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Drug monographs on drugs which are frequently analysed in the context of 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 were published last year by the working group "Drug Monitoring" of the Swiss Society of Clinical Chemistry (SSCC) [1], new monographs have been written. The aim of these monographs is to give an overview of the most important information necessary for ordering a drug analysis or interpreting the results. Therefore, the targeted readers comprise laboratory health professionals and all receivers of laboratory reports. There is information provided on the indication for therapeutic drug monitoring, protein binding, metabolic pathways and enzymes involved, elimination half-life and elimination routes, and on therapeutic or toxic concentrations.

Preanalytical considerations are of particular importance for therapeutic drug monitoring. Therefore, information is provided regarding a reasonable timing for the determination of drug concentrations as well as steady-state concentrations 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 in drug analysis, references to important publications are given.

The number of 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 and look forward to receiving comments from the audience.

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Keywords: cyclosporine A; haloperidol; lamotrigine; mirtazepine; mycophenolate; paroxetine; phenobarbital; sertralin; valproic acid.

Zusammenfassung

In Ergänzung zu den im letzten Jahr publizierten Arzneimittelmonographien der Arbeitsgruppe Medikamente der Schweizerischen Gesellschaft für Klinische Chemie (SGKC) [1] 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.

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 gemacht, zu welchem Zeitpunkt eine Bestimmung der Arzneimittelkonzentration sinnvoll ist und wann, nach einer Dosisänderung, der "steady-state" erreicht ist. Außerdem werden Informationen zur Stabilität der Medikamente bzw. ihrer Metaboliten nach der Blutentnahme gegeben. 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 Ihnen diese Monographien im Umgang mit dem Therapeutic Drug Monitoring hilfreich sein werden und freuen uns über Kommentare und Bemerkungen.

Schlüsselwörter: Ciclosporin A; Haloperidol; Lamotrigin; Mirtazepin; Mycophenolat; Paroxetin; Phenobarbital; Sertralin; Valproinsäure.

Cyclosporine

General	
• Class of the drug	Immunosuppressants
• Synonym(s)	
• Common trade name(s) in Germany	Cicloral® HEXAL®, Immunosporin®, Sandimmun®, Sandimmun Optoral®
• Conversion factors	*μg/L × 0.83 = nmol/L* *nmol/L × 1.20 = μg/L*
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	41–58% localized in erythrocytes; in plasma 90% bound to proteins, mainly lipoproteins
• Elimination half-life	5–18 h
• Volume of distribution	3–5 L/kg
• Metabolism	
– Main metabolic pathways	CYP3A4
– Active metabolite(s)	AM1 and AM9 have about 10% of the activity of cyclosporine
– Inhibitor or inducer of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions	P-glycoprotein substrate and inducer (e.g. St. John's Worth)
• Elimination of parent drug	Hepatic >94%, renal <6%
• Typical therapeutic range	Dependent on combination therapy and indication
• Potentially toxic concentration	>500 μg/L (C0)
Pre-analytics	
• Time to steady-state from beginning of treatment or change of posology	~2 days
• Time for blood sampling	Before next dose at steady state (C0) or 2 h after administration (C2)
• Type(s) of sample	Whole blood on EDTA
• Stability	5 days at 25°C
References	• Arzneimittelkompendium Schweiz, Basel: Documed 2005. • Armstrong VW, Oellerich M. New developments in the immunosuppressive drug monitoring of cyclosporine, tacrolimus, and azathioprine. Clin Biochem 2001;34:9–16. • Holt DW, Armstrong VW, Griesmacher A, Morris RG, Napoli KL, Shaw L. International Federation of Clinical Chemistry/International Association of Therapeutic Drug Monitoring. Therap Drug Monit 2002;24:59–67. • Kelly P, Kahan BD. Metabolism of immunosuppressant drugs. Curr Drug Metabol 2002;3:275–87. • Macphee IA, Fredericks S, Tai T, Syrris P, Carter N, Johnston A, et al. Tacrolimus pharmacogenetics: polymorphisms associated with expression of cytochrome p4503A5 and p-glycoprotein correlate with dose requirement. Transplantation 2002;74:1486–9. • 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.

