AMIK2

cobas®

ONLINE TDM Amikacin

Order information

REF		CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
08105383190	08105383500	ONLINE TDM Amikacin (200 tests)	System-ID 2015 001	**cobas c** 303, **cobas c** 503, **cobas c** 703

Materials required (but not provided):

03375781190	Preciset TDM II CAL A-F (1 x 5 mL) Diluent (1 x 10 mL)	Codes 20743-20748	
04521536190	TDM Control Set Level I (2 x 5 mL) Level II (2 x 5 mL) Level III (2 x 5 mL)	 Code 20310 Code 20311 Code 20312	

English

System information

AMIK2: ACN 20150

Intended use

In vitro test for the quantitative determination of amikacin in serum and plasma on **cobas c** systems.

Summary

Amikacin measurements performed with this assay, in human serum and plasma, are used for monitoring amikacin treatment to ensure appropriate therapy.

Amikacin is a semisynthetic aminoglycoside antibiotic used in the treatment of serious Gram-negative infections.[1] Like all aminoglycoside antibiotics, amikacin blocks the production of protein by inhibiting messenger RNA translation in the bacterial cells.[1,2] It is excreted unchanged by glomerular filtration by the kidney.[1] For patients with impaired renal function, elderly patients and critically ill patients, serum amikacin concentrations should be monitored by appropriate assay procedures and doses should be adjusted accordingly.[1,2,3,4,5]

Toxicity associated with aminoglycosides manifests as ototoxicity (delayed-onset vestibular or cochlear sensory cell destruction) and nephrotoxicity.[2] The degree and severity of cell damage are variable among the different drugs, but they all cause cell damage if the concentrations are high.[2]

Amikacin therapeutic drug monitoring is recommended by manufacturers and guidelines to maximize the efficacy of aminoglycosides and reduce incidences of drug toxicity.[1,3,6,7,8]

Test principle

Kinetic interaction of microparticles in solution (KIMS) as measured by changes in light transmission.

The assay is a homogeneous immunoassay based on the principle of measuring changes in scattered light or absorbance which result when activated microparticles aggregate. The microparticles are coated with amikacin and rapidly aggregate in the presence of an amikacin antibody solution. When a sample containing amikacin is introduced, the aggregation reaction is partially inhibited, slowing the rate of the aggregation process. Antibody bound to sample drug is no longer available to promote microparticle aggregation, and subsequent particle lattice formation is inhibited. Thus, a classic inhibition curve with respect to amikacin concentration is obtained, with the maximum rate of aggregation at the lowest amikacin concentration. By monitoring the change in scattered light or absorbance, a concentration-dependent curve is obtained.

Reagents - working solutions

R1 Anti-amikacin antibody (mouse monoclonal) and human-sourced material in buffer with preservative

R3 Conjugated amikacin derivative microparticles, human-sourced material, and preservative

R1 is in position B and R3 is in position C.

Precautions and warnings

For in vitro diagnostic use for health care professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste:
Warning: handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards:
Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

Product safety labeling follows EU GHS guidance.

All human material should be considered potentially infectious. All products derived from human blood are prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg and antibodies to HCV and HIV. The testing methods use assays that have been approved or cleared by the FDA or that are in compliance with the legal rules of the European Union (IVDR 2017/746/EU, IVDD 98/79/EC, Annex II, List A). However, as no testing method can rule out the potential risk of infection with absolute certainty, the material should be handled with the same level of care as a patient specimen. In the event of exposure, the directives of the responsible health authorities should be followed.[9,10]

Reagent handling

Ready for use

Carefully invert reagent container several times prior to use to ensure that the reagent components are mixed.

Storage and stability

Shelf life at 2-8 °C:	See expiration date on **cobas c** pack label
On-board in use and refrigerated on the analyzer:	26 weeks

Do not freeze.

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.
Serum: Collect serum using standard sampling tubes.
Plasma: K_2- or K_3-EDTA or Na or Li heparin plasma.

Stability:	8 hours capped at 15-25 °C
	48 hours capped at 2-8 °C
	4 weeks capped at -20 °C (± 5° C)

Freeze only once.

Do not induce foaming of specimens.

Invert thawed specimens several times prior to testing.

Centrifuge samples containing precipitates before performing the assay.

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.

See the limitations and interferences section for details about possible sample interferences.

Usual sampling time varies dependent upon desired measurement of peak or trough values.[11]

Materials provided

See "Reagents – working solutions" section for reagents.

Materials required (but not provided)

See "Order information" section

General laboratory equipment

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.

The performance of applications not validated by Roche is not warranted and must be defined by the user.

Application for serum and plasma

Test definition

Reporting time	10 min		
Wavelength (sub/main)	– /700 nm		
Reagent pipetting		Diluent (H_2O)	
R1	84 µL	–	
R3	25 µL	–	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (H_2O)*
Normal	1.0 µL	–	–
Decreased	1.0 µL	–	–
Increased	1.0 µL	–	–

For further information about the assay test definitions refer to the application parameters setting screen of the corresponding analyzer and assay.

