TDM monograph Clobazam and clonazepam

Indication:	Based on current available information, TDM is not advised for all patients treated with clobazam or clonazepam. TDM might be used in specific cases, for example for monitoring therapy adherence, in case of adequate dosing and an insufficient response, in case of therapeutic dosing and side effects, in case of a suspicion of overdose, in case of drug interactions, or in case of impaired renal function or impaired liver function.
Sample material:	Plasma or serum [2-4]
Time of sampling:	Trough based monitoring: sample before next dose
Storage conditions:	2-8 °C after sample collection and for transport. Store at -20 ºC in the freezer.
Interpretation:	**Clobazam** - Efficacy 30-300 ug/L [1-3] - Toxicity > 3000 ug/L [1] **N-desmethylclobazam** - Efficacy 300-3000 ug/L [3] - Toxicity > 12000 ug/L [1] **Clonazepam** - Efficacy 20-70 ug/L [3;7] - Toxicity > 100 ug/L [2]
Evidence level:	4

Introduction

Clobazam (CLB) and clonazepam (CZP) are benzodiazepines. Benzodiazepines potentiate the central depressive effect of gamma-aminobutyric acid (GABA) by binding to specific sites on the GABA receptor. Binding to this receptor results in the opening of the chloride channels. The chloride ion flux causes hyperpolarization (i.e. reduced excitability) of the membrane [9].

Clobazam has both anxiolytic and anticonvulsant activity [8], while clonazepam (in animal studies) has pronounced anticonvulsant properties [10]. Pharmacotherapeutically, both benzodiazepines are therefore classified as anticonvulsants. Clobazam has been registered for pathological anxiety and stress and as adjuvant therapy in epileptic seizures [8;9]. Clonazepam has been registered for various forms of epilepsy, in particular absence seizures, tonic-clonic seizures and status epilepticus [9;10].

Indications for TDM

Many patients develop a benzodiazepine tolerance for the effects and side effects. Therefore, there is no clear concentration-effect relationship [3].

Given the wide variation in clearance of clonazepam, determination of serum concentrations may be useful.

Determination of the plasma concentration of clonazepam or clobazam is recommended during dose titration, for special indications, and solving the following problems:

- Monitoring therapy adherence
- Adequate dosing and a lack of response or insufficient response
- Suspicion of overdose
- Therapeutic dosing and side effects

- Drug interactions
- Impaired renal function or impaired liver function

Dosing guidelines

For dosing guidelines with clobazam and clonazepam, see KNMP Kennisbank: http://kennisbank.knmp.nl [9], UpToDate Lexicomp: https://uptodate.com, or Medscape: https://medscape.com/.
For dosing guidelines for children, see Kinderformularium: Kinderformularium [11].

Reference values

Efficacy

Clobazam
There is no clear relationship between drug exposure (serum concentrations) and efficacy in clobazam or N-desmethylclobazam. This may be due to tolerance [1,3]. Clobazam has a large therapeutic window [1]. Steady state serum clobazam and N-desmethylclobazam concentrations are linearly related to clobazam dose [1;3]. In patients using therapeutic doses of clobazam, serum trough concentrations have been reported of 30 – 300 ng/mL clobazam and 300 – 3000 ng/mL N-desmethylclobazam [1-3;5]. In therapeutic ranges N-desmethylclobazam/clobazam ratios are usually < 10 [1].
After a single dose of 20 mg clobazam maximum plasma concentrations have been reported of 222 – 709 ng/mL [8].

Clonazepam
Steady-state serum clonazepam concentrations increase linearly with dose [3,8]. A correlation between serum clonazepam concentrations and efficacy has not been identified because tolerance in clonazepam develops in many patients [3].

In patients using therapeutic doses of clonazepam, serum concentrations of 20 – 70 ng/mL have been reported [3;10]. The steady-state plasma concentration of clonazepam with once-daily dosing is three-fold higher than after a single dose; the predicted accumulation ratio with twice and thrice daily dosing is, respectively, 5 and 7. After repeated oral dosing of 2 mg three times daily, the mean steady-state plasma concentration of clonazepam before dosing was 55 ng/mL [10].

