J Lab Med 2008;32(5):372–381 © 2008 by Walter de Gruyter • Berlin • New York. DOI 10.1515/JLM.2008.047

Monographs on drugs which are frequently analyzed in therapeutic drug monitoring

Arzneimittel-Monographien für Medikamente, die regelmäßig im Rahmen des Therapeutic Drug Monitorings analysiert werden

Working group "Drug Monitoring" of the SSCC: Katharina Rentsch[1,*], Chin Bin Eap[2], Marc Fathi[3], Nathalie Grignaschi[4], Jean-Luc Magnin[5], Wolfgang Thormann[6], Liliane Todesco[4] and Dominique Werner[2]

[1] University Hospital Zurich, Zurich, Switzerland
[2] University Hospital Lausanne, Lausanne, Switzerland
[3] University Hospital Geneva, Geneva, Switzerland
[4] University Hospital Basle, Basle, Switzerland
[5] Kantonsspital Freiburg, Freiburg, Switzerland
[6] University of Berne, Berne, Switzerland

Abstract

In addition to the monographs which have been published recently by the working group "Drug Monitoring" of the Swiss Society of Clinical Chemistry (SSCC) [1, 2], new monographs have been written. The aim of these monographs is to provide an overview on the information which is important for the request and interpretation of the results. Therefore, the targeted readers are laboratory health professionals and the receivers of the reports. In this series, aminoglycoside as well as glycopeptide antibiotics are presented. In addition, two antimycotic drugs, which are regularly quantified in sera of intensive care patients, are described. Also, the monograph on mebendazole is shown. This drug is often used in high doses for the treatment of infections with *Echinococcus multilocularis* for which the measurement of drug concentrations in serum is recommended. Information on the indication for therapeutic drug monitoring (TDM), protein binding, metabolic pathways and enzymes involved, elimination half-life and elimination routes, and therapeutic or toxic concentrations is provided. Because pre-analytical considerations are of particular importance for therapeutic drug monitoring, there is also information given at which time the determination of the drug concentration is reasonable and when steady-state concentrations are reached after changing the dose. Furthermore, the stability of the drug and its metabolite(s) after blood sampling is described. For readers with a specific interest, references to important publications are provided. The number of the monographs will be continuously increased. The updated files are presented on the homepage of the SSCC (www.sscc.ch). We hope that these monographs are helpful for the better handling of therapeutic drug monitoring and we are looking forward to comments by the readers.

Keywords: amikacin; gentamicin; itraconazole; mebendazole; netilmicin; teicoplanin; tobramycin; vancomycin; voriconazole.

*Correspondence: Dr. Katharina Rentsch, Universitätsspital Zürich, Institut für Klinische Chemie, Rämistraße 100, CH-8091 Zürich, Switzerland
Tel.: +41 (044) 2552290
Fax: +41 (044) 2554590
E-Mail: rentsch@ikc.uzh.ch

Zusammenfassung

In Ergänzung zu den in den letzten Jahren publizierten Arzneimittelmonographien der Arbeitsgruppe Medikamente der Schweizerischen Gesellschaft für Klinische Chemie (SGKC) [1, 2], sind nun weitere Monographien erstellt worden. Ziel dieser Monographien ist es, dem Labormediziner bzw. dem Empfänger der Befunde eine Übersicht über die wichtigsten Informationen zu geben, die für die Veranlassung einer Analyse bzw. für die Interpretation der Resultate hilfreich sind. In dieser Serie werden die Aminoglykosid- und Glykopeptidantibiotika präsentiert, wie auch zwei Antimykotika, bei denen vor allem bei Intensivpatienten immer häufiger Messungen im Serum durchgeführt werden. Zusätzlich wird die Monographie von Mebendazol präsentiert, das im Rahmen der Infektionen mit *Echinococcus multilocularis* (Fuchsbandwurm) in hohen Dosen verabreicht und im Serum bestimmt wird. In den einzelnen Monographien werden klinisch pharmakologische Angaben wie zum Beispiel Indikation für das Therapeutic Drug Monitoring (TDM), Proteinbindungen, Metabolisierungswege und daran beteiligte Enzyme, Halbwertszeiten und Eliminationswege der Muttersubstanz, sowie Informationen zu therapeutischen bzw. toxischen Bereichen, zur Verfügung gestellt. Da die Präanalytik gerade beim Therapeutic Drug Monitoring eine wichtige Rolle spielt werden auch hier Angaben gemacht zu welchem Zeitpunkt eine Bestimmung der Arzneimittelkonzentration sinnvoll ist und wann, nach einer Dosisänderung, der steady-state erreicht ist. Außerdem werden Angaben über die Stabilität der Medikamente bzw. ihrer Metaboliten nach der

