

Quinidine

Order information

REF	CONTENT	Analyzer(s) on which cobas c pack(s) can be used
20737909 322	Quinidine (200 tests)	System-ID 07 3790 9 COBAS INTEGRA 400 plus COBAS INTEGRA 800
03375781 190	Preciset TDM II Calibrators A-F (6 × 1 × 5 mL) Diluent (1 × 10 mL)	System-ID 07 6829 4
04521536 190	TDM Control Set Level I (2 × 5 mL) Level II (2 × 5 mL) Level III (2 × 5 mL)	System-ID 07 6900 2 System-ID 07 6901 0 System-ID 07 6902 9
20720720 322	COBAS FP Sample Dilution Reagent II (1 × 200 mL)	System-ID 07 2072 0

English

System information

Test QUINM, test ID 0-290

Intended use

In vitro diagnostic test for the quantitative determination of quinidine in serum or heparinized plasma on COBAS INTEGRA systems.

Summary

Quinidine is used for the prevention and treatment of ventricular arrhythmias, junctional (nodal) arrhythmias, and supraventricular (atrial) arrhythmias. The quinidine dosage required to achieve therapeutic serum levels is dependent on the drug formulation, patient age, and individual variability in absorption and metabolism.

Test principle

Fluorescence polarization

COBAS INTEGRA therapeutic drug monitoring measurements are made on the COBAS INTEGRA systems using the principle of fluorescence polarization. When a fluorescent molecule, or fluorophore, is irradiated with light of the proper wavelength (the excitation wavelength) some of the light is absorbed. Within a few nanoseconds the absorbed light is emitted, although at a longer wavelength (the emission wavelength). Whether or not the emitted light is polarized depends on the freedom of the fluorophore to rotate in solution. A small molecule, such as fluorescein, can rotate rapidly before light emission occurs, resulting in depolarization of the emitted light. In contrast, a fluorescent macromolecule, such as a fluorescein-labeled protein, will rotate much more slowly. Thus, in the time frame between excitation and emission, the macromolecule will have rotated only very slightly and the emitted light will be polarized.¹ Fluorescence polarization is a reproducible function of the drug concentration, and is suitable for the quantitative determination of drug concentrations in serum for the purpose of therapeutic drug monitoring.

Surface active agents are used to ensure dissociation of the drug from serum proteins and to prevent nonspecific binding of the tracer.

Reagents - working solutions

- R1** Antibody reagent
Anti-quinidine monoclonal antibody (mouse) in buffer, pH 7.5, with stabilizer and preservative.
- SR** Tracer reagent
Fluorescein-labeled quinidine derivative in buffer, pH 6.5, with stabilizer and preservative.

R1 is in position B and SR is in position C.

Precautions and warnings

Pay attention to all precautions and warnings listed in Section 1 / Introduction of this Method Manual.

For USA: For prescription use only.

Reagent handling

Ready for use

Storage and stability

Shelf life at 2-8 °C

See expiration date on
cobas c pack label

COBAS INTEGRA 400 plus system

On-board in use at 10-15 °C 10 weeks

COBAS INTEGRA 800 system

On-board in use at 8 °C 26 weeks

Specimen collection and preparation

For specimen collection and preparation only use suitable tubes or collection containers.

Only the specimens listed below were tested and found acceptable:

Unhemolyzed serum

Unhemolyzed heparinized plasma

The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

Centrifuge samples containing precipitates before performing the assay.

Specimens should be tested within 8 hours of collection if kept capped at 15-25 °C. If specimens must be stored for later testing, they may be kept capped at 2-8 °C for up to 48 hours or at -20 °C for 4 weeks. Specimens should not be repeatedly frozen and thawed.

Invert thawed specimens several times prior to testing.

Materials provided

See "Reagents – working solutions" section for reagents.

Materials required (but not provided)

COBAS FP Sample Dilution Reagent (SDR II), Cat. No. 20720720322

The SDR II is placed as special diluent in its predefined rack position and is stable for 7 days on-board COBAS INTEGRA 400 plus/800 analyzers.

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator's manual for analyzer-specific assay instructions.

Application for serum and plasma

COBAS INTEGRA 400 plus test definition

Measuring mode	FP
Reaction mode	R1-SDR2/S-SR
Wavelength	excitation 485 nm
	emission 515 nm
Reading cycle blank/test	29/45
Unit	µg/mL

Pipetting parameters

		Diluent (H ₂ O)
R1	140 µL	10 µL
Sample	2 µL	5 µL

Special diluent SDR II	18 µL	
SR	20 µL	10 µL
Total volume	205 µL	

COBAS INTEGRA 800 test definition

Measuring mode	FP
Reaction mode	R1-SDR2/S-SR
Wavelength	excitation 485 nm
	emission 515 nm
Reading cycle blank/test	40/60
Unit	µg/mL

Pipetting parameters

		Diluent (H ₂ O)
R1	140 µL	10 µL
Sample	2 µL	5 µL
Special diluent SDR II	18 µL	
SR	20 µL	10 µL
Total volume	205 µL	

Calibration

Calibrators	Preciset TDM II
	Calibrators A-F
Calibration mode	Logit/log 4
Calibration replicate	Duplicate recommended
Deviation low/high	< 10 % at ≥ 0.5 µg/mL (≥ 1.5 µmol/L)
Calibration interval	
COBAS INTEGRA 400 plus analyzers	Each lot, every 10 weeks and as required following quality control procedures
COBAS INTEGRA 800 analyzers	Each lot, every 26 weeks and as required following quality control procedures

A calibration curve must be prepared using the Preciset TDM II calibrators. Calibrators must be placed from the highest concentration (F) first, to the lowest (A) last, on the CAL/QC rack. This curve is retained in memory by the COBAS INTEGRA systems and recalled for later use.

Traceability: The Preciset TDM II calibrators are prepared to contain known quantities of quinidine in normal human serum and are traceable to USP reference standards.

Note

Calibrators should be assayed within 2 hours after placing on-board the instrument.

Quality control

Quality control	TDM Control Set
Control interval	24 hours recommended
Control sequence	User defined
Control after calibration	Recommended

For quality control, use control materials as listed in the "Order information" section. In addition, other suitable control material can be used.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

Follow the applicable government regulations and local guidelines for quality control.

Note

Controls should be assayed within 2 hours after placing on-board the instrument.

Calculation

COBAS INTEGRA analyzers automatically calculate the analyte concentration of each sample. For more details, please refer to Data Analysis in the Online Help (COBAS INTEGRA 400 plus/800 analyzers).

Conversion factor: µg/mL x 3.08 = µmol/L

Limitations - interference

See the Analytical specificity section of this method sheet for information on substances tested for cross-reactivity in this assay. There is the possibility that other substances and/or factors may interfere with the test and cause erroneous results (e.g., technical or procedural errors).

Specimens with assay values greater than the highest calibrator will be flagged by the system and must be repeated after appropriate dilution of the original sample with the Preciset TDM II Diluent (0 µg/mL). Specimens with high fluorescent backgrounds or those giving polarization values greater than the zero calibrator will also be flagged by the system.

Serum/plasma

Criterion: Recovery within ± 10 % of initial value at a quinidine concentration of 3 µg/mL (9.2 µmol/L).

Icterus:² No significant interference up to a bilirubin concentration of 404 µmol/L or 23.6 mg/dL.

Hemolysis:² No significant interference up to a hemoglobin concentration of 621 µmol/L or 1000 mg/dL.

Lipemia:² No significant interference up to a triglycerides concentration of 921 mg/dL.

Total protein: No significant interference up to a total protein concentration of 2-12 g/dL.

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.³

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

ACTION REQUIRED

Special Wash Programming: The use of special wash steps is mandatory when certain test combinations are run together on COBAS INTEGRA analyzers. Refer to the CLEAN Method Sheet for further instructions and for the latest version of the Extra wash cycle list.

Where required, special wash/carry-over evasion programming must be implemented prior to reporting results with this test.

Limits and ranges**Measuring range**

COBAS INTEGRA 400 plus analyzer:
0.19-8 µg/mL (0.58-24.6 µmol/L)

COBAS INTEGRA 800 analyzer:
0.09-8 µg/mL (0.28-24.6 µmol/L)

Lower limits of measurement

Lower detection limit of the test:

COBAS INTEGRA 400 plus analyzer:
0.19 µg/mL (0.58 µmol/L)

COBAS INTEGRA 800 analyzer:
0.09 µg/mL (0.28 µmol/L)

The lower detection limit represents the lowest measurable analyte level that can be distinguished from the zero calibrator at a 95 % confidence level.

Expected values

Quinidine is approximately 75 % bound to serum protein.⁴ The elimination half-life of quinidine ranges from 4-10 hours in healthy individuals and may be prolonged in the elderly. From 60-80 % of the dose is metabolized by the liver with renal excretion of the unchanged drug accounting for much of the remainder.^{4,5}

Serum quinidine levels of 1.5-5 µg/mL (4.6-15.4 µmol/L) have been reported as therapeutic, based on nonspecific methodologies that measure quinidine metabolites as well as quinidine.^{4,6} The therapeutic range using newer, more specific assays has not been established. However, effective reduction of premature ventricular contractions has been reported with

Quinidine

blood levels less than 1.0 µg/mL (3.1 µmol/L).⁴ Toxicity has been reported at a level of 6 µg/mL (18.5 µmol/L).⁷ Toxic side effects include ventricular tachycardia, heart block, thrombocytopenia and "cinchonism", a group of symptoms including headache, dizziness, tinnitus, nervousness, blurred vision, nausea, and vomiting. Measured quinidine levels are lower using specific methods (HPLC and immunoassays). Clinicians requesting serum quinidine determinations should ask that the method of analysis be specified.⁴

Metabolites of quinidine which may be found in serum are 3(S)-hydroxyquinidine, 2'-oxoquinidinone, quinidine-N-oxide, o-desmethylquinidine, and the quinidine 10,11-dihydrodiols. Most of these have been shown to have pharmacological activity in human or animal studies, and some quinidine metabolites may be as potent as the parent drug.^{5,6,8,9} Because of variability seen in patient metabolism, relative proportions of these metabolites are reported in the literature in differing amounts.^{5,10,11,12} Quinidine serum specimens may also contain dihydroquinidine, an analog contained in quinidine formulations at levels of 5-10 % of the dosage. Dihydroquinidine has anti-arrhythmic activity comparable to quinidine.^{6,13}

Recent reports indicate that plasma concentrations of digoxin increase when quinidine is given concurrently. Patients on concomitant therapy should be carefully monitored.⁴

Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.

Specific performance data

Representative performance data on the COBAS INTEGRA analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using controls in accordance with the NCCLS EP5-T2¹⁴ requirements with repeatability (n = 80) and intermediate precision (2 aliquots per run, 2 runs per day, 20 days). The following results were obtained.

COBAS INTEGRA 400 analyzer

Repeatability	Mean µg/mL (µmol/L)	SD µg/mL (µmol/L)	CV %
Level 1	0.9 (2.8)	0.05 (0.15)	5.5
Level 2	2.6 (8.0)	0.03 (0.09)	0.9
Level 3	4.3 (13.6)	0.05 (0.15)	1.1

Intermediate precision	Mean µg/mL (µmol/L)	SD µg/mL (µmol/L)	CV %
Level 1	0.9 (2.8)	0.09 (0.28)	10.0
Level 2	2.6 (8.0)	0.11 (0.34)	4.2
Level 3	4.3 (13.6)	0.05 (0.15)	2.6

COBAS INTEGRA 700 analyzer

Repeatability	Mean µg/mL (µmol/L)	SD µg/mL (µmol/L)	CV %
Level 1	1.4 (4.3)	0.03 (0.09)	2.1
Level 2	3.5 (10.8)	0.07 (0.22)	2.2
Level 3	5.4 (16.6)	0.11 (0.34)	2.0

Intermediate precision	Mean µg/mL (µmol/L)	SD µg/mL (µmol/L)	CV %
Level 1	1.4 (4.3)	0.04 (0.12)	3.2
Level 2	3.5 (10.8)	0.12 (0.37)	3.5
Level 3	5.4 (16.6)	0.17 (0.52)	3.2

Method comparison

Quinidine values for human serum samples obtained on a COBAS INTEGRA 700 analyzer using the COBAS INTEGRA

Quinidine reagent (y) were compared with those determined using a commercially available enzyme immunoassay method (x).

