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Drug Monitoring und Toxikologie Redaktion: V.W. Armstrong

Monographies on drugs, which are frequently analysed in the course of Therapeutic Drug Monitoring

Monographien über Medikamente, die regelmässig im Rahmen des Therapeutic Drug Monitorings analysiert werden

K. Rentsch[1,*], M. Fathi[2], N. Grignaschi[3], J.L. Magnin[4], G. Printzen[5], W. Thormann[6], M. Wenk[3] and D. Werner[7]

[1] Chair person, UniversitätsSpital Zürich
[2] Universitätsspital Genf
[3] Universitätsspital Basel
[4] Kantonsspital Freiburg
[5] Inselspital Bern
[6] Universität Bern
[7] Universitätsspital Lausanne

Abstract

In 1995 the working group "Drug Monitoring" of the Swiss Society of Clinical Chemistry (SSCC) has already published a printed version of drug monographs, which are now newly compiled and presented in a standardised manner. The aim of these monographs is to give an overview on the most important informations that are necessary in order to request a drug analysis or is helpful to interpret the results. Therefore, the targeted audience are laboratory health professionals or the receivers of the reports.

There is information provided on the indication for therapeutic drug monitoring, protein binding, metabolic pathways and enzymes involved, elimination half life time and elimination routes as well as information on therapeutic or toxic concentrations.

Because preanalytical 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), respectively, after blood sampling is described.

For readers with a specific interest, references to important publications are given.

The number of the monographs will be continuously enlarged. The updated files are presented on the homepage of the SSCC (www.sscc.ch).

We hope that these monographs are helpful for you handling therapeutic drug monitoring and look forward to comments of the audience.

Keywords: acetaminophen; albendazole; amiodarone; carbamazepin; clozapine; conversion factors; elimination; flecainide; lidocaine; paracetamol; pre-analytics; protein-binding; rapamycine; sirolismus; stability; tacrolismus.

Zusammenfassung

Nachdem bereits 1995 eine gedruckte Version von Arzneimittelmonographien durch die Arbeitsgruppe Medikamente der Schweizerischen Gesellschaft für Klinische Chemie (SGKC) erarbeitet worden war, werden jetzt alle Monographien neu und in einheitlicher Form erstellt. 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.

Es werden klinisch pharmakologische Angaben wie zum Beispiel Indikation für das Therapeutic Drug Monitoring, 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 darüber 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 Stab-

Arbeitsgruppe Medikamente der Schweizerischen Gesellschaft für Klinische Chemie (SGKC)/Working group "Drug Monitoring" of the SSCC.

*Korrespondenz: PD Dr. Katharina Rentsch, Institut für Klinische Chemie, Universitätsspital Zürich, Rämistrasse 100, CH-8091 Zürich/Schweiz
Tel.: +41 1 255 2290
Fax: +41 1 255 4590
E-mail: rentsch@ikc.unizh.ch

ilität der Medikamente bzw. ihrer Metaboliten nach der Blutentnahme gemacht.

Für die interessierten Leser sind die verwendeten Referenzen 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 Ihnen diese Monographien im Umgang mit dem Therapeutic Drug Monitoring hilfreich sein werden und freuen uns über Kommentare und Bemerkungen.

Schlüsselwörter: Albendazol; Amiodaron; Carbamazepin; Clozapin; Elimination; Flecainid; Lidocain; Metabolismus; Paracetamol; Präanalytik; Proteinbindung; Sirolismus; Stabilität; Tacrolismus; Umrechnungsfaktoren.