Toxicity

The most important adverse events/reactions of clobazam and clonazepam are drowsiness, lethargy, fatigue, slowed reaction time, dizziness, light headednedd, ataxia, muscle hypotonia, and muscle weakness. These side effects occur mainly at the beginning of treatment and are largely preventable by starting with low doses and increasing them gradually [9]. Clobazam is less sedative and shows less tolerance than clonazepam and clobazam shows [2;9]. Overdose may also cause tachycardia, reflex tachycardia, respiratory depression and coma [20].

Clobazam
Plasma concentrations of clobazam (>3000 µg/L) and/or N-desmethylclobazam (>12000 µg/L) can confirm whether it is concerns a clobazam intoxication (estimate references of de Leon et al [1]).
High ratios (>25) of N-desmethylclobazam/clobazam can indicate genetic mutations in CYP2C19 or concomitant use of a CYP3A4 inducer [1;12].

Clonazepam
Serious toxic effects including increased seizure frequency occurred in the majority of patients with steady-state plasma concentrations above 100 ng/ml. A plasma concentration >100 µg/L is considered to be potentially toxic [10].

See the Benzodiazepines monograph at www.toxicologie.org (http://toxicologie.org/) for toxicology treatment information.

Summary

Efficacy clobazam:

- Clobazam trough concentration 30 – 300 ug/L
- N-desmethylclobazam trough concentration 300 – 3000 ug/L

Toxicity clobazam:

- Clobazam trough concentration > 3000 ug/L
- N-desmethylclobazam trough concentration > 12000 ug/L

Ratio N-desmethylclobazam/clobazam:

- <10: Normal
- 10-25: Possible concomitant use of CYP3A4 inducer
- >25: Possible CYP2C19 PM, concomitant use of CYP3A4 inducer, or CYP2C19 inhibitor

Efficacy clonazepam:

- Trough concentration 20 – 70 ug/L

Toxicity clonazepam:

- Trough concentration > 100 ug/L

Sampling conditions

Clobazam

- Trough based monitoring, sample before next dose

Sampling should occur at seven days after start of therapy to measure steady state concentrations of clobazam. N-desmethylclobazam steady state occurs after more than three weeks [1;4-5;9].

Clonazepam

- Trough based monitoring, sample before next dose

Sampling should occur at seven days after start of therapy to measure steady state concentrations of clonazepam [9].

Interpretation results

Bio-analytical assay

Clobazam
Different chromatographic methods can be used to determine clobazam and N-desmethylclobazam concentrations in serum. GC-MS, (U)HPLC-UV or (U)HPLC-MS [2-4].

Clonazepam
Many chromatographic methods have been described for quantitation of clonazepam in serum. These include GC-MS, (U)HPLC-UV [2;3].

Toxicity

See under Reference Values.

Background information [extended]

Pharmacokinetics

- #### Absorption
  Clobazam
  Clobazam is well absorbed after oral ingestion. No influence of food on bioavailability is expected. Clobazam is lipophilic and quickly crosses the blood-brain barrier [2].
  Steady state of clobazam occurs within seven days. N-desmethylclobazam steady state occurs after 28 days and is approximately 8 times higher than clobazam steady state concentration [8].

  Clonazepam
  Clonazepam is well absorbed after oral ingestion. No influence of food on bioavailability is expected [9;10].

- #### Distribution
  Clobazam
  Clobazam is lipophilic and distributes quickly throughout the body. Based on population pharmacokinetic analysis, the apparent volume of distribution at steady state was approximately 102 L and is independent of the drug concentration throughout the therapeutic range. Clobazam binding to plasma protein is approximately 80 – 90 % [8].

