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Drug Monitoring und Toxikologie/
Drug Monitoring and Toxicology

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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

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Abstract

In addition to the monographs which have been published in the last 6 years by the working group "Drug Monitoring" of the Swiss Society of Clinical Chemistry (SSCC) [1–5], new monographs have been written. The data presented in these monographs provide an overview of the information which is important for the request and interpretation of the results. Therefore, laboratory health professionals and the receivers of the reports are the targeted readers. With the exception of digoxin, the drugs presented in this series are not administered frequently and are only analyzed in special situations.

First, information about pharmacology and pharmacokinetics of these drugs (protein binding, metabolic pathways and enzymes involved, elimination half-life time and elimination route(s) of the parent drug and therapeutic as well as toxic concentrations) is given. Secondly, the indications for therapeutic drug monitoring are listed. Last but not least, important preanalytical information is provided, including time points of blood sampling and time interval after which steady-state concentrations are reached after changing the dose. Furthermore, the stability of the drug and its metabolite(s) after blood sampling are described.

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

The number of the monographs will be further enlarged. 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 receiving comments from the readers.

Keywords: caffeine; digoxin; fluphenazine; methadone; methotrexate; olanzapine; ribavirin, salicylate, theophylline

Zusammenfassung

Ergänzend zu den in den letzten sechs Jahren publizierten Arzneimittelmonographien der Arbeitsgruppe Medikamente der Schweizerischen Gesellschaft für Klinische Chemie (SGKC) [1–5], sind weitere Monographien erstellt worden. Wiederum sollen diese Monographien dem Labormediziner bzw. dem Empfänger der Befunde eine Übersicht über die wichtigsten Informationen geben, die für die Veranlassung einer Analyse bzw. für die Interpretation der Resultate hilfreich sind. In dieser Serie werden verschiedene Medikamente vorgestellt, die mit Ausnahme von Digoxin nur noch selten verordnet oder deren Konzentration nur in speziellen Fällen im Blut bestimmt werden.

Die einzelnen Monographien beinhalten einerseits Angaben zu klinisch-pharmakologischen Daten wie zum Beispiel zu den Proteinbindungen, Metabolisierungswegen und daran beteiligten Enzymen, Halbwertszeiten und Eliminationswege der Muttersubstanz, sowie Informationen zu therapeutischen bzw. toxischen Bereichen. Andererseits werden bei jeder Substanz die Indikationen für das Therapeutic Drug Monitoring aufgelistet und wichtige Angaben zur Präanalytik gemacht (Zeitpunkt der Blutentnahme und Zeitpunkt des Erreichens einer steady-state-Situation nach einer Dosisänderung). 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.

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Die Zahl der Monographien wird weiterhin 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.

Caffeine

General	
• Class of the drug:	Analeptics
• Synonym(s):	
• Common trade name(s) in Germany:	No commercial products available for this indication
• Conversion factors:	mg/l × 5.15 = µmol/l µmol/l × 0.194 = mg/l
Clinical pharmacology	
• Indications for TDM:	Prevention and treatment of apnoeas in newborns
• Protein binding:	35%
• Elimination half-life:	84–120 h in newborns
• Volume of distribution:	0.5 l/kg
• Metabolism:	
– Main metabolic pathways:	CYP1A2
– Active metabolite(s)?	Paraxanthine (84%), theobromine and theophylline
– Inhibitor or inductor of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions:	No
• Elimination of parent drug:	Mainly hepatic (>90%)
• Typical therapeutic range:	4–10 mg/l (20.6–51.5 µmol/)
• Potentially toxic concentration:	>15–20 mg/l (>77–103 µmol/)
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology:	20 days in neonates
• Time for blood sampling:	Before next dose (trough levels)
• Type(s) of sample:	Serum or plasma
• Stability:	1 week at 4 °C
Remarks	None
References	• Baselt, RC. Disposition of toxic drugs and chemicals in man, Foster City, CA: Biomedical Publications: 2002. • Schweizerische Gesellschaft für Klinische Pharmakologie und Toxikologie, Grundlagen der Arzneimitteltherapie (15. Auflage). Basel: Documed, 2001. • Natarajan G, Lulic-Botica M, Aranda JV. Pharmacology Review: Clinical Pharmacology of caffeine in the newborn. NeoReviews 2007;8:e214–21.