Haloperidol

General	
• Class of the drug	Neuroleptics
• Synonym(s)	
• Common trade name(s) in Germany	Haldol®, Haldol® decanoas
• Conversion factors	*μg/L × 2.66 = nmol/L* *nmol/L × 0.38 = μg/L*
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	92%
• Elimination half-life	24 h (12–38 h)
• Volume of distribution	7.9±2.5 L/kg
• Metabolism	
– Main metabolic pathways	CYP3A4, CYP2D6 and reduction
– Active metabolite(s)	None
– Inhibitor or inducer of the cytochrome P450 system?	Reduced haloperidol (metabolite; inhibits CYP2D6)
– Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Mainly hepatic
• Typical therapeutic range	3.8–38.0 μg/L (10–100 nmol/L)
• Potentially toxic concentration	49.4 μg/L (>130 nmol/L)
Pre-analytics	
• Time to steady-state from beginning of treatment or change of posology	~5 days
• Time for blood sampling	Before next dose at steady state
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C
References	• Arzneimittelkompendium Schweiz, Basel: Documed 2005. • 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. • Helle A, Peterson A. Therapeutic drug monitoring of haloperidol, perphenazine, and zuclopenthixol in serum by a fully automated sequential solid phase extraction followed by high-performance liquid chromatography. Ther Drug Monit 2001;23:157–62. • Llerena A, Dahl ML, Ekqvist B, Bertilsson L. Haloperidol disposition is dependent on debrisoquine hydroxylation phenotype. Ther Drug Monit 1992;14:92–7. • Pan L, Rosseel MT, Belpaire FM. Comparison of two high-performance liquid chromatographic methods for monitoring plasma concentrations of haloperidol and reduced haloperidol. Ther Drug Monit 1998;20:224–30.

Lamotrigine

General	
• Class of the drug	Antiepileptics
• Synonym(s)	
• Common trade name(s) in Germany	Lamictal®, elmendos®
• Conversion factors	*mg/L* × *3.90* = *μmol/L* *μmol/L* × *0.256* = *mg/L*
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, verification of compliance
• Protein binding	55%
• Elimination half-life	25 h (60 h in presence of valproate, 15 h in presence of phenytoin, carbamazepine or phenobarbital)
• Volume of distribution	1–1.4 L/kg
• Metabolism	
– Main metabolic pathways	N-glucuronidation
– Active metabolite(s)	None
– Inhibitor or inducer of the cytochrome P450 system?	Not known
– Other significant pharmacokinetic interactions	• Coadministration with valproic acid results in decreased elimination of lamotrigine • Coadministration with enzyme inducing drugs, including carbamazepine, phenytoin and phenobarbital, results in increased elimination
• Elimination of parent drug	Mainly hepatic, renal 10%
• Typical therapeutic range	3–14 mg/L (12–56 μmol/L)
• Potentially toxic concentration	Not known
Pre-analytics	
• Time to steady-state from beginning of treatment or change of posology	4–5 days
• Time for blood sampling	Before next dose at steady state
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C
References	• Arzneimittelkompendium Schweiz, Basel: Documed 2005. • Johannessen SI, Battino D, Berry DJ, Bialer M, Kramer G, Tomson T, et al. Therapeutic drug monitoring of the newer antiepileptic drugs. Ther Drug Monit 2003;25:347–63. • Morris RG, Black AB, Harris AL, Batty AL, Sallustio BC. Lamotrigine and therapeutic drug monitoring: retrospective survey following the introduction of a routine service. Br J Clin Pharmacol 1998;46:547–51. • Morris RG, Lee MY, Cleanthous X, Black AB. Long-term follow-up using a higher target range for lamotrigine monitoring. Ther Drug Monit 2004;26:626–32. • Neels HM, Sierens AC, Naelaerts K, Scharpe SL, Hatfield GM, Lambert WE. Therapeutic drug monitoring of old and newer anti-epileptic drugs. Clin Chem Lab Med 2004;42:1228–55.

Mirtazapine

General	
• Class of the drug	Antidepressants
• Synonym(s)	
• Common trade name(s) in Germany	Remergil®
• Conversion factors	
Mirtazapine:	*μg/L × 3.77 = nmol/L*
	nmol/L × 0.26 = μg/L
Desmethylmirtazapine:	*μg/L × 3.97 = nmol/L*
	nmol/L × 0.25 = μg/L
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	85%
• Elimination half-life	20–40 h
• Volume of distribution	4.5 L/kg
• Metabolism	
– Main metabolic pathways	CYP3A4, CYP2D6, CYP1A2
– Active metabolite(s)	Desmethylmirtazapine
– Inhibitor or inducer of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Hepatic >80%, renal <20%
• Typical therapeutic range	
Mirtazapine:	10.4–31.2 μg/L (40–120 nmol/L)
Desmethylmirtazapine:	5.0–20.0 μg/L (20–80 nmol/L)
• Potentially toxic concentration	Not known
Pre-analytics	
• Time to steady-state of treatment or change of posology	~5 days from beginning
• Time for blood sampling	Before next dose at steady state
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C
References	• Arzneimittelkompendium Schweiz, Basel: Documed 2005. • 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. • Delbressine LP, Moonen ME, Kaspersen FM, Wagenaars GN, Jacobs PL, Timmer CJ, et al. Pharmacokinetics and biotransformation of mirtazapine in human volunteers. Clin Drug Invest 1998;15:45–56. • Pistos C, Koutsopoulou M, Panderi I. A validated liquid chromatographic tandem mass spectrometric method for the determination of mirtazapine and desmethylmirtazapine in human plasma: application to a pharmacokinetic study. Anal Chim Acta 2004;514:15–26. • Shams M, Hiemke C, Hartter S. Therapeutic drug monitoring of the antidepressant mirtazapine and its N-demethylated metabolite in human serum. Ther Drug Monit 2004;26:78–84.

Mycophenolate (MPA)

General	
• Class of the drug	Immunosuppressants
• Synonym(s)	Mycophenolic acid
• Common trade name(s) in Germany	CellCept®, Myfortic®
• Conversion factors	*mg/L* × *3.12* = *μmol/L* *μmol/L* × *0.32* = *mg/L*
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, symptoms of rejection or toxicity
• Protein binding	97–99% (mainly to albumin)
• Elimination half-life	17 h
• Volume of distribution	4 L/kg
• Metabolism:	
– Main metabolic pathways	Glucuroconjugation to form 7-O-MPA-glucuronide (MPAG); two other metabolites are 7-O-glucoside-MPA and acylglucuronide-MPA (AcMPAG)
– Active metabolite(s)	AcMPAG
– Inhibitor or inducer of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Mainly hepatic
• Typical therapeutic range	Dependent on combination therapy and indication
• Potentially toxic concentration	>10 mg/L
Pre-analytics	
• Time to steady-state from beginning of treatment or change of posology	~3 days
• Time for blood sampling	Before next dose at steady state or at different time points for the determination of the area-under-the-curve (AUC)
• Type(s) of sample	Plasma on EDTA
• Stability	5 days at 25°C
Remarks	• Mycophenolate mofetil (MMF) is a prodrug for the active MPA. • Most immunoassays cross-react with the active metabolite. • The AUC correlates better with the inhibition of the inosine monophosphate dehydrogenase (IMPDH) than the trough level.
References	• Arzneimittelkompendium Schweiz, Basel: Documed 2005. • Holt DW, Armstrong VW, Griesmacher A, Morris RG, Raymond G, Napoli K, et al. International Federation of Clinical Chemistry/International Association of Therapeutic Drug Monitoring and Clinical Toxicology working group on immunosuppressive drug monitoring. Therap Drug Monit 2002;24:59–67. • Shaw LM, Nicholls A, Hale M, Holt DW, Venkataramanan R, Haley J, et al. Therapeutic drug monitoring of mycophenolic acid: A consensus panel. Clin Biochem 1998;31:317–22.

