OCULAR MANIFESTATIONS FOLLOWING SYSTEMIC MEDICATION

SEI Spring Educational – March 20, 2019

ER called….

- 29 YO CF
- Woke up with severe, bilateral eye pain and bilateral decrease in vision
- Went to ER for evaluation of pain/decreased vision
  - Normal, (-) CT, unable to check intraocular pressure at ER
  - given 4 units of Morphine
- ER sent patient to SEI for evaluation of ocular symptoms.

Exam 1

29 year old Caucasian female

CC: Blurry vision:

- Woke up with blurry vision after nap,
- Can only see objects within 1 inch of her face
- Light sensitive
- Extremely painful eyes
- Severe headache

Exam 1

- **Medical History:**
  - Heart ablation 2011
  - Migraines
  - Depression
  - **Medications:**
    - Lexapro
    - Imitrex
    - Topomax

ROS:
Headache
Nausea

Social History:
Current everyday smoker

Exam 1

VA sc: Big E at 2 ft OD and OS
IOP (applanation): 15mmHg OU
Slit Lamp:
Anterior Segment: Anterior shift of iris and lens, shallow anterior chamber, rest is WNL
Posterior Segment: ON: 0.2/0.1 perfused, no edema OU
+ FLR, retina attached, normal vessels OU
BP: Not checked

Exam 1

Auto refraction:
OD:-5.75 +0.75 096
OS:-6.50 +0.75 066

Refraction:
OD: -5.75 20/50
OS: -6.00 20/40

DDx:

- Acute bilateral myopic shift
- Bilateral = Systemic
1. Diabetes
2. Migraine headaches
3. Angle-closure glaucoma (early pupillary block)
4. CVA
5. Choroidal effusion syndrome

- Any recent changes to medical history?
  - Started Lexapro and Topamax 1 week ago, titrating dosage of Topamax to higher level

Exam 1

1 gtt Atropine instilled in office

IOP s/p dilation: 16 mmHg OU

Exam 1

Diagnosis: Ciliochoroidal effusion syndrome: Topamax induced myopic shift

Plan: Notify clinic if eye pain worsens, and/or redness occurs. Ed that eye will be dilated for 1 week.

- D/C Topamax
- PCP notified
- RTC 1 day

Exam 2

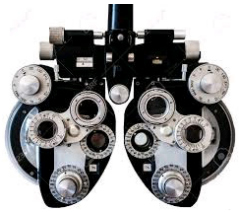
CC: Improved vision, but still blurry, still painful, but not as bad
ROS: Headache
VA sc: OD: 20/80 PH: 20/40
OS: 20/300 PH: 20/150

IOP (applination): 13mmHg OU
Slit Lamp:

- Anterior Segment: Anterior shift of iris and lens, shallow anterior chamber, Mydriatic pupil OU, rest is WNL

Exam 2

Auto refraction:
OD:-1.00 SPH
OS:-2.50 +0.50 x001



Impression/Plan
Topamax induced myopic shift:
Vision improving.
1 gtt 1% Cyclopentolate instilled.
RTC 3 days

Exam 3

CC

- Pain/headache significantly improved
- Vision improved, distance is fine, reading and up close vision is blurry

VA sc OD: 20/50 PH: 20/20
OS: 20/30 PH: 20/25

IOP (applanation): 15/14 mmHg

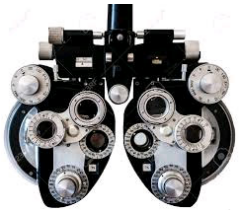
Slit Lamp:

- Anterior Segment: Improved anterior shift of iris and lens, deep anterior chamber, mydriatic pupil OU

Exam 3

Auto refraction

OD: +0.75 +0.25 x010
OS: +0.25 +0.50 x005



Impression/Plan

Improved AC depth

Improved auto-refraction and vision

Dilation responsible for near blur, should be improving. RTC 1 week.

Exam 4

CC

- Pain/headache gone
- Vision is good, no problems

VA sc OD: 20/30 PH: 20/25
OS: 20/25

IOP (applanation): 15/14 mmHg

Slit Lamp

- Anterior Segment: Resolved anterior shift of iris and lens, deep anterior chamber, reactive pupils OU

Exam 4

Auto refraction

OD: +0.75 SPH
OS: +0.25 SPH

Impression/Plan

Resolved cilichoroidal effusion syndrome resulting in acute myopic shift secondary to Topamax

Normal AC depth, improved auto-refraction and vision.

Consider MRx with local optometrist in 1 month.

RTC PRN.