Blutentnahme gemacht. Für die interessierten Leser sind die verwendeten Referenzen als Zitate aufgeführt. Die Zahl der Monographien wird fortlaufend ergänzt. Die aktuellsten Versionen der Monographien sind auf der Homepage der SGKC abrufbar (www.sscc.ch). Wir hoffen, dass diese Monographien im Umgang mit dem Therapeutic Drug Monitoring hilfreich sein werden und freuen uns über Kommentare und Bemerkungen.

Schlüsselwörter: Amikacin; Gentamicin; Itraconazol; Mebendazol; Netilmicin; Teicoplanin; Tobramycin; Vancomycin; Voriconazol.

Amikacin

General	
• Class of the drug	Aminoglycoside antibiotics
• Synonym(s)	–
• Common trade name(s) in Germany	Biklin®
• Conversion factors	mg/L × 1.71 = μmol/L μmol/L × 0.58 = mg/L
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, suspicion of toxicity, side effects
• Protein binding	4–11% (albumin)
• Elimination half-life	1–4 h Neonates/infants: 3–8 h (see remarks)
• Volume of distribution	0.3–0.4 L/kg
• Metabolism	
Main metabolic pathways	No metabolism
Active metabolite(s)?	None
Inhibitor or inducer of the cytochrome P450 system?	No
Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Renal 100%
• Typical therapeutic range	Multiple dosing Peak concentration: 20–30 mg/L (34–51 μmol/L) Trough concentration: ≤7 mg/L (≤12 μmol/L) Once-daily dosing Trough concentration: ≤1.5 mg/L (≤2.6 μmol/L)
• Potentially toxic concentration	Multiple dosing Peak concentration: >35 mg/L (>60 μmol/L) Trough concentration: >10 mg/L (>17 μmol/L) Once-daily dosing Trough concentration: >1.5 mg/L (>2.6 μmol/L)
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	Steady-state is generally achieved after 3 doses for multiple dosing
• Time for blood sampling	Peak: 1 h after beginning of infusion Trough: within 30 min of next dose Once-daily dosing: trough level only
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C When combined therapy with penicillins and/or cephalosporins: in vitro inactivation → freeze sample
Remarks	• Elimination is strongly dependent on renal function • Avoid gel tubes if possible, unless having confirmed that no binding occurs
References	• Arzneimittelkompendium Schweiz. Basel: Documed 2005 • Schweizerische Gesellschaft für Klinische Pharmakologie und Toxikologie, Grundlagen der Arzneimitteltherapie (16. Auflage). Basel: Documed, 2005 • Taylor WJ, Diers Caviness MH. A textbook for the clinical application of therapeutic drug monitoring. Irving, TX: Abbott Laboratories, 1986 • Thomson Micromedex® Healthcare series • Begg EJ, Barclay ML. Aminoglycosides – 50 years on. Br J Clin Pharm 1995;39:597–603 • Schulz M, Schmoldt A. Therapeutic and toxic blood concentrations of more than 800 drugs and other xenobiotics. Pharmazie 2003;58:447–74 • Touw DJ, Neef C, Thomson AH, Vinks AA. Cost-effectiveness of therapeutic drug monitoring committee of the international association for therapeutic drug monitoring and clinical toxicology. Ther Drug Monit 2005;27:10–7

