Quantitative Assay of Topiramate by LC-MS/MS (Reference — 2013.03.010)

Notice of Assessment

April 2014

1 GENERAL INFORMATION

1.1 Requestor

CHUM

1.2 Application for Review Submitted to MSSS

September 30, 2013

1.3 Application Received by INESSS

November 1, 2013

1.4 Notice Issued

February 28, 2014

Note:
This notice is based on the scientific and commercial information submitted by the requestor and on a complementary review of the literature according to the data available at the time that this test was assessed by INESSS.

2 TECHNOLOGY, COMPANY, AND LICENCE(S)

2.1 Name of the Technology

Liquid chromatography-tandem mass spectrometry (LC-MS/MS).

2.2 Brief Description of the Technology, and Clinical and Technical Specifications

The technique comprises three steps:

1) sample preparation;
2) liquid chromatography (LC);
3) mass spectrometry analysis (MS).

The aim of sample preparation is to purify it by removing proteins and other substances before analysis. There are several methods for doing so; the three most common are solid phase extraction (SPE), liquid-liquid extraction (LLE), and protein precipitation (PP) [Adaway and Keevil, 2012]. The requestor uses the PP method.

With LC, molecules can be separated from a complex mixture (serum or plasma) based on their physicochemical properties (molecular weight, hydrophobicity, etc.). The principle behind LC involves a liquid mobile phase and a solid stationary phase (in the column or in a thin layer). The composition of the liquid and solid phases varies based on the type of molecule to be purified. In the case at hand, the stationary phase is hydrophobic and the mobile phase is hydrophilic.

MS determines the mass of molecules present in the sample to be analyzed. Mass is measured based on the deflection of molecules previously ionized by an electric or magnetic field; a molecule's trajectory is proportional to its mass and charge.

The mass spectrometer consists of the following:

1) An ion source to alter the molecules' charge and convert them to the gas phase (e.g., electrospray ionization [ESI], atmospheric pressure chemical ionization [APCI], and others);
2) An analyzer that separates ions by their mass-to-charge ratio (m/z).

Analyzers can be coupled sequentially. Mass spectrometry is in several stages (tandem in this case, therefore MS/MS). The first analyzer selects ions based on a given m/z (purification). The purified ion is then fragmented in a collision cell. A second analyzer measures the fragments' m/z [Adaway and Keevil, 2012; Grebe and Singh, 2011].

2.3 Company or Developer

In-house method.

2.4 Licence(s)

Not applicable.

2.5 Patent, If Any

Not applicable.

2.6 Approval Status (Health Canada, FDA)

Not applicable. The requestor uses an in-house method for the test with an internal (UTAK) and external (Arvecon) quality control.

2.7 Weighted Value

51.0[11]

3 CLINICAL INDICATIONS, PRACTICE SETTINGS, AND TESTING PROCEDURES

3.1 Targeted Patient Group

Therapeutic monitoring of patients with epilepsy to optimize topiramate dosages, and those with specific clinical situations (e.g., kidney failure, coadministration of other anticonvulsants[12]).

3.2 Targeted Disease(s)

3.2.1 Epilepsy and its Treatment

Epilepsy is the most common neurological disease after migraines; its estimated prevalence ranges from 0.5% to 1% in the Western world [Forsgren et al., 2005]. It is characterized by recurrent seizures caused by excessive brain activity.

Several anticonvulsants are often used in combination for seizure control. Because of interindividual variation in the clinical manifestation of epileptic seizures, therapeutic drug monitoring can determine optimum doses while reducing adverse effects [Collins and Janis, 2012].

[11] According to the requestor, analysis can be performed at the same time as quantitation of levetiracetam (another antiepileptic); the cost per test would then be less than this value.

[12] Information provided by the requestor, electronic communication on December 20, 2013.

Topiramate, a new-generation antiepileptic,[13] is used as monotherapy for the management of patients[14] with newly diagnosed epilepsy. It is also indicated as adjunctive therapy for the management of patients whose epilepsy[15] is "not satisfactorily controlled with conventional therapy" [CPhA, 2013]. Topiramate can also be used for prophylaxis of migraine.