Albendazole (data refer to albendazole sulfoxide)

General	
• Class of the drug:	Anthelmintics
• Synonym(s):	
• Common trade name(s) in Germany:	Eskazole®
• Conversion factors:	mg/L × 3.77 = μmol/L μmol/L × 0.265 = mg/L
Clinical pharmacology	
• Indications for TDM:	Extrahepatic cholestasis, uncertain response or suspected toxicity
• Protein binding:	Not known
• Elimination half-life:	8.5 h (large interindividual variability)
• Volume of distribution:	Not known
• Metabolism:	
– Main metabolic pathways:	Rapid hepatic transformation of albendazole (achiral) to albendazole sulfoxide (chiral) and further to albendazole sulfone (achiral)
– Active metabolite(s)?	Albendazole sulfoxide (is determined), albendazole sulfone?
– Inhibitor or inductor of the cytochrome P450 system?	Not known
– Other significant pharmacokinetic interactions:	Not known
• Elimination:	Via bile, small amount in urine
• Typical therapeutic range:	> 0.27 mg/L (> 1 μmol/L) albendazole sulfoxide for treatment of echinococcosis
• Potentially toxic concentration:	Not known
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology:	2–4 days
• Time for blood sampling:	4 h after drug administration
• Type(s) of sample:	Serum or plasma
• Stability:	At 4°C many days
References	• Marriner SE, Morris DL, Dickson B, Bogan JA. Pharmacokinetics of albendazole in man. Eur J Clin Pharmacol 1986;30:705–8 • Cotting J, Zeugin T, Steiger U, Reichen J. Albendazole kinetics in patients with echinococcosis: delayed absorption and impaired elimination in cholestasis. Eur J Clin Pharmacol 1990;38:605–8 • Zeugin T, Zysset T, Cotting J. Therapeutic monitoring of albendazole: a high-performance liquid chromatography method for determination of its active metabolite albendazole sulfoxide. Ther Drug Monit 1990;12:187–90 • Gottstein B. and Reichen J., Echinococcosis/hydatosis. In G.C. Cook (ed.). Manson's Tropical Diseases. London: Saunders 1996:1486–1508 • Bresson-Hadni S, Mignet JP, Vuitton DA. Echinococcosis of the liver. In: Bircher J, Benhamou JP, McIntyre N, Rizzetto M, Rodés J. Oxford Textbook of Clinical Hepatology. Vol. I (2nd ed.). Oxford: Oxford University Press 1999:1066–76

Amiodarone

General	
• Class of the drug:	Antiarrhythmics
• Synonym(s):	
• Common trade name(s) in Germany:	Cordarex®
• Conversion factors:	Amiodarone: mg/L × 1.55 = μmol/L μmol/L × 0.645 = mg/L DEA: mg/L × 1.62 = μmol/L μmol/L × 0.617 = mg/L
Clinical pharmacology	
• Indications for TDM:	Uncertain response or suspected toxicity. Routine monitoring of amiodarone is questioned.
• Protein binding:	96–98% (α_1-acid glycoprotein)
• Elimination half-life:	Amiodarone: 55 (21–78) days DEA: 129 days
• Volume of distribution:	70 L/kg
• Metabolism:	
– Main metabolic pathways:	Via CYP3A4 to desethyl-amiodarone (DEA) and other metabolites
– Active metabolite(s)?	DEA: 2–3 times more potent than amiodarone
– Inhibitor or inductor of the cytochrome P450 system?	Inhibitor of CYP2C9, CYP2D6, CYP3A4
– Other significant pharmacokinetic interactions:	Trimetoprim and ofloxacin decreases renal tubular secretion
• Elimination of parent drug:	Hepatic >98%
• Typical therapeutic range:	0.8–2.6 mg/L (1.2–4.0 μmol/L), not defined for DEA
• Potentially toxic concentration:	>2.6 mg/L (>4.0 μmol/L) for amiodarone >2.0 mg/L (>3.2 μmol/L) for DEA (not well defined)
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology:	Up to six month (!), faster with a loading dose
• Time for blood sampling:	Before next dose at steady state
• Type(s) of sample:	Serum or plasma
• Stability:	2 days at room temperature; decreases up to 23% within a week (independent of storage temperature); binds to barrier gels in blood collection tubes!
Remarks	During therapy the ratio amiodarone to DEA is >1. May be used as index for compliance.
References	• Natel S, Davies M, Quantz M. The antiarrhythmic efficacy of amiodarone and desethylamiodarone, alone and in combination, in dogs with acute myocardial infarction. Circulation1988;77:200–8 • Somani P. Basic and clinical pharmacology of amiodarone: relationship of antiarrhythmic effects, dose and drug concentrations to intracellular inclusion bodies. J Clin Pharmacol 1998;29:405–12 • Valdes R Jr, Jortani SA, Gheorghiade M. Standards of laboratory practice: cardiac drug monitoring. National Academy of Clinical Biochemistry. Clin Chem 1998;44:1096–109 • Campbell TJ, Williams KM. Therapeutic drug monitoring: antiarrhythmic drugs. Br J Clin Pharmacol 1998;46:307–19 • Jürgens G, Graudal NA, Kampmann JP. Therapeutic drug monitoring of antiarrhythmic drugs. Clin Pharmacokinet 2003;42:647

