CYP2D6: Clomipramine

AUC: 'area under the concentration-time curve', BID: twice a day, Clomi: clomipramine, Css: steady state plasma concentration, Clor: oral clearance, DC: desmethylclomipramine, EM: extensive metabolizer, HC: 8-hydroxyclomipramine, HDC: 8-hydroxydesmethylclomipramine, IM: intermediate metabolizer, MR: metabolic ratio, NS: not statistically significant, PM: poor metabolizer, S: statistically significant, t1/2: half life, UM: ultrarapid metabolizer.

Reference	Level of evidence	Clinical relevance	Effect	Remarks
ref. 1 Stephan PL et al. Adverse drug reactions following nonresponse in a depressed patient with CYP2D6 deficiency and low CYP 3A4/5 activity. Pharmacopsychiatry 2006;39:150-2. PMID: 16871470	2	PM: C	A 47-year-old male patient experienced multiple adverse drug reactions during therapy with C 225-300 mg/day and quetiapine 700 mg/day. Drug serum concentrations of CMI and quetiapine were significantly increased. Css Clomi + DC was 1228 ng/ml (therapeutic range 175-400 ng/ml). Genotyping showed a PM status for CYP2D6 (*4/*6), low CYP3A4/5 activity and normal CYP2C19 genotype (EM). After reduction of the Clomi dose to 75/mg/day and discontinuation of quetiapine, all adverse drug reactions subsided except for the increase in liver enzymes. Css Clomi + DC was decreased to 374 ng/ml	
ref. 2 Vandel P et al. Clomipramine, fluoxetine and CYP2D6 metabolic capacity in depressed patients. Hum Psychopharmacol 2004;19:293-8. PMID: 15252821	3	IM: C	45 patients, 20x *1/*2, 25x *1/*4. Clomi 100-150 mg/day for 3 weeks. Concomitant use of benzodiazepines allowed. Compared to EM: IM: - Percentage of patients with side effects increased from 30% to 56% - Mean CYP2D6 activity was lower in the group with side effects. Dextrorphan / dextromethorphan ratios of 5.5 and 13.3 in the groups with and without side effects respectively.	
ref. 3	4	IM: AA	51 patients, 8x *1/*1, 4x *1/*2, 1x *2/*2, 17x *1/*10, 9x	Conclusion authors:

Yokono A et al. The effect of CYP2C19 and CYP2D6 genotypes on the metabolism of clomipramine in Japanese psychiatric patients. Clin Psychopharmacol 2001;21:549-55. PMID: 11763000			*2/*10, 1x *1/*5, 2x *2/*5, 9x *10/*10. Clomi 10-250 mg/day or 0.14-4.82 mg/kg/day. No relevant concomitant medication. Compared to EM: *10/*10: - Ratio Css DC/HDC is 1.72 (NS decrease by 11%) 1 mutation (*5 or *10): - Ratio Css DC/HDC is 1.77 (NS decrease by 9%) No mutation: - Ratio Css DC/HDC is 1.94. Note: for CYP2C19 2 mutations results in an 1.7 times increased Clomi Css and ratio Css C/DC compared to no CYP2C19 mutation	'The genotyping of CYP2D6 is not useful for predicting the individual capacity to hydroxylate DC.'
ref. 4 Danish University Antidepressant Group. Clomipramine dose effect study in patients with depression: clinical end points and pharmacokinetics. Clin Pharmacol Ther 1999;66:152-65. PMID: 10460069	4	PM: AA	109 patients, 97 EM, 12 PM (Phenotyped with sparteine), Clomi 25-200 mg/day. No relevant concomitant medication. Compared to EM: PM, 50 mg/day: - Css Clomi+DC decreased from 2.6 to 4.5 nM[a] (NS, by 73%) - Css Clomi decreased from 1.5 to 0.8 nM[a] (NS, by 47%) - Ratio HC/Clomi decreased from 0.8 to 0.7 (NS, by 13%) - Ratio HDC/DC decreased from 0.6 to 0.2 (NS, by 67%) PM ,75 mg/day: - Css clomi+DC increased from 3.2 to 8.2 nM[a] (NS, by 156%) - Css clomi increased from 1.6 to 2.1 nM[a] (NS, by 31%) - Ratio HC/Clomi decreased from 0.7 to 0.3 (NS, by 57%) - Ratio HDC/DC decreased from 0.6 to 0.1 (NS, by 83%)	Css Clomi+DC compared to EM at a dose of 125 mg/day: PM: 200% Css Clomi compared to EM at a dose of 200 mg/day: PM: 76%

