 and to a lesser extent by CYP3A4 to N-desmethylcitalopram. Desmethylcitalopram has antidepressant effects but is much less potent than the parent compound, and at a normal citalopram dose not clinically significant. N-desmethylcitalopram is metabolized to didesmethylcitalopram by CYP2D6.