TDM monograph Topiramate

Synonyms: Epitomax, Topamax

Summary

Indication:	Patients treated with topiramate as monotherapy or adjunctive therapy for partial-onset seizures and/or generalized tonic-clonic seizures and as adjunctive therapy for Lennox-Gastaut syndrome-related seizures.
Sample material:	Serum, plasma or Dry blood spot.
Time of sampling:	After at least 5 days at a steady dosage level (= steady state concentration in patients with adequate renal function), obtain sample material (serum/plasma) just prior to administration of the next dose (through-based monitoring).
Storage conditions:	No special handling, transportation or storage conditions. Suitable for storage at -20° C.
Interpretation:	Target level: 2(5) - 20 mg/L Toxicity level: > 25 mg/L
Evidence level:	2

Contents

Introduction

Topiramate is part of the class of newer (non-classic) antiepileptic drugs. In The Netherlands, topiramate is approved as monotherapy or adjunctive therapy for partial-onset seizures and/or generalized tonic-clonic seizures as well as adjunctive therapy for seizures associated with Lennox-Gastaut syndrome. Additionally, topiramate is approved as a prophylactic drug to prevent episodes of migraine following failure of first line treatment. In addition to its licensed indications, topiramate is used off-label to treat various different types of epilepsy syndromes (i.e. juvenile myoclonus epilepsy), neuropathic pain, binge eating disorders, several forms of personality and/or depressive disorders and cluster headache prevention. [1-3]

Dosing guidelines

Adults (maintenance) [1]	Adjuvant: 200-400 mg per 24 hours, divided in 2 doses Monotherapy: 100-200 mg (max. 500 mg) per 24 hours, divided in 2 doses
Children >2 years (maintenance) [4]	Adjuvant: 5-9 mg/kg (max. 400 mg) per 24 hours, divided in 2 doses Monotherapy: 2 mg/kg per 24 hours, divided in 2 doses

The recommended starting dose for topiramate in adults is 25-50 mg once daily for one week. The dose is titrated with increments of 25-50 mg per 24 hours divided in 1-2 doses every 1-2 weeks until the maintenance dose is reached [1].

Dosing guidelines in children and adolescents

For children, the starting dose is 1-3 mg/kg once daily for one week, titrated with increments of 1-3 mg/kg per 24 hours divided in 2 doses every 1-2 weeks when used as adjunctive therapy. When used as monotherapy, the starting dose is 0,5-1 mg/kg once daily for one week, titrated with increments of 0,5-1 mg/kg per 24 hours divided in 2 doses every 1-2 weeks. [4]

Dosing guidelines in patients with altered pharmacokinetics

At a creatinine clearance of 10-50 ml/min: 50% of the usual dosage; this applies to both the titration and maintenance schedules [1].

Indications/Criteria for TDM

This protocol will not address indications other than epilepsy/seizures, as TDM is not considered useful for these other indications.

Reference values

Target level
adults: 2 – 20 mg/L
children (>2 years): 5 – 20 mg/L
Toxicity level: > 25 mg/L

The aforementioned ranges are based on population data acquired from drug trials and research in the field of TDM and/or PK/PD of topiramate. Concentrations below the lower limit of the therapeutic range are less likely to provide an appropriate therapeutic response, while concentrations above the upper limit are less likely to produce further efficacy, with side effects and/or toxic consequences becoming more likely to develop. For more information see the 'interpretation of results' section.

Efficacy

On the basis of pooled data from three RCTs, Reife et al. [20] reported in 1995 that rising plasma concentrations appear to result in increased efficacy with an optimal concentration between 3,4-5,2 mg/L. A few years later, in 1997, Penovich et al. [21] studied a cohort of 62 patients and concluded that serum levels >4 mg/L are required for successful therapy. In 1999, Twyman et al. [22] measured plasma concentrations in 125 patients treated with various topiramate dosage regimens. They defined three strata, i.e.. ≤1.8 mg/L (N=72), >1.8 – 9.9 mg/L (N=70), and >9.9 mg/L (N=73) and found that the median seizure-free period increased considerably with increasing concentrations. Christensen et al. [23] conducted a randomized, concentration controlled, triple-blind clinical trial in 2003. A total of 65 patients were randomized and their topiramate concentrations were titrated to low (2 mg/L), medium (10.5 mg/L) and high (19 mg/L). The median reduction in seizures was 39% for those with the low target, 85% for those with the medium target and 39% for those with the high target. Based on these findings, the authors conclude that the optimal topiramate concentration range should be between 2 and 10,5 mg/L. In 2005, Stephen et al. [24] published the results of their prospective observational study, in which they administered adjunctive topiramate therapy to 170 patients until seizure freedom for 6 months, 50% seizure reduction at maximum tolerated dose or discontinuation of therapy due to lack of efficacy or adverse effects. They found that 23% of patients achieved seizure freedom (dosing range 50-800 mg/day), 47% reached 50% seizure reduction (dosing range 25-1200 mg/day) and 30% stopped the medication (dosing range 25-800 mg/day). With corresponding averages of 7.0 mg/L, 8.9 mg/L and 5.9 mg/L, topiramate concentrations varied substantially across all groups. Yamamoto et al. [25] report an association between continuation of medication and plasma concentrations more than 5 mg/L based on a 2017 retrospective cohort study of 610 patients and 1217 plasma samples. The 2017 AGNP (Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie) consensus guideline recommends a therapeutic range of 2-10 mg/L (alert level 16 mg/L) [27]. After the Norwegian association of clinical pharmacology changed therapeutic range of topiramate from 5- 20 mg/L to 2-10 mg/L in 2018, Koristkova et al. [26] evaluated the efficacy of topiramate treatment for both therapeutic ranges in a cohort of 294 plasma samples. They concluded that children with plasma concentrations greater than 5 mg/L experienced fewer seizures. There was no substantial impact in adults.