			PM, 125 mg/day: - Css clomi+DC EM increased from 5.0 to 10.0 nM[a] (NS, by 100%) - Css clomi increased from 2.1 to 2.8 nM[a] (NS, by 33%) - Ratio HC/Clomi decreased from 0.6 to 0.4 (NS, by 33%) -Ratio HDC/DC decreased from 0.6 to 0.2 (NS, by 67%) PM, 200 mg/day: - Css clomi+DC increased from 7.5 to 11.7 nM[a] (NS, by 56%) - Css clomi decreased from 3.2 to 2.1 nM[a] (NS, by 34%) - Ratio HC/Clomi unchanged - Ratio HDC/DC decreased from 0.3 to 0.1 (NS, by 67%) Serum levels of clomi+DC showed weak correlation with depression ratings. A few blood pressure measurements and a few typical side-effect ratings showed a statistically significant dose-effect and concentration-effect relationship. Note: genotype not reported	
ref. 5 Baumann P et al. Ultrarapid metabolism of clomipramine in a therapy resistant depressive patient, as confirmed by CYP2D6 genotyping. Pharmacopsychiatry 1998;31:72. PMID: 9562213	2	UM: C	A 62-year-old patient who did not respond to various antidepressants over a ten-year period. He had unusual low plasma concentrations of clomi and DC during treatment with clomi 150-225 mg/day. Clomi concentration increased fivefold after addition of 100 mg/day fluvoxamine (CYP2D6 substrate and CYP1A2 inhibitor) and he showed rapid and consistent response to the treatment. The patient was found to have a duplication of the CYP2D6 gene	
ref. 6 Nielsen KK et al.	3	PM: A	25 healthy subjects, 15x EM (5x CYP2C19 PM), 10x PM (1 CYP2C19 1x PM). Phenotyping with sparteine. 100	

Single-dose kinetics of clomipramine: relationship to the sparteine and S-mephenytoin oxidation polymorphisms. Clin Pharmacol Ther 1994;55:518-27. PMID: 8181196			mg clomi single dose. No concomitant medication. Compared to EM: PM: - Clor decreased from 98.6 to 65.2 l/hr (S, by 34%) - t½ increased from 18.7 to 22.7 hour (NS, by 21%) Note: genotype not reported	Clor clomipramine compared to EM: PM: 76%
ref. 7 Bertilsson L et al. Molecular basis for rational megaprescribing in ultrarapid hydroxylators of debrisoquine. Lancet 1993;341:63. PMID: 8093319	2	UM: C	A patient with agoraphobia was treated with 150 mg/day clomi daily. Since there was no response, the dose was increased to 225 mg/day. Plasma concentrations were much lower than expected with 150 nM for clomi, DC concentration was below the level of quantitation (<100 nM). The patient was stabilized on 300 mg/day clomi.	Maintenance dose compared to standard dose: UM: 200%
ref. 8 Nielsen KK et al. Steady-state plasma levels of clomipramine and its metabolites: impact of the sparteine/debrisoquine oxidation polymorphism. Danish University Antidepressant Group. Eur J Clin Pharmacol 1992;43:405-11. PMID: 1451721	4	PM: AA	36 patients, 35x EM, 1x PM (phenotyping with sparteine), Clomi 75 mg BID. No relevant concomitant medication. Compared to EM: PM: - Css Clomi+DC increased from 710 to 2120 nM (NS, by 199%) - Css Clomi increased from 200 to 570 nM (NS, by 185%) - Ratio Css Clomi/DC unchanged - Ratio Clomi/HC increased from 1.9 to 4.7 (NS, by 147%) - Ratio DH/HDC increased from 1.6 to 7.1 (NS, by 343%) - Ratio (Clomi+DC)/(HC+HDC) increased from 1.7 to 6.1 (NS, by 259%).	Conclusion authors: 'Phenotyping before treatment may be a valuable guideline for selecting the appropriate initial dose of clomipramine, which in PM should be only 1/4 of that in EM.' Css Clomi+DC compared to EM: PM: 299% Css Clomi+DC compared to EM: PM: 285%