Safety and effectiveness in children under the age of two years have not been established for adjunctive therapy. There is limited information for the use of topiramate in adults aged 65 years and older, but the possibility of age-associated renal function abnormalities should be considered. Additionally, patients should be warned about the potential significant risk for metabolic acidosis. Topiramate is contraindicated in pregnancy and in women of childbearing potential who are not using an effective method of contraception because of the risk of fetal toxicity [CPhA, 2013]. Therefore, the benefits and risks of topiramate should be considered when it is used to treat these patient categories.

Most adverse effects are mild to moderate and dose-related. The most common[16] are paresthesia, headaches, fatigue, drowsiness, dizziness, depression, anorexia, nausea, and upper respiratory tract infections [CPhA, 2013]. Adverse effects with the highest rate of incidence are often central nervous system-related [CPhA, 2013; Goswami et al., 2009].
Topiramate has been listed in the Quebec formulary since 1997.[17] It has been available in the United Kingdom, United States, France, and Germany since 1995, 1996, 1997, and 1999, respectively [Bentué-Ferrer et al., 2010; Froscher et al., 2005; Privitera, 1997].

3.2.2 Drug Pharmacokinetics and Dosage

Topiramate is absorbed rapidly. Food has no clinically significant effect on bioavailability. Peak serum concentrations are achieved approximately 1 to 4 hours after oral administration [Johannessen and Tomson, 2006]. Topiramate exhibits low interindividual variability in plasma concentrations, and concentration increases are dose-proportional [CPA, 2013]. Elimination is primarily through the urinary tract, and plasma half-life is approximately 19 to 25 hours [CPhA, 2013; Goswami et al., 2009]. Steady state is achieved in 4 to 8 days in patients with normal kidney function [CPhA, 2013].

In children,[18] mean topiramate clearance is approximately 50% higher than in adults. Therefore, plasma concentrations for the same dose per kilogram body mass are expected to be approximately 33% lower in children [CPhA, 2013].

Phenytoin and carbamazepine decrease plasma concentrations of topiramate. Therefore, the addition or withdrawal of these antiepileptics during adjunctive therapy with topiramate may require adjustment of the dose of topiramate until the desired clinical effect is achieved [CPhA, 2013].

[13] In the last two decades, so-called new-generation antiepileptics have come on the market. They have a wider spectrum and are associated with fewer adverse effects than "first-generation" antiepileptics. [Krasowski, 2010]. Topiramate [TPM,2,3,4,5-bis-O-(1-methylethylidene)-b-D-fructopyranose sulfamate] is a second-generation antiepileptic [Patsalos and Perucca, 2003] with a broad spectrum of activity and multiple mechanisms of action [Goswami et al., 2009].
[14] Adults and children 6 years and older [CPhA, 2013].
[15] Adults and children 2 years and older [CPhA, 2013].
[16] Adverse effects in adults and children aged 6 to 16 years [CPhA, 2013].
[17] Institut national d'excellence en santé et en services sociaux (INESSS). Extract from the Notice: Topamax [website]. Assessment published July 1, 1997. Available at: http://www.inesss.qc.ca/activites/evaluation-des-medicaments/evaluation-des-medicaments/extrait-davis-au-ministre/topamax.html.
[18] Children with epilepsy aged 4 to 7 years.

Given the unpredictable nature of epileptic seizures and the difficulties associated with determining clinical parameters, clinical assessment to adjust anticonvulsant dosages is often complex. Determining the concentration of the drug allows the dosage to be adjusted based on tangible data rather than proceeding by trial and error[19].

3.3 Number of Patients Targeted

Twenty to thirty tests are expected per year. Quantitative measurement of topiramate can be performed at the same time as that of levetiracetam.[20]

Twelve tests were sent outside Quebec to the Hospital In-Common Laboratory (Ontario) during the 2012–2013 fiscal year at a unit price of $28,000.[21]

3.4 Medical Specialties and Other Professions Involved

Neurology, biochemistry.