Gentamicin

General	
• Class of the drug	Aminoglycoside antibiotics
• Synonym(s)	–
• Common trade name(s) in Germany	Refobacin®
• Conversion factors	mg/L × 2.1 = μmol/L (mean) μmol/L × 0.48 = mg/L (mean)
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, suspicion of toxicity, side effects
• Protein binding	0–30% (albumin)
• Elimination half-life	1–3 h Neonates/infants: 3–8 h (see remarks)
• Volume of distribution	0.3 L/kg
• Metabolism	
Main metabolic pathways	No metabolism
Active metabolite(s)?	None
Inhibitor or inducer of the cytochrome P450 system?	No
Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Renal 100%
• Typical therapeutic range	Multiple dosing Peak concentration: 6–10 mg/L (13–21 μmol/L) Trough concentration: ≤1 mg/L (≤2.1 μmol/L) Once-daily dosing Trough concentration: ≤0.5 mg/L (≤1.1 μmol/L)
• Potentially toxic concentration	Multiple dosing Peak concentration: >12 mg/L (>25 μmol/L) Trough concentration: >2 mg/L (>4 μmol/L) Once-daily dosing Trough concentration: >0.5 mg/L (>1.1 μmol/L)
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	Steady-state is generally achieved after 3 doses for multiple dosing
• Time for blood sampling	Peak: 1 h after beginning of infusion Trough: within 30 min of next dose Once-daily dosing: trough level only
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C When combined therapy with penicillins and/or cephalosporins: in vitro inactivation → freeze sample
Remarks	• Elimination is strongly dependent on renal function • Avoid gel tubes if possible, unless having confirmed that no binding occurs
References	• Arzneimittelkompendium Schweiz. Basel: Documed 2005 • Schweizerische Gesellschaft für Klinische Pharmakologie und Toxikologie, Grundlagen der Arzneimitteltherapie (16. Auflage). Basel: Documed, 2005 • Taylor WJ, Diers Caviness MH. A textbook for the clinical application of therapeutic drug monitoring. Irving, TX: Abbott Laboratories, 1986 • Thomson Micromedex® Healthcare series • Begg EJ, Barclay ML, Duffull SB. A suggested approach to once-daily aminoglycoside dosing. Br J Clin Pharm 1995;39:605–9 • Modi N, Maggs AF, Clarke C, Chapman C, Swann RA. Gentamicin concentration and toxicity. Lancet 1998;352:70 • Touw DJ, Neef C, Thomson AH, Vinks AA. Cost-effectiveness of therapeutic drug monitoring committee of the international association for therapeutic drug monitoring and clinical toxicology. Ther Drug Monit 2005;27:10–7

Netilmicin

General	
• Class of the drug	Aminoglycoside antibiotics
• Synonym(s)	–
• Common trade name(s) in Germany	Certomycin®
• Conversion factors	mg/L × 2.1 = μmol/L μmol/L × 0.476 = mg/L
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, suspicion of toxicity, side effects
• Protein binding	0–30% (albumin)
• Elimination half-life	1–3 h Neonates: 3–8 h (see remarks)
• Volume of distribution	0.3 L/kg
• Metabolism	
Main metabolic pathways	No metabolism
Active metabolite(s)?	None
Inhibitor or inducer of the cytochrome P450 system?	No
Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Renal 100%
• Typical therapeutic range	Multiple dosing Peak concentration: 6–10 mg/L (13–21 μmol/L) Trough concentration: ≤1 mg/L (≤2.1 μmol/L) Once-daily dosing Trough concentration: <0.5 mg/L (<1.1 μmol/L)
• Potentially toxic concentration	Multiple dosing Peak concentration: >12 mg/L (>25 μmol/L) Trough concentration: >2 mg/L (>4.2 μmol/L) Once-daily dosing Trough concentration: >0.5 mg/L (>1.1 μmol/L)
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	Steady-state is generally achieved after 3 doses for multiple dosing
• Time for blood sampling	Peak: 1 h after beginning of infusion Trough: within 30 min of next dose Once-daily dosing: trough level only
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C When combined therapy with penicillins and/or cephalosporins: in vitro inactivation → freeze sample
Remarks	• Elimination is strongly dependent on renal function • Avoid gel tubes if possible, unless having confirmed that no binding occurs
References	• Arzneimittelkompendium Schweiz. Basel: Documed 2005 • Schweizerische Gesellschaft für Klinische Pharmakologie und Toxikologie, Grundlagen der Arzneimitteltherapie (16. Auflage). Basel: Documed, 2005 • Taylor WJ, Diers Caviness MH. A textbook for the clinical application of therapeutic drug monitoring. Irving, TX: Abbott Laboratories, 1986 • Thomson Micromedex® Healthcare series • Begg EJ, Barclay ML, Duffull SB. A suggested approach to once-daily aminoglycoside dosing. Br J Clin Pharm 1995;39:605–9 • Touw DJ, Neef C, Thomson AH, Vinks AA. Cost-effectiveness of therapeutic drug monitoring committee of the international association for therapeutic drug monitoring and clinical toxicology. Ther Drug Monit 2005;27:10–7

