

Systemic Management of Glaucoma

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Objectives of presentation

- ❖ Meet requirement for non-topical therapeutic licensure in optometry
- ❖ Present successful practices and pitfalls of systemic prescriptive drug management
- ❖ Review foundational terminology, anatomy and physiology of the eye and body pertinent to systemic management of glaucoma
- ❖ Present pharmaceuticals and biologicals that can be used in non-topical formulations to manage glaucoma
 - Mechanism of action
 - Common clinical use (if there is one)
 - Cautions and adverse effects
 - Case examples

We make the assumption that we understand that glaucomas have one thing in common: characteristic damage to the optic nerve in association with abnormal intraocular pressure (IOP). An association; not necessarily a direct cause and effect. We treat it primarily by reduction of IOP.

Treatment of Glaucoma

- ❖ Different forms of glaucoma
 - POAG
 - Most common
 - Acute angle closure glaucoma
 - Secondary glaucomas
 - Pediatric glaucomas
- ❖ Different mechanisms of treatment
 - Increased outflow
 - Through traditional channels
 - Schlemm' canal
 - ◆ Schlemm's canal, right there at the base of the angle where the trabecular tissue passes the fluid through the inner wall of the sclera and then to the blood vessels that surround the eye.
 - Uveoscleral channels
 - ◆ The iris and uvea which also return fluid to the bloodstream.
 - ◆ We really take advantage of uveoscleral channels when we use hyperosmotic
 - Other outflow (osmotic)
 - Decreased inflow
 - Reducing production of fluid into the eye
- ❖ Different forms of treatment
 - Natural remedies
 - Topical agents
 - Systemic agents

- Orals
- Injectables
- Surgical interventions

Systemic Agents

- ❖ Oral Carbonic anhydrase inhibitors (CAI)
 - Acetazolamide (Diamox®)
 - Methazolamide (Neptazane®)
 - Dichlorphenamide (Daranide®)
 - Ethoxzolamide (Cardrase®, Ethamide®)

We currently have CAIs in topicals in Trusopt and Azopt (which are hard on corneas). If you have patients that have problems with Fuch's or have corneal transplants with reduced cell counts and cell quality, you may end up finding these patients developing corneal edema. They can also produce discomfort with keratitis where they have dry eye and marginal corneas. Keep that in mind with Trusopt and Azopt. The orals aren't as bad in my experience.

Acetazolamide is the gold standard. Methazolamide is less commonly used but is very effective when needed for chronic treatment. If I was asked what drug do I need to have to do an acute intervention with a systemic CAI for an eye problem (high IOP), I'm going to go with acetazolamide. Acetazolamide is going to be your drug of choice for rapid response intervention with a systemic CAI. There are couple of dosages and forms of it. I'm not big into having people remember specific drug names and dosages because I can use Epocrates. If you have a patient who needs rapid reduction of pressure, you want to use the tablet form of acetazolamide. There is also a capsule form which is extended release; they are called Diamox sequels and they don't get in to the system nearly as fast because they are slow release.

What's nice about Neptazane is that it doesn't work as effectively as Diamox. Generally, drugs that have really strong positive effects often have strong adverse effects. If you have a patient that doesn't tolerate acetazolamide, even if you try to go to a sequel which is better tolerated because it's slow released, you can go to Neptazane. Neptazane is a good drug.

The other two are generally used more for systemic cardiac applications and I don't have experience with Daranide or Cardrase.

Systemic Agents

- ❖ Hyperosmotics
 - Glycerin (Osmoglyn®)
 - Isosorbide (Ismotic®)
 - Ethanol
 - Urea (Ureaphil®)
 - Mannitol

The first two used to have brand names (Osmoglyn and Ismotic) which are no longer available commercially. You can get glycerin without any problem from the pharmacy. Technically, it wouldn't be pharmacy grade. We get ours from a pharmacy down in California. If you find any compounding pharmacy, they can put that together for you. I think every office should have a bottle of 50% glycerin in house. It can make the difference between breaking an angle closure attack in a patient and not. It's pretty inexpensive stuff. Oral glycerin is definitely important for clinical practice.

The Ismotic was a form that didn't metabolize to a form of glucose so it was better for diabetics.

Ethanol, I guess if you don't have a bottle of glycerin, you can always send them down to the local pub and have it work out that way. But is effective in terms of it being a hyperosmotic.

Urea and mannitol are IV delivered drugs. We have always been successful with orals so I haven't done that IV approach. You can do the CAIs IV and it is faster. It really will hit the system quickly. By the time you make your diagnosis and your working with the patient in your office, it's quicker if they are able to get pills down, than to get them to an urgent care [facility] or hospital where you can get the IV started. That would be more for an in-patient application.