3.5 Testing Procedure

Blood is drawn for a plasma or serum sample in the usual manner. There are no specifications regarding where the sample is to be collected.

4 TECHNOLOGY BACKGROUND

4.1 Nature of the Diagnostic Technology

"Unique" test.

4.2 Brief Description of the Current Technological Context

Different methods of analysis can be used for assaying topiramate in plasma or serum: high-performance liquid chromatography (HPLC) with UV[22] or fluorescence detection, fluorescence polarization immunoassay (FPIA), immunological methods, gas chromatography (GC), capillary gas chromatography, liquid chromatography coupled with mass spectrometry (LC-MS), or tandem mass spectrometry (LC-MS/MS) [Popov et al., 2013; Kim et al., 2011; Krasowski, 2010; Neels et al., 2004; Britzi et al., 2003; Johannessen et al., 2003 Perucca, 2000]. The literature does not indicate a reference method for this test.

4.3 Brief Description of the Advantages Cited for the New Technology

The protein precipitation (PP) purification method is the simplest and can be automated, but it can be less sensitive than the other two methods (SPE and LLE) because the resulting sample is not as clean and can be diluted by the solvents used for precipitation [Adaway and Keevil, 2012].

LC-MS/MS is quicker and simpler than other quantification methods for monitoring antiepileptic drugs [Kim et al., 2011]. Immunoassays are limited to detection of a single drug, and they are subject to cross-reactions between drug metabolites [Shibata et al., 2012]. Additionally, topiramate and its metabolites undergo thermal decomposition during gas chromatography, which is why LC-MS is the preferred method [Christensen et al., 2002].

19. Information provided by the requestor, electronic communication on January 7, 2014.
20. Information provided by the requestor.
21. Information provided by MSSS.
22. Detection by ultraviolet light. However, topiramate does not have a UV-visible absorption spectrum and it is not fluorescent [Bentué-Ferrer *et al.*, 2010; Subramanian *et al.*, 2008].

4.4 Cost of Technology and Options

LC-MS/MS necessitates expensive equipment, but compared with other chromatography techniques (e.g., HPLC or GC), smaller volume samples (50 to 200 µl) can be used [Adaway and Keevil, 2012]. With little handling, run time is short, specificity is better, and several anticonvulsants can be detected in the same sample [Collins and Janis, 2012; Kim et al., 2011; Tai et al., 2011; Subramanian et al., 2008].

5 EVIDENCE

5.1 Clinical Relevance

5.1.1 Other Tests Replaced

This will replace sending tests outside Quebec (Hospital In-Common Laboratory, Ontario).

5.1.2 Diagnostic or Prognostic Value

No studies showed a relationship between serum or plasma measurements of topiramate and mortality, morbidity, quality of life, or clinical results. One study was unable to show a direct relationship between high serum concentrations of topiramate (dosage) and efficacy (seizure control) or tolerability (occurrence of adverse effects) [Zanotta et al., 2006]. The results of another study of topiramate indicate that the correlation between the occurrence of adverse effects and dosage and the correlation between adverse effects and serum concentrations of topiramate are comparable [Froscher et al., 2005].

5.1.3 Therapeutic Value

The requestor used 5 to 20 µg/mL[23] as reference values in plasma and serum. These values correspond to those indicated in the literature as a therapeutic concentration range for topiramate [Bentué-Ferrer et al., 2010; Subramanian et al., 2008; Johannessen and Tomson, 2006].

Several authors have studied the usefulness of therapeutic drug monitoring for topiramate [Bentué-Ferrer et al., 2010; Patsalos et al., 2008; Johannessen and Tomson, 2006; Zanotta et al., 2006; Neels et al., 2004; Johannessen et al., 2003; Perucca, 2000; Tomson and Johannessen, 2000]. There is insufficient data to support a recommendation for therapeutic drug monitoring of this antiepileptic.

First, there is a linear relationship between the dose of topiramate (dosage) and serum or plasma concentrations in adults and children [Bentué-Ferrer et al., 2010; Johannessen and Tomson, 2006]. Therefore, pharmacokinetics are predictable, since interindividual variability is low. Second, a wide range of dosages and serum concentrations have been associated with optimal clinical response [Johannessen and Tomson, 2006].

