Monographs on drugs which are frequently analyzed in therapeutic drug monitoring

Rentsch, K; Buhl, Daniela; Eap, Chin Bin; Fathi, Marc; Jöchle, Wolfgang; Magnin, Jean-Luc; Thormann, Wolfgang; Werner, Dominique

Abstract: In addition to the monographs which have been published in the past 4 years by the working group ”Drug Monitoring” of the Swiss Society of Clinical Chemistry (SSCC) [1-4], new monographs have been written. The data presented in these monographs provide an overview of important information for the request and interpretation of results. Therefore, laboratory health professionals and the receivers of the reports are the targeted readers. In this series, several antiepileptic drugs are presented. Monographs on carbamazepine [1], lamotrigine [2], phenobarbital [2], and valproic acid [2] have been published previously. 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. Second, the indications for therapeutic drug monitoring are listed. Last but not least, important pre-analytical 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 is 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 comments from the readers

DOI: https://doi.org/10.1515/jlm.2010.024

Other titles: Arzneimittel-Monographien für Medikamente, die regelmäßig im Rahmen des Therapeutic Drug Monitorings analysiert werden

Posted at the Zurich Open Repository and Archive, University of Zurich
ZORA URL: https://doi.org/10.5167/uzh-155091
Journal Article
Published Version

Originally published at:
Rentsch, K; Buhl, Daniela; Eap, Chin Bin; Fathi, Marc; Jöchle, Wolfgang; Magnin, Jean-Luc; Thormann, Wolfgang; Werner, Dominique (2010). Monographs on drugs which are frequently analyzed in therapeutic drug monitoring. Journal of Laboratory Medicine, 34(3):129-139.
DOI: https://doi.org/10.1515/jlm.2010.024
Drug Monitoring und Toxikologie

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 past 4 years by the working group “Drug Monitoring” of the Swiss Society of Clinical Chemistry (SSCC) [1–4], new monographs have been written. The data presented in these monographs provide an overview of important information for the request and interpretation of results. Therefore, laboratory health professionals and the receivers of the reports are the targeted readers. In this series, several antiepileptic drugs are presented. Monographs on carbamazepine [1], lamotrigine [2], phenobarbital [2], and valproic acid [2] have been published previously. 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. Second, the indications for therapeutic drug monitoring are listed. Last but not least, important pre-analytical 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 is 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 comments from the readers.

Keywords: antiepileptics; clonazepam; ethosuximide; gabapentin; levetiracetam; oxcarbazepin; phenytoin; primidone; topiramate; vigabatrin.

Zusammenfassung


Schlüsselwörter: Antiepileptika; Clonazepam; Ethosuximid; Gabapentin; Levetiracetam; Oxcarbazepin; Phenytoin; Primidon; Topiramat; Vigabatrin.
## Clonazepam

### General
- **Class of the drug:** Antiepileptics
- **Synonym(s):**
- **Common trade name(s) in Germany:** Rivotril®
- **Conversion factors:**
  - \( \mu g/L \times 3.167 = nmol/L \)
  - \( nmol/L \times 0.316 = \mu g/L \)

### Clinical pharmacology
- **Indications for TDM:** Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
- **Protein binding:** 85%
- **Elimination half-life:** 20–60 h
- **Volume of distribution:** 3 L/kg
- **Metabolism:**
  - Main metabolic pathways: CYP3A4
  - Active metabolite(s): 7-amino-clonazepam
  - Inhibitor or inductor of the cytochrome P450 system: No
  - Other significant pharmacokinetic interactions: None
- **Elimination of parent drug:** Hepatic
- **Typical therapeutic range:** 20–40 \( \mu g/L \) (63–127 nmol/L)
- **Potentially toxic concentration:** > 100 \( \mu g/L \) (> 316 nmol/L)

### Pre-analytics
- **Time to steady-state since beginning of treatment or change of posology:** ~4–10 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
**Ethosuximide**

### General
- **Class of the drug:** Antiepileptics
- **Synonym(s):**
- **Common trade name(s) in Germany:** Petnidan®, Suxilep®
- **Conversion factors:**
  \[ \text{mg/L} \times 7.082 = \mu\text{mol/L} \]
  \[ \mu\text{mol/L} \times 0.141 = \text{mg/L} \]

### Clinical pharmacology
- **Indications for TDM:** Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
- **Protein binding:** No
- **Elimination half-life:** 48–60 h
- **Volume of distribution:** 0.7 L/kg
- **Metabolism:**
  - **Main metabolic pathways:** CYP3A
  - **Active metabolite(s)?** No
  - **Inhibitor or inductor of the cytochrome P450 system?** No
  - **Other significant pharmacokinetic interactions:** None
- **Elimination of parent drug:** Mainly hepatic, 20% renal
- **Typical therapeutic range:** 40–100 mg/L (280–700 μmol/L)
- **Potentially toxic concentration:** >141 mg/L (>1000 μmol/L)

### 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
- **Type(s) of sample:** Serum or plasma
- **Stability:** 1 week at 4°C

### Remarks
None

### References
Gabapentine

General

• Class of the drug: Antiepileptics
• Synonym(s):
• Common trade name(s) in Germany: Neurontin®
• Conversion factors: mg/L × 5.840 = μmol/L
μmol/L × 0.171 = mg/L

Clinical pharmacology

• Indications for TDM: Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding: No
• Elimination half-life: 5–15 h
• Volume of distribution: 58 L/kg
• Metabolism:
  – Main metabolic pathways: No metabolites identified
  – Active metabolite(s)? No
  – Inhibitor or inducer of the cytochrome P450 system?: No
  – Other significant pharmacokinetic interactions: None
• Elimination of parent drug: Renal
• Typical therapeutic range: 1.7–20.5 mg/L (10–120 μmol/L)
• Potentially toxic concentration: Not known

Pre-analytics

• Time to steady-state since beginning of treatment or change of posology: ~ 30 h
• Time for blood sampling: Before next dose at steady-state
• Type(s) of sample: Serum or plasma
• Stability: 1 week at 4°C

Remarks

Nonlinear kinetics of absorption

References

### Levetiracetam

#### General
- **Class of the drug:** Antiepileptics
- **Synonym(s):**
- **Common trade name(s) in Germany:** Keppra®
- **Conversion factors:**
  \[ \text{mg/L} \times 5.875 = \mu\text{mol/L} \]
  \[ \mu\text{mol/L} \times 0.1702 = \text{mg/L} \]

#### Clinical pharmacology
- **Indications for TDM:** Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
- **Protein binding:** <10%
- **Elimination half-life:** 6–8 h
- **Volume of distribution:** 0.5–0.7 L/kg
- **Metabolism:**
  - Main metabolic pathways: Enzymatic hydrolysis in blood
  - Active metabolite(s)? No
  - Inhibitor or inducer of the cytochrome P450 system? No
  - Other significant pharmacokinetic interactions: None
- **Elimination of parent drug:** Renal
- **Typical therapeutic range:** 5–30 mg/L (29.4–176 μmol/L)
- **Potentially toxic concentration:** >400 mg/L (>2350 μmol/L)

#### Pre-analytics
- **Time to steady-state since beginning of treatment or change of posology:** ~2 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
- Schulz M, Schmoldt A. Therapeutic and toxic blood concentrations of more than 800 drugs and other xenobiotics. Pharmazie 2003;58:447–74.
### Oxcarbazepine

#### General
- **Class of the drug:** Antiepileptics
- **Synonym(s):** Trileptal®, Apydan®, Timox®
- **Common trade name(s) in Germany:**
  - Oxcarbazepine: mg/L × 4.0 = µmol/L
  - Monohydroxy-oxcarbazepine (MHD): mg/L × 3.94 = µmol/L

#### Clinical pharmacology
- **Indications for TDM:** Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
- **Protein binding:** MHD: 40% (albumin)
- **Elimination half-life:**
  - Oxcarbazepine: 1–3 h
  - MHD: 11–15 h
- **Volume of distribution:**
  - Oxcarbazepine: 3–15 L/kg
  - MHD: 0.7 L/kg
- **Metabolism:**
  - **Main metabolic pathways:** Hydroxylation
  - **Active metabolite(s)?** Yes (MHD)
  - **Inhibitor or inducer of the cytochrome P450 system?** Inhibitor of CYP2C19; inducer of CYP3A4
  - **Other significant pharmacokinetic interactions:** None
- **Elimination of parent drug:**
  - Oxcarbazepine: mainly hepatic
  - MHD: mainly renal
- **Typical therapeutic range:**
  - Oxcarbazepine: 0.025–0.33 mg/L (0.1–1.3 µmol/L)
  - MHD: 7.6–20.3 mg/L (30–80 µmol/L)
- **Potentially toxic concentration:** Not known

#### Pre-analytics
- **Time to steady-state since beginning of treatment or change of posology:** ~ 2 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
- Schulz M, Schmoldt A. Therapeutic and toxic blood concentrations of more than 800 drugs and other xenobiotics. Pharmazie 2003;58:447–74.
**Phenytoin**

### General
- **Class of the drug:** Antiepileptics
- **Synonym(s):** Diphenylhydantoin
- **Common trade name(s) in Germany:** Zentropil®, Phenhydan®, Zentropil®, Phenhydan®
- **Conversion factors:** 
  
  \[
  \text{mg/L} \times 3.96 = \mu \text{mol/L} \\
  \mu \text{mol/L} \times 0.252 = \text{mg/L}
  \]

### Clinical pharmacology
- **Indications for TDM:** Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
- **Protein binding:** 90% (albumin)
- **Elimination half-life:** 20–60 h (concentration-dependent; increases at higher levels due to saturation of metabolism)
- **Volume of distribution:** 0.5–0.8 L/kg
- **Metabolism:**
  - **Main metabolic pathways:** Hydroxylation by CYP2C9 and CYP2C19 (main metabolite: p-hydroxy-diphenylhydantoin) followed by glucuroconjugation
  - **Active metabolite(s)?** No
  - **Inhibitor or inductor of the cytochrome P450 system?** Numerous other interactions
- **Elimination of parent drug:** Mainly hepatic
- **Typical therapeutic range:** 10–20 mg/L (40–80 μmol/L)
- **Potentially toxic concentration:** > 20 mg/L (> 80 μmol/L)

### Pre-analytics
- **Time to steady-state since beginning of treatment or change of posology:** 5–14 days (concentration-dependent)
- **Time for blood sampling:** Before next dose at steady-state
- **Type(s) of sample:** Serum or plasma
- **Stability:** 48 h at 4°C

### Remarks
- A small increase of the dose might produce a disproportional increase in plasma concentration due to the nonlinear kinetics of phenytoin.
- In case of hypoalbuminemia or diminished binding, the free fraction of phenytoin increases.
- Slow hydroxylators could develop toxic effects at a common posology.

### References
## Primidone

### General
- **Class of the drug:** Antiepileptics
- **Synonym(s):**
- **Common trade name(s) in Germany:** Mylepsinum®
- **Conversion factors:**
  - Primidone: \( \text{mg/L} \times 4.58 = \mu\text{mol/L} \)
  - Phenobarbital: \( \mu\text{mol/L} \times 0.218 = \text{mg/L} \)
  - Phenylethylmalonamide: \( \mu\text{mol/L} \times 0.232 = \text{mg/L} \)

