QMS® Lidocaine (LIDO)

Thermo SCIENTIFIC

IVD **For In Vitro Diagnostic Use Only**

Rx Only

REF **0374686**

This Quantitative Microsphere System (QMS) package insert must be read carefully prior to use. Package insert instructions must be followed accordingly. Reliability of assay results cannot be guaranteed if there are any deviations from the instructions in this package insert.

Intended Use

The QMS® Lidocaine assay is intended for the quantitative determination of lidocaine in human serum or plasma on automated clinical chemistry analyzers.

The results obtained are used in the diagnosis and treatment of lidocaine overdose and in monitoring levels of lidocaine to help ensure appropriate therapy.

Summary and Explanation of the Test

Lidocaine is an anti-arrhythmic agent administered intravenously by either injection or continuous infusion. It is specifically indicated in the acute management of ventricular arrhythmias such as those occurring in relation to acute myocardial infarction, or during cardiac manipulation, such as cardiac surgery.[1] Lidocaine is metabolized primarily by the liver. N-ethylglycyl-2,6-xylidide (MEGX), glycyl-2,6-xylidide (GX), and 4-hydroxy-2,6-xylidine (4-OH-XY) are the major metabolites.[2] 4-OH-XY, which comprises 73% of the dose is found in urine. Other metabolic products recovered in urine in amounts less than 1% are 3-hydroxy lidocaine, 3-hydroxy MEGX, and 2,6-xylidine. MEGX has 80 to 90% and GX has 10 to 26% of the anti-arrhythmic potency of lidocaine.[3] Concentration monitoring is warranted by lidocaine's extensive interpatient variability in disposition and by its narrow therapeutic index.[3]

Principles of the Procedure

The QMS Lidocaine assay is a homogeneous particle-enhanced turbidimetric immunoassay. The assay is based on competition between drug in the sample and drug coated onto a microparticle for antibody binding sites of the lidocaine antibody reagent. The lidocaine-coated microparticle reagent is rapidly agglutinated in the presence of the antilidocaine antibody reagent and in the absence of any competing drug in the sample. The rate of absorbance change is measured photometrically. When a sample containing lidocaine is added, the agglutination reaction is partially inhibited, slowing down the rate of absorbance change. A concentration-dependent classic agglutination inhibition curve can be obtained with maximum rate of agglutination at the lowest lidocaine concentration and the lowest agglutination rate at the highest lidocaine concentration.

Reagents

Reagent Kit

QMS Lidocaine, **REF** 0374686, is supplied as a liquid, ready-to-use, two-reagent kit that contains:

R1 Reagent 1 2 x 18 mL
R2 Reagent 2 2 x 9 mL

Reactive Ingredients

INGRED	Ingredient	Concentration
R1	Anti-lidocaine Monoclonal Antibody (Mouse)	≤5.0%
	Sodium azide	≤0.05%
R2	Lidocaine-coated Microparticles	<0.6%
	Sodium azide	≤0.09%

Reagent Handling and Storage

- **R1** and **R2** Ready for Use.
- Before use, invert several times, avoiding the formation of bubbles.
- Remove air bubbles, if present in the reagent cartridge, with a new applicator stick. Alternatively, allow the reagent to sit at the appropriate storage temperature to allow the bubbles to dissipate. To minimize volume depletion, do not use a transfer pipette to remove the bubbles.
- When either the **R1** or the **R2** reagent cartridge becomes empty, replace both cartridges and verify calibration with at least two levels of controls according to the established Quality Control requirements for your laboratory. If control results fall outside acceptable ranges, recalibration may be necessary.
- Refer to the analyzer specific Assay System Parameters sheet for reagent on-board stability and other system specific information.

⚠ **CAUTION:** Reagent bubbles may interfere with proper detection of reagent level in the cartridge, causing insufficient reagent aspiration that could impact results.

2°C 8°C The unopened reagents are stable until the expiration date when stored at 2 to 8°C. **Do not freeze reagents or expose them to temperatures above 32°C.**

Warnings and Precautions

Precautions for Users

- For in vitro diagnostic use.
- Do not mix materials from different kit lot numbers.