Carbamazepine

General	
• Class of the drug:	Antiepileptics
• Synonym(s):	
• Common trade name(s) in Germany:	Fokalepsin®, Tegretal®, Timonil®
• Conversion factors:	mg/L × 4.23 = μmol/L μmol/L × 0.236 = mg/L
Clinical pharmacology	
• Indications for TDM:	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding:	70–80% (mainly to albumin and to a lesser extent to α1-acid glycoprotein)
• Elimination half-life:	– 30 to 45 h during first days of treatment – 20 h on average when auto-induction of metabolism is maximal (achieved after around 4 weeks of treatment) – 10 h on average when given with other inductors (phenytoin, phenobarbital, ...)
• Volume of distribution:	0.8–1.9 L/kg
• Metabolism:	
– Main metabolic pathways:	"10,11-epoxide diol pathway" in the liver: oxydation to carbamazepine 10,11-epoxide mostly by CYP 3A4 followed by almost complete transformation to the transdiol-10,11 derivative (= dihydroxy-10,11-carbamazepine) and its glucuronides
– Active metabolite(s)?	Carbamazepine 10,11-epoxide
– Inhibitor or inductor of the cytochrome P450 system?	Inductor of cytochrome CYP 3A4 (auto-induction!)
– Other significant pharmacokinetic interactions:	Numerous interactions, mostly with inductors and inhibitors of CYP 3A4
• Elimination of parent drug:	Hepatic > 98% Renal < 2%
• Typical therapeutic range:	4–10 mg/L (17–42 μmol/L)
• Potentially toxic concentration:	> 10 mg/L (> 42 μmol/L) (variable)
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology:	4 weeks (for metabolic induction to be complete)
• Time for blood sampling:	Before next dose at steady state
• Type(s) of sample:	Serum or plasma
• Stability:	48 h at 4°C (for longer conservation, freeze at −20°C)
Remarks	For immunoassays, cross-reaction with the active metabolite carbamazepine 10,11-epoxide might occur; the extent of this cross-reaction depends on the method
References	• Arzneimittelkompendium Schweiz, Basel: Documed, 2004 • Schweizerische Gesellschaft für Klinische Pharmakologie und Toxikologie, Grundlagen der Arzneimitteltherapie (15. Auflage), Basel: Documed, 2001 • Barre et al., in Commission Médicaments de la SFBC, Méthodes de dosage et suivi thérapeutique: aminosides, antiépileptiques, hétérosides cardiotoniques, isoniazide, théophylline., Expansion Scientifique Française, 1989, 26–48 • MacKichan and Kutt. In: Taylor WJ, Finn AL. Individualizing Drug Therapy – Practical Applications of Drug Monitoring, Vol. 2, New York: Gross, Townsend, Frank, Inc 1981, 1–25 • Regenthal R, Krueger M, Koeppel C, Preiss R. Drug levels: therapeutic and toxic serum/plasma concentrations of common drugs. J Clin Monit Comput 1999;15:529–44 • Warner A, Privitera M, Bates D. Standards of laboratory practice: antiepileptic drug monitoring. National Academy of Clinical Biochemistry Clin Chem 1998;44:1085–95 • Yukawa E. Optimisation of antiepileptic drug therapy. The importance of serum drug concentration monitoring. Clin Pharmacokinet 1996;31:120–30