### Clinical pharmacology
- **Indications for TDM:** Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
- **Protein binding:** < 20%
- **Elimination half-life:**
  - Primidone: 5–16 h
  - Phenobarbital: 50–150 h
  - Phenylethylmalonamide: 16–50 h
- **Volume of distribution:** 0.6 L/kg
- **Metabolism:**
  - Main metabolic pathways: CYP2C9 and CYP2C19
  - Active metabolite(s)? Phenobarbital
  - Inhibitor or inducer of the cytochrome P450 system? Inducer of cytochromes CYP2C9, CYP2C19, and CYP3A4
  - Other significant pharmacokinetic interactions: Numerous interactions, e.g., with other antiepileptics, oral anticoagulants, steroids
- **Elimination of parent drug:**
  - Hepatic: 17%–73%
  - Renal: 15%–65%
- **Typical therapeutic range:**
  - Primidone: 5–12 mg/L (23–55 \( \mu\text{mol/L} \))
  - Phenobarbital: 15–40 mg/L (64–172 \( \mu\text{mol/L} \))
- **Potentially toxic concentration:**
  - Primidone: > 15 mg/L (> 69 \( \mu\text{mol/L} \))

### Pre-analytics
- **Time to steady-state since beginning of treatment or change of posology:** Primidone: 2 days
  - Phenobarbital: 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

### Remarks
- TDM of primidone must include measurement of its main active metabolite phenobarbital

### References
# Topiramate

**General**
- **Class of the drug:** Antiepiletics
- **Synonym(s):**
- **Common trade name(s) in Germany:** Topamax®, Topiramat-Jansen®
- **Conversion factors:**
  \[
  mg/L \times 4.23 = \mu\text{mol/L} \\
  \mu\text{mol/L} \times 0.236 = mg/L
  \]

## Clinical pharmacology
- **Indications for TDM:** Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
- **Protein binding:** 13%–17%
- **Elimination half-life:** 21 h
- **Volume of distribution:** 0.55–0.8 L/kg (lower in women than in men)
- **Metabolism:**
  - **Main metabolic pathways:** Not known
  - **Active metabolite(s)?** No
  - **Inhibitor or inducer of the cytochrome P450 system?** Strong inductor of CYP3A4, strong inhibitor of CYP2C19
  - **Other significant pharmacokinetic interactions:** Not known
- **Elimination of parent drug:** Mainly renal, hepatic 20% (50% if treated with other antiepileptics)
- **Typical therapeutic range:** 4.0–12.2 mg/L (16.9–51.6 μmol/L)

## Pre-analytics
- **Time to steady-state since 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

**Remarks**
- None

**References**
- [http://www.kardiolab.ch/CYP450_2J51.html](http://www.kardiolab.ch/CYP450_2J51.html).
### Vigabatrin

**General**
- **Class of the drug:** Antiepileptics
- **Synonym(s):** Gamma-vinyl GABA
- **Common trade name(s) in Germany:** Sabril®
- **Conversion factors:**
  - $\text{mg/L} \times 7.7 = \mu\text{mol/L}$
  - $\mu\text{mol/L} \times 0.130 = \text{mg/L}$

**Clinical Pharmacology**
- **Indications for TDM:** Verification of compliance
- **Protein binding:** No
- **Elimination half-life:** 5–8 h (elderly 12–13 h)
- **Volume of distribution:** 1.0–1.4 L/kg
- **Metabolism:**
  - Main metabolic pathways: No metabolites identified
  - Active metabolite(s)? No
  - Inhibitor or inducer of the cytochrome P450 system? No
- **Other significant pharmacokinetic interactions:**
  - A gradual reduction of approximately 20%–30% in plasma phenytoin concentration has been observed following add-on therapy with vigabatrin
- **Elimination of parent drug:** Mainly renal
- **Typical therapeutic range:** No direct correlation between concentration and effectiveness. Because vigabatrin acts irreversibly, it would be unlikely to have a therapeutic range
- **Potentially toxic concentration:** Not known

**Pre-analytics**
- **Time to steady-state since beginning of treatment or change of posology:** 2 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**
- S-enantiomer pharmacologically active
- Irreversible enzyme inhibition (GABA transaminase): half-life of the drug is clinically not relevant

**References**
References