TDM monograph Quinidine (Kinidine)

Indication:	Prophylaxis for atrial fibrillation / flutter, paroxysmal atrial fibrillation/flutter, maintenance of sinus rhythm, Ventricular arrhythmias, Paroxysmal Supraventricular Tachycardia (PSVT) [1,2] and Brugada-syndrome in children (off-label) [2]
Sample material	Plasma or serum
Time of sampling:	Trough sample
Storage conditions	-20°C
Interpretation:	Trough level: 2 – 5 mg/L [3–5] Toxic level: > 8 mg/L [4,5]
Evidence level	4

Introduction

Quinidine is a class 1A antiarrhythmic agent. It is a stereoisomer of anti-malaric agent quinine. However, quinidine is not used to treat malaria in the Netherlands. Due to the risk of adverse drug reactions (e.g. urticaria, exanthema, fever, hepatitis, pancytopenia, photosensitivity and systemic lupus) it is advised to administer a test dosage first. In many trials in which antiarrhythmic therapy was used for non–life-threatening arrhythmias, active antiarrhythmic therapy was associated with increased mortality. This increased risk of mortality is probably most profound in patients with structural heart disease. [6] Also, due to the greater efficacy and tolerability of sotalol and the greater efficacy of amiodarone the use of quinidine is limited. [6]

Indications for TDM

- Optimalization of treatment
- Toxicity assessment

Dosing guidelines

Dosing for adults and children >12 years

Prophylaxis for atrial fibrillation / flutter	Oral (sulfate): 200 - 400 mg every 6 to 8 hours.
Arrhythmias	Oral (sulfate): 200 mg every 3 hours until the desired effect is reached. Maximum of 3 grams per day. Afterwards, reduce dosage gradually to 200 mg – 400 mg every 6 to 8 hours.
Dosing in children[7]	
Brugada-syndrome:	In children a higher dosage is needed per kg of body weight due to a faster metabolism. 1 month – 18 years: 15-60 mg/kg/day in 4-6 doses. Maximum of 1600 mg/day.
Kidney impairment: no specific dosage adjustments needed. [3]	

Reference values

Efficacy

In two studies a relation between the serum concentration and the efficacy of quinidine was observed. The study of Kessler et al. showed that quinidine serum concentrations of 2.3 – 5.0 mg/L were associated with therapeutic effectiveness in 14 patients with arrhythmias and 12 patients with congestive heart failure.[3] Sokolow et al. documented their experience with over 200 conversion attempts with quinidine in patients with chronic atrial fibrillation. [5] In their study conversion as well as toxicity usually occurred about the time of the peak level in the blood. A large individual variation in serum concentration by patients on similar doses was observed. As blood concentrations exceeded 8 mg/L, the likelihood of conversion decreased and also the toxicity increased. Myocardial infarction was infrequent at levels below 6.0 mg/L but increased proportional as this level was exceeded. In total, 80% of the successful conversions were achieved with a blood concentrations below 8 mg/L, the average concentration required for conversion was 6.1 mg/L. [5]

Sampling conditions

To monitor quinidine a trough sample should be collected 8 -12 hours after the last dose. [8]

Sampling should occur at 24 – 36 hours after start of therapy when steady-state concentrations are reached. The elimination half time of quinidine is 6-8 hours but can be prolonged in case of hepatic impairment. In children, the elimination half time is 2.5-6.7 hours.

Interpretation results

A decreased free fraction due to an increase in orosomucoid (ORM) or alpha-1-acid glycoprotein after, for example, myocardial infarction or cardiac surgery can cause a disturbance in the concentration-effect relation. [9,10]

Toxicity

There is a relation between toxicity and serum concentrations above 8 mg/L. [5] Some patients however may have toxic effects at the upper limit of the therapeutic window. [4,5] Toxic symptoms are nausea, diarrhea, hypotension, prolongation of the QRS-interval and extrasystole. Also delirium, convulsions and coma can occur. The dose-response curve for torsades de pointes does not correlate with the toxic concentration of 8 mg/L. Action potential prolongation and hazard for torsades de pointes are actually higher at the lower end of the therapeutic range. [8,11] Therefore, this toxicity occurs either early after initiation of the therapy, or after quinidine has been ceased. Treatment of quinidine toxicity should be symptomatic. Arrhythmias can be treated with lidocaine or phenytoin.

Background information

- ### Pharmacokinetics
  After oral administration bioavailability is variable between patients (45 – 100%). The time to peak concentration is 2 hours after administration of an immediate release form and 3 to 5 hours in an extended release form. Quinidine is extensively metabolised by the liver (50-90%) to inactive compounds. [2]

- ### Food interactions
  Quinidine serum levels can increase if taken with food. Food has a variable effect on the absorption of sustained release formulation. Also, grapefruit juice may decrease the rate of absorption of quinidine. [2]

- ### Pharmacogenetics
  Quinidine is a minor substrate for CYP2C9 and CYP2E1 and a major substrate for CYP3A4. Also quinidine inhibits CYP2D6 (strong), CYP3A4 (weak) and P-glycoprotein/ABCB1. However, no clinically relevant drug-gene interactions have been identified.

- ### Renal replacement therapy

  Hemodialysis: increase in clearance
  CAPD: increase in clearance
  Dosage adjustments after dialysis: measuring serum trough concentration after dialysis can be of use to determine the dosage.

