

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.sccc.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.sgcc.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: $\text{mg/l} \times 5.15 = \mu\text{mol/l}$
 $\mu\text{mol/l} \times 0.194 = \text{mg/l}$

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 $\mu\text{mol/l}$)
- Potentially toxic concentration: >15–20 mg/l (>77–103 $\mu\text{mol/l}$)

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: $\mu\text{g/l} \times 1.28 = \text{nmol/l}$
 $\text{nmol/l} \times 0.781 = \mu\text{g/l}$

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 inducer 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 Wort).
- Elimination of parent drug: Hepatic: 5–20%
Renal: 60–80%
- Typical therapeutic range: 0.8–2 $\mu\text{g/l}$ (1.0–2.6 nmol/l)
- Potentially toxic concentration: >2.5 $\mu\text{g/l}$ (>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 $\mu\text{g/l}$)

References

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- 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: $\mu\text{g/l} \times 2.28 = \text{nmol/l}$
 $\text{nmol/l} \times 0.43 = \mu\text{g/l}$

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: $11 \pm 10 \text{ l/kg}$ (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: $0.5\text{--}2.0 \mu\text{g/l}$ ($1.14\text{--}4.57 \text{ nmol/l}$)
- Potentially toxic concentration: $>43 \mu\text{g/l}$ ($>100 \text{ nmol/l}$)

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

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- Glazer WM. Fluphenazine decanoate, its steady-state pharmacologic profile and relationship to tardive dyskinesia. *Schizophr Res.* 1988;6:425–9.
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Methadone

General

- Class of the drug: Analgesics
- Synonym(s):
- Common trade name(s) in Germany: Eptadone[®], Methaddict[®]
- Conversion factors: $\text{mg/l} \times 3.23 = \mu\text{mol/l}$
 $\mu\text{mol/l} \times 0.309 = \text{mg/l}$

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 inducer 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 $\mu\text{mol/l}$)
Pain treatment: 0.02–0.09 mg/l (0.064–0.29 $\mu\text{mol/l}$)
- Potentially toxic concentration: Non tolerant patients: toxic > 0.5 mg/l (1.61 $\mu\text{mol/l}$)
coma: > 1.0 mg/l (3.23 $\mu\text{mol/l}$)

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

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- Baselt, RC. Disposition of toxic drugs and chemicals in man, Foster City, CA: Biomedical Publications: 2002.
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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: $\text{mg/l} \times 2.20 = \mu\text{mol/l}$
 $\mu\text{mol/l} \times 0.455 = \text{mg/l}$

Clinical pharmacology

- Indications for TDM: To ensure that plasma concentrations after infusion are $<0.46 \text{ mg/l}$ at 48 h and $<0.046 \text{ mg/l}$ at 72 h and to adapt leucovorin rescue
- Protein binding: 50%–60% (albumin)
- Elimination half-life: 5–9 h ($t_{\alpha} = 0.75 \text{ h}$; $t_{\beta} = 2\text{--}3 \text{ h}$; $t_{\gamma} = 6\text{--}20 \text{ h}$)
- 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: $>4.6 \text{ mg/l}$ after 24 h
 $>0.46 \text{ mg/l}$ after 48 h
 $>0.046 \text{ mg/l}$ 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, Grundlegend er 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: $\mu\text{g/l} \times 3.20 = \text{nmol/l}$
 $\text{nmol/l} \times 0.31 = \mu\text{g/l}$

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: $21.9 \pm 3.2 \text{ l/kg}$
- Metabolism:
 - Main metabolic pathways: CYP1A2, CYP2D6 (moderate)
 - Active metabolite(s)? Desmethylolanzapine, minor activity
 - Inhibitor or inducer of the cytochrome P450 system? Not known
 - Other significant pharmacokinetic interactions: Not known
- Elimination: Mainly hepatic
- Typical therapeutic range: 20–80 $\mu\text{g/l}$ (64–256 nmol/l)
- Potentially toxic concentration: $>186 \mu\text{g/l}$ ($>600 \text{ nmol/l}$)

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 $-20 \text{ }^\circ\text{C}$

Remarks

Fluvoxamine, a specific inhibitor of CYP1A2, inhibits significantly the olanzapine metabolism

References

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Ribavirin

General

- Class of the drug: Antiviral drugs
- Synonym(s):
- Common trade name(s) in Germany: Copegus[®], Rebetol[®], Virazol[®]
- Conversion factors: mg/l \times 4.09 = μ mol/l
 μ mol/l \times 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 inducer 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 μ mol/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

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Salicylate

General

- Class of the drug: Analgesics
- Synonym(s): Salicylic acid
- Common trade name(s) in Germany: Acesal[®], Aspirin[®], Godamed[®], Togonal[®] ASS (acetylsalicylic acid = ASA)
- Conversion factors: $\text{mg/l} \times 0.00724 = \text{mmol/l}$
 $\text{mmol/l} \times 138 = \text{mg/l}$

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 inducer 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 (C_{max})
- 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

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Theophylline

General

- Class of the drug: Bronchodilators
- Synonym(s):
- Common trade name(s) in Germany: Afonilum[®], Afpred[®], Bronchoretard[®], Euphyllong[®], Solosin[®], Theo CT[®], Uniphyllin[®]
- Conversion factors: $\text{mg/l} \times 5.55 = \mu\text{mol/l}$
 $\mu\text{mol/l} \times 0.180 = \text{mg/l}$

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 $\mu\text{mol/l}$)
- Potentially toxic concentration: > 20 mg/l (>111 $\mu\text{mol/l}$)

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

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- Arzneimittelkompendium Schweiz. Basel: Documed 2005.
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Schlüsselwörter: Coffein; Digoxin; Fluphenazin; Methadon; Methotrexat; Olanzapin; Ribavirin, Salicylat, Theophyllin

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