Teicoplanin	
General	
• Class of the drug	Glycopeptide antibiotics
• Synonym(s)	–
• Common trade name(s) in Germany	Targocid®
• Conversion factors	Not applicable
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, suspicion of toxicity, side effects
• Protein binding	90% (albumin)
• Elimination half-life	70–150 h Pediatric: 58 h
• Volume of distribution	1.1 L/kg
• Metabolism	
Main metabolic pathways	No metabolites identified
Active metabolite(s)?	None
Inhibitor or inducer of the cytochrome P450 system?	No
Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Renal (80%)
• Typical therapeutic range	Trough concentration: $<$15 mg/L
• Potentially toxic concentration	Not known
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	Not relevant
• Time for blood sampling	Trough: within 30 min of next dose
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C
Remarks	• Elimination is strongly dependent on renal function • Avoid gel tubes if possible, unless having confirmed that no binding occurs
References	• Arzneimittelkompendium Schweiz. Basel: Documed 2005 • Thomson Micromedex® Healthcare series • Begg EJ, Barclay ML, Kirkpatrick CJ. The therapeutic monitoring of antimicrobial agents. Br J Clin Pharm 1999;47:23–30 • Schulz M, Schmoldt A. Therapeutic and toxic blood concentrations of more than 800 drugs and other xenobiotics. Pharmazie 2003;58:447–74 • Touw DJ, Neef C, Thomson AH, Vinks AA. Cost-effectiveness of therapeutic drug monitoring committee of the international association for therapeutic drug monitoring and clinical toxicology. Ther Drug Monit 2005;27:10–7

Tobramycin

General	
• Class of the drug	Aminoglycoside antibiotics
• Synonym(s)	–
• Common trade name(s) in Germany	Gernebcin®
• Conversion factors	mg/L × 2.14 = μmol/L μmol/L × 0.467 = mg/L
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, suspicion of toxicity, side effects
• Protein binding	0–30% (albumin)
• Elimination half-life	1–3 h Neonates/infants: 3–8 h (see remarks)
• Volume of distribution	0.3 L/kg
• Metabolism	
Main metabolic pathways	No metabolism
Active metabolite(s)?	None
Inhibitor or inducer of the cytochrome P450 system?	No
Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Renal 100%
• Typical therapeutic range	Multiple dosing Peak concentration: 6–10 mg/L (13–21 μmol/L) Trough concentration: ≤1 mg/L (≤2.1 μmol/L) Once-daily dosing Trough concentration: ≤0.5 mg/L (≤1.1 μmol/L)
• Potentially toxic concentration	Multiple dosing Peak concentration: >12 mg/L (>26 μmol/L) Trough concentration: >2 mg/L (>4.3 μmol/L) Once-daily dosing Trough concentration: >0.5 mg/L (>1.1 μmol/L)
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	Steady-state is generally achieved after 3 doses for multiple dosing
• Time for blood sampling	Peak: 1 h after beginning of infusion Trough: within 30 min of next dose Once-daily dosing: trough level only
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C When combined therapy with penicillins and/or cephalosporins: in vitro inactivation → freeze sample
Remarks	• Elimination is strongly dependent on renal function • Avoid gel tubes if possible, unless having confirmed that no binding occurs
References	• Arzneimittelkompendium Schweiz. Basel: Documed 2005 • Schweizerische Gesellschaft für Klinische Pharmakologie und Toxikologie, Grundlagen der Arzneimitteltherapie (16. Auflage). Basel: Documed, 2005 • Taylor WJ, Diers Caviness MH. A textbook for the clinical application of therapeutic drug monitoring. Irving, TX: Abbott Laboratories, 1986 • Thomson Micromedex® Healthcare series • Begg EJ, Barclay ML. Aminoglycosides – 50 years on. Br J Clin Pharm 1995;39:597–603 • Touw DJ, Neef C, Thomson AH, Vinks AA. Cost-effectiveness of therapeutic drug monitoring committee of the international association for therapeutic drug monitoring and clinical toxicology. Ther Drug Monit 2005;27:10–7