Digoxin

General	
• Class of the drug:	Cardiac glycosides
• Synonym(s):	
• Common trade name(s) in Germany:	Digacin®, Lanicor®, Lenoxin®
• Conversion factors:	µg/l × 1.28 = nmol/l nmol/l × 0.781 = µg/l
Clinical pharmacology	
• Indications for TDM:	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding:	20%–30% (albumin)
• Elimination half-life:	40 h
• Volume of distribution:	5–7 l/kg
• Metabolism:	
– Main metabolic pathways:	Sequential cleavage of sugar molecules and reduction followed by conjugations
– Active metabolite(s)?	Digoxigenine and dihydrodigoxin have some cardiac effects (not clinically relevant)
– Inhibitor or inductor of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions:	Antacids inhibit absorption of oral digoxin from the GI tract. Quinidine decreases clearance and volume of distribution; amiodarone, verapamil, propafenone reduce digoxin clearance. Interferences with the transport protein P-glycoprotein can affect digoxin levels (e.g. St. John's Worth).
• Elimination of parent drug:	Hepatic: 5–20% Renal: 60–80%
• Typical therapeutic range:	0.8–2 µg/l (1.0–2.6 nmol/l)
• Potentially toxic concentration:	>2.5 µg/l (>3.2 nmol/l)
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology:	1 week
• Time for blood sampling:	Before next dose at steady state or at least 6–8 hours after the last dose
• Type(s) of sample:	Serum or plasma
• Stability:	1 week at 4 °C
Remarks	Digoxin-like immunoreactive factors (DLIFs) may result in falsely elevated digoxin levels with immunoassays. New trend: lower therapeutic range (0.6–1.2 nmol/l; 0.5–0.9 µg/l)
References	• Wettrell G, Andersson KE. Cardiovascular drugs II: digoxin. Ther Drug Monit 1986;8:129–39. • Mooradian AD. Digitalis: An update of clinical pharmacokinetics, therapeutic monitoring techniques and treatment recommendations. Clin Pharmacokinet 1988;15:133–64. • Matzuk MM, Shlomchik M, Shaw LM. Making digoxin therapeutic drug monitoring more effective. Ther Drug Monit 1991;13:215–9. • Dobbs RJ, O'Neill CJA, Deshmukh AA, Nicholson PW, Dobbs SM. Serum concentration monitoring of cardiac glycosides: how helpful is it for adjusting dosage regimens? Clin Pharmacokinet 1991;20:175–93. • Valdes R Jr., Jortani SA, Gheorghiade M. Standards of laboratory practice: cardiac drug monitoring. Clin Chem 1998;44:1096–109. • Ahmed A, Rich MW, Love TE, Lloyd-Jones DM, Aban IB, Colucci WS, et al. Digoxin and reduction in mortality and hospitalization in heart failure: a comprehensive post hoc analysis of the DIG trial. Eur Heart J 2006;27:178–86.

Fluphenazine

General	
• Class of the drug:	Neuroleptics
• Synonym(s):	
• Common trade name(s) in Germany:	Fluphenazin-neuraxpharm© D, Lyogen©, Lyogen Depot©
• Conversion factors:	µg/l × 2.28 = nmol/l nmol/l × 0.43 = µg/l
Clinical pharmacology	
• Indications for TDM:	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding:	>90%
• Elimination half-life:	13–58 h (oral formulation), 7 to 10 days (Fluphenazine decanoate)
• Volume of distribution:	11 ± 10 l/kg (oral formulation)
• Metabolism:	
– Main metabolic pathways:	CYP1A2, CYP2D6
– Active metabolite(s)?	Not known
– Inhibitor or inductor of the cytochrome P450 system?	Not known
– Other significant pharmacokinetic interactions:	Not known
• Elimination of parent drug:	Mainly hepatic
• Typical therapeutic range:	0.5–2.0 µg/l (1.14–4.57 nmol/l)
• Potentially toxic concentration:	>43 µg/l (>100 nmol/l)
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology:	~30–50 days (Fluphenazine decanoate)
• Time for blood sampling:	Before next dose at steady state
• Type(s) of sample:	Serum or plasma
• Stability:	1 week at 4 °C
Remarks	None
References	• Arzneimittelkompendium Schweiz, www.kompendium.ch. • Glazer WM. Fluphenazine decanoate, its steady-state pharmacologic profile and relationship to tardive dyskinesia. Schizophr Res. 1988;6:425–9. • Marder SR, Hubbard JW, Van Putten T, Midha KK. Pharmacokinetics of long-acting injectable neuroleptic drugs: clinical implications. Psychopharmacology 1989;98:433–9. • Luo JP, Hubbard JW, Midha KK. Sensitive method for the simultaneous measurement of fluphenazine decanoate and fluphenazine in plasma by high-performance liquid chromatography with coulometric detection. J Chromatogr B 1997;688:303–8. • Molero-Monfort M, Escuder-Gilabert L, Villanueva-Camanas RM, Sagrado S, Medina-Hernandez MJ. Biopartitioning micellar chromatography: an in vitro technique for predicting human drug absorption. J Chromatogr B 2001;753:225–36. • Baumann PB, 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;37:246–65. • Berellini G, Springer C, Waters NJ, Lombardo F. In silico prediction of volume of distribution in human using linear and nonlinear models on a 669 Compound Data Set. J Med Chem 2009;52:4488–95.

