THEO2

cobas®

ONLINE TDM Theophylline

Order information

REF	CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
04491025 190	ONLINE TDM Theophylline 100 tests	System-ID 07 6927 4	Roche/Hitachi **cobas c** 501/502

Materials required (but not provided):

03375790 190	Preciset TDM I calibrators CAL A-F (1 x 5 mL) Diluent (1 x 10 mL)	Codes 691-696	
04521536 190	TDM Control Set Level I (2 x 5 mL) Level II (2 x 5 mL) Level III (2 x 5 mL)	 Code 310 Code 311 Code 312	

English

System information

For **cobas c** 501 analyzer:

THEO2: ACN 415

For **cobas c** 502 analyzer:

THEO2: ACN 8415

Intended use

In vitro test for the quantitative determination of theophylline in serum and plasma on Roche/Hitachi **cobas c** systems.

Summary

Theophylline (1,3-dimethylxanthine), a bronchodilator, is widely used to treat patients with asthma, apnea (temporary asphyxia), and other obstructive lung diseases.

Monitoring of theophylline concentrations in serum is essential, since individuals can vary in their rates of theophylline clearance,[1,2] and severe toxicity has been observed without prior occurrence of minor side effects.[3] Moreover, several factors can alter theophylline elimination. Theophylline elimination is slowed in obese patients, patients with hepatic disease, and in those on a high carbohydrate, low protein diet. Premature infants have very low rates of theophylline elimination.[4] Conversely, theophylline elimination is more rapid among cigarette smokers.[5] In combination with other clinical data, monitoring serum theophylline levels may provide the physician with useful information to aid in adjusting patient dosage to achieve optimal therapeutic effect while avoiding drug toxicity.

Test principle

The assay is based on the kinetic interaction of microparticles in a solution (KIMS). Theophylline antibody is covalently coupled to microparticles and the drug derivative is linked to a macromolecule. The kinetic interaction of microparticles in solutions is induced by binding of drug-conjugate to the antibody on the microparticles and is inhibited by the presence of theophylline in the sample. A competitive reaction takes place between the drug conjugate and theophylline in the serum sample for binding to the theophylline antibody on the microparticles. The resulting kinetic interaction of microparticles is indirectly proportional to the amount of drug present in the sample.

Reagents - working solutions

R1 Theophylline conjugate; piperazine-N,N'-bis (ethanesulfonic acid) (PIPES) buffer, pH 7.2; preservative

R2 Anti-theophylline antibody (mouse monoclonal); latex microparticle; 3-(N-morpholino) propane sulfonic acid (MOPS) buffer, pH 7.5; stabilizer; preservative

R1 is in position B and R2 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.

For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

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:	12 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, sodium citrate, or sodium, lithium or ammonium heparin plasma.

Stability:[6]	1 week capped at 2-8 °C
	60 days capped at -20 °C

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 not be repeatedly frozen and thawed.

Invert thawed specimens several times prior to testing.

Usual sampling time varies dependent upon desired measurement of peak or trough values.[7]

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

Deselect Automatic Rerun for these applications in the Utility menu, Application screen, Range tab.

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cobas c 501/502 **test definition**

Assay type	2-Point End		
Reaction time /Assay points	10 / 15-49		
Wavelength (sub/main)	800/600 nm		
Reaction direction	Increase		
Unit	µg/mL		
Reagent pipetting		Diluent (H_2O)	
R1	97 µL	–	
R2	92 µL	–	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	2.0 µL	–	–
Decreased	2.0 µL	–	–
Increased	2.0 µL	–	–

Calibration

Calibrators	S1-6: Preciset TDM I calibrators
Calibration mode	RCM
Calibration frequency	6-point calibration • after reagent lot change • every 6 weeks • 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.[8] The calibrators are prepared to contain known quantities of theophylline 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. 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

Roche/Hitachi **cobas c** systems automatically calculate the analyte concentration of each sample.

Conversion factor:[9] µg/mL x 5.55 = µmol/L

Limitations - interference

Criterion: Recovery within ± 10 % of initial value at theophylline levels of approximately 5 and 15 µg/mL (27.8 and 83.3 µmol/L).

Serum/Plasma

Icterus:[10] 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:[10] No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 1000 mg/dL or 621 µmol/L).

Lipemia (Intralipid):[10] No significant interference up to an L index of 300. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

No significant interference from triglycerides up to 1000 mg/dL (11.3 mmol/L).

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

Total protein: No interference from total protein up to 12 g/dL.

Theobromine: No significant interference up to 49 µg/mL theobromine. Concentrations above this toxic level may result in negative bias of > 10 %.