Calibration

Calibrators (full calibration)	S1-6: Preciset TDM II calibrators
Calibrators (2-point calibration)	S2: Preciset TDM II-B S6: Preciset TDM II-F
Calibration mode	Non-linear
Calibration frequency **cobas c** 303 and **cobas c** 703 analyzers	2-point calibration - every 4 days on-board Full calibration - after reagent lot change - every 6 weeks during shelf life - as required following quality control procedures
Calibration frequency **cobas c** 503 analyzer	2-point calibration - every 14 days on-board Full calibration - after reagent lot change - every 6 weeks during shelf life - as required following quality control procedures

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Traceability: This method has been standardized against USP reference standards. The calibrators are prepared to contain known quantities of amikacin in normal human serum.

Quality control

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. It is recommended to perform quality control always after lot calibration and subsequently at least every 26 weeks.

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.

Calculation

cobas c systems automatically calculate the analyte concentration of each sample in the unit µg/mL (µmol/L, mg/L).

Conversion factors:[12] µg/mL x 1.71 = µmol/L

Limitations - interference

Criterion: Recovery within ± 10 % of initial value at amikacin levels of approximately 5.0 and 30 µg/mL (8.6 and 51.3 µmol/L).

Icterus:[13] No significant interference up to an I index of 50 for conjugated bilirubin and unconjugated bilirubin (approximate conjugated and unconjugated bilirubin concentration: 50 mg/dL or 855 µmol/L).

Hemolysis:[13] No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 1000 mg/dL or 621 µmol/L).

Lipemia (Intralipid):[13] No significant interference up to an L index of 2000. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Triglycerides: No significant interference from triglycerides up to a concentration of 800 mg/dL (9.0 mmol/L).

Rheumatoid factors: No significant interference from rheumatoid factors up to a concentration of 100 IU/mL.

Total protein: No significant interference from total protein in the concentration range of 2-12 g/dL.

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[14]

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 c** systems. All special wash programming necessary for avoiding carry-over is available via the **cobas** link. The latest version of the carry-over evasion list can be found with the NaOHD/SMS/SCCS Method Sheet. For further instructions, refer to the operator's manual.

Limits and ranges

Measuring range

0.8-40 µg/mL (1.4-68.4 µmol/L)

Manually dilute samples above the measuring range 1 + 1 with the Preciset TDM II Diluent (0 µg/mL) and reassay. Multiply the result by 2 to obtain the specimen value.

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank	= 0.8 µg/mL (1.4 µmol/L)
Limit of Detection	= 0.8 µg/mL (1.4 µmol/L)
Limit of Quantitation	= 1.2 µg/mL (2.05 µmol/L)

The Limit of Blank, Limit of Detection and Limit of Quantitation were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17-A2 requirements.

The Limit of Blank is the 95th percentile value from n ≥ 60 measurements of analyte-free samples over several independent series. The Limit of Blank corresponds to the concentration below which analyte-free samples are found with a probability of 95 %.

The Limit of Detection is determined based on the Limit of Blank and the standard deviation of low concentration samples.

The Limit of Detection corresponds to the lowest analyte concentration which can be detected (value above the Limit of Blank with a probability of 95 %).

The Limit of Quantitation is the lowest analyte concentration that can be reproducibly measured with a total error of 20 %. It has been determined using low concentration amikacin samples.

Expected values

Although optimum values may vary, peak serum values of amikacin in the range of 20 to 25 µg/mL (34.2 to 42.8 µmol/L) and trough values in the range of 5 to 10 µg/mL (8.6 to 17.1 µmol/L) are generally accepted for therapeutic effectiveness. Toxicity is associated with peak levels greater than 35 µg/mL (59.9 µmol/L) and trough values greater than 10 µg/mL (17.1 µmol/L).[15] The most serious toxic effect is permanent damage to the vestibular division of the eighth cranial nerve, which has been reported to occur most frequently in patients with renal failure. Since amikacin is inherently stable, is not metabolized, and is excreted primarily by glomerular filtration, the presence of renal impairment drastically alters its pharmacokinetics. If dosage regimens are not adjusted, excess accumulation leading to ototoxicity and further renal impairment could be encountered.[16,17,18,19] While serum levels can be toxic, indiscriminately low dosages of amikacin will result in ineffective treatment for many strains of gram-negative bacteria. Organisms which are resistant to amikacin will often show increased resistance to all other available aminoglycosides. This observation[20] points out the possibility that the indiscriminate use of low dosages of amikacin could engender the emergence of drug-resistant organisms and possibly render the drug ineffective in treating infectious disease.[21,22]

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

Expected values reflect the data and information provided in the reference and do not necessarily represent therapeutic recommendations and/or dosage instructions. For therapeutic recommendations and dosage instructions refer to applicable guidelines and the full prescription information of the drug.

Specific performance data

Representative performance data on the analyzers are given below. These data represent the performance of the analytical procedure itself.