Formation of Aqueous

❖ Mechanisms

- Diffusion- passive / concentration
- Ultrafiltration: passive / pressure
 - fluid pressure from the blood pressure across the capillary walls
- Secretion: active / energy dependent
 - active secretion with produces aqueous by active energy utilization

❖ Non-pigmented ciliary epithelium

- $\text{H}_2\text{O} + \text{CO}_2 \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{H}^+ + \text{HCO}_3^-$
- HCO_3^- is secreted into the posterior chamber
- Na^+ is associated with HCO_3^-
- H_2O follows the Na^+

Carbonic Anhydrase

- ❖ Catalyzes the formation of H_2CO_3 from H_2O and CO_2
- ❖ Increases reaction by a factor of 1000x
- ❖ Seven known isoenzymes of CA
 - CA-II is found in ciliary epithelium
 - Also found in kidneys, GI tract brain, RBC's

We got the ciliary processes, the ciliary body, the zonules attach to the crystalline lens. Here's a histological slide (figure 1) showing a process with a capillary here, some corpuscles in the capillary lumen, the pigmented epithelium, and the non-pigmented epithelium. It's in the non-pigmented epithelium where this active secretion takes place. In terms of the diffusion, that's just going to be by osmotic gradient across the capillary wall through the pigmented and non-pigmented epithelium through the posterior chamber. But the actual active secretion into the posterior chamber takes place in the non-pigmented epithelium, is energy requiring, and influenced by the effect of carbonic anhydrase which is the enzyme that catalyzes active secretion process

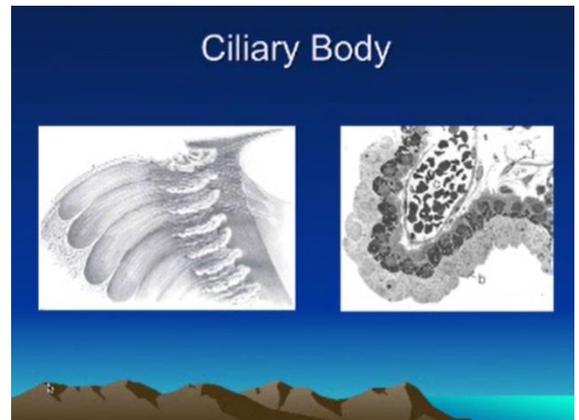


Figure 1

This is the chemical formula for that process involved in producing aqueous by active secretion. The bicarbonate passes across the ciliary epithelium into the posterior chamber, sodium follows that and in term water follows it. CAIs block the enzyme carbonic anhydrase which is critical to secretion [of aqueous]. Another thing that is important to realize is that there are a number of types of carbonic anhydrase which are prevalent throughout the body. It has a role in cardiac function, kidney function, and in respiration. That's where we have to be thinking about the adverse effects or the other effects besides what's happening to the eye.

If you block carbonic anhydrase, it will reduce the production of aqueous greatly.

CAIs by impairing that chemical equation will reduce the amount of bicarbonate ion that produced in that equation. Bicarbonate, that ion, is important to transmission of carbon dioxide and getting that off the body. If you block that, that's going to increase the respiratory load. Are there any climbers here? Individuals, in preparation for climbs, if they're getting up to real high altitudes where oxygen is going to be reduced, they will sometimes be treated for a week before their climb [with a CAI]. What it's doing is it's chemically conditioning and training them by increasing the respiratory load because they will be in an environment where there is less oxygen available. [If you put patients with pulmonary problems on high dose Diamox], you just may well aggravate respiratory problems.

The fat, the thin, the young, the old, and patients with multiple illnesses, those are the people you have to be aware of the adverse effects. For example, the more they're in those categories: they're 70 pounds overweight, they have congestive heart failure, have a history of asthma, they're allergic to 10 different medicines, you know what? I'm going to call your personal physician and ask them what they think about me putting you on this drug. But then you have a patient with no illnesses and normal body weight, but they had an angle closure attack because they're a hyperope. They're probably going to be fine [because they have] no drug allergies and are otherwise pretty healthy. The CAIs add a respiratory load is an important thing for you to keep in mind in terms of patients. There are some interactions that are important. For patients

with congestive heart failure that are treated with digitalis, that drug has a very narrow therapeutic index so carbonic anhydrase can impact the heart. It is actually used to treat patients with congestive heart failure, but you have to be careful. When we are treating patients when their pressure rises, we are generally going to do high doses of Diamox so you want to be aware that patients with congestive heart failure, they're compromised. You're going to hit them with a drug that impacts cardiac and lung function. It doesn't mean you're not going to treat them; you will have to consult [with other physicians] or send them to the ER because of these other issues.

CA= carbonic anhydrase

Other CA Functions

- ❖ Body
 - CO_2 (HCO_3^-) carried to lungs by RBC's
- ❖ Kidney
 - CA enhances H^+ secretion/ Na^+ retention
 - CAI = metabolic acidosis
- ❖ Lung
 - CO_2 "blown off"
 - Reduced lung function = respiratory acidosis

When you give patients CAIs, it does have some diuresis effect. If they're taking CAIs along with other drugs that cause diuresis, it can get them out of balance. Patients who have kidney problems who are treated with drugs that impact their kidneys and you're thinking about putting them on a drug like Diamox that's going to impact the kidneys, just be aware and take a look at your references. [Also] talk to your colleagues.

CAIs make it harder for the patient to breathe

CAIs are also used in patients with sleep apnea which I thought was interesting. "Wait a minute, this person has got trouble with respiratory function." In low doses, what it does, is that it increases the drive, like it does for the mountain climber, to breathe. It adds a load to it and their problem with respiration is not a primary pulmonary problem, [but] it helps to regulate their breathing during sleