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Monographs on drugs which are frequently analyzed in therapeutic drug monitoring

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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 recently by the working group “Drug Monitoring” of the Swiss Society of Clinical Chemistry (SSCC) [1–3], new monographs have been written. The aim of these monographs is to provide an overview on the information which is important for the request and interpretation of the results. Therefore, the targeted readers are laboratory health professionals and the receivers of the reports. In this series, several antidepressant and antipsychotic drugs are presented. It is worth noting that the monograph on the antipsychotic clozapine has already been published in 2005 [1]. Information on the indications for therapeutic drug monitoring (TDM), protein binding, metabolic pathways and enzymes involved, elimination half-life time and elimination route(s) of the parent drug and therapeutic or toxic concentrations is provided. Because pre-analytical considerations are of particular importance for therapeutic drug monitoring, information regarding the optimal point in time for the determination of drug concentrations and achievement of steady-state concentrations after changing the dose is given. Furthermore, the stability of the drug and its metabolite(s) after blood sampling is described. For readers with a specific interest, references to important publications are provided. The number of the monographs will be continuously increased. The updated files are presented on the

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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 comments by the readers.

Keywords: antidepressants; antipsychotics.

Zusammenfassung

In Ergänzung zu den in den letzten vier Jahren publizierten Arzneimittelmonographien der Arbeitsgruppe Medikamente der Schweizerischen Gesellschaft für Klinische Chemie (SGKC) [1–3], sind nun weitere Monographien erstellt worden. Ziel dieser Monographien ist es, dem Labormediziner bzw. dem Empfänger der Befunde eine Übersicht über die wichtigsten Informationen zu geben, die für die Veranlassung einer Analyse bzw. für die Interpretation der Resultate hilfreich sind. In dieser Serie werden eine große Zahl von Antidepressiva und Antipsychotika präsentiert. Es muss noch darauf hingewiesen werden, dass die Monographie zu Clozapin, Neuroleptikum, bereits 2005 publiziert worden ist [1]. In den einzelnen Monographien 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 Angaben über die Stabilität der Medikamente bzw. ihrer Metaboliten nach der Blutentnahme gemacht. Für die interessierten Leser sind die verwendeten Referenzen als Zitate aufgeführt. Die Zahl der Monographien wird fortlaufend ergänzt. Die aktuellsten Versionen der Monographien sind auf der Homepage der SGKC abrufbar (www.sccc.ch). Wir hoffen, dass diese Monographien im Umgang mit dem Therapeutic Drug Monitoring hilfreich sein werden und freuen uns über Kommentare und Bemerkungen.

Schlüsselwörter: Antidepressiva; Antipsychotika.

Amisulpride

General

• Class of the drug	Antipsychotics
• Synonym(s)	–
• Common trade name(s) in Germany	Solian®
• Conversion factors	$\mu\text{g/L} \times 2.706 = \text{nmol/L}$ $\text{nmol/L} \times 0.370 = \mu\text{g/L}$

Clinical pharmacology

• Indications for TDM	Individual dose adaptation, verification of compliance, suspicion of toxicity, side effects
• Protein binding	16%
• Elimination half-life	12 h
• Volume of distribution	6 L/kg
• Metabolism	
– Main metabolic pathways	Weakly metabolized (approximately 12% of the dose)
– Active metabolite(s)?	None
– Inhibitor or inducer of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Renal (approximately 70%)
• Typical therapeutic range	100–400 $\mu\text{g/L}$ (270–1080 nmol/L)
• Potentially toxic concentration	Not known [overdose: 10,000 $\mu\text{g/L}$ (27,060 nmol/L), fatality: 42,000 $\mu\text{g/L}$ (113,652 nmol/L)]

Pre-analytics

• Time to steady-state since beginning of treatment or change of posology	2–3 days
• 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. Basel: Documed, 2007.
- Moffat AC, Osselton D, Widdop B, editors. Clarke's analysis of drugs and poisons in pharmaceuticals, body fluids and post-mortem material. 3rd ed. London/Chicago, IL: Pharmaceutical Press, 2003.
- Service of Pharmacology and Clinical Toxicology, University Hospital of Geneva.
http://pharmacoclin.hug-ge.ch/_library/pdf/cytp450.pdf (accession date 27 December 2007).
- 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.