Methadone

General	
• Class of the drug:	Analgesics
• Synonym(s):	
• Common trade name(s) in Germany:	Eptadone®, Methaddict®
• Conversion factors:	mg/l × 3.23 = µmol/l µmol/l × 0.309 = mg/l
Clinical pharmacology	
• Indications for TDM:	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding:	90%
• Elimination half-life:	15–55 h (depending on urine pH)
• Volume of distribution:	4–5 l/kg
• Metabolism:	
– Main metabolic pathways:	Demethylation to EDDP (Ethyl-dimethyl-diphenylpyrrolidine) and EMDP (Ethyl-methyl-diphenylpyrrolidine) (major: CYP3A4 and CYP2B6, minor: CYP2D6)
– Active metabolite(s)?	None
– Inhibitor or inductor of the cytochrome P450 system?	CYP3A4, CYP2D6 (moderate inhibitor)
– Other significant pharmacokinetic interactions:	No
• Elimination of parent drug:	Hepatic 75% Renal 25%
• Typical therapeutic range:	Substitution: 0.4–0.6 mg/l (1.29–1.94 µmol/l) Pain treatment: 0.02–0.09 mg/l (0.064–0.29 µmol/l)
• Potentially toxic concentration:	Non tolerant patients: toxic > 0.5 mg/l (1.61 µmol/l) coma: > 1.0 mg/l (3.23 µmol/l)
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology:	3–6 days
• Time for blood sampling:	Before next dose at steady state or 12–16h after last dose
• Type(s) of sample:	Serum or plasma
• Stability:	7 days at 4 °C
Remarks	• Chiral drug • Enantiomers differ by their metabolism and pharmacology • R-enantiomer is active (therapeutic ranges are given for the racemate)

References

- Arzneimittelkompendium Schweiz. Basel: Documed 2005.
- Baselt, RC. Disposition of toxic drugs and chemicals in man, Foster City, CA: Biomedical Publications: 2002.
- Iten, P. Fahren unter Drogen- oder Medikamenteneinfluss, Forensische Interpretation und Begutachtung, Institut für Rechtsmedizin der Universität Zürich: 1994.
- Schweizerische Gesellschaft für Klinische Pharmakologie und Toxikologie, Grundlagen der Arzneimitteltherapie (16. Auflage). Basel: Documed, 2006
- Baumann PB, 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;37:246–65.