Clozapine

General	
• Class of the drug:	Antipsychotics
• Synonym(s):	
• Common trade name(s) in Germany:	Leponex®, Elcrit®
• Conversion factors:	Clozapine: μg/L × 0.0031 = μmol/L μmol/L × 327 = μg/L Norclozapine: μg/L × 0.0032 = μmol/L μmol/L × 313 = μg/L
Clinical pharmacology	
• Indications for TDM:	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding:	95% (α_1-acid glycoprotein)
• Elimination half-life:	6–26 h
• Volume of distribution:	1.6 L/kg
– Metabolism:	
– Main metabolic pathways:	CYP1A2 (Norclozapine), CYP3A4 (Clozapine-N-oxide), CYP2D6
– Active metabolite(s)?	Norclozapine (partial activity) (is determined)
– Inhibitor or inductor of the cytochrome P450 system?	Not yet found
– Other significant pharmacokinetic interactions:	Cigarette smoking decreases clozapine serum levels
– Elimination of parent drug:	Hepatic > 30% Renal > 50%
– Indicative therapeutic range:	350–810 μg/L (1.07–2.48 μmol/L) (Clozapine)
– Indicative toxic concentration:	> 1000 μg/L (3.1 μmol/L) (Clozapine)
Pre-analytics	
– Time to steady-state since beginning of treatment or change of posology:	3–5 days
– Time for blood sampling:	Before next dose at steady state
– Type(s) of sample:	Serum or plasma
– Stability:	At 4°C several days in serum
Remarks	Plasma levels are 10% higher (clozapine) and 16% higher (norclozapine) than serum levels.
References	• Arzneimittelkompendium Schweiz, Basel: Documed 2004 • Baselt RC. Disposition of Toxic Drugs and Chemicals in Man, 6th edition, Foster City, (USA): Biomedical Publikations 2002 • Kaladjian A, Bery B, Deturmeny E, Bruguerolle B. Clozapine monitoring: plasma or serum levels? Therap Drug Monit 1999;21:327–9 • Mitchell P. Therapeutic drug monitoring of psychotropic medications. Br J Clin Pharmacol 2001;52:45S • Baumann P, Hiemke C, Ulrich S, Eckermann G, Gaertner I, Gerlach M, et al. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. Pharmacopsychiatry 2004;37:243–65

Flecainide

General	
• Class of the drug:	Antiarrhythmics
• Synonym(s):	
• Common trade name(s) in Germany:	Tambocor®
• Conversion factors:	mg/L × 2.41 = μmol/L μmol/L × 0.414 = mg/L
Clinical pharmacology	
• Indications for TDM:	Dose adaptation during reduced liver and/or kidney function. Avoidance of toxic levels in CYP2D6 poor metabolizers
• Protein binding:	40% (α_1-acid glycoprotein)
• Elimination half-life:	12–20 h
• Volume of distribution:	8.5 L/kg
• Metabolism:	
– Main metabolic pathways:	Via CYP2D6 (stereoselective) and conjugated metabolites
– Active metabolite(s)?	Meta-o-dealkyl-flecainide (activity approx. 20%, clinically not relevant)
– Inhibitor or inductor of the cytochrome P450 system?	Inhibitor of CYP2D6
– Other significant pharmacokinetic interactions:	Inhibitors of CYP2D6 (e.g., amiodarone, cimetidine) increase flecainide serum levels
• Elimination of parent drug:	Hepatic > 70% Renal < 30%
• Typical therapeutic range:	0.2–0.8 mg/L (0.5–1.9 μmol/L)
• Potentially toxic concentration:	> 1 mg/L (> 2.4 μmol/L)
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology:	3–5 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	Heart, kidney, and liver failure reduce flecainide clearance
References	• Valdes R Jr, Jortani SA, Gheorghiade M. Standards of laboratory practice: cardiac drug monitoring. National Academy of Clinical Biochemistry. Clin Chem 1998;44: 1096–109 • Campbell TJ, Williams KM. Therapeutic drug monitoring: antiarrhythmic drugs. Br J Clin Pharmacol 1998; 46:307–19 • Jürgens G, Graudal NA, Kampmann JP. Therapeutic drug monitoring of antiarrhythmic drugs. Clin Pharmacokinet 2003;42:647–63