Amitriptyline

General

• Class of the drug	Antidepressants
• Synonym(s)	–
• Common trade name(s) in Germany	Saroten [®]
• Conversion factors	Amitriptyline: $\text{mg/L} \times 3.61 = \mu\text{mol/L}$ $\mu\text{mol/L} \times 0.277 = \text{mg/L}$ Nortriptyline: $\text{mg/L} \times 3.80 = \mu\text{mol/L}$ $\mu\text{mol/L} \times 0.263 = \text{mg/L}$

Clinical pharmacology

• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	90%–95% (albumin, α 1-acid glycoprotein)
• Elimination half-life	17–40 h
• Volume of distribution	6–10 L/kg
• Metabolism	
– Main metabolic pathways	CYP2D6, CYP3A, CYP2C19
– Active metabolite(s)?	Nortriptyline, 10-hydroxyamitriptyline and 10-hydroxynortriptyline
– Inhibitor or inducer of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Mainly hepatic
• Typical therapeutic range	0.080–0.200 mg/L (0.288–0.722 $\mu\text{mol/L}$) (amitriptyline + nortriptyline)
• Potentially toxic concentration	>0.500 mg/L (>1.80 $\mu\text{mol/L}$) (amitriptyline + nortriptyline)

Pre-analytics

• Time to steady-state since beginning of treatment or change of posology	7–10 days
• Time for blood sampling	Before next dose at steady-state or 12–16 h after last dose
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C

Remarks

None

References

- Arzneimittelkompendium Schweiz. Basel: Documed, 2006.
- Baselt RC. Disposition of toxic drugs and chemicals in men, 7th ed. Foster City, CA: Biomedical Publications, 2004.
- Schweizerische Gesellschaft für Klinische Pharmakologie und Toxikologie, Grundlagen der Arzneimitteltherapie (16. Auflage). Basel: Documed, 2005.
- Evans WE, Oellerich M, Holt DW. Therapeutic drug monitoring: clinical guide, 2nd ed. Wiesbaden: Abbott Laboratories, Diagnostic Division, 1994.
- 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.

Aripiprazole

General

• Class of the drug	Antipsychotics
• Synonym(s)	–
• Common trade name(s) in Germany	Abilify®
• Conversion factors	Aripiprazole: $\mu\text{g/L} \times 2.23 = \text{nmol/L}$ $\text{nmol/L} \times 0.448 = \mu\text{g/L}$ Dehydroaripiprazole: $\mu\text{g/L} \times 2.24 = \text{nmol/L}$ $\text{nmol/L} \times 0.446 = \mu\text{g/L}$

Clinical pharmacology

• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	99%
• Elimination half-life	75 h
• Volume of distribution	5 L/kg
• Metabolism	
– Main metabolic pathways	CYP3A4, CYP2D6
– Active metabolite(s)?	Dehydroaripiprazole
– Inhibitor or inducer of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Mainly hepatic
• Typical therapeutic range	Preliminary data: Aripiprazole: 100–300 $\mu\text{g/L}$ (220–670 nmol/L)
• Potentially toxic concentration	Not known

Pre-analytics

• Time to steady-state since beginning of treatment or change of posology	~ 2 weeks
• Time for blood sampling	Before next dose at steady-state
• Type(s) of sample	Serum or plasma
• Stability	Several days at 4°C

Remarks

Almost no studies available on TDM of aripiprazole and its main active metabolite dehydroaripiprazole.

References

- Arzneimittelkompendium Schweiz. Basel: Documed, 2006.
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- Kirschbaum KM, Müller MJ, Zernig G, Saria A, Moascher A, et al. Therapeutic drug monitoring of aripiprazole by HPLC with column-switching and spectrophotometric detection. *Clin Chem* 2005;51:1718–21.

Clomipramine

General

- | | |
|-----------------------------------|---|
| • Class of the drug | Antidepressants |
| • Synonym(s) | – |
| • Common trade name(s) in Germany | Anafranil® |
| • Conversion factors | mg/L × 3.18 = μmol/L
μmol/L × 0.315 = mg/L |

Clinical pharmacology

- | | |
|--|---|
| • Indications for TDM | Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity |
| • Protein binding | 90–98% (albumin, α1-glycoprotein) |
| • Elimination half-life | Clomipramine: 19–37 h
N-Desmethyldomipramine: 54–77 h |
| • Volume of distribution | 12–17 L/kg |
| • Metabolism | |
| – Main metabolic pathways | CYP2D6, CYP3A4, CYP1A2 |
| – Active metabolite(s)? | N-Desmethyldomipramine |
| – Inhibitor or inductor of the cytochrome P450 system? | No |
| – Other significant pharmacokinetic interactions | None |
| • Elimination of parent drug | Mainly hepatic |
| • Typical therapeutic range | Clomipramine + N-Desmethyldomipramine: 0.175–0.450 mg/L (0.557–1.43 μmol/L) |
| • Potentially toxic concentration | >0.450 mg/L (>1.272 μmol/L) |

Pre-analytics

- | | |
|---|---|
| • Time to steady-state since beginning of treatment or change of posology | 7–14 days |
| • Time for blood sampling | Before next dose at steady-state or 12–16 h after last dose |
| • Type(s) of sample | Serum or plasma |
| • Stability | 1 week at 4°C |

Remarks

None

References

- Arzneimittelkompendium Schweiz. Basel: Documed, 2005.
- Baselt RC. Disposition of toxic drugs and chemicals in men, 7th ed. Foster City, CA: Biomedical Publications, 2004.
- Schweizerische Gesellschaft für Klinische Pharmakologie und Toxikologie, Grundlagen der Arzneimitteltherapie (16. Auflage). Basel: Documed, 2005.
- Evans WE, Oellerich M, Holt DW. Therapeutic drug monitoring: clinical guide, 2nd ed. Abbott Laboratories, Diagnostic Division, 1994.
- 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.