Paroxetine

General	
• Class of the drug	Antidepressants
• Synonym(s)	
• Common trade name(s) in Germany	Seroxat®, Tagonis®
• Conversion factors	*μg/L × 3.03 = nmol/L* *nmol/L × 0.33 = μg/L*
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	95%
• Elimination half-life	24 h (6–71 h)
• Volume of distribution	17 L/kg
• Metabolism	
– Main metabolic pathways	CYP2D6 and other CYP enzymes
– Active metabolite(s)	None
– Inhibitor or inducer of the cytochrome P450 system?	Inhibitor of CYP2D6
– Other significant pharmacokinetic interactions	Not known
• Elimination of parent drug	Hepatic 36%, renal 64%
• Typical therapeutic range	39.6–122 μg/L (120–370 nmol/L)
• Potentially toxic concentration	Not known
Pre-analytics	
• Time to steady-state from beginning of treatment or change of posology	~5 days
• Time for blood sampling	Before next dose at steady state
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C
References	• Arzneimittelkompendium Schweiz, Basel: Documed 2005. • 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. • Foglia JP, Sorisio D, Kirshner M, Pollock BG. Quantitative determination of paroxetine in plasma by high-performance liquid chromatography and ultraviolet detection. J Chrom B 1997;693:147–51. • Linder MW, Keck PE Jr. Standards of laboratory practice: antidepressant drug monitoring. National Academy of Clinical Biochemistry. Clin Chem 1998;44:1073–84. • Lucca A, Gentilini G, Lopez-Silva S, Soldarini A. Simultaneous determination of human plasma levels of four selective serotonin reuptake inhibitors by high-performance liquid chromatography. Ther Drug Monit 2000;22:271–6. • Montgomery SA. Efficacy of long-term treatment of depression. J Clin Psychiatry 1996;57:24–30.

Phenobarbital

General	
• Class of the drug	Antiepileptics
• Synonym(s)	
• Common trade name(s) in Germany	Luminal®, Luminaletten®
• Conversion factors	*mg/L × 4.31 = μmol/L* *μmol/L × 0.232 = mg/L*
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	50% (to albumin)
• Elimination half-life	50–150 h (varies with age, urinary pH, hepatic and renal function)
• Volume of distribution	0.7 L/kg
• Metabolism	
– Main metabolic pathways	Hydroxylation by P450 cytochromes to form p-hydroxyphenobarbital followed by glucuro- or sulfoconjugation
– Active metabolite(s)	None
– Inhibitor or inducer of the cytochrome P450 system?	Inducer of cytochromes CYP3A4 and CYP2C9 (also auto-induction)
– Other significant pharmacokinetic interactions	Interaction with valproic acid (phenobarbital levels increase)
• Elimination of parent drug	Hepatic 75%, renal 25%
• Typical therapeutic range	15–40 mg/L (64–172 μmol/L)
• Potentially toxic concentration	>50 mg/L (>216 μmol/L)
Pre-analytics	
• Time to steady-state from beginning of treatment or change of posology	10–30 days
• 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)
References	• Arzneimittelkompendium Schweiz, Basel: Documed 2005. • Schweizerische Gesellschaft für Klinische Pharmakologie und Toxikologie, Grundlagen der Arzneimitteltherapie (16. Auflage), Basel: Documed, 2005. • Neels HM, Sierens AC, Naelaerts K, Scharpe SL, Hatfield GM, Lambert WE. Therapeutic drug monitoring of old and newer anti-epileptic drugs. Clin Chem Lab Med 2004;42:1228–55. • Warner A, Privitera M, Bates D. Standards of laboratory practice: antiepileptic drug monitoring. Clin Chem 1998;44:1085–95.