Auto refractions

	OD	OS
9/24/2018	-6.50 +0.75 066	-6.50 +0.75 066
9/25/2018	-1.00 SPH	-2.50 +0.50 x001
9/28/2018	+0.75 +0.25 x010	+0.25 +0.50 x005
10/5/2018	+0.75 SPH	+0.25 SPH

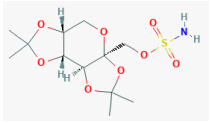
Objectives

- Review Topamax (Topiramate)
- Introduce ciliochoroidal effusion syndrome (CES)
- Discuss sulfonamides roll in CES
- Discuss primary vs. secondary angle closure
- Treatment for ciliochoroidal effusion syndrome

DV2

Topamax (Topiramate)- sulfamate substituted fructose analog

- **1996**- FDA approved epilepsy prophylaxis
- **2004**- Approved for migraine prophylaxis
- **2012**- 1st line migraine prophylaxis (previously a 3rd tier migraine prophylaxis, no 1st line based on clinic trial results)



DV1

MOA:

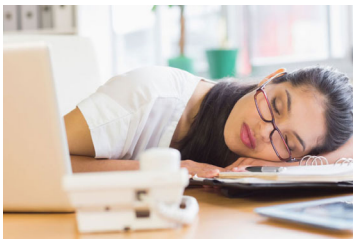
Molecular Activity	Consequences of Action
Negatively modulates voltage-activated Na^+ channels	1. Block action potential propagation
	2. Stabilize neuronal membranes
	3. Decrease neurotransmitter release
	4. Decrease focal firing
	5. Decrease seizure spread
Negative modulation of high-voltage activated Ca^{2+} channels	1. Decrease neurotransmitter release
	2. Decrease sustained membrane depolarization
Positive modulation of $GABA_A$ receptor	1. Increase membrane hyperpolarization
	2. Elevate seizure threshold
	3. Decrease focal firing
Negative modulator of AMPA/kainate receptor-mediated excitatory neurotransmission	1. Decrease fast excitatory neurotransmission
	2. Attenuate focal firing
Inhibits carbonic anhydrase activity	1. Decrease excitatory neurotransmission
	2. Enhance inhibitory neurotransmission
	3. Activate a hyperpolarizing K^+ conductance
	4. Stabilize neuronal membranes

Other Uses….

- Depression
- Neuropathic pain
- Obesity
- IIH
- Substance abuse
- Bipolar disorder
- PTSD
- Essential tremor
- Tourette's disorder

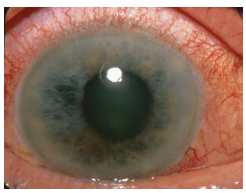
Topamax: Common Systemic Side Effects

- Somnolence
- Psychomotor slowing
- Fatigue
- Cognitive disorders
- Nephrolithiasis



Topamax: Ocular Side Effects

- Acute angle closure glaucoma
- Acute myopia
- Ocular pain
- Headache
- Hyperemia
- Mydriasis
- Uveitis
- Visual field defects
- Ciliochoroidal effusions
- Blepharospasm
- Oculogyric crisis
- Scleritis
- Retinal hemorrhage



Cilichoroidal Effusion Syndrome (CES)

- Spectrum of clinical manifestations ranging from TiMS to TiACG
  - -Term originated in 2002
  - -Describes mechanism of Topamax induced myopic shift (TiMS) and Topamax induced angle closure glaucoma (TiACG)
- Uveal effusions can occur secondary to:
  - -Hypotony (glaucoma surgeries)
  - -Primary angle closure
  - -Idiopathic
  - -Nanophthalmos
  - -Dural arteriovenous fistula
  - -Scleritis
  - -Harada disease
  - -Diffuse tumors of the uveal tract
  - -Drug induced: **SULFONAMIDES**

Slide 19

DV2 Highlight sulfa substitution
Daniel VanElk, 1/29/2019

Slide 20

DV1 Molecular Pharmacology of Topiramate: Managing Seizures and Preventing Migraine
Daniel VanElk, 1/29/2019

Cilichoroidal effusion syndrome: TiACG and TiMS

- Onset?
- When occurs?
- Who gets it?
- How many people are affected?
- Why? (Mechanism)
- Treatment?

Ciliochoroidal effusion syndrome in TPM use

- Onset
  - -Days to weeks
  - -Generally within 2 weeks
  - -Mean: 7 days
- The patient's onset was 7 days

Why does ciliochoroidal effusion syndrome occur?

- Dose dependent?
  - -50% of cases 50 mg or less
- Idiosyncratic
  - -Occurs in very small proportion of patients
  - -Not dosage dependent
  - -TPM intoxication without ACG

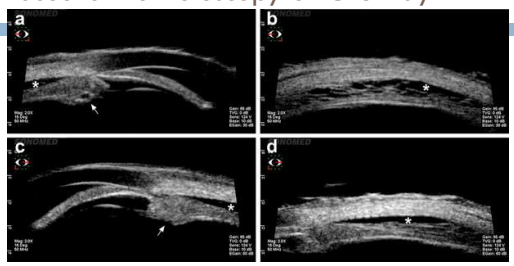
Incidence of ciliochoroidal effusion syndrome

- 3/100,000 (FDA)
  - -over 100 cases have been reported
  - -AACG most common reported ocular adverse effect
- Female>>>Males
  - -75%-89% of all reported cases
  - -Why?
- Mean age
  - -34

How does TiMS and TiACG occur?

