CYP2D6: Aripiprazole

AP: aripiprazole, AUC: 'area under the concentration-time curve', Clor: oral clearance, Css: steady state plasma concentration, DAP: dehydroaripiprazole, EM: extensive metabolizer, 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 Hendset M et al. Impact of the CYP2D6vgenotype on steadystate serum concentrations of aripiprazole and dehydroaripiprazole. Eur J Clin Pharmacol 2007;63:1147-51. PMID: 17828532	4	PM: A IM: A	62 patients, 37x EM (*1/*1), 17x IM (16x *1/*4, 1x *1/*5), 8x PM (4x *4/*4, 3x *4/*5, 1x *5/*6). Aripiprazole 5-40 mg/day. Concomitant use of strong CYP2D6 / CYP3A4 inhibitors and CYP3A4 inducers excluded. Data were extracted from a routine therapeutic drug monitoring database. Compared to EM: PM: - Median Css[a] AP+DAP increased from 37.0 to 53.9 nM/mg (S, by 46%) - Median Css[a] AP increased from 26.3 tor 45.5 nM/mg (S, by 73%) - Median Css[a] DAP increased from 7.9 to 8.4 nM/mg (NS, by 6%) IM: - Median Css[a] AP+DAP increased from 37.0 to 42.6 nM/mg (S, by 15%) - Median Css[a] AP increased from 26.3 tor 33.5 nM/mg (S, by 27%) - Median Css[a] DAP increased from 7.9 to 8.2 nM/mg (NS, by 4%) Note: *3-*8 and gene duplication were assessed.	Conclusion authors: "The present study demonstrates that serum concentrations of both ARI and the active sum of ARI + DARI in psychiatric patients were significantly affected by CYP2D6 genotype. The observed differences in median C/D ratios indicate that PMs typically need 30–40% lower doses to achieve a similar steady-state serum concentration as EMs." Css[a] AP+DAP compared to EM: PM: 146% IM: 115%
ref. 2 Kubo M et al.	4	IM: A	20 healthy Japanese subjects. 9x EM (1x *1/*1, 2x *1/*2, 5x *1/*10, 1x *2/*41), 11x IM (5x *10/*10, 4x *5/*10, 1x	AUC AP+DAP compared to EM[#]:

Pharmacokinetics of aripiprazole, a new antipsychotic, following oral dosing in healthy adult Japanese volunteers: influence of CYP2D6 polymorphism. Drug Metab Pharmacokinet 2007;22:358-66. PMID: 17965519			*1/*5, 1x *41/*41). Aripiprazol 6 mg single dose. Compared to EM: IM: - AUC AP increased from 1459 to 2487 ng.hour/ml (S, by 70%) - Clor AP decreased from 4186 to 2569 ml/hour (S, by 38%) 15 healthy Japanese subjects. 11x EM# (2x*1/*1, 2x *1/*2, 6x *1/*10, 1x *1/*5), 1x IM (*10/*10), 3x type *2 (1x *2/*2, 1x *2/*5, 1x *2/*10). Aripiprazole 3 mg/day for 2 weeks. Compared to EM#: IM: - AUC24hr AP+DAP increased from 731.5 to 1977.7 ng.hour/ml (NS, by 170%) - AUC24hr AP increased from 556.13 to 1683.2 ng.hour/ml (NS, by 203%) - AUC24hr DAP increased from 175.33 to 294.5 ng.hour/ml (NS, by 68%) Type *2 (IM+EM) compared to EM#: - AUC24hr AP+DAP increased from 731.5 to 977.2 ng.hour/ml (NS, by 34%) - AUC24hr AP increased from 556.13 to 789.6 ng.hour/ml (NS, by 42%) - AUC24hr DAP increased from 175.33 to 187.53 ng.uur/ml (NS, by 7%)	IM: 270%
ref. 3 Oosterhuis M et al. Safety of aripiprazole: high serum levels in a CYP2D6 mutated	2	PM: C	Case report of a 51-year-old patient diagnosed with schizophrenia. After little antipsychotic effect being observed, her aripiprazole dose was increased from 15 mg to 30 mg per day. She then developed progressive symptoms of lethargy and memory loss. The serum level of aripiprazole was 2990 ng/ml, approx. 7x the expected	Conclusion authors: “The high serum levels of aripiprazole, not the adverse events, are disconcerting. Assuming our patient to represent all poor metabolizers, many patients