Serum levels of topiramate would be useful for guiding dosage, particularly in young children who often require higher daily doses [Schwabe and Wheless, 2001] because they eliminate the drug faster [Krasowski, 2010]. This remains the authors' opinion since no supporting data have been presented.

[23] These values correspond to molar concentrations of 15 to 60 µmol/L [Bentué-Ferrer *et al.*, 2010; Johannessen *et al.*, 2003].

According to the requestor, because of the unpredictable nature of epileptic seizures and the difficulties associated with assessing these parameters (e.g., using EEG[24]), dosages could be adjusted more accurately by assaying drug concentrations rather than by relying on clinical parameters.

5.2 Clinical Validity

No studies assessing clinical validity were found.

5.3 Analytical (or Technical) Validity

TERM	PRESENCE	ABSENCE	NOT APPLICABLE
Repeatability	x		
Reproducibility	x		
Analytical sensitivity	x		
Analytical specificity	x		
Matrix effect	x		
Concordance		x	
Correlation between test and comparator	x		
Other depending on the type of test		x	

Table 1 presents the nine validation studies of LC-MS/MS identified. They use different purification and ionization methods.

5.3.1 Analytical Sensitivity

Few studies indicate the detection limit for the method (Table 1). For those that do, it is approximately 0.2 pg (picograms) to 0.01 µg/mL. The lower limit of quantification ranges from 0.01 to 0.8 µg/mL.

Calibration curves show high linearity with coefficients approaching or achieving a value of 1.

[24] EEG: electroencephalogram.

Table 1: Validation studies of topiramate quantitation using LC-MS/MS

Study	Type of Sample	Number of Specimens	Volume (µL)	Analysis Using LC-MS/MS						
				Purification Method	Internal Control	Ionization	LOD (µg/mL)	LLOQ (µg/mL)	Linearity (µg/mL)	Coefficient of Linearity
Britzi et al., 2003	Plasma	12 specimens (a single patient)	10	SPE	Topiramate-d_{12}	ESI (positive ion)	n.a.	0.625	0.625 – 40	r^2 = 0.9960
Christensen et al., 2002	Plasma	37 patients	10	PP	Structural isomer of topiramate†	APCI	n.a.	n.a.	20 – 20,000	r^2 = 0.9998
Goswami et al., 2009	Plasma	16 Indian patients	10	SPE coupled with centrifugation	Amlodipine	ESI in MRM mode (negative ion)	0.010	0.0104	0.0104 – 2.045	r = 0.998
Kim et al., 2011	Plasma	n.a.	5	PP	Valproic acid-d_6	ESI in SRM mode (negative ion)	n.a.	0.8	0.8 – 40	r = 0.9992
Matar, 2010	Plasma	n.a.	10	n.a.	Topiramate-d_{12}	ESI in MRM mode	n.a.	0.5	0.5 – 30	n.a.
Park et al., 2008	Plasma	24 Korean patients	5	LLE	Prednisone‡	ESI in MRM mode (negative ion)	n.a.	0.020	0.020 – 5	r^2 = 1.0
Popov et al., 2013	Plasma	n.a.	50	SPE	Topiramate-d_{12}	ESI in SRM mode	n.a.	0.010	0.010 – 2	n.a.
Subramanian et al., 2008	Plasma	n.a.	20	SPE	$^2H_{12}$-topiramate	APCI-MS in SIM mode	0.00047 (0.47 ng/mL)	n.a.	0.375 – 30*	r^2 = 0.9998
Tai et al., 2011	Serum	n.a.	1 – 2	SPE	Topiramate-d_{12}	ESI in MRM mode (negative ion)	0.2 pg	n.a.	44 – 47 µg/g	n.a.

Abbreviations: APCI = atmospheric pressure chemical ionization; APCI-MS = atmospheric pressure chemical ionization-mass spectrometry; ESI = electrospray ionization; FPIA = fluorescence polarization immunoassay; IMS = positive- and negative-ion mode switching; LLE = liquid-liquid extraction; LLOQ in the article (perhaps ng/mL).

