CYP2D6: methylphenidate 2527/2528/2529

AUC = area under the concentration-time curve, IM = intermediate metaboliser (gene dose 0.25-1) (reduced CYP2D6 enzyme activity), NM = normal metaboliser (gene dose 1.25-2.5) (normal CYP2D6 enzyme activity), NS = non-significant, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), $t_{1/2}$ = half-life, UM = ultra-rapid metaboliser (gene dose ≥ 2.75) (elevated CYP2D6 enzyme activity)

The table below follows the KNMP definition for NM, PM, IM and UM. The definition of NM, PM, IM and UM used in the table below may therefore differ from the definition used by the authors in the article.

Source	Code	Effect	Comments
ref. 1 DeVane CL et al. Single-dose pharmacokinetics of methylphenidate in CYP2D6 extensive and poor metabolizers. J Clin Psychopharmacol 2000;20:347-9.	3 PM: AA	6 healthy volunteers, 4x NM#, 2x PM, single dose of 10 mg methylphenidate, no co-medication, caffeine, alcohol or smoking; PM versus NM#: - No difference in methylphenidate AUC, $t_{1/2}$ and AUC of the metabolite α-phenyl-2-piperidine acetic acid (all NS). - In a pharmacokinetic model, the CYP2D6 phenotype as a covariate did not explain the pharmacokinetics of methylphenidate or α-phenyl-2-piperidine acetic acid. The CYP2D6 inhibitor quinidine did not significantly alter methylphenidate pharmacokinetics. Note: genotype not known. Phenotyping can only distinguish between PM and other phenotypes. NM# is therefore equal to NM + IM + UM.	Authors' conclusion: 'These data suggest a lack of involvement of CYP2D6 in the metabolism of methylphenidate.'

Risk group	--

Comments:

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Date of literature search: 13 December 2021

	Phenotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working Group decision	PM	3 AA	no	no	31 January 2022
	IM	--	no	no	
	UM	--	no	no	

Mechanism:
Methylphenidate is mainly converted by the carboxylesterase CES1A1 and hydrolysis to the major metabolite α-phenyl-2-piperidine acetic acid. This metabolite is inactive.