Toxicity

Topiramate toxicity can cause a wide range of side effects, such as paresthesia, sedation (e.g. dizziness, fatigue), cognitive dysfunction (e.g. attention deficit, impaired memory, language issues) and psychiatric

disturbances (e.g. aggressiveness, anxiety, depression) [1, 32]. According to Reife et al. [20] adversed drug reactions and/or signs of toxicity (mostly for symptoms associated with cognitive and emotional state) occur more frequently at increasing plasma concentrations. Christensen et al. [23]. observed a greater incidence of side effects (mainly psychiatric) in groups with medium (10.5 mg/L) or high (19 mg/L) target levels than compared to the group with low (2 mg/L) target levels. Koristkova et al. [26] noticed no difference in the incidence of adversed drug reactions between samples with a topiramate concentration.

Specific patient groups

There are no clear data on the TDM of topiramate during pregnancy. Arfman et al. [28] propose adjusting the dosage if the topiramate concentration reduces by >25% compared to TDM findings before pregnancy, and if the concentration decreased by 15-25% in presence of seizure risks factors.

Sampling conditions

After at least 5 days at a steady dosage level (= steady state concentration in patients with adequate renal function), obtain sample material (serum/plasma) just prior to administration of the next dose (through-based monitoring).

Background information [extended]

Topiramate is quickly and steadily absorbed after oral administration (Tmax 2-3 hours, F > 81%) and approximately 80% of the dosage is excreted in urine (mainly unchanged, about 20% as mostly inactive metabolites produced by the liver). About 15% of topiramate is bound to plasma proteins and its distribution volume is 0,55-0,8 L/kg. On the basis of its stated elimination half-life of 19 to 25 hours in healthy volunteers, steady state concentrations are expected to be attained in around 5 days. Clearance is enhanced by hemodialysis (by a factor of 4-6), reduced with renal impairment (-42% at CrCl 30-69 mL/min/1,73 m2 and -54% at CrCl < 30 ml/min/1,73 m2) and reduced in the presence of severe hepatic impairment (-26%) [1,5]. In pediatric patients, clearance is accelerated, resulting in a shorter elimination half-life: 7.7-8 hours at ages 4-7, 11.3-11.7 hours at ages 8-11 and 12.3-12.8 hours at ages 12-17 [4].

Interactions

Topiramate induces CYP3A4 and inhibits CYP2C19. CYP3A4 (partially) metabolizes topiramate. In addition to CYP-related interactions, hydrochlorothiazide raises the AUC of topiramate and influences the AUC of lithium, metformin, pioglitazone and glibenclamide [1,33].

PK parameters

	F (%)	**Cl** (L/h^{-1})	**Vd** (L/kg)	**$t_{1/2}$** (h^{-1})	Protein binding	Tmax (h)	Ref.
Adults	> 81%	1.2 – 2.4	0.6-0.8	20-30	9 - 17	2-3	[33,39]
Children		42-66% higher					[40]
+ enzyme inducers		3					[39]

Population models

Several pharmacokinetic models for topiramate have been developed. It is essential to pick a suitable population pharmacokinetic model by matching patient characteristics to those of the population used to create the model.
- Jovanović et al. 2013 [34] – Adults (patients), covariates: renal function, carbamazepine dose.
- Bouillon-Pichault et al. 2011 [35] – Children aged 6 months to 4 years (patients), covariates: body weight, age and the usage of enzyme inducers.
- Ahmed et al. 2015 [36] – Adults (healthy volunteers), covariates: body weight.
- Takeuchi et al. 2017 [37] – Children >2 years and adults (patients), covariates: body weight, carbamazepine or phenytoin use.
- Bae et al. 2016 [38] – Adults (patients), covariates: renal function, dose, usage of carbamazepine, oxcarbazepine, phenytoin and phenobarbital.

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Colophon

This guideline has been constituted by A.J. Wilhelm, Clinical Pharmacist & Clinical Pharmacologist 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

Not applicable

Revision

This guideline has been revised by R.P. Zuidema, PharmD and L.A.A. van Gendt – de Jong, PharmD, PhD
The guidelines was updated based on most recent literature and translated to English.
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