† 1,2:3,4-bis-o-(1-methylethylidene-α-D-galactopyranose sulfamate).

‡ 1,4-pregnadiene-17-α,21-diol-3,11,20-trione.

5.3.2 Repeatability and Reproducibility

Tables 2 and 3 present data on repeatability and reproducibility of topiramate quantitation by LC-MS/MS. The coefficient of variation is approximately 0.2% to 14% for repeatability and 0.7% to 10.5% for reproducibility. Accuracy ranges from 92.4% to 116.63%.

5.3.3 Analytical Specificity, Matrix Effect, and Interference

All studies found have a recovery rate greater than 84%, except for the study by Goswami et al. [2009] in which values fall between 55.2% and 58.5% (Tables 2 and 3).

For all studies, the matrix effect was calculated at 96.5% to 111.96%. No significant interference was observed with respect to topiramate retention time (Table 4).

5.3.4 Correlation Between Test and Comparator

Only one study compared LC-MS/MS with another method, fluorescence polarization immunoassay (FPIA), on plasma samples [Christensen et al., 2002]. Least squares regression yielded $r^2 = 0.9965$ ($P < 0.001$), which indicates that both techniques provide similar results.

5.4 Recommendations From Other Organizations

None of the organizations found recommend topiramate quantitation for therapeutic drug monitoring of epileptic patients.

Clinical practice guidelines by National Institute for Health and Clinical Excellence (NICE) and Scottish Intercollegiate Guidelines Network (SIGN) recommend against conducting routine therapeutic monitoring of antiepileptics [NICE 2013; SIGN, 2005 and 2003]. This monitoring may be indicated in cases of nonadherence to medication, when toxicity [SIGN, 2003] or a drug interaction is suspected, and in specific clinical conditions such as status epilepticus, organ failure, and certain situations associated with pregnancy [NICE, 2013]. However, none of the guidelines deal specifically with topiramate monitoring.

Table 2: Repeatability (intratrial) and reproducibility (intertrial) of topiramate quantitation by LC-MS/MS

Study	Number of Specimens	Nominal Concentration* (µg/mL)	Intratrial			Intertrial			Total Accuracy (%)
			CV (%)	Relative Standard Deviation (%)	Accuracy or Bias (%)	CV (%)	Relative Standard Deviation (%)	Accuracy or Bias (%)	
Christensen et al., 2002	N/A	0.04	14.0			10.5			107
		0.4	1.4			2.6			100
		4.0	2.5			1.7			100
		16.0	1.8			0.9			101
Matar, 2010	7 (intratrial) 15 (intertrial for each conc. in 4 weeks)	2.0		2.71	–10.0		7.76	1.0	
		12.0		0.69	–5.3		2.97	2.1	
		25.0		0.81	–5.8		3.52	–0.3	
Subramanian et al., 2008	15 (triplicates over 5 days)	0.625	8.3			6.4			99.4
		2.5	6.5			7.1			101.5
		25	6.9			7.8			101.1
Tai et al., 2011	3	6.86†	0.2 – 0.6			0.8			
	3	19.0†	0.3 – 1.0			0.7			

Abbreviations: conc. = concentration; CV = coefficient of variation
*The units used in the studies were converted for uniformity.
†Mean concentration (ng/g).

Table 3: Reproducibility (intra-day and inter-day) of topiramate quantitation by LC-MS/MS