⚠ **CAUTION:** This product contains human sourced and/or potentially infectious components. Components sourced from human blood have been tested by FDA-approved methods and found to be nonreactive for HBsAg, anti-HIV 1/2, and anti-HCV. No known test method can offer complete assurance that products derived from human sources or inactivated microorganisms will not transmit infection. Therefore, it is recommended that all human sourced materials be considered potentially infectious and handled with appropriate biosafety practices.

DANGER: QMS Lidocaine Immunoassay contains ≤5.0% Drug-specific antibody (mouse) and ≤2.0% Human Serum Albumin (HSA).
H317 - May cause allergic skin reaction.
H334 - May cause allergy or asthma symptoms or breathing difficulties if inhaled.

Avoid breathing mist or vapor. Contaminated work clothing should not be allowed out of the workplace. Wear protective gloves/eye protection/face protection. In case of inadequate ventilation wear respiratory protection. If on skin: Wash with plenty of soap and water. IF INHALED: If breathing is difficult, remove victim to fresh air and keep at rest in a position comfortable for breathing. If skin irritation or rash occurs: Get medical advice/attention. If experiencing respiratory symptoms: Call a POISON CENTER or doctor/physician. Wash contaminated clothing before reuse. Dispose of contents/container to location in accordance with local/regional/national/international regulations.

Specimen Collection and Handling

The following specimen collection tubes may be used for the QMS Lidocaine assay:

	Glass	Plastic
Serum	• Serum Separator Tube	• No Additive
Plasma	• EDTA (K_3) • Lithium Heparin Tube • Sodium Heparin Tube (Sprayed Sodium Heparin)	• EDTA (K_2)

Other specimen collection tubes have not been validated for use with the QMS Lidocaine assay. Follow the manufacturer's processing instructions for serum or plasma collection tubes.

- Some specimens, especially those from patients receiving anticoagulant or thrombolytic therapy may exhibit increased clotting time.
- Centrifuge samples containing precipitates before performing the assay. Inadequate centrifugation of the specimen may cause an erroneous result.
- Ensure specimens are free of fibrin, red blood cells, other particulate matter, and bubbles.
- Remove the plasma or serum from the cells, clot, or gel as soon as possible after collection. Some serum or plasma tubes may not be suitable for use with therapeutic drug monitoring assays; refer to information provided by the tube manufacturer.[4]
- 2°C 8°C Specimens removed from the cells, clot, or gel may be stored up to 7 days at 2 to 8°C.

Procedure

Materials Provided

- QMS Lidocaine Reagent Kit, **REF** 0374686

Materials Required but not Provided

- Lidocaine Calibrators (6-Level)
- Lidocaine Controls

Assay Procedure

For a detailed description of how to run and calibrate an assay, refer to the calibrator instructions and instrument specific operations manual.

Calibration

The QMS Lidocaine assay must be calibrated using a full calibration (6-point) procedure.

Calibration is required with each new lot number. Verify the calibration curve with at least two levels of controls according to the established Quality Control requirements for your laboratory. If control results fall outside acceptable ranges, recalibration may be necessary.

Quality Control

As appropriate, refer to your laboratory's Standard Operating Procedure(s) and/or Quality Assurance Plan for additional quality control requirements and potential corrective actions.

Recommended control requirements for the QMS Lidocaine assay:

- A minimum of two levels of controls spanning the medical decision range should be run every 24 hours.
- If more frequent control monitoring is required, follow the applicable local, state, and federal Quality Control procedures for your laboratory.
- If quality control results do not fall within an acceptable range defined by your laboratory, patient values may be suspect and corrective action should be taken.

Results

The result unit for the QMS Lidocaine assay can be reported as µg/mL or µmol/L. To convert results from µg/mL lidocaine to µmol/L lidocaine, multiply µg/mL by 4.27.[5]

As with all analyte determinations, the lidocaine value should be used in conjunction with information available from clinical evaluations and other diagnostic procedures.

Result Error Codes

Some results may contain Result Error Codes. Refer to the instrument specific operations manual for a description of the error codes.