Duloxetine

General

• Class of the drug	Antidepressants
• Synonym(s)	–
• Common trade name(s) in Germany	Yentreve®
• Conversion factors	$\mu\text{g/L} \times 3.37 = \text{nmol/L}$ $\text{nmol/L} \times 0.297 = \mu\text{g/L}$

Clinical pharmacology

• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	>90%
• Elimination half-life	8–17 h
• Volume of distribution	23 L/kg
• Metabolism	
– Main metabolic pathways	CYP1A2 and CYP2D6
– Active metabolite(s)?	None
– Inhibitor or inductor of the cytochrome P450 system?	Not known
– Other significant pharmacokinetic interactions	Not known
• Elimination of parent drug	Hepatic
• Typical therapeutic range	15–150 $\mu\text{g/L}$ (50–500 nmol/L)
• Potentially toxic concentration	Not known

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	Serum or plasma
• Stability	1 week at 4°C

Remarks

None

References

- Arzneimittelkompendium Schweiz. Basel: Documed, 2007.
- Anderson D, Reed S, Lintemoot J, Kegler S, De Quintana S, Sandberg M, et al. A first look at duloxetine (Cymbalta) in a postmortem laboratory. *J Anal Toxicol* 2006;30:576–80.
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Fluvoxamine

General

- | | |
|-----------------------------------|--|
| • Class of the drug | Antidepressants |
| • Synonym(s) | – |
| • Common trade name(s) in Germany | Fevarin® |
| • Conversion factors | $\mu\text{g/L} \times 3.141 = \text{nmol/L}$
$\text{nmol/L} \times 0.318 = \mu\text{g/L}$ |

Clinical pharmacology

- | | |
|---|---|
| • Indications for TDM | Individual dose adaptation, verification of compliance, suspicion of toxicity, side effects |
| • Protein binding | 80% (mainly to albumin) |
| • Elimination half-life | 17–22 h |
| • Volume of distribution | 25 L/kg |
| • Metabolism | |
| – Main metabolic pathways | CYP2D6 (major) |
| – Active metabolite(s)? | None |
| – Inhibitor or inducer of the cytochrome P450 system? | Strong inhibition: CYP1A2, CYP2C19
Moderate inhibition: CYP2C9, CYP2D6, CYP3A4/5 |
| – Other significant pharmacokinetic interactions | None |
| • Elimination of parent drug | Hepatic |
| • Typical therapeutic range | 150–300 $\mu\text{g/L}$ (470–940 nmol/L) |
| • Potentially toxic concentration | Not known |

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 | Serum or plasma |
| • Stability | 1 week at 4°C |

Remarks

None

References

- Arzneimittelkompendium Schweiz. Basel: Documed, 2007.
- Moffat AC, Osselton D, Widdop B, editors. Clarke's analysis of drugs and poisons in pharmaceuticals, body fluids and post-mortem material, 3rd ed. London/Chicago, IL: Pharmaceutical Press, 2003.
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- 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.

Haloperidol

General

• Class of the drug	Neuroleptics
• Synonym(s)	–
• Common trade name(s) in Germany	Haldol [®] , Haldol [®] decanoat
• Conversion factors	$\mu\text{g/L} \times 2.66 = \text{nmol/L}$ $\text{nmol/L} \times 0.38 = \mu\text{g/L}$

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	No
• Elimination of parent drug	Mainly hepatic
• Typical therapeutic range	$5.0\text{--}17.0$ $\mu\text{g/L}$ ($13.0\text{--}45.2$ nmol/L)
• Potentially toxic concentration	49.4 $\mu\text{g/L}$ (> 130 nmol/L)

Pre-analytics

• Time to steady-state since 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	One week at 4°C

Remarks

None

References

- Arzneimittelkompendium Schweiz. Basel: Documed, 2005.
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- Angelo HR, Petersen 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.
- 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.