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[11]

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 Roche/Hitachi **cobas c** systems. The latest version of the carry-over evasion list can be found with the NaOHD-SMS-SmpCln1+2-SCCS Method Sheets. For further instructions refer to the operator's manual. **cobas c** 502 analyzer: All special wash programming necessary for avoiding carry-over is available via the **cobas** link, manual input is not required.

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

Limits and ranges

Measuring range

0.8-40.0 µg/mL (4.4-222 µmol/L)

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

Lower limits of measurement

Lower detection limit of the test

0.8 µg/mL (4.4 µmol/L)

The lower detection limit represents the lowest measurable analyte level that can be distinguished from zero. It is calculated as the value lying 2 standard deviations above that of the 0 µg/mL calibrator (standard 1 + 2 SD, repeatability, n = 21).

Expected values

Various methodologies have been used to evaluate theophylline preparations and routes of administration,[12] to study pharmacokinetics of the drug,[13] and to define the relationship between serum concentration and the drug's therapeutic and toxic effects.[14] For most patients, the range of 10 to 20 µg/mL (55.5 to 111 µmol/L) suppresses chronic asthmatic symptoms.[15,16,17,18] Wide discrepancies between drug dosage and serum concentrations were observed among patients.[12,15] A major factor accounting for the variability is individual variation in the rate of theophylline metabolism and elimination.

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 analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using human samples and controls in a modified NCCLS EP5-T2 protocol (repeatability n = 63, intermediate precision n = 63). The following results were obtained on a Roche/Hitachi **cobas c** 501 analyzer.

Serum/Plasma

Repeatability	*Mean*		*SD*		*CV*
	µg/mL	*µmol/L*	*µg/mL*	*µmol/L*	*%*
Control 1	4.25	23.6	0.07	0.4	1.7
Control 2	14.3	79.4	0.2	1.1	1.3
Control 3	34.1	189	0.4	2	1.2
HS 1	5.78	32.1	0.08	0.4	1.4
HS 2	20.0	111	0.3	2	1.4
Intermediate precision	*Mean*		*SD*		*CV*
	µg/mL	*µmol/L*	*µg/mL*	*µmol/L*	*%*

Control 1	4.25	23.6	0.12	0.7	2.8
Control 2	14.3	79.4	0.2	1.1	1.7
Control 3	34.1	189	0.6	3	1.9
HS 1	5.78	32.1	0.12	0.7	2.1
HS 2	20.0	111	0.4	2	1.8

Method comparison

Serum/plasma

Theophylline values for human serum and plasma samples obtained on a Roche/Hitachi **cobas c** 501 analyzer (y) were compared with those determined using the corresponding reagent on a Roche/Hitachi 917 analyzer (x) and on a COBAS INTEGRA 800 analyzer (x).

Roche/Hitachi 917 analyzer	Sample size (n) = 72
Passing/Bablok[19]	Linear regression
y = 0.975x + 0.136 µg/mL	y = 0.982x + 0.032 µg/mL
τ = 0.985	r = 0.999

The sample concentrations were between 3.98 and 39.0 µg/mL (22.1 and 217 µmol/L).

COBAS INTEGRA 800 analyzer	Sample size (n) = 72
Passing/Bablok[19]	Linear regression
y = 1.017x + 0.091 µg/mL	y = 1.013x + 0.143 µg/mL
τ = 0.981	r = 0.999

The sample concentrations were between 3.71 and 39.0 µg/mL (20.6 and 217 µmol/L).

Analytical specificity

The following compounds were tested for cross-reactivity.

Compound	Concentration Tested (µg/mL)	% Cross-reactivity
Aminophylline	15	79.6
8-Chlorotheophylline	200	5.97
1,7-Dimethylxanthine	150	5.24
3-Methylxanthine	150	2.73
Ephedrine	12	1.00
Acetaminophen	200	< 1.0
Allopurinol	50	< 1.0
Caffeine	150	< 1.0
Dihydroxypropyl theophylline	200	< 1.0
Diphenhydramine	10	< 1.0
Epinephrine	16	< 1.0
β-Hydroxyethyl theophylline	200	< 1.0
7-β-Hydroxypropyl theophylline	200	< 1.0
Hypoxanthine	150	< 1.0
Isoproterenol	50	< 1.0
1-Methyluric acid	400	< 1.0
Phenobarbital	200	< 1.0
Phenylbutazone	400	< 1.0
Uric acid	210	< 1.0
1,3-Dimethyluric acid	700	< 0.1
Phenytoin	200	< 0.1

Tests were performed on 15 drugs. No significant interference with the assay was found.

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

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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 (for USA: see dialog.roche.com for definition of symbols used):

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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