CYP2D6: quinidine 2533/2534/2535

AUC = area under the time-concentration curve, Cl_{or} = oral clearance, IM = intermediate metaboliser (gene dose 0.25-1) (reduced CYP2D6 enzyme activity), NM = normal metaboliser (gene dose 1.5-2.5) (normal CYP2D6 enzyme activity), NS = non-significant, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), S = significant, $t_{1/2}$ = half-life, UM = ultra-rapid metaboliser (gene dose ≥ 2.75) (elevated CYP2D6 enzyme activity)

Source	Code	Effect	Comments
ref. 1 Nielsen F et al. Lack of relationship between quinidine pharmacokinetics and the sparteine oxidation polymorphism. Eur J Clin Pharmacol 1995;48:501-4.	3 PM: AA	16 volunteers, 8x PM and 8x NM# (phenotyped using sparteine), single dose of 200 mg oral quinidine, no co-medication reported. PM versus NM#: - No significant decrease in Cl_{or} and $t_{1/2}$ (NS, by 13% and 1% respectively). - No significant decrease in clearance via metabolite formation (NS, by 11%). - No significant decrease in clearance via 3-hydroxyquinidine or via quinidine-N-oxide (NS, by 29% and 24% respectively). Note: genotype not known.	Authors' conclusion: 'CYP2D6 is not an important enzyme for the oxidation of quinidine.'
ref. 2 Brøsen K et al. Quinidine kinetics after a single oral dose in relation to the sparteine oxidation polymorphism in man. Br J Clin Pharmacol 1990;29:248-53.	3 PM: AA	8 volunteers, 4x PM and 4x NM# (phenotyped using sparteine), single dose of 400 mg oral quinidine sulphate, no co-medication. PM versus NM#: - No significant decrease in Cl_{or} and $t_{1/2}$ (NS, by 28% and 8% respectively). - No significant decrease in clearance via metabolite formation (NS, by 33%). - Decrease in clearance via 3-hydroxyquinidine by 23% (S; from 3.1 to 2.4 L/h). Note: genotype not known.	Authors' conclusion: 'The panel study ruled out a major involvement of P450dbl in the metabolism of quinidine. However, the 20% lower formation clearance of 3-OH-quinidine found in PM compared with NM at a significance level of 5% suggests that a fraction of the quinidine dose might be metabolised by P450dbl.'
ref. 3 Mikus G et al. Pharmacokinetics and metabolism of quinidine in extensive and poor metabolisers of sparteine. Eur J Clin Pharmacol 1986;31:69-72.	3 PM: AA	6 volunteers, 3x PM and 3x NM# (phenotyped using sparteine), single dose of 3 mg/kg intravenous quinidine sulphate, no co-medication, smoking not excluded. PM versus NM#: - No significant decrease in AUC (NS, by 5%). - No significant increase in Cl and $t_{1/2}$ (NS, by 11% and 7% respectively). Note: genotype not known.	Authors' conclusion: 'It is unlikely that quinidine metabolism is controlled by the sparteine/debrisoquine gene locus.'

NM#: It is not possible to distinguish NM, IM and UM by phenotyping. NM# is therefore equal to NM + IM + UM.

Risk group	--

Comments:
-

Date of literature search: 11 July 2022.

	Phenotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working Group decision	PM	3 AA	no	no	12 September 2022
	IM	--	no	no	
	UM	--	no	no	

Mechanism:
Quinidine is primarily metabolised by CYP3A4.
Quinidine is a strong inhibitor of CYP2D6, but is hardly if at all metabolised by CYP2D6.