Imipramine

General

• Class of the drug	Antidepressants
• Synonym(s)	–
• Common trade name(s) in Germany	Tofranil®
• Conversion factors	mg/L × 3.57 = μmol/L μmol/L × 0.280 = mg/L

Clinical pharmacology

• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	63–96%
• Elimination half-life	6–28 h (11–37 h)
• Volume of distribution	16–20 L/kg
• Metabolism	
– Main metabolic pathways	CYP2D6, CYP3A4, CYP2C19, CYP1A2
– Active metabolite(s)?	2-OH-imipramine, desipramine, 2-OH-desipramine
– Inhibitor or inducer of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions	None
• Elimination	Mainly hepatic
• Typical therapeutic range	Imipramine + Desipramine: 0.15–0.25 mg/L (0.54–0.89 μmol/L)
• Potentially toxic concentration	> 1.0 mg/L (> 3.57 μmol/L)

Pre-analytics

• Time to steady-state since beginning of treatment or change of posology	2–5 days
• Time for blood sampling	Before next dose at steady-state
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C

Remarks

None

References

- Arzneimittelkompendium Schweiz. Basel: Documed, 2005.
- Baselt RC. Disposition of toxic drugs and chemicals in men, 7th ed. Foster City, CA: Biomedical Publications, 2004.
- Schweizerische Gesellschaft für Klinische Pharmakologie und Toxikologie, Grundlagen der Arzneimitteltherapie (16. Auflage). Basel: Documed, 2005.
- Evans WE, Oellerich M, Holt DW. Therapeutic drug monitoring: clinical guide, 2nd ed. Abbott Laboratories, Diagnostic Division, 1994.
- 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.

Levomepromazine

General

- | | |
|-----------------------------------|---|
| • Class of the drug | Antipsychotics |
| • Synonym(s) | Methotrimeprazine |
| • Common trade name(s) in Germany | Neurocil® |
| • Conversion factors | $\mu\text{g/L} \times 3.05 = \text{nmol/L}$
$\text{nmol/L} \times 0.328 = \mu\text{g/L}$ |

Clinical pharmacology

- | | |
|--|---|
| • Indications for TDM | Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity |
| • Protein binding | 99% |
| • Elimination half-life | 15–30 h |
| • Volume of distribution | 30 L/kg |
| • Metabolism | |
| – Main metabolic pathways | CYP2D6 |
| – Active metabolite(s)? | None |
| – Inhibitor or inductor of the cytochrome P450 system? | Inhibition of CYP2D6 |
| – Other significant pharmacokinetic interactions | None |
| • Elimination of parent drug | Mainly hepatic |
| • Typical therapeutic range | 15–60 $\mu\text{g/L}$ (46–183 nmol/L) |
| • Potentially toxic concentration | >3660 $\mu\text{g/L}$ (> 1200 nmol/L) |

Pre-analytics

- | | |
|---|----------------------------------|
| • Time to steady-state since 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 |

Remarks

None

References

- Arzneimittelkompendium Schweiz. Basel: Documed, 2007.
- Brown G, Scott W, Walker S. Sedation in the intensive care unit. *Can J Hosp Pharm* 1996;49:279–80.
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Lithium

General

- | | |
|-----------------------------------|--|
| • Class of the drug | Antidepressant |
| • Synonym(s) | – |
| • Common trade name(s) in Germany | Quilonorm®: lithium carbonate
Togal CLASSIC®: lithium citrate |
| • Conversion factors | mmol/L × 6.94 = mg/L
mg/L × 0.144 = mmol/L |

Clinical pharmacology

- | | |
|---|---|
| • Indications for TDM | Mandatory for individual dose adaptation, verification of compliance, side effects, suspicion of toxicity |
| • Protein binding | 0% |
| • Elimination half-life | 15–30 h |
| • Volume of distribution | 0.7–0.9 L/kg |
| • Metabolism | |
| – Main metabolic pathways | No metabolism |
| – Active metabolite(s)? | None |
| – Inhibitor or inducer of the cytochrome P450 system? | No |
| – Other significant pharmacokinetic interactions | Numerous interactions with anti-inflammatory non-steroidal drugs, ACE inhibitors, various diuretics, ... |
| • Elimination of parent drug | Renal >95% |
| • Typical therapeutic range | 0.5–1.2 mmol/L |
| • Potentially toxic concentration | >1.5 mmol/L |

Pre-analytics

- | | |
|---|---|
| • Time to steady-state since beginning of treatment or change of posology | 5–7 days |
| • Time for blood sampling | Before next dose at steady-state |
| • Type(s) of sample | Serum |
| • Stability | 4 days at 4°C
For longer conservation, freeze at –20°C |

Remarks

None

References

- Arzneimittelkompendium Schweiz. Basel: Documed, 2005.
- Schweizerische Gesellschaft für Klinische Pharmakologie und Toxikologie, Grundlagen der Arzneimitteltherapie (15. Auflage). Basel: Documed, 2001.
- Magnin J-L. Lithium: médicament et outil diagnostic. *Labolife* 1997; 2:21.