Study	Number of Specimens	Nominal Concentration * (µg/mL)	Intra-day			Inter-day		
			CV (%)	Relative Standard Deviation (%)	Accuracy† (%)	CV (%)	Relative Standard Deviation (%)	Accuracy† (%)
Britzi et al., 2003	6 (3 different days)	0.625				6		103
		1.25				8		99
		10				10		106
		20				9		104
Goswami et al., 2009	6 (intra-day) 18 (inter-day)	0.0271	4.3		98.6	4.1		99.9
		0.7731	3.9		106.2	6.4		104.3
		1.5463	2.4		107	5.5		106.4
Kim et al., 2011	6 (intra-day) 6 (inter-day)	0.8		2.1	112		11	105
		1.0		2.3	109		5.8	108
		6.0		3.4	94.3		7.1	92.4
		30.0		9.6	97.7		7.8	96.4
Park et al., 2008	5 (3 different days)	0.02	6.2		112.7	5.2		106.1
		0.1	4.1		116.6	4.2		108.7
		0.5	5.6		99.2	1.9		93.4
		2.0	2.2		101.4	1.8		96.3
		5.0	1.1		99.3	2.9		98.0
Popov et al., 2013	8 (intra-day) 21 (inter-day)	0.01	4.5		107.4	7.1		111.4
		0.03	4.5		97.0	4.4		95.7
		0.25	1.6		96.2	3.5		96.4
		1.75	2.3		95.9	3.2		92.9

Abbreviations: CV = coefficient of variation; wk = week.

* The units used in the studies were converted for uniformity.

† Mean measured concentration/nominal concentration * 100.

Table 4: Topiramate matrix effect, recovery, and interference

Study	N	Nominal Concentration (µg/mL)	Recovery (%)	Matrix Effect (%)	Endogenous Interference
Christensen et al., 2002	n.a.	2,000	104	n.a.	n.a.
Goswami et al., 2009	6	0.0271	58.5	96.5 Matrix factor not observed	No significant interference
	6	0.7731	55.2	n.a.	n.a.
	6	1.5463	56.4	107.8	n.a.
Kim et al., 2011	n.a.	1	97.1	106	No interference
		30	95.7	105	
Matar, 2010	6	2.0	89.9	111.96	No interference with endogenous compounds
		12.0	86.2	103.0	
		25.0	84.1	97.1	
Park et al., 2008	n.a.	n.a.	n.a.	No data on recovery	No significant interference No peak from endogenous substances
Popov et al., 2013	8	0.030	103.0 – 105.5	Matrix effect found in 1 of 8 plasma samples Topiramate matrix factor of 0.669	No peak found
		0.250			
		1.750			
Subramanian et al., 2008	3	2.5	86.3	n.a.	n.a.
Tai et al., 2011	4	2 µg/g	99.5	n.a.	No interference
		9 µg/g	100.1		
		25 µg/g	99.0		

Abbreviations: N = number of specimens; n.a. = not available.

6 OUTCOMES OF INTRODUCING THE TEST

6.1 Impact on Material and Human Resources

The test is performed with materials and equipment already found in several hospitals. It can be performed simultaneously with quantification of other antiepileptics. Availability of qualified staff should be taken into consideration.

6.2 Economic Consequences of Introducing Test Into Quebec's Health Care and Social Services System

Not analyzed.

6.3 Main Organizational, Ethical and Other (Social, Legal, Political) Issues

Not analyzed.

7 IN BRIEF

7.1 Clinical Relevance

None of the studies found show the effect of therapeutic monitoring of topiramate on clinical results. Additionally, there is insufficient data to support a recommendation for therapeutic drug monitoring of this antiepileptic.

7.2 Clinical Validity

No studies assessing clinical validity were found.

7.3 Analytical Validity

There are several validation studies of LC-MS/MS. The method is relatively selective, sensitive, precise, and reproducible.

7.4 Recommendations From Other Organizations

No recommendations supporting therapeutic monitoring of topiramate in epileptic patients were found.

8 INESSS NOTICE IN BRIEF

Quantitative Assay of Topiramate by LC-MS/MS

Status of the Diagnostic Technology

☐ Established
☒ Innovative for the indication requested
☐ Experimental (for research purposes only)
☐ Replacement for technology: _____, which becomes obsolete

INESSS Recommendation

☐ Include test in the Index
☒ Do not include test in the Index
There is little documentation of clinical usefulness and relevance.
☐ Reassess test

Additional Recommendation

☐ Draw connection with listing of drugs, if companion test
☐ Produce an optimal use manual
☐ Identify indicators, when monitoring is required

NOTE
We encourage the requestor to submit a new request with more thorough documentation and a clinical use algorithm.

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