Sertraline

General	
• Class of the drug	Antidepressants
• Synonym(s)	
• Common trade name(s) in Germany	Gladem®, Zoloft®
• Conversion factors	*μg/L × 3.26 = 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	98%
• Elimination half-life	22–36 h for sertraline 62–104 h for N-desmethylsertraline
• Volume of distribution	>20 L/kg
• Metabolism	
– Main metabolic pathways	CYP3A4, CYP2D6, CYP2B6, CYP2C9
– Active metabolite(s)	N-Desmethylsertraline
– Inhibitor or inducer of the cytochrome P450 system?	Weak inhibitor of CYP2D6 and CYP3A4
– Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Hepatic 50%, renal 50%
• Typical therapeutic range	12.4–62.0 μg/L (40–200 nmol/L)
• Potentially toxic concentration	Not known
Pre-analytics	
• Time to steady-state from beginning of treatment or change of posology	~5 days
• Time for blood sampling	Before next dose at steady state
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C
References	• Arzneimittelkompendium Schweiz, Basel: Documed 2005. • 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. • Linder MW, Keck PE Jr. Standards of laboratory practice: antidepressant drug monitoring. National Academy of Clinical Biochemistry. Clin Chem 1998;44:1073–84. • Lucca A, Gentilini G, Lopez-Silva S, Soldarini A. Simultaneous determination of human plasma levels of four selective serotonin reuptake inhibitors by high-performance liquid chromatography. Ther Drug Monit 2000;22:271–6. • Montgomery SA. Efficacy of long-term treatment of depression. J Clin Psychiatry 1996;57:24–30.

Valproic acid

General	
• Class of the drug	Antiepileptics
• Synonym(s)	Valproate
• Common trade name(s) in Germany	Convulex®, Ergenyl®, Orfiril®
• Conversion factors	*mg/L × 6.93 = μmol/L* *μmol/L × 0.144 = mg/L*
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	85 to 95% at low concentration, decreases to 70% with higher dosing (mainly to albumin)
• Elimination half-life	5–20 h
• Volume of distribution	0.13–0.15 L/kg
• Metabolism	
– Main metabolic pathways	Glucuroconjugation by uridine diphosphate glucuronosyltransferases (~50%), mitochondrial β-oxydation (~40%) and P-450 oxidation (~10%)
– Active metabolite(s)	Present but not clinically relevant
– Inhibitor or inducer of the cytochrome P450 system?	Inhibitor of cytochromes CYP2C9 and CYP3A4
– Other significant pharmacokinetic interactions	Numerous interactions, in particular with other antiepileptics (e.g. phenytoin, lamotrigine, phenobarbital)
• Elimination of parent drug	Hepatic >95%, renal <3%
• Typical therapeutic range	50–100 mg/L (347–693 μmol/L)
• Potentially toxic concentration	>120 to 150 mg/L (>832–1040 μmol/L)
Pre-analytics	
• Time to steady-state from beginning of treatment or change of posology	2–4 days
• 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	In patients with renal insufficiency the free valproic acid concentration should be determined due to reduced protein binding.
References	• Arzneimittelkompendium Schweiz, Basel: Documed 2005. • Schweizerische Gesellschaft für Klinische Pharmakologie und Toxikologie, Grundlagen der Arzneimitteltherapie (16. Auflage), Basel: Documed, 2005. • DeVane CL. Pharmacokinetics, drug interactions, and tolerability of valproate. Psychopharmacol Bull 2003;37(Suppl 2):25–42. • 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. Clin Chem 1998;44:1085–95.

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