Maprotiline

General

- | | |
|-----------------------------------|---|
| • Class of the drug | Antidepressants |
| • Synonym(s) | – |
| • Common trade name(s) in Germany | Ludiomil® |
| • Conversion factors | $\mu\text{g/L} \times 3.61 = \text{nmol/L}$
$\text{nmol/L} \times 0.277 = \mu\text{g/L}$ |

Clinical pharmacology

- | | |
|---|---|
| • Indications for TDM | Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity |
| • Protein binding | 90% |
| • Elimination half-life | 43–45 h |
| • Volume of distribution | 23–27 L/kg |
| • Metabolism | |
| – Main metabolic pathways | CYP2D6 |
| – Active metabolite(s)? | Desmethylmaprotiline |
| – Inhibitor or inducer of the cytochrome P450 system? | Not known |
| – Other significant pharmacokinetic interactions | None |
| • Elimination of parent drug | Mainly hepatic |
| • Typical therapeutic range | 125–200 $\mu\text{g/L}$ (451–720 nmol/L) |
| • Potentially toxic concentration | >554 $\mu\text{g/L}$ (>2000 nmol/L) |

Pre-analytics

- | | |
|---|----------------------------------|
| • Time to steady-state since beginning of treatment or change of posology | ~ 8 days |
| • 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. Basel: Documed, 2007.
- Kuss HJ, Sirch S, Zhao DY. Assay for maprotiline in human serum with improved sensitivity and selectivity. *J Chromatogr B Biomed Appl* 1994;656:245–9.
- König F, Wolfersdorf M, Löble M, Hauger B. Trimipramine and maprotiline plasma levels during combined treatment with moclobemide in therapy-resistant depression. *Pharmacopsychiatry* 1997;30:154–7.
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- Firkusny L, Gleiter CH. Maprotiline metabolism appears to co-segregate with the genetically-determined CYP2D6 polymorphic hydroxylation of debrisoquine. *Br J Clin Pharmacol* 1994;37:383–8.

Mianserin

General

• Class of the drug	Antidepressants
• Synonym(s)	–
• Common trade name(s) in Germany	Tolvin®
• Conversion factors	Mianserin: $\mu\text{g/L} \times 3.78 = \text{nmol/L}$ $\text{nmol/L} \times 0.26 = \mu\text{g/L}$ Desmethyilmianserin: $\mu\text{g/L} \times 3.99 = \text{nmol/L}$ $\text{nmol/L} \times 0.25 = \mu\text{g/L}$

Clinical pharmacology

• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	90%
• Elimination half-life	Mianserin: 15–22 h Desmethyilmianserin: 5–21 h
• Volume of distribution	13 L/kg
• Metabolism	
– Main metabolic pathways	CYP1A2, CYP2D6
– Active metabolite(s)?	Desmethyilmianserin
– Inhibitor or inducer of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Mainly hepatic
• Typical therapeutic range	Mianserin: 15–70 $\mu\text{g/L}$ (57–265 nmol/L)
• Potentially toxic concentration	>500 $\mu\text{g/L}$ (>1900 nmol/L)

Pre-analytics

• Time to steady-state since 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

Remarks

Chiral drug: enantiomers differ by their metabolism and pharmacology

References

- Arzneimittelkompendium Schweiz. Basel: Documed, 2005.
- 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.
- Eap CB, Yasui N, Kaneko S, Baumann P, Powell K, Otani K. Effects of carbamazepine coadministration on plasma concentrations of the enantiomers of mianserin and of its metabolites. *Ther Drug Monit* 1999;21:166–70.

Mirtazapine

General

• Class of the drug	Antidepressants
• Synonym(s)	–
• Common trade name(s) in Germany	Remergil®
• Conversion factors	Mirtazapine: $\mu\text{g/L} \times 3.77 = \text{nmol/L}$ $\text{nmol/L} \times 0.26 = \mu\text{g/L}$ Desmethylmirtazapine: $\mu\text{g/L} \times 3.97 = \text{nmol/L}$ $\text{nmol/L} \times 0.25 = \mu\text{g/L}$

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
– Active metabolite(s)?	Desmethylmirtazapine
– Inhibitor or inducer of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions	No
• Elimination of parent drug	Hepatic 80% Renal <20%
• Typical therapeutic range	Mirtazapine: 40–80 $\mu\text{g/L}$ (150–300 nmol/L) Desmethylmirtazapine: 5.0–20.0 $\mu\text{g/L}$ (20–80 nmol/L)
• Potentially toxic concentration	Not known

Pre-analytics

• Time to steady-state since 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

Remarks

- Chiral drug
- Enantiomers differ by their metabolism and pharmacology

References

- Arzneimittelkompendium Schweiz. Basel: Documed, 2005.
- 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;15:45–55.
- 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.
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- 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.