patient. Am J Psychiatry 2007;164:175. PMID: 17202571			plasma concentration at the maximum dose of 30 mg per day (320-584 ng/ml). The patient was CYP2D6*4/*4. When aripiprazole was substituted by quetiapine 400 mg daily, the adverse symptoms improved. The patient showed serum levels in the range of the toxic effects in animal studies. Although aripiprazole is well tolerated in general, PMs may potentially be at risk of long-term toxicity. Note: the normal aripiprazole maximum dose is 15 mg/day. The problems described in this case report only occurred after increasing the dose to 30 mg/day.	would potentially be at risk of long-term toxicity because of the good tolerability of aripiprazole."
ref. 4 Kim E et al. Effects of DRD2 and CYP2D6 genotypes on delta EEG power response to aripiprazole in healthy male volunteers: a preliminary study. Hum Psychopharmacol 2006;21:519-28. PMID: 16981227	3	IM: AA	17 healthy subjects, 5x EM (3x *1/*1, 1x *2/*2, 1x *2/*41), 2x IM (2x *1/*5), 9x IM+EM (4x *10/*10, 5x *1/*10), (1x UM (*2N/*10). 10 mg aripiprazole single dose. Absolute delta power in the Cz channel, obtained from a quantitative EEG was used as a pharmacodynamic parameter. Absolute delta power exhibited a significant change in patients with schizophrenia on aripiprazole. Compared to EM+UM (gene dose = 2): *1/*5 : - AUC72hr AP increased from 1557.2 to 1957.1 ng.hour/ml (NS, by 26%) - Clor AP decreased from 4.7 to 3.5 l/hour (NS, by 26%) - t1/2 AP increased from 46.0 to 54.7 hour (NS, by 19%) - Trend towards larger 'area under the EEG response-time curve' (AUEC6hr) IM+EM (*10/*10 + *1/*10): - AUC72hr AP increased from 1557.2 to 1749 ng.hour/ml (NS, by 12%) - Clor AP decreased from 4.7 to 3.6 l/hour (NS, by 23%) - t1/2 AP increased form 46.0 to 64.0 hours (NS, by 39%) Because the plasma concentrations of DAP were much lower than those of AP, they were excluded in pharmacokinetic– pharmacodynamic analysis.	Conclusion authors: "The linear relationship between AUC and AUEC and the trend of different AUC according to CYP2D6 genotypes suggest that the clinical effects of aripiprazole could be influenced by CYP2D6 genotypes and that dose adjustment of aripiprazole could be needed according to CYP2D6 genotypes."

			After the exclusion of 2 outliers, a significant linear relationships between AUC AP and AUEC in the 2nd hour and the 6th hour was observed. In addition to *1/*5, *1/*10 also showed a trend towards a higher AUEC6hr. Note: *2, *5, *10, *17, *41 and gene duplication were assessed.	
ref. 5 Kubo M et al. Influence of itraconazole coadministration And CYP2D6 genotype on the pharmacokinetics of the new antipsychotic aripiprazole. Drug Metab Pharmacokinet. 2005;20:55-64. PMID: 15770075	3	IM: A	24 healthy subjects, 18x EM (4x *1/*1, 10x *1/*10, 4x *2/*10), 6x IM (3x*10/*10, 3x *1/*5.) Aripiprazole 3 mg single dose. No relevant concomitant medication. Compared to EM: IM: - AUC AP+DAP increased form 990 to 1011 ng.hour/ml (significance not reported, by 2%) - AUC AP increased from 702 to 800 ng.hour/ml (significance nor reported, by 14%) - AUC DAP decreased from 288 to 211 ng.hour/ml (significance not reported, by 27%) Compared to *1/*1: *10/*10: - AUC AP+DAP increased from 931 to 1176 ng.hour/ml (significance not reported, by 26%) - AUC AP increased from 612 to 960 ng.hour/ml (S, by 87%) - AUC DAP decreased from 319 to 216 ng.hour/ml (NS, by 32%) Note: - *2, *4, *5, *10, *14, *18 and *36 were assessed. - *2 could be *2 or *41 (Kubo, 2007).	AUC AP+DAP compared to EM: IM: 102%
ref. 6	0	PM: AA	Mean t1/2 is approximately 75 hours in extensive and 146	

SPC Abilify (aripirazol) 04-06-04.			hours in poor CYP2D6 metabolizers.	
ref. 7 US-label text Abilify.	0	PM: AA	Compared to EM: PM: - AUC AP+DAP is increased by 60% - AUC AP is increased by 80% - AUC DAP is increased by 30%	AUC AP+DAP compared to EM: PM: 160%

[a] adjusted for dose

Groups at risk	Concomitant use of a CYP3A4 inhibitor

Remarks
Date literature search: 13 February 2008

	Phenotype	**Code**	**Gene-Drug Interaction**	**Action Required**	**Date**
Decision DPWG	PM	4 C	Yes	Yes	26 March 2008
	IM	4 A	Yes	No	
	UM	--	Yes	No	

Action Pharmacy Technician	PM: > 10 mg/day: consult pharmacist. ≤ 10 mg/day: dispense.
	IM: --
	UM: --

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 plasma concentrations of aripiprazole and its active metabolite. Reduce maximum dose to 10 mg/day (67% of the maximum recommended daily dose)
	IM: --
	UM: --

Considerations

IM, UM: Based on the limited available data and the large therapeutic window of aripiprazole no dose adjustment or selection of alternative drug is not considered useful.

PM: There is a case report describing aripiprazole toxicity in a PM. The authors of the case report emphasize that PMs may potentially be at risk for long-term toxicity since high aripiprazole concentrations might remain undetected due to the absence of acute toxicity. However, the aripiprazole concentration increase in the case report was much larger than the increase observed in other studies with PMs (700% vs. 73-80&). For this reasons, the recommendation is limited to a dose restriction to the maximum aripiprazole dose. The population size-weighted mean of the dose adjustments calculated for the individual papers is 63-68% of the recommended dose. For clinical applicability this is translated to a reduction to 67% (=10mg) of the recommended maximum dose

Mechanism

Aripiprazole is mainly metabolized by CYP2D6, and CYP3A4 to the active metabolite dehydroaripiprazole. Dehydroaripiprazole is metabolized by CYP2D6, and CYP3A4 to inactive metabolites. A genetic polymorphism in CYP2D6 can result in altered plasma concentrations of aripiprazole and dehydroaripiprazole.