Lidocaine

General	
• Class of the drug:	Antiarrhythmic drugs, local anesthetics
• Synonym(s):	Lignocaine
• Common trade name(s) in Germany	Xylocain®
• Conversion factors:	mg/L × 4.27 = μmol/L μmol/L × 0.234 = mg/L
Clinical pharmacology	
• Indications for TDM:	To control lidocaine levels after heart failure, shock, hepatic disease or suspected toxicity. Drug monitoring is not routinely performed
• Protein binding:	60–70% (α_1-acid glycoprotein)
• Elimination half-life:	1–2 h
• Volume of distribution:	1.1 L/kg
• Metabolism:	
– Main metabolic pathways:	Via CYP1A2 and CYP3A4 to monoethylglycinexylide (MEGX) and glycinexilide (GX)
– Active metabolite(s)?	MEGX and GX
– Inhibitor or inductor of the cytochrome P450 system?	Not known
– Other significant pharmacokinetic interactions:	Inducers or inhibitors of CYP1A2 or CYP3A4 can influence lidocaine levels
• Elimination of parent drug:	> 97% hepatic < 3% renal
• Typical therapeutic range:	2–5 mg/L (8.5–21 μmol/L)
• Potentially toxic concentration:	> 6 mg/L (> 26 μmol/L)
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology:	30–90 min after a loading dose; 5–10 h without an initial loading dose
• Time for blood sampling:	2 h after loading dose or 5–10 h after beginning of the infusion (without an initial loading dose)
• Type(s) of sample:	Serum or plasma
• Stability:	6 h at 4°C; 8 weeks at −25°C. Binds to barrier gels in blood collection tubes!
Remarks	Determination of MEGX can be used as liver function test (e.g., after liver transplantation)
References	• Valdes R Jr, Jortani SA, Gheorghiade M. Standards of laboratory practice: cardiac drug monitoring. National Academy of Clinical Biochemistry. Clin Chem 1998; 44:1096–109 • Campbell TJ, Williams KM. Therapeutic drug monitoring: antiarrhythmic drugs. Br J Clin Pharmacol 1998;46:307–19 • Jürgens G, Graudal NA, Kampmann JP. Therapeutic drug monitoring of antiarrhythmic drugs. Clin Pharmacokinet 2003;42:647–63 • Orlando R, Piccoli P, De Martin S, Padrini R, Floreani M, Palatini P. Cytochrome P450 1A2 is a major determinant of lidocaine metabolism *in vivo*: effects of liver function. Clin Pharmacol Ther 2004;75:80–8 • Tanaka E, Inomata S, Yasuhara H. The clinical importance of conventional and quantitative liver function tests in liver transplantation. J Clin Pharm Therap 2000;25:411–9

Paracetamol (DCI)

General

• Class of the drug:	Analgesics
• Synonym(s):	Acetaminophen, N-acetyl-*p*-aminophenol
• Common trade name(s) in Germany:	numerous
• Conversion factors:	mg/L × 6.62 = μmol/L μmol/L × 0.151 = mg/L

Clinical pharmacology

• Indications for TDM:	Suspicion of toxicity
• Protein binding:	5–15% at therapeutic concentration until 50% in overdose
• Elimination half-life:	1–4 h (may be higher in case of intoxication = toxicity indication)
• Volume of distribution:	0,75–1 L/kg
• Metabolism:	
– Main metabolic pathways:	Extensive by hepatic route; forms inactive sulfates (main children pathway) and glucuronides (main adult pathway)
– Active metabolite(s)?	Toxic metabolite in case of intoxication (oxydase pathway, essentially CYP2E1): N-acetyl-p-benzoquinonimine, normally rapidly detoxified by glutathione in the liver. In overdose, production of the toxic metabolite exceeds glutathione capacity and the metabolite reacts directly with hepatic macromolecules, causing liver injury.
– Inhibitor or inductor of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions:	Enzymatic inductors may promote oxidative pathway (CYP2E1) to toxic metabolite. Chronic alcoholism: enzymatic induction, lowered glutathione capacity, higher risk of liver injury
• Elimination of parent drug:	Hepatic > 90% Renal < 5%
• Typical therapeutic range:	5–20 mg/L
• Potentially toxic concentration:	Nomogram for prediction of acetaminophen hepatotoxicity (Figure 1): – > 150–200 mg/L 4 h after ingestion (Alcoholic, cirrhotic, associated hepatotoxic substances: > 100 mg/L at 4 h) – > 100 mg/L at 8 h – > 50 mg/L at 12 h – > 30 mg/L at 15 h