Nortriptyline

General

• Class of the drug	Antidepressants
• Synonym(s)	–
• Common trade name(s) in Germany	Nortrilen®
• Conversion factors	mg/L × 3.80 = μmol/L μmol/L × 0.263 = mg/L

Clinical pharmacology

• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	87–93%
• Elimination half-life	18–56 h
• Volume of distribution	20–57 L/kg
• Metabolism	
– Main metabolic pathways	CYP2D6
– Active metabolite(s)?	10-hydroxynortriptyline
– Inhibitor or inducer of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Mainly hepatic
• Typical therapeutic range	0.070–0.170 mg/L (0.266–0.646 μmol/L)
• Potentially toxic concentration	>0.500 mg/L (>1.805 μmol/L)

Pre-analytics

• Time to steady-state since beginning of treatment or change of posology	4–20 days
• 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. Basel: Documed, 2005.
- Baselt RC. Disposition of toxic drugs and chemicals in men, 7th ed. Foster City, CA: Biomedical Publications, 2004.
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- Evans WE, Oellerich M, Holt DW. Therapeutic drug monitoring: clinical guide, 2nd ed. Abbott Laboratories, Diagnostic Division, 1994.
- 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.

Paroxetine

General

- | | |
|-----------------------------------|--|
| • Class of the drug | Antidepressants |
| • Synonym(s) | – |
| • Common trade name(s) in Germany | Seroxat [®] , Tagonis [®] |
| • Conversion factors | $\mu\text{g/L} \times 3.03 = \text{nmol/L}$
$\text{nmol/L} \times 0.33 = \mu\text{g/L}$ |

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 |
| – 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 | 70–120 $\mu\text{g/L}$ (200–365 nmol/L) |
| • Potentially toxic concentration | Not known |

Pre-analytics

- | | |
|---|----------------------------------|
| • Time to steady-state since 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 |

Remarks

None

References

- Arzneimittelkompendium Schweiz. Basel: Documed, 2006.
- Foglia JP, Sorisio D, Kirshner M, Pollock BG. Quantitative determination of paroxetine in plasma by high-performance liquid chromatography and ultraviolet detection. *J Chromatogr B Biomed Sci Appl* 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 in long-term treatment of depression. *J Clin Psychiatry* 1996;57(Suppl 2):24–30.
- 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.

Quetiapine

General

- | | |
|-----------------------------------|---|
| • Class of the drug | Antipsychotics |
| • Synonym(s) | – |
| • Common trade name(s) in Germany | Seroquel® |
| • Conversion factors | $\mu\text{g/L} \times 2.607 = \text{nmol/L}$
$\text{nmol/L} \times 0.38 = \mu\text{g/L}$ |

Clinical pharmacology

- | | |
|---|---|
| • Indications for TDM | Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity |
| • Protein binding | 83% |
| • Elimination half-life | 5–7 h |
| • Volume of distribution | 7–10 L/kg |
| • Metabolism | |
| – Main metabolic pathways | CYP3A4 (quetiapine sulfoxide formation) |
| – Active metabolite(s)? | Clinically not relevant |
| – Inhibitor or inducer of the cytochrome P450 system? | No |
| – Other significant pharmacokinetic interactions | None |
| • Elimination of parent drug | Mainly hepatic |
| • Typical therapeutic range | 70–170 $\mu\text{g/L}$ (182–443 nmol/L) |
| • Potentially toxic concentration | Not known [fatality: 18,000 $\mu\text{g/L}$ (47,000 nmol/L)] |

Pre-analytics

- | | |
|---|----------------------------------|
| • Time to steady-state since beginning of treatment or change of posology | 2–3 days |
| • Time for blood sampling | Before next dose at steady-state |
| • Type(s) of sample | Serum or plasma |
| • Stability | 1 week at 4°C |

Remarks

Quetiapine plasma concentrations show a wide interindividual variation

References

- Arzneimittelkompendium Schweiz. Basel: Documed, 2006.
- De Vane CL, Nemeroff CB. Clinical pharmacokinetics of quetiapine: an atypical antipsychotic. *Clin Pharmacokinet* 2001;40:509–22.
- Hasselstrom J, Linnet K. Quetiapine serum concentrations in psychiatric patients: the influence of comedication. *Ther Drug Monit* 2004;26:486–91.
- Fernandes PP, Marcil WA. Death associated with quetiapine overdose. *Am J Psychiatr* 2002;159:2114.
- 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.