Methotrexate

General	
• Class of the drug:	Cytostatics
• Synonym(s):	Amethopterin
• Common trade name(s) in Germany:	Bendatrexat®, Lantarel®, metex®, Methotrexat HEXAL®, Methotrexat Lederle®, Methotrexat medac®, MTX HEXAL®, MTX medac®, Neotrexat®
• Conversion factors:	mg/l × 2.20 = µmol/l µmol/l × 0.455 = mg/l
Clinical pharmacology	
• Indications for TDM:	To ensure that plasma concentrations after infusion are <0.46 mg/l at 48 h and <0.046 mg/l at 72 h and to adapt leucovorin rescue
• Protein binding:	50%–60% (albumin)
• Elimination half-life:	5–9 h (t_α = 0.75 h; t_β = 2–3 h; t_γ = 6–20 h)
• Volume of distribution:	2.6 l/kg
• Metabolism:	
– Main metabolic pathways:	Hydroxylation to 7-hydroxymethotrexate
– Active metabolite(s)?	7-hydroxymethotrexate (aldehyde oxidase, xanthine oxidase)
– Inhibitor or inductor of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions:	Folic acid and precursors/inhibitors, triamteren (increase of metabolism)
• Elimination of parent drug:	Renal 94% Hepatic 6%
• Typical therapeutic range:	No typical therapeutic range
• Potentially toxic concentration:	>4.6 mg/l after 24 h >0.46 mg/l after 48 h >0.046 mg/l after 72 h
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology:	20–36 h after chronic dosing
• Time for blood sampling:	Depends on the applied protocol
• Type(s) of sample:	Serum or plasma, cerebrospinal fluid
• Stability:	48 h at 4 °C (screened from light)
Remarks	None
References	• Arzneimittelkompendium Schweiz. Basel: Documed 2005. • Baselt, RC. Disposition of toxic drugs and chemicals in man, Foster City, CA: Biomedical Publications: 2002. • Schweizerische Gesellschaft für Klinische Pharmakologie und Toxikologie, Grundlagender Arzneimitteltherapie (16. Auflage). Basel: Documed, 2006.

Olanzapine

General	
• Class of the drug:	Neuroleptics
• Synonym(s):	
• Common trade name(s) in Germany:	Zyphadera®, Zyprexa®
• Conversion factors:	µg/l × 3.20 = nmol/l nmol/l × 0.31 = µg/l
Clinical pharmacology	
• Indications for TDM:	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding:	93%
• Elimination half-life:	Adults: 29–39 h, elderly people: 49–55 h
• Volume of distribution:	21.9 ± 3.2 l/kg
• Metabolism:	
– Main metabolic pathways:	CYP1A2, CYP2D6 (moderate)
– Active metabolite(s)?	Desmethylolanzapine, minor activity
– Inhibitor or inductor of the cytochrome P450 system?	Not known
– Other significant pharmacokinetic interactions:	Not known
• Elimination:	Mainly hepatic
• Typical therapeutic range:	20–80 µg/l (64–256 nmol/l)
• Potentially toxic concentration:	>186 µg/l (>600 nmol/l)
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology:	~7 days
• Time for blood sampling:	Before next dose at steady state
• Type(s) of sample:	Serum or plasma
• Stability:	At least 1 week at –20 °C
Remarks	Fluvoxamine, a specific inhibitor of CYP1A2, inhibits significantly the olanzapine metabolism
References	• Arzneimittelkompendium Schweiz, www.kompendium.ch. • Zhang G, Terry AV Jr., Bartlett MG. Sensitive liquid chromatography/tandem mass spectrometry method for the simultaneous determination of olanzapine, risperidone, 9-hydroxyrisperidone, clozapine, haloperidol and ziprasidone in rat brain tissue. J Chromatogr B 2007;858:276–281. • Baumann PB, 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;37:246–65. • Gervasini G, Vizcaíno S, Herraiz AG, Benitez J, Carrillo JA. Applicability of an assay for routine monitoring of highly variable concentrations of olanzapine based on HPLC with mass spectrometric detection. Clin Chem 2003;49:2088–91. • Carrillo JA, Herraiz AG, Ramos SI, Gervasini G, Vizcaino S, Benitez J. Role of the smoking-induced cytochrome P450 (CYP)1A2 and polymorphic CYP2D6 in steady-state concentration of olanzapine. J Clin Psychopharmacol 2003;23:119–27. • Gex-Fabry M, Balant-Gorgia AE, Balant LP. Therapeutic drug monitoring of olanzapine: the combined effect of age, gender, smoking, and comedication. Ther Drug Monit 2003;25:46–53.