Vancomycin

General	
• Class of the drug	Glycopeptide antibiotics
• Synonym(s)	–
• Common trade name(s) in Germany	Vancomycin "Lederle"®
• Conversion factors	mg/L × 0.69 = μmol/L μmol/L × 1.45 = mg/L
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, suspicion of toxicity, side effects
• Protein binding	30–55% (albumin)
• Elimination half-life	4–6 h Neonates: 4–22 h
• Volume of distribution	0.2–1.3 L/kg
• Metabolism	
Main metabolic pathways	No metabolism
Active metabolite(s)?	None
Inhibitor or inducer of the cytochrome P450 system?	No
Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Renal 100%
• Typical therapeutic range	Peak concentration: 20–40 mg/L (14–28 μmol/L) Trough concentration: 5–10 mg/L (3.5–6.9 μmol/L)
• Potentially toxic concentration	Peak concentration: lack of evidence for toxicity associated with peak levels in patients with normal renal function Trough concentration: >15 mg/L (>10 μmol/L)
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	Steady-state is generally achieved after 3 doses
• Time for blood sampling	Peak: 1 h after beginning of infusion Trough: within 30 min of next dose
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C
Remarks	• Accumulation of vancomycin crystalline degradation products (CDP) in renally impaired patients may cause falsely elevated serum vancomycin concentrations with certain immunoassays • Incompatibility with heparin, CAVE portacath • Elimination is strongly dependent on renal function • Avoid gel tubes if possible, unless having confirmed that no binding occurs
References	• Arzneimittelkompendium Schweiz. Basel: Documed 2005 • Schweizerische Gesellschaft für Klinische Pharmakologie und Toxikologie, Grundlagen der Arzneimitteltherapie (16. Auflage). Basel: Documed, 2005 • Taylor WJ, Diers Caviness MH. A textbook for the clinical application of therapeutic drug monitoring. Irving, TX: Abbott Laboratories, 1986 • Thomson Micromedex® Healthcare series • Schulz M, Schmoldt A. Therapeutic and toxic blood concentrations of more than 800 drugs and other xenobiotics. Pharmazie 2003;58:447–74 • Touw DJ, Neef C, Thomson AH, Vinks AA. Cost-effectiveness of therapeutic drug monitoring committee of the international association for therapeutic drug monitoring and clinical toxicology. Ther Drug Monit 2005;27:10–7 • Saunders, J. Vancomycin administration and monitoring reappraisal. Antimicrob Chemother 1995;36:279–82

Itraconazole

General	
• Class of the drug	Antimycotics
• Synonym(s)	–
• Common trade name(s) in Germany	Sempera®
• Conversion factors	Itraconazole: mg/L × 1.42 = μmol/L μmol/L × 0.71 = mg/L Hydroxyitraconazole: mg/L × 1.39 = μmol/L μmol/L × 0.72 = mg/L
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, verification of compliance
• Protein binding	> 99% (albumin)
• Elimination half-life	1.0–1.5 days
• Volume of distribution	10.7 L/kg
• Metabolism	
Main metabolic pathways	Hydroxylation by CYP3A4 to hydroxyitraconazole (stereoselective biotransformation) and a number of other metabolites
Active metabolite(s)?	Hydroxyitraconazole (should be determined as well)
Inhibitor or inducer of the cytochrome P450 system?	Inhibits CYP3A4
Other significant pharmacokinetic interactions	Inhibitor of P-gp
• Elimination of parent drug	Mainly hepatic
• Typical therapeutic range	> 0.50 mg/L (> 0.71 μmol/L) for itraconazole > 1.0 mg/L (> 1.42 μmol/L) for itraconazole + hydroxyitraconazole
• Potentially toxic concentration	Not known
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	7–14 days
• Time for blood sampling	Before next dose at steady-state
• Type(s) of sample	Serum or plasma
• Stability	Several days at 4°C
Remarks	None
References	• Arzneimittel Kompendium Schweiz. Basel: Documed 2005 • Breadmore MC, Thormann, W. Capillary electrophoresis: evidence for the stereoselective metabolism of itraconazole in man. Electrophoresis 2003;24:2588–97 • Glasmacher A, Hahn C, Leutner C, Molitor E, Wardelmann E, Losem C, Sauerbruch T, et al. Breakthrough invasive fungal infections in neutropenic patients after prophylaxis with itraconazole. Mycoses 1999;42:443–51 • Heykants J, Vanpeer A, Vandevelde V, Vanrooy P, Meuldermans W, Lavrijsen K, et al. The clinical pharmacokinetics of itraconazole – an overview. Mycoses 1989;32:67–87 • Poirier JM, Cheymol G. A rapid and specific liquid chromatographic assay for the determination of itraconazole and hydroxyitraconazole in plasma. Ther Drug Monit 1997;19:247–8