Interactions

Acetazolamide
Acetazolamide alkalizes the urine, reducing the renal excretion of quinidine. The quinidine serum concentration might increase.

CYP2D6-substrates
Quinidine inhibits the CYP2D6 iso-enzyme increasing serum concentrations of drugs metabolized by CYP2D6 (e.g. tricyclic antidepressants).

CYP3A4-inhibitors and inductors
CYP3A4 inhibitors (e.g. azoles and antiretrovirals) increase the quinidine serum concentration. On the contrary, CYP3A4 inductors (e.g. phenobarbital, phenytoin) reduce the quinidine serum concentration.

Digoxin
Quinidine increases the serum concentration of digoxin. Due to inhibition of the P-glycoproteins, the renal clearance of digoxin is inhibited. In 90% of patients using digoxin, the digoxin serum concentration increases with 25-100% after start of quinidine. This effect is dose dependent. Other risk factors are impaired renal function and age. When introducing quinidine new steady-state concentrations are reached after 5 – 7 days.

P-gp- substrates
As quinidine is a P-gp-inhibitor, concomitant use may lead to higher serum concentrations of P-gp-substrates such as DOACS. For instance, for dabigatran, an 1.5x rise in AUC and 1.6 in Cmax was reported.

QTc-prolongation
Quinidine prolongs the QTc-interval increasing the risk of torsades de pointes when given with other QTc-prolonging drugs.

PK parameters

	F (%)	**Cl** (l/kg/h)	**Vd** (l/kg)	**t½**,ß (h)	%protein	**Tmax** (h)	Tmax* (h)
adults	0,9	0,27	2-3,5	6-8	75-95	1-2	4

* extended release formulation

Population models

	Vd)	**Kelm** (h-1)	Kelr (h1/ml/min)	F	Ka (h-1)	Literature
General	2,7±1,2	0,086±0,04	0,00021±0,00 01	0,8±0,2	0,7±0,2 *	MWPharm

Literature

1. Informatorium Medicamentorium. Kinidine. https://kennisbank.knmp.nl/article/Informatorium_Medicamentorum/S500.html. Accessed July 13, 2022.
2. UpToDate/Lexicomp. Quinidine: Drug information. https://www.uptodate.com/contents/quinidine-drug-information?search=quinidine&source=panel_search_result&selectedTitle=1~148&usage_type=panel&kp_tab=drug_general&display_rank=1. Accessed July 13, 2022.
3. Kessler KM, Lowenthal DT, Warner H, Gibson T, Briggs W, MM R. Quinidine elimination in patients with congestive heart failure or poor renal function. *New Engl J Med Engl J Med*. 1974;28(290(13)):706-709.
4. Lexicomp. QuiNIDine Level, Serum (Lab Tests and Diagnostic Procedures). https://online.lexi.com/lco/action/doc/retrieve/docid/lthdph/382868?cesid=2NJF04Ncmz9&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dquinidine%26t%3Dname%26acs%3Dfalse%26acq%3Dquinidine. Accessed July 13, 2022.
5. Sokolow M, Ball RE. Factors influencing conversion of chronic atrial fibrillation with special reference to serum quinidine concentration. *Circulation*. 1956;14(4 Part 1):568-583. doi:10.1161/01.cir.14.4.568
6. Grace A, Camm AJ. Quinidine. *N Engl J Med*. 1998:35-45.
7. Kinderformularium. kinidine (sulfaat). https://www.kinderformularium.nl/geneesmiddel/401/kinidine-sulfaat. Accessed July 13, 2022.
8. Campbell TJ, Williams KM. Therapeutic drug monitoring: Antiarrhythmic drugs. *Br J Clin Pharmacol*. 2001;52(SUPPL. 1):21-33. doi:10.1046/j.1365-2125.2001.00768.x
9. Huang JL, Morgan DJ. Effect of alpha-1-acidglycoprotein on myocardial uptake and pharmacodynamics of quinidine in perfused rat heart. *Biochem pharmacol*. 1933;49:1705-1711.
10. Giardina EG, Raby K, Freilich D, Vita J, Brem R, Louie, M. Time course of alpha-1-acid glycoprotein and its relation to myocardial enzymes after acute myocardial infarction. *Am j cardiol*. 1985;56(4):262-265.
11. Wyse KR, Ye V, Campbell TJ. Action Potential Prolongation Exhibits Simple Dose-Dependence for Sotalol, but Reverse. *J Cardiovasc Pharmacol*. 1993;21(2):316-322.

Colophon

This guideline was constituted by: D.J. Touw, J.M. Bos, A.C. van Loenen, E.L. Swart and A.J. Wilhem in 1997

This guideline has been revised in July of 2022 by Jurjen Kingma, hospital pharmacist in training St. Antonius Ziekenhuis Nieuwegein/Utrecht and dr. Ankie Harmsze, hospital pharmacist – clinical pharmacologist St. Antonius Ziekenhuis Nieuwegein/Utrecht

Under the auspices of TDM, Toxicology and Pharmacogenetics committee (TTF) of the Dutch Association of Hospital Pharmacists (NVZA) and the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT).

July 2022

Appendices

Revision

July 2022: the guideline was translated to English and the new format was applied. Also the paragraphs efficacy, toxicity and background information were amended.