- Choroidal effusion
  - anterior rotation of the ciliary body
  - Zonules loosen
  - Lens thickens
- Forward displacement of lens-iris diaphragm
  - -Leads to myopic shift and anterior chamber shallowing (80-90%)
  - -Iridocorneal angle change occurs secondary to effusion

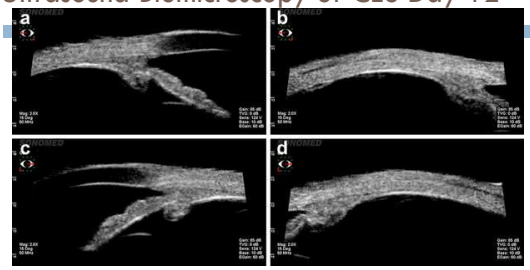
Ultrasound Biomicroscopy of CES Day 2



Right eye Left eye

Lan, YW. & Hsieh, JW. Int Ophthalmol (2018) 38: 2639. https://doi-org.ezproxy.ferris.edu/10.1007/s10792-017-0740-y

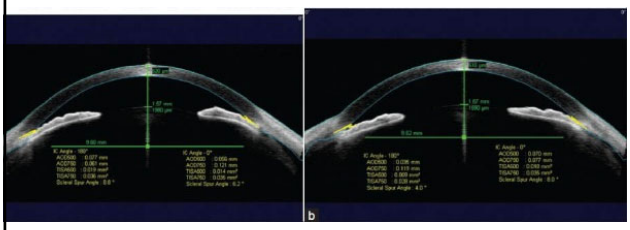
Ultrasound Biomicroscopy of CES Day 12



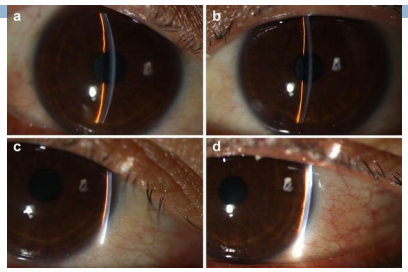
Right eye Left eye

Lan, YW. & Hsieh, JW. Int Ophthalmol (2018) 38: 2639. https://doi-org.ezproxy.ferris.edu/10.1007/s10792-017-0740-y

Anterior Segment OCT



Anterior segment photos

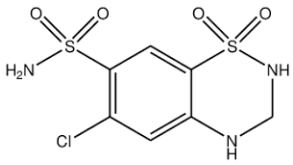


Proposed mechanism of cilichoroidal effusion:

- Sulfonamides decrease carbonic anhydrase inhibitor levels
  - -All sulfonamides have CAI activity
  - -CAIs reduce aqueous production
- Long-term decrease in CAI levels leads to rebound increase to serum aqueous and accumulation of suprachoroidal fluid.
- Critique:
  - -Doesn't explain idiosyncrasy
  - -Most have onset of 1 week….not long-term.

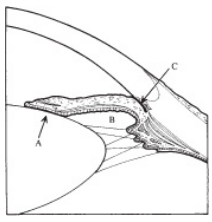
Sulfonamides

- Furosemide
- Hydrochlorothiazide
- Sumatriptan (Imitrex)
- Indapamide
- Acetazolamide
- Sulfamethoxazole/trimethoprim
- Topamax



Primary ACG vs. TiACG

- Primary occurs mostly in 6th or 7th decade
  - -Hyperopes with shallow AC
  - -Asian
  - -Female
  - -Most are unilateral
  - -LPI, pilocarpine, ocular hypotensives, oral CAI
- Topamax (and sulfonamides) can cause secondary angle closure
  - -Mechanism is different than pupil block
- Pupil block
  - -Not involved in TiACG



Treatment

- Decrease IOP with ocular hypotensives
  - -avoid acetazolamide!
  - -NO LPI!
  - -No Pilocarpine!
- Discontinue TPM
  - -Notify neurologist/PCP
  - -Seek alternative
- Use cycloplegics
  - -Help reduce IOP
  - -Cause retraction of the ciliary processes
  - -Help deepen AC: posterior displacement of lens-iris diaphragm

Treatment (continued)

- Refractory cases of TiACG?
  - -Mannitol
  - -Steroids?
  - -Argon laser iridoplasty?
    - Low energy burns to peripheral iris: widens AC angle and can break peripheral anterior synechiae.

TPM and CCT, Anterior chamber depth and Refractive error

- Does TPM cause changes to central corneal thickness (CCT)?
  - -Yes, 531.43 to 537.51 at 90 day f/u
  - -Not good LASIK/PRK candidates when taking TPM
- Does TPM cause changes to anterior chamber depth?
  - -No
- Does TPM cause changes to refractive error?
  - -Maybe… --0.23D to -0.61D at 90 day f/u
  - -Recheck MRx before dispensing glasses/CLs in patients who start TPM

Takeaways:

- Thorough patient history
- Topamax and other sulfonamides can result in idiosyncratic choroidal effusion syndrome
- Choroidal effusion syndrome: myopic shift to angle closure
- Use cycloplegics, stop TPM, notify prescriber
- Primary vs. Secondary angle closure