Voriconazole

General	
• Class of the drug	Antimycotics
• Synonym(s)	–
• Common trade name(s) in Germany	Vfend®
• Conversion factors	mg/L × 2.86 = μmol/L μmol/L × 0.35 = mg/L
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation
• Protein binding	58%
• Elimination half-life	Approximately 6 h for 200 mg (non-linear pharmacokinetics)
• Volume of distribution	2–4.6 L/kg
• Metabolism	
Main metabolic pathways	N-oxidation and hydroxylation by CYP2C19, CYP2C9, CYP3A4
Active metabolite(s)?	None
Inhibitor or inducer of the cytochrome P450 system?	Inhibits CYP2C19, CYP2C9 and CYP3A4
Other significant pharmacokinetic interactions	No
• Elimination of parent drug	Mainly hepatic Renal < 2%
• Typical therapeutic range	1–6 mg/L (2.9–17.2 μmol/L)
• Potentially toxic concentration	Not known
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	5–6 days (approximately 1 day with loading dose)
• Time for blood sampling	Before next dose at steady-state
• Type(s) of sample	Serum or plasma
• Stability	Several days at 4°C
Remarks	• Genotype status for CYP2C19 and/or co-administration of drugs that modulate CYP2C19 and CYP3A4 activities could affect voriconazole drug levels • The target range for CSF (cerebrospinal fluid) and aqueous humor is only 50% of the respective value in serum or plasma, due to missing proteins
References	• Arzneimittel Kompendium Schweiz. Basel: Documed 2005 • Hyland R, Jones BC, Smith DA. Identification of the cytochrome P450 enzymes involved in the N-oxidation of voriconazole. Drug Metab Dispos 2003;31:540–7 • Johnson LB, Kauffman CA. Voriconazole: a new triazole antifungal agent. Rev Antiinfect Agents 2003;36:630–7 • Purkins L, Wood N, Greenhalgh K, Eve MD, Oliver SD, Nichols D. The pharmacokinetics and safety of intravenous voriconazole – a novel wide-spectrum antifungal agent. Br J Clin Pharmacol 2003;56:2–9 • Roffey SJ, Cole S, Comby P, Gibson D, Jezequel SG, Nedderman ANR, et al. The disposition of voriconazole in mouse, rat, rabbit, guinea pig, dog and human. Drug Metab Dispos 2003;31:731–41

Mebendazole	
General	
• Class of the drug	Anthelmintics
• Synonym(s)	–
• Common trade name(s) in Germany	Vermox®, Surfont®
• Conversion factors	mg/L × 3.39 = μmol/L μmol/L × 0.295 = mg/L
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation
• Protein binding	90%
• Elimination half-life	2.5–5.5 h
• Volume of distribution	Not known
• Metabolism	
Main metabolic pathways	Formation of amino- and hydroxymetabolites (larger plasma concentration compared to mebendazole)
Active metabolite(s)?	Non-significant activity of major metabolites
Inhibitor or inducer of the cytochrome P450 system?	Inducer of hepatic microsomal oxidizing system (enzyme(s) not known)
Other significant pharmacokinetic interactions	Not known
• Elimination of parent drug	Mainly hepatic
• Typical therapeutic range	> 0.074 mg/L (> 0.25 μmol/L) for treatment of echinococcosis
• Potentially toxic concentration	> 1 mg/L (> 3.39 μmol/L) should be avoided
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	2–4 days
• Time for blood sampling	4 h after last dose
• Type(s) of sample	Serum or plasma
• Stability	Several days at 4°C
Remarks	• The large inter- and intra-individual variability is due to the low bioavailability that is related to the low solubility of mebendazole; bioavailability is increased with concomitant intake of a fatty meal • Cholestasis increases blood levels • Only serum or plasma samples should be shipped (mebendazole is not stable in the collected blood samples)
References	• Arzneimittel Kompendium Schweiz. Basel: Documed 2005 • Bresson-Hadni S, Miguet JP, Vuitton DA. Echinococcosis of the liver. In: Bircher J, Benhamou J-P, McIntyre N, Rizzetto M, Rodés J, editors. Oxford textbook of clinical hepatology, vol. I (2nd ed.). Oxford: Oxford University Press, 1999:1066–76 • Gottstein B, Reichen J. Echinococcosis/hydatidosis. In: Cook GC, editor. Manson's tropical diseases. London: Saunders, 1996:1486–508 • Witassek F, Burkhardt B, Eckert J, Bircher J. Chemotherapy of alveolar echinococcosis. Eur J Clin Pharmacol 1981;20:427–33

References

1. Rentsch K, Fathi M, Grignaschi N, Magnin JL, Printzen G, Thormann W, et al. Monographies on drugs, which are frequently analysed in the course of therapeutic drug monitoring. J Lab Med 2005;29:287–97.
2. Rentsch K, Baumann P, Fathi M, Grignaschi N, Magnin JL, Thormann W, et al. Drug monographs on drugs, which are frequently analysed in the context of therapeutic drug monitoring. J Lab Med 2006;30:443–52.