Results obtained in individual laboratories may differ due to heterogenous sample materials, aging of analyzer components and mixture of reagents running on the analyzer.

Precision

Precision was determined using human samples and controls in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP05-A3 requirements with repeatability (n = 84) and intermediate precision (2 aliquots per run, 2 runs per day, 21 days). Results for repeatability and intermediate precision were obtained on the **cobas c** 503 analyzer.

Repeatability	*Mean* µg/mL	*SD* µg/mL	*CV* %
TDMC1[a)]	5.14	0.152	2.9
TDMC2[b)]	14.5	0.203	1.4
TDMC3[c)]	27.4	0.694	2.5
Human serum 1	2.18	0.147	6.8
Human serum 2	10.7	0.159	1.5
Human serum 3	20.1	0.231	1.1
Human serum 4	24.2	0.283	1.2
Human serum 5	35.4	0.549	1.6

Intermediate precision	*Mean* µg/mL	*SD* µg/mL	*CV* %
TDMC1[a)]	5.14	0.215	4.2
TDMC2[b)]	14.4	0.252	1.7
TDMC3[c)]	27.4	0.694	2.5
Human serum 1	1.96	0.223	11.4
Human serum 2	10.7	0.220	2.0
Human serum 3	20.2	0.289	1.4
Human serum 4	24.2	0.331	1.4
Human serum 5	35.4	0.589	1.7

a) TDM Control Set Level I
b) TDM Control Set Level II
c) TDM Control Set Level III

The data obtained on **cobas c** 503 analyzer(s) are representative for **cobas c** 303 analyzer(s) and **cobas c** 703 analyzer(s).

Method comparison

Amikacin values for human serum and plasma samples obtained on a **cobas c** 503 analyzer (y) were compared with those determined using the corresponding reagent on a **cobas c** 501 analyzer (x).

Sample size (n) = 75

Passing/Bablok[23]	Linear regression
y = 0.975x + 0.209 µg/mL	y = 0.991x + 0.0137 µg/mL
τ = 0.965	r = 0.997

The sample concentrations were between 1.20 and 37.5 µg/mL.

Amikacin values for human serum and plasma samples obtained on a **cobas c** 303 analyzer (y) were compared with those determined using the corresponding reagent on a **cobas c** 501 analyzer (x).

Sample size (n) = 75

Passing/Bablok[23]	Linear regression
y = 0.967x + 0.110 µg/mL	y = 0.978x - 0.0391 µg/mL
τ = 0.981	r = 0.998

The sample concentrations were between 1.30 and 37.2 µg/mL.

Amikacin values for human serum and plasma samples obtained on a **cobas c** 703 analyzer (y) were compared with those determined using the corresponding reagent on a **cobas c** 503 analyzer (x).

Sample size (n) = 74

Passing/Bablok[23]	Linear regression
y = 0.972x + 0.0175 µg/mL	y = 0.974x - 0.0517 µg/mL
τ = 0.975	r = 0.999

The sample concentrations were between 0.995 and 37.1 µg/mL.

Analytical specificity

The following compounds were tested for cross-reactivity.

Compound	**Concentration tested (µg/mL)**	**% cross-reactivity**
Amphotericin	20	ND
Ampicillin	90	ND
Carbenicillin	500	ND
Cephalexin	500	ND
Cephalosporin C	500	ND
Cephalothin	60	ND
Chloramphenicol	300	ND
Clindamycin	5	ND
Erythromycin	200	ND
Ethacrynic acid	500	ND
5-Fluorocytosine	700	ND
Furosemide	100	ND
Fusidic acid	500	ND

Gentamicin	100	ND
Kanamycin A	25	ND
Kanamycin B	25	ND
Lincomycin	30	ND
Methotrexate	23	ND
Methylprednisolone	500	ND
Neomycin	100	ND
Netilmycin	80	ND
Oxytetracycline	40	ND
Penicillin V	50	ND
Prednisolone	500	ND
Rifampin	320	ND
Spectinomycin	200	ND
Streptomycin	200	ND
Sulfadiazine	1500	ND
Sulfamethoxazole	2000	ND
Tetracycline	40	ND
Tobramycin	100	ND
Trimethoprim	120	ND
Vancomycin	400	ND

ND = Not detectable

Tests were performed on 16 drugs. No significant interference with the assay was found.

Acetaminophen	Doxycycline
Acetyl cysteine	Ibuprofen
Acetylsalicylic acid	Levodopa
Ampicillin-Na	Methyldopa + 1.5 H_2O
Ascorbic acid	Metronidazole
Ca-Dobesilate	Phenylbutazone
Cefoxitin	Rifampicin
Cyclosporine	Theophylline

References

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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.

Any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.

The Summary of Safety & Performance Report can be found here: https://ec.europa.eu/tools/eudamed

Symbols

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

CONTENT	Contents of kit

AMIK2

ONLINE TDM Amikacin

→	Volume for reconstitution
GTIN	Global Trade Item Number
Rx only	For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

CE 0123

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