Ribavirin

General	
• Class of the drug:	Antiviral drugs
• Synonym(s):	
• Common trade name(s) in Germany:	Copegus®, Rebetol®, Virazol®
• Conversion factors:	mg/l × 4.09 = µmol/l µmol/l × 0.244 = mg/l
Clinical pharmacology	
• Indications for TDM:	Tailoring dosing of ribavirin as comedication with pegylated interferon-alpha2 for the treatment of chronic hepatitis C infection
• Protein binding:	Not known
• Elimination half-life:	Up to 300 h (comedication dependent, large interindividual variability)
• Volume of distribution:	Not known
• Metabolism:	
– Main metabolic pathways:	1) reversible phosphorylation, 2) deribosylation and amide hydrolysis
– Active metabolite(s)?	Phosphorylated ribavirin (intracellular)
– Inhibitor or inductor of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions:	Not known
• Elimination:	Renal
• Typical therapeutic range:	Not defined; 3.0–4.0 mg/l (12.27–16.36 µmol/l) anticipated for treatment of chronic hepatitis C in combination with interferon-alpha2
• Potentially toxic concentration:	Not known
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology:	4–8 weeks
• Time for blood sampling:	4 h after drug administration
• Type(s) of sample:	Plasma or serum (plasma preferred)
• Stability:	1 week at 4 °C
Remarks	Samples should be centrifuged shortly after blood collection
References	• Tsubota A, Hirose Y, Izumi N, Kumada H. Pharmacokinetics of ribavirin in combined interferon-alpha 2b and ribavirin therapy for chronic hepatitis C virus infection. Br J Clin Pharmacol 2003;55:360–7. • Larrat S, Stanke-Labesque F, Plages A, Zarski JP, Bessard G, Souvignet C. Ribavirin quantification in combination treatment of chronic hepatitis C. Antimicrob Agents Chemother 2003;47:124–9. • Martin P, Jensen DM. Ribavirin in the treatment of chronic hepatitis C. J Gastroenterol Hepatol 2008;23:844–55. • Stanke-Labesque F, Loustaud-Ratti V, Babany G, Gagnieu Mc, Marquet P. Ribavirin therapeutic drug monitoring: why, when and how? Fundam Clin Pharmacol 2010;24:401–6. • Marquet P, Sauvage FL, Loustaud-Ratti V, Babany G, Rousseau A, Lachâtre G. Stability of ribavirin concentrations depending on the type of blood collection tube and preanalytical conditions. Ther Drug Monit 2010;32:237–41. • Bosch ME, Sanchez AJ, Rojas FS, Ojeda CB. Ribavirin: analytical determinations since the origin until today. J Pharm Biomed Anal 2007;45:185–93. • Breadmore MC, Theurillat R, Thormann W. Determination of ribavirin in human serum and plasma by capillary electrophoresis. Electrophoresis 2004;25:1615–22.

Salicylate

General	
• Class of the drug:	Analgesics
• Synonym(s):	Salicylic acid
• Common trade name(s) in Germany:	Acesal©, Aspirin©, Godamed©, Togal© ASS (acetylsalicylic acid = ASA)
• Conversion factors:	mg/l × 0.00724 = mmol/l mmol/l × 138 = mg/l
Clinical pharmacology	
• Indications for TDM:	Intoxication
• Protein binding:	90%–95% at < 100 mg/l, 50% at >400 mg/l (albumin), saturable in case of intoxication
• Elimination half-life:	ASA: 15 minutes Salicylate: 2–4.5 hours (15–30 hours if dose >3 g and in intoxications)
• Volume of distribution:	0.1–0.2 l/kg (dose and pH dependent)
• Metabolism:	
– Main metabolic pathways:	Hepatic: ASA esterolysis to salicylate; metabolism of salicylic acid to salicyluric acid and gentisic acid and their glucuronides
– Active metabolite(s)?	Salicylic acid is the active metabolite of ASA
– Inhibitor or inductor of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions:	None
• Elimination of parent drug:	ASA: mainly hepatic Salicylic acid: mainly hepatic
• Typical therapeutic range:	Analgesia, antipyresis: <100 mg/l (<0.724 mmol/l) Anti-inflammatory: 150–300 mg/l (1.086–2.172 mmol/l)
• Potentially toxic concentration:	>400 mg/l (>2.896 mmol/l) 6 hours after ingestion Limited utility of the Done nomogram as it can not be used to predict chronic toxicity. ***Caution: at high concentrations (800–1000 mg/l, 5.8–7.2 mmol/l) the plasma concentration could underestimate the total body salicylate.***
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology:	Therapeutic dosage: time to steady state 1–5 days (dose dependent) Intoxication: modified kinetic parameters
• Time for blood sampling:	Acute intoxication: min. 6 hours after ingestion Therapeutic: 1–3 hours after ingestion (Cmax)
• Type(s) of sample:	Serum or plasma
• Stability:	8 h at room temperature 48 h at 4 °C
Remarks	Alkalinization of the urine (pH 8) increases renal clearance.
References	• Fenton, J. The laboratory and the poisoned patient, AACC Press, Washington: 1998, 304–309. • Olson, KK. Poisoning and drug overdose, Appleton & Lange, Hemel Hempstead: 1990, 261–264. • Tietz, NW. Clinical guide to laboratory tests, 3rd Edition, Saunders, Philadelphia: 1995, 856–859Arzneimittelkompendium Schweiz. Basel: Documed 2006. • White S, Wong SH. Standards of laboratory practice: analgesic drug monitoring. National Academy of Clinical Biochemistry. Clin Chem 1998;44:1110–23. • Dargan PI, Wallace CI, Jones AL. An evidence based flowchart to guide the management of acute salicylate (aspirin) overdose. Emerg Med J 2002;19:206–9.