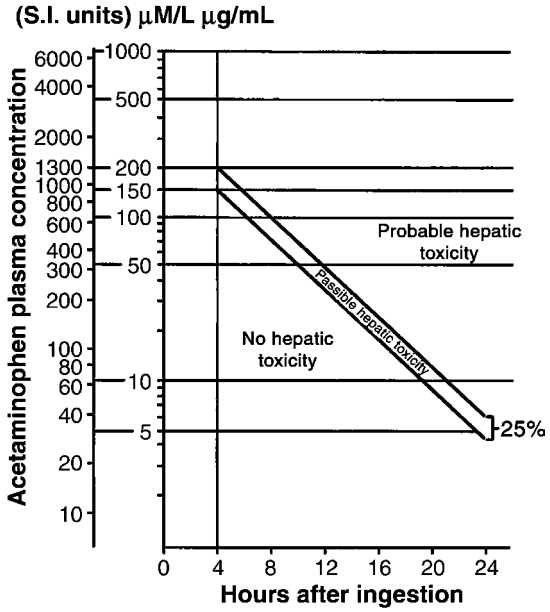

Figure 1 The Rumack-Matthew nomogram relating expected severity of liver toxicity to serum paracetamol concentrations.

Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology:	Acute intoxication: modified kinetic if massive ingestion Therapeutic dosage: time to steady state 5–20 h (orally, continuous treatment)
• Time for blood sampling:	Acute intoxication: min. 4 h after ingestion, max. 24 h. Therapeutic: 1 h after ingestion (Cmax)
• Type(s) of sample:	Serum or plasma
• Stability:	8 h at room temperature, 48 h at 4–8°C, for longer conservation freeze at −20°C
Remarks	Variable, method related, cross-reactivity with toxic metabolite Possible interference (false positive) of hyperbilirubinemic samples (Clin Chem 49 (2003) 695) Antidotes: N-acetylcysteine
References	• Fenton J. The laboratory and the poisoned patient, Washington: AACC Press 1998, 31–36 • Olson K. Poisoning and drug overdose, Stanford (USA): Appleton&Lange 1990:57–58 • Tietz NW. Clinical guide to laboratory tests, 3rd ed., Philadelphia: Saunders 1995:788–9 • Arzneimittelkompendium Schweiz, Basel: Documed 2004 • White S, Wong SHY. Standards of laboratory practice: analgesic drug monitoring. National Academy of Clinical Biochemistry. Clin Chem 1998;44:1110–23 • Manyike PT, Kharasch ED, Kalhorn TF, Slattery JT. Contribution of CYP2E1 and CYP3A to acetaminophen reactive metabolite formation. Clin Pharmacol Ther 2000;67:275–82