Risperidone

General

• Class of the drug	Antipsychotics
• Synonym(s)	–
• Common trade name(s) in Germany	Risperdal®, Risperdal Consta®
• Conversion factors	Risperidone: $\mu\text{g/L} \times 2.436 = \text{nmol/L}$ $\text{nmol/L} \times 0.411 = \mu\text{g/L}$ 9-OH-risperidone: $\mu\text{g/L} \times 2.345 = \text{nmol/L}$ $\text{nmol/L} \times 0.426 = \mu\text{g/L}$

Clinical pharmacology

• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	90% (risperidone), 77% (9-OH-risperidone)
• Elimination half-life	Risperidone: 3–4 h 9-OH-risperidone: 15–25 h
• Volume of distribution	1 L/kg
• Metabolism	
– Main metabolic pathways	CYP2D6
– Active metabolite(s)?	9-OH-risperidone
– Inhibitor or inducer of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions	CYP2D6 inhibitors increase risperidone, with a non-fully compensating decrease of 9-OH-risperidone
• Elimination of parent drug	Mainly hepatic (active metabolite mainly renal)
• Typical therapeutic range	Risperidone + 9-OH-risperidone (= “active moiety”): 20–60 $\mu\text{g/L}$ (49–146 nmol/L)
• Potentially toxic concentration	Not known

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	1 week at 4°C

Remarks

With long acting (depot) risperidone, steady-state conditions are only reached after 4 injections every 2 weeks (8 weeks after 1st injection). Apparent half-life of “active moiety”, after administration of long acting risperidone: 3–6 days
The active metabolite 9-OH-risperidone undergoes renal elimination

References

- Arzneimittelkompendium Schweiz. Basel: Documed, 2006.
- Grant S, Fitton A. Risperidone. A review of its pharmacology and therapeutic potential in the treatment of schizophrenia. *Drugs* 1994;48:253–73.
- Marder SR, Conley R, Ereshefsky L, Kane JM, Turner MS. Clinical guidelines: dosing and switching strategies for long-acting risperidone. *J Clin Psychiatry* 2003;64:41–6.
- Harrison TS, Goa KL. Long-acting risperidone: a review of its use in schizophrenia. *CNS Drugs* 2004;18:113–32.
- 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.
- Wilson WH. A visual guide to expected blood levels of long-acting injectable risperidone in clinical practice. *J Psychiatr Pract* 2004;10:393–401.

Sertraline

General

- | | |
|-----------------------------------|--|
| • Class of the drug | Antidepressants |
| • Synonym(s) | – |
| • Common trade name(s) in Germany | Gladem [®] , Zoloft [®] |
| • Conversion factors | $\mu\text{g/L} \times 3.26 = \text{nmol/L}$
$\text{nmol/L} \times 0.31 = \mu\text{g/L}$ |

Clinical pharmacology

- | | |
|---|---|
| • Indications for TDM | Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity |
| • Protein binding | 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 | CYP2B6 |
| – Active metabolite(s)? | N-Desmethylsertraline |
| – Inhibitor or inducer of the cytochrome P450 system? | Weak inhibitor of CYP2D6 and CYP3A4 |
| – Other significant pharmacokinetic interactions | No |
| • Elimination of parent drug | Hepatic 50%
Renal 50% |
| • Typical therapeutic range | 10–50 $\mu\text{g/L}$ (33–163 nmol/L) |
| • Potentially toxic concentration | Not known |

Pre-analytics

- | | |
|---|----------------------------------|
| • Time to steady-state since 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 |

Remarks

None

References

- Arzneimittelkompendium Schweiz. Basel: Documed, 2005.
- 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 in long-term treatment of depression. J Clin Psychiatry 1996;57(Suppl 2):24–30.
- Baumann PB, Hienke 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.

Trazodone

General

- | | |
|-----------------------------------|--|
| • Class of the drug | Antidepressants |
| • Synonym(s) | – |
| • Common trade name(s) in Germany | Thombran® |
| • Conversion factors | $\mu\text{g/L} \times 0.027 = \mu\text{mol/L}$
$\mu\text{mol/L} \times 372 = \mu\text{g/L}$ |

Clinical pharmacology

- | | |
|---|---|
| • Indications for TDM | Individual dose adaptation, verification of compliance, suspicion of toxicity, side effects |
| • Protein binding | 90% |
| • Elimination half-life | 4–7 h |
| • Volume of distribution | Unknown |
| • Metabolism | |
| – Main metabolic pathways | CYP3A4 |
| – Active metabolite(s)? | m-chlorophenyl-piperazine or mCPP (minor) |
| – Inhibitor or inducer of the cytochrome P450 system? | No |
| – Other significant pharmacokinetic interactions | Reported cases of increased levels of digoxin and phenytoin |
| • Elimination of parent drug | Hepatic |
| • Typical therapeutic range | 650–1500 $\mu\text{g/L}$ (1.75–4.03 $\mu\text{mol/L}$) |
| • Potentially toxic concentration | Not known [fatalities: 9000–33,000 $\mu\text{g/L}$ (243–891 $\mu\text{mol/L}$)] |