			Note: genotype not reported	
ref. 9 Balant-Gorgia et al. High blood concentrations of imipramine or clomipramine and therapeutic failure: a case report study using drug monitoring data. Ther Drug Monit 1989;11:415-20. PMID: 2741190	2	IM: C PM: C	2 patients were prescribed clomi: - Patient 1 was suffering from a 1st episode of major depression. He received clomi 150 mg/day for 3 weeks. No clinical improvement was observed but side effects were reported. Css Clomi+DC was 1215 ng/ml, Css clomi was 235 ng/ml, Css DC was 980 ng/ml. Patient was found to be 'slow metabolizer'. - Patient 2 had been suffering from episodes of major depression for ~1 year. He received clomi 225 mg/day for 8 weeks. No clinical improvement was observed but severe side effects were reported. Css Clomi+DC was 1120 ng/ml, Css clomi was 160 ng/ml, Css DC was 960 ng/ml. Patient was found to be 'slow metabolizer'. Note: genotype not reported	
ref. 10 Balant-Gorgia AE et al. High plasma concentrations of desmethylclomipramine after chronic administration of clomipramine to a poor metabolizer. Eur J Clin Pharmacol 1987;32:101-2. PMID: 3582462	2	PM: A	Patient, PM, receives clomi 100 mg/day for 2 months for a major depressive syndrome. Blood concentrations were analyzed at 2 time-points: Css Clomi+DC were 598 ng/ml and 558 ng/ml. Compared to the reference values of this laboratory (125-350 ng/ml) this was an increase by 135-152% (NS). Increased concentrations were mainly the result of increased DC concentration. Css Clomi is increased by 6-14% compared to the mean reference values (25-100 ng/ml) (NS)	Css Clomi+DC compared to laboratory reference values: PM: 243% Css Clomi+DC compared to laboratory reference values: PM: 110%.

[a] dose corrected

Note: IM, EM and UM phenotypes are not separated by phenotyping. In phenotyping studies EM therefore consists of IM+EM+UM.

Groups at risk	IMs prescribed a concomitant CYP2D6 inhibitor

Remarks
Date literature search: 02 January 2008

- The active metabolite desmethylclomipramine lacks serotonin-reuptake-activity and does not contribute to the treatment of obsessive-compulsive disorder or anxiety.

	Phenotype	Code	Gene-Drug Interaction	Action Required	Date
Decision DPWG	PM	4 C	Yes	Yes	26 March 2008
	IM	4 C	Yes	Yes	
	UM	2 C	Yes	Yes	

Action Pharmacy Technician	PM: First prescription: Consult pharmacist Subsequent prescription: Dispense. If genotype was not previously known, consult pharmacist.
	IM: First prescription: Consult pharmacist Subsequent prescription: Dispense. If genotype was not previously known, consult pharmacist.
	UM: First prescription: Consult pharmacist Subsequent prescription: Dispense. If genotype was not previously known, consult pharmacist.
Action Pharmacist, Physician	PM: Reduce dose to 50% of the recommended dose. Monitor clomipramine and desmethylclomipramine plasma concentrations. For the treatment of obsessive-compulsive disorder or anxiety only clomipramine are relevant. For toxicity and depression both clomipramine and desmethylclomipramine plasma concentrations are of importance.
	IM: Insufficient data to allow calculation of dose adjustment. Monitor clomipramine and desmethylclomipramine plasma concentrations. For the treatment of obsessive-compulsive disorder or anxiety only clomipramine are relevant. For toxicity and depression both clomipramine and desmethylclomipramine plasma concentrations are of importance.
	UM: Select alternative drug that is less metabolized by CYP2D6 e.g. citalopram or sertraline. If this is not possible, monitor clomipramine and desmethylclomipramine plasma concentrations. For the treatment of obsessive-compulsive disorder or anxiety only clomipramine are relevant.

	For toxicity and depression both clomipramine and desmethylclomipramine plasma concentrations are of importance.

Considerations

Dose adjustments were calculated based on the sum concentration of clomipramine + desmethylclomipramine since this is related to toxicity. The clomipramine + desmethylclomipramine is also related to efficacy for the indication depression. For anxiety disorders only the clomipramine concentration has been related with efficacy.

PM: The population size-weighted mean of the dose adjustments calculated for the individual papers is 43% of the recommended dose (33% - 55%). For clinical applicability this is translated to a reduction to 50% of the recommended dose. Monitor plasma concentrations after dose adjustment.

IM: Insufficient data to allow calculation of dose adjustment. As a precaution it is advised to monitor clomipramine and desmethylclomipramine plasma concentrations.

UM: Insufficient data to allow calculation of dose adjustment. Theoretically both the risks for decreased efficacy as well as cardiotoxicity are increased. Therefore, as a precaution, the selection of an alternative drug or monitoring of clomipramine and desmethylclomipramine plasma concentrations is recommended.

Mechanism

Clomipramine and the active metabolite desmethylclomipramine are mainly metabolized by CYP2D6 to inactive hydroxymetabolites. It has been suggested that the hydroxymetabolites are cardiotoxic. Clomipramine is metabolized to desmethylclomipramine by CYP2C19. A genetic polymorphism in CYP2D6 can result in altered concentrations of clomipramine, desmethylclomipramine and the (possibly cardiotoxic) hydroxymetabolites.