Theophylline

General	
• Class of the drug:	Bronchodilators
• Synonym(s):	
• Common trade name(s) in Germany:	Afonilum©, Afpred©, Bronchoretard©, Euphylong©, Solosin©, Theo CT©, Uniphyllin©
• Conversion factors:	mg/l × 5.55 = μmol/l μmol/l × 0.180 = mg/l
Clinical pharmacology	
• Indications for TDM:	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding:	60% (40% in newborns)
• Elimination half-life:	4–9 h (3–5 h for children <12 years old; 30 h for newborns)
• Volume of distribution:	0.5 l/kg
• Metabolism:	
– Main metabolic pathways:	Oxidation and N-demethylation to 3-methylxanthine and 1,3-dimethyluric acid (CYP1A2, CYP2E1)
– Active metabolite(s)?	3-methylxanthine (20–50% activity of theophylline), caffeine in newborns
– Inhibitor or inductor of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions:	Increased metabolism in smokers
• Elimination of parent drug:	Hepatic >87% Renal <10% (greater in newborn)
• Typical therapeutic range:	10–20 mg/l (55.5–111 μmol/l)
• Potentially toxic concentration:	> 20 mg/l (>111 μmol/l)
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology:	2–3 days (adults), 1–2 days (children), 1–5 days (infants), 5 days (newborns)
• Time for blood sampling:	Before next dose at steady-state
• Type(s) of sample:	Serum or plasma
• Stability:	3 months at 25 °C
Remarks	None
References	• Arzneimittelkompendium Schweiz. Basel: Documed 2005. • Baselt, RC. Disposition of toxic drugs and chemicals in man, Foster City, CA: Biomedical Publications: 2002. • Schweizerische Gesellschaft für Klinische Pharmakologie und Toxikologie, Grundlagen der Arzneimitteltherapie (16. Auflage). Basel: Documed, 2005. • Guder WG, Narayanan S, Wisser H, Zawta B. List of Analytes Preanalytical Variables, German Society of Clinical Chemistry, 1996.

Schlüsselwörter: Coffein; Digoxin; Fluphenazin; Methadon; Methotrexat; Olanzapin; Ribavirin, Salicylat, Theophyllin

References

1. Rentsch K, Fathi M, Grignaschi N, Magnin JL, Printzen G, Thormann W, et al. Monographs 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.
3. Rentsch K, Eap CB, Fathi M, Grignaschi N, Magnin JL, Thormann W, et al. Monograph on drugs which are frequently analysed in therapeutic drug monitoring. J Lab Med 2008;32:372–81.
4. Rentsch K, Eap CB, Fathi M, Grignaschi N, Magnin JL, Thormann W, et al. Monographs on drugs which are frequently analysed in therapeutic drug monitoring. J Lab Med 2009;33:99–120.
5. Rentsch K, Buhl D, Eap CB, Fathi M, Jöchle W, Magnin JL, et al. Monographs on drugs which are frequently analysed in therapeutic drug monitoring. J Lab Med 2010;34:129–39.