Sirolimus

General	
• Class of the drug:	Immunosuppressants
• Synonym(s):	Rapamycine
• Common trade name(s) in Germany:	Rapamune®
• Conversion factors:	μg/L × 1.09 = nmol/L nmol/L × 0.91 = μg/L
Clinical pharmacology	
• Indications for TDM:	Individual dose adaptation, symptoms of rejection or toxicity
• Protein binding:	95–97% localized in erythrocytes; in plasma 92% bound to albumin
• Elimination half-life:	46–78 h
• Volume of distribution:	5–19 L/kg
• Metabolism:	
– Main metabolic pathways:	Liver, mainly through CYP3A4
– Active metabolite(s)?	Desmethylmetabolites and hydroxymetabolites represent a maximum of 30% of sirolimus activity
– Inhibitor or inductor of the cytochrome P450 system?	Inductor of CYP3A4
– Other significant pharmacokinetic interactions:	PGP substrate and inhibitor
• Elimination of parent drug:	Hepatic > 90% Renal < 3%
• Typical therapeutic range:	Dependent on combination therapy and indication
• Potentially toxic concentration:	> 30 μg/L
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology:	~4 days
• Time for blood sampling:	Before next dose at steady state
• Type(s) of sample:	Whole blood on EDTA
• Stability:	1 day at 25°C, 2–3 days at 4°C, for longer conservation freeze at −20°C
Remarks	Samples should be shipped frozen
References	• Arzneimittelkompendium Schweiz, Basel: Documed 2004 • Napoli KL, Taylor PJ. From beach to bedside: history of the development of sirolimus. Ther Drug Monit 2001;23:559–86 • Macphee IA, Fredericks S, Tai T, Syrris P, Carter ND, Johnston A. Tacrolimus pharmacogenetics: polymorphisms associated with expression of cytochrome p4503A5 and P-glycoprotein correlate with dose requirement. Transplantation 2002;74:1486–9 • Ingle GR, Sievers TM, Holt CD. Sirolimus: continuing the evolution of transplant immunosuppression. Ann Pharmacother 2000;34:1044–55 • Marzolini C, Paus E, Buclin T, Kim RB. Polymorphisms in human MDR1 (P-glycoprotein): recent advances and clinical relevance. Clin Pharmacol Ther 2004;75:13–33

Tacrolimus

General	
• Class of the drug:	Immunosuppressants
• Synonym(s):	FK506
• Common trade name(s) in Germany:	Prograf®
• Conversion factors:	μg/L × 1.24 = nmol/L nmol/L × 0.80 = μg/L
Clinical pharmacology	
• Indications for TDM:	Individual dose adaptation, symptoms of rejection or toxicity
• Protein binding:	92–98% localized in erythrocytes; in plasma 98.8% bound to albumin
• Elimination half-life:	12–15 h
• Volume of distribution:	2.5 L/kg
• Metabolism:	
– Main metabolic pathways:	Liver, high affinity for CYP3A4
– Active metabolite(s)?	31-O-desmethyltacrolimus, has a similar activity to tacrolimus
– Inhibitor or inductor of the cytochrome P450 system?	Strongly inhibitor for CYP1A2 and 3A4
– Other significant pharmacokinetic interactions:	PGP substrate and inhibitor
• Elimination of parent drug:	Hepatic > 99% Renal < 1%
• Typical therapeutic range:	Dependent on combination therapy and indication
• Potentially toxic concentration:	> 30 μg/L
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology:	~3 days
• Time for blood sampling:	Before next dose at steady state
• Type(s) of sample:	Whole blood on EDTA
• Stability:	5 days at 25°C
References	• Arzneimittelkompendium Schweiz, Basel: Documed 2004 • Holt DW, Armstrong VW, Griesmacher A, Morris RG, Napoli KL, Shaw LM, et al. International Federation of Clinical Chemistry/International Association of Therapeutic Drug Monitoring and Clinical Toxicology working group on immunosuppressive drug monitoring. Ther Drug Monit 2002;24:59–67 • Macphee IA, Fredericks S, Tai T, Syrris P, Carter ND, Johnston A. Tacrolimus pharmacogenetics: polymorphisms associated with expression of cytochrome p4503A5 and P-glycoprotein correlate with dose requirement. Transplantation 2002;74:1486–9 • Armstrong VW, Oellerich M. New developments in the immunosuppressive drug monitoring of cyclosporine, tacrolimus, and azathioprine. Clin Biochem 2001;34:9–16 • Marzolini C, Paus E, Buclin T, Kim RB. Polymorphisms in human MDR1 (P-glycoprotein): recent advances and clinical relevance. Clin Pharmacol Ther 2004; 75:13–33