  Clonazepam
  Clonazepam is rapidly distributed in various organs and tissues, but is mainly incorporated into the structures of the brain. The distribution half-life is approximately 0.5-1 hour. The volume of distribution is 3 l/kg. The extent to which clonazepam is bound to plasma protein, amounts to 82-86% [10].

- #### Metabolism
  Clobazam
  Clobazam is metabolised in the liver to the active metabolite N-desmethylclobazam. This is mainly due to CYP3A4, and to a lesser extent CYP2C19 and CYP2B6 [21]. N-desmethylclobazam is mainly metabolised by CYP2C19 [21].

  Clonazepam
  Clonazepam is extensively metabolised in the liver, mainly to the inactive 7-amino-clonazepam followed by N-acetylation to 7-acetamino-clonazepam [9;10]. CYP3A4 is involved in the nitro reduction of clonazepam to inactive metabolites [10].

- #### Excretion
  Clobazam
  81-97% of the clobazam is recovered in the urine, of which 2% is found as unchanged clobazam [20]. The remaining clobazam is excreted in the faeces. Elimination half-life of clobazam is 18 to

30 hours. Elimination half-life of N-desmethylclobazam is approximately 50 hours [8].

Clonazepam
Within 10 days clobazam is excreted mainly as metabolites, 2% is excreted unchanged. 50-70% of the dose is excreted in the urine and 10-30% in the faeces [10]. The mean elimination half-life is between 30 and 40 hours and is independent of dose [10].

- Organ dysfunction

  Clobazam
  In the case of impaired liver function, clobazam may result in increased response and sensitivity with an accelerated onset of encephalopathy [8].

  Clonazepam
  Renal impairment does not affect the pharmacokinetics of clonazepam. No dose adjustment is necessary in patients with reduced kidney function [10]. Due to the large volume of distribution and high protein binding, dialysis and perfusion do not affect clearance.
  Plasma protein binding of clonazepam in patients with cirrhosis is significantly different than in healthy humans (free fraction 17.1±1.0% versus 13.9±0.2%). Although the influence of a reduced liver function on the pharmacokinetics of clonazepam has not been further investigated, experience with a other closely related nitrobenzodiazepine (nitrazepam) from that clearance of unbound clonazepam may be reduced in patients with liver cirrhosis [10].

- Pharmacogenetics

  Clobazam
  CYP2C19 poor metabolizers may have a higher plasma concentration of N-desmethylclobazam compared to extensive metabolizers [8;21], resulting in a higher ratio of N-desmethylclobazam/clobazam. However, evidence for this is not conclusive [1].

  Clonazepam
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- Special populations

  Clobazam

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  Clonazepam
  Paediatric: elimination kinetics are comparable to adults. After therapeutic dosing, trough serum concentrations of clonazepam were in the same window as adults (13 – 72 ng/mL) [10].
  In neonates, a dose of 0.10 mg/kg resulted in plasma concentrations between 28 and 117 ng/ml at the end of a 5 minute infusion. After 30 minutes this fell to 18-60 ng/ml [10].

Interactions

For interactions with clobazam or clonazepam, see KNMP Kennisbank: https://kennisbank.knmp.nl/ [9] or the Lexicomp® Drug Interactions checker: https://uptodate.com/drug-interactions/.

Cannabidiol and stiripentol are moderate CYP2C19 inhibitors and may increase may increase serum concentrations of clobazam and N-desmethylclobazam.

PK parameters

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Population models

Not relevant

Literature

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Colophon

This guideline has been constituted by A.M. Schimmel and A.J. Wilhelm, hospital pharmacists, on January 5th 2015. The guideline has been revised by Simone Baan, hospital pharmacist in training, on June 10th 2022.

Under the auspices of TDM, Toxicology and Pharmacogenetics committee (TTF) of the Dutch Association of Hospital Pharmacists (NVZA) and the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT)

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Appendices

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Revision

Translation to English
New format with added information.
Revised reference value for clobazam.