Limitations of the Procedure

In very rare cases, patient samples may contain heterophile antibodies, which may produce low results with the QMS Lidocaine assay.

Interfering heterophile antibodies occur at low frequency in the general population. These antibodies can cause autoagglutination of the microparticle reagent leading to underdetected erroneously low results.

For diagnostic purposes, interfering heterophile antibodies occur at low frequency in the general population. These antibodies can cause auto-agglutination of the microparticle reagent leading to erroneous results that may be unexpectedly low or unexpectedly high. An erroneous result could lead to incorrect patient management; incorrect patient management could potentially cause serious injury or death. Test results should not be used in isolation to make patient management decisions. Results should always be assessed in conjunction with the patient's medical history, clinical examinations, and other clinicopathological findings. An alternative test method should be used to confirm results when results are inconsistent with clinical expectations.

See the SPECIMEN COLLECTION AND HANDLING and SPECIFIC PERFORMANCE CHARACTERISTICS sections of this package insert.

Expected Values

The therapeutic range for total concentration is stated as 1.5 to 6 µg/mL.[5] Suppression of ventricular arrhythmias at concentrations above 2 µg/mL are likely, but prevention of primary ventricular fibrillation may require higher concentrations in AMI patients. At concentrations exceeding 6 µg/mL the frequency of CNS toxicity increases.[3] A significant number of patients may require concentrations of 6 to 9 µg/mL for arrhythmia control.[6] The benefits and risks of lidocaine concentrations above 6 µg/mL must be determined carefully.[3]

The time to collect the specimen is determined by the reason for monitoring. If the blood concentration is intended to document an adequate concentration early in therapy, the specimen should be collected 30 minutes after the loading dose, or 5 to 7 hours after therapy is initiated if no loading dose is given.[7]

Lidocaine metabolites may contribute to toxicity in patients receiving prolonged (>24 hours) infusions or in patients with renal insufficiency.[3] Lidocaine is 60 to 80% bound to plasma proteins. Of the fraction bound, approximately 70% is associated with alpha-1-acidglycoprotein (AAGP) and 30% with albumin.[8] AAGP concentrations have been reported to increase twofold by the third post-bypass day.[8] Plasma concentrations of AAGP have been reported higher in patients receiving phenytoin, carbamazepine, primidone and phenytoin plus phenobarbital. Females receiving estrogen-progestogen oral contraceptives have lower AAGP concentrations and higher free lidocaine concentrations.[3] Cardiopulmonary bypass patients receive very large doses of heparin. Heparin releases lipoprotein lipase from tissues, which in turn increases free fatty acids and alters free lidocaine concentrations.[8] Therapeutic concentrations of quinidine and disopyramide significantly increases the concentrations of free lidocaine.[3]

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 Characteristics

Representative performance results obtained on a commercially available automated clinical chemistry analyzer that employs turbidimetric quantitative analysis are shown below.

Sensitivity

Limit of Quantitation (LOQ)

The LOQ of the QMS Lidocaine assay is defined as the lowest concentration for which acceptable inter-assay precision and recovery is observed (≤20% CV with ±10% recovery). The LOQ was determined to be 0.8 µg/mL.

Assay Range

The range of the assay is 0.8 to 10 µg/mL. Report results below this range as <0.8 µg/mL.

Linearity

Linearity by Dilution

A commercially available calibrator (10.0 µg/mL) was diluted with a commercially available "zero" calibrator (0 µg/mL) to achieve samples with concentrations at 80, 60, 40, and 20% of the 10 µg/mL calibrator. Samples were run in duplicate using QMS Lidocaine reagents. The results are shown below.

Theoretical Concentration (µg/mL)	Rep 1	Rep 2	Mean Recovered Concentration	% Recovery
2	1.88	1.86	1.87	93.5
4	3.81	3.64	3.73	93.3
6	5.66	5.74	5.70	95.0
8	7.68	8.18	7.93	99.1
10	9.28	9.49	9.39	93.9

Mean Percent Recovery 95.0

Method Comparison

A study was conducted to compare accuracy of recovery of lidocaine in serum and plasma samples ranging from 0.4 to 9.1 µg/mL assayed by the QMS Lidocaine assay to that of a commercially available FPIA immunoassay.