Pre-analytics

- | | |
|---|----------------------------------|
| • Time to steady-state since beginning of treatment or change of posology | 2–3 days |
| • 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. Basel: Documed, 2007.
- Moffat AC, Osselton D, Widdop B, editors. Clarke's analysis of drugs and poisons in pharmaceuticals, body fluids and post-mortem material, 3rd ed. London/Chicago, IL: Pharmaceutical Press, 2003.
- Service of Pharmacology and Clinical Toxicology, University Hospital of Geneva. http://pharmacoclin.hug-ge.ch/_library/pdf/cytp450.pdf (accession date 27 December 2007).
- 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.

Trimipramine

General

- | | |
|-----------------------------------|--|
| • Class of the drug | Antidepressants |
| • Synonym(s) | – |
| • Common trade name(s) in Germany | Stangyl® |
| • Conversion factors | $\mu\text{g/L} \times 0.00397 = \mu\text{mol/L}$
$\mu\text{mol/L} \times 294 = \mu\text{g/L}$ |

Clinical pharmacology

- | | |
|---|--|
| • Indications for TDM | Individual dose adaptation, verification of compliance, suspicion of toxicity, side effects |
| • Protein binding | 94% |
| • Elimination half-life | 16–40 h (mean 24 h) |
| • Volume of distribution | 20–50 L/kg |
| • Metabolism | |
| – Main metabolic pathways | CYP2D6 |
| – Active metabolite(s)? | N-desmethyltrimipramine |
| – Inhibitor or inducer of the cytochrome P450 system? | No |
| – Other significant pharmacokinetic interactions | None |
| • Elimination of parent drug | Hepatic |
| • Typical therapeutic range | 150–350 $\mu\text{g/L}$ (0.51–1.19 $\mu\text{mol/L}$) |
| • Potentially toxic concentration | > 1000 $\mu\text{g/L}$ (> 3.4 $\mu\text{mol/L}$) [fatalities: 9000–12,000 $\mu\text{g/L}$ (30.6–47.6 $\mu\text{mol/L}$)] |

Pre-analytics

- | | |
|---|----------------------------------|
| • Time to steady-state since beginning of treatment or change of posology | 4–7 days |
| • 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. Basel: Documed, 2007.
- Moffat AC, Osselton D, Widdop B, editors. Clarke's analysis of drugs and poisons in pharmaceuticals, body fluids and post-mortem material, 3rd ed. London/Chicago, IL: Pharmaceutical Press, 2003.
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- 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

Venlafaxine

General

• Class of the drug	Antidepressants
• Synonym(s)	–
• Common trade name(s) in Germany	Trevilor®
• Conversion factors	Venlafaxine: $\mu\text{g/L} \times 3.605 = \text{nmol/L}$ $\text{nmol/L} \times 0.277 = \mu\text{g/L}$ O-desmethylvenlafaxine: $\mu\text{g/L} \times 3.797 = \text{nmol/L}$ $\text{nmol/L} \times 0.263 = \mu\text{g/L}$

Clinical pharmacology

• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	30% (venlafaxine)
• Elimination half-life	4 h (venlafaxine), 10 h (O-desmethylvenlafaxine)
• Volume of distribution	7 L/kg
• Metabolism	
– Main metabolic pathways	CYP2D6
– Active metabolite(s)?	Mainly O-desmethylvenlafaxine
– Inhibitor or inducer of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Mainly hepatic
• Typical therapeutic range	Venlafaxine + O-desmethylvenlafaxine: 195–400 $\mu\text{g/L}$ (721–1480 nmol/L)
• Potentially toxic concentration	Not known

Pre-analytics

• Time to steady-state since beginning of treatment or change of posology	2–3 days
• Time for blood sampling	Before next dose at steady-state
• Type(s) of sample	Serum or plasma
• Stability:	1 week at 4°C

Remarks

Chiral drug: enantiomers of the parent compound and the active metabolite differ by their metabolism and pharmacology. The extended release (ER) form is preferentially used. The active metabolite O-desmethylvenlafaxine undergoes renal elimination.

References

- Arzneimittelkompendium Schweiz. Basel: Documed, 2006.
- Holliday SM, Benfield P. Venlafaxine. A review of its pharmacology and therapeutic potential in depression. *Drugs* 1995;49:280–94.
- Eap CB, Lessard, E, Baumann P, Brawand-Amey M, Yessine MA, O'Hara G, Turgeon J. Role of CYP2D6 in the stereoselective disposition of venlafaxine in humans. *Pharmacogenetics* 2003;13:39–47.
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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 analyzed in therapeutic drug monitoring. *J Lab Med* 2008;32:372–81.