	Enzyme Immunoassay
Number of samples	154
Range of values	min. 0.16 µg/mL max. 5.7 µg/mL
Slope	0.941
Intercept	-0.024 µg/mL
Correlation coefficient	0.991

Analytical specificity

The following cross-reactive substances were evaluated on the COBAS INTEGRA systems in normal human serum spiked with quinidine at 5 µg/mL (15.4 µmol/L). Each substance was tested at 10 times the highest concentration for its therapeutic or normal range, as per the protocol described by NCCLS.¹⁵ The imprecision of the assay was taken into account when determining cross-reactivity. Cross-reactivity was designated as "not detectable" (ND) if the obtained value was less than the sensitivity of the assay.

$$\text{Cross-reactivity (\%)} = \frac{100 \times (\text{analytical result} - \text{analyte concentration})}{\text{concentration of interferent}}$$

Drug	Level tested µg/mL	Cross-reactivity %
Dihydroquinidine	1	107.8
10,11-Dihydroquinidinediol	100	ND
O-desmethylquinidine	10	27.9
3(S)-Hydroxyquinidine	100	2.2
2'-Oxoquinidinone	500	0.4
Quinidine-N-oxide	100	2.6

ND = Not Detectable

In a similar study, the following structurally related or potentially co-administered compounds were tested on the COBAS FARA II using normal human serum spiked with quinidine at 2.4 µg/mL (7.4 µmol/L).

Drug	Level tested µg/mL	Cross-reactivity %
Digitoxin	0.4	ND
Digoxin	0.022	ND
Disopyramide	80	ND
Ephedrine	1.2	ND
Furosemide	100	ND
Hydrochlorothiazide	4.5	ND
Isoproterenol	5.0	ND
Lidocaine	50	ND
N-Acetylprocainamide	200	ND
Ouabain	0.002	ND
Phenytoin(DPH)	200	ND
Procainamide	80	ND
Propranolol	3.4	ND
Quinine	1000	ND
Reserpine	0.006	ND

ND = Not Detectable

Any modification of the instrument as set forth in this labeling requires validation by the laboratory.

References

- 1 Dandliker WB, Feigen GA. Quantification of the antigen-antibody reaction by the polarization of fluorescence. *Biochem Biophys Res Comm* 1961;5:299-304.
- 2 Glick MR, Ryder KW, Jackson SA. Graphical Comparisons of Interferences in Clinical Chemistry Instrumentation. *Clin Chem* 1986;32:470-475.
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- 4 Physicians' Desk Reference 47th ed. Montvale NJ: Medical Economics Data 1993;688-689.
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- 7 Goodman, Gilman. *The Pharmacological Basis of Therapeutics*. 8th ed. Paragon, NY 1990;1704-1705.
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- 9 Drayer DE, Restivo K, Reidenberg MM. Specific determination of quinidine and (3S)-3-hydroxyquinidine in human serum by high-pressure liquid chromatography. *J Lab Clin Med* 1977;90(5):816-822.
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- 12 Leroyer R, Varoquaux O, Advenier C, et al. Quinidine oxidative metabolism. Identification and biosynthesis of quinidine 10,11-dihydrodiol stereoisomers. *Biomedical Chromatography* 1980;4(2):61-64.
- 13 Drayer DE, Hughes M, Lorenzo B, et al. Prevalence of high (3S)-3-hydroxyquinidine/quinidine ratios in serum, and clearance of quinidine in cardiac patients of age. *Clin Pharmacol Ther* 1980;27(1):72-75.
- 14 National Committee for Clinical Laboratory Standards. *User Evaluation of Precision Performance of Clinical Chemistry Devices; Tentative Guideline*. Villanova, PA.: NCCLS;1992;4(12). NCCLS Publication EP5-T2.
- 15 National Committee for Clinical Laboratory Standards. *Interference Testing in Clinical Chemistry; Proposed Guideline*. Villanova, PA.: NCCLS; 1986;6(13). NCCLS Publication EP7-P.

A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard:

CONTENT

Contents of kit



Volume after reconstitution or mixing

GTIN

Global Trade Item Number

FOR US CUSTOMERS ONLY: LIMITED WARRANTY

Roche Diagnostics warrants that this product will meet the specifications stated in the labeling when used in accordance with such labeling and will be free from defects in material and workmanship until the expiration date printed on the label. THIS LIMITED WARRANTY IS IN LIEU OF ANY OTHER WARRANTY, EXPRESS OR IMPLIED, INCLUDING ANY IMPLIED WARRANTY OF MERCHANTABILITY OR FITNESS FOR PARTICULAR PURPOSE. IN NO EVENT SHALL ROCHE DIAGNOSTICS BE LIABLE FOR INCIDENTAL, INDIRECT, SPECIAL OR CONSEQUENTIAL DAMAGES.

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