Results of the Passing-Bablok[9] regression analysis for the study are shown below.

Slope	1.076 (1.044 to 1.104)
Y-Intercept	-0.096 (-0.153 to -0.024)
Correlation Coefficient (R^2)	0.986
Number of Samples	52

Precision

Precision was determined as described in CLSI (NCCLS) Protocol EP5-A2.[10]

A tri-level human serum based commercially available control set containing lidocaine was used in the study. Each level of control was assayed in duplicate twice a day for 20 days on one analyzer, by one operator using one reagent and calibrator lot. Calibration was performed initially and at day 10 of the study. Each of the runs per day was separated by at least two hours. The means were calculated and the between day, within run, total SD, and percent CVs were calculated. Results are shown below.

			Within Run		Between Day		Total	
Control	N	Mean (µg/mL)	SD	CV (%)	SD	CV (%)	SD	CV (%)
1	80	1.76	0.10	5.66	0.10	5.41	0.14	8.13
2	80	4.42	0.15	3.48	0.11	2.44	0.22	5.06
3	80	8.83	0.24	2.73	0.19	2.17	0.46	5.27

Acceptance Criteria of <10% total CV

Interfering Substances

The following compounds, when tested with the QMS Lidocaine assay at the concentrations indicated, resulted in less than 10% error in detecting lidocaine.

Interfering Substance	Interferent Concentration	n	Lidocaine (µg/mL)	Percent Recovery
Bilirubin	15 mg/dL	2	7.3	91.4
Hemoglobin	10 g/dL	2	5.3	102.0
HAMA type 1*	Normal human level	2	4.4	92.0
HAMA type 2*	Normal human level	2	4.4	92.0
Triglyceride	2000 mg/dL	3	5.2	97.8
Rheumatoid Factor	1500 IU/mL	3	5.2	98.5
Total Protein	2-12 g/dL	3	6.9	103

*HAMA = human anti-mouse antibodies

Metabolite Cross-Reactivity

The two major metabolites of lidocaine were tested for cross-reactivity. Results are shown below.

	Metabolite Concentration (µg/mL)	Lidocaine Concentration (µg/mL)	% Cross-Reactivity
GX	10	4.0	0.8
MEGX	100	4.9	0.8

Drug Interference

Cross-reactivity was tested with drugs that are routinely administered with lidocaine. Testing also determined whether these compounds affect the quantitation of lidocaine concentrations using the QMS Lidocaine assay. Cross-reactants were analyzed in a lidocaine spiked serum pool at 5 µg/mL. The samples were assayed and the lidocaine concentrations of spiked samples were compared to a control serum. Results are shown below.

Compound	Concentration Tested (µg/mL)	% Cross-Reactivity
Mepivacaine	10	63
Bupivacaine	40	20
Acetaminophen	200	ND
Acetyl cysteine	1660	ND
Acetylsalycilic acid	650	ND
Ampicillin-Na	53	ND
Ascorbic Acid	60	ND
Cefoxitin	660	ND
Cyclosporine	0.5	ND
Digoxin	0.01	ND
Disopyramide	10	ND
d-Methamphetamine	10	ND
Ephedrine	0.1	ND
Flecainide	10	ND
Furosemide	60	ND
Hydrochlorothiazide	6	ND
Ibuprofen	500	ND
Isoproterenol	0.01	ND
Levodopa	80	ND
Lidocaine-N-ethyl Bromide	100	ND
Methylodopa+1,5	15	ND
Metronidazole	120	ND
Mexiletine	100	ND
Phenybutazone	100	ND
Phenytoin (DPH)	50	ND
PPX (L-Pipecolicacid-2,6-xylidide)	10	3.4
Procainamide	24	ND
Propanolol	2.0	ND
Quinidine	12	ND
Rifampicin	64	ND
Tetracycline	15	ND
Theophylline	40	ND
Tocainide	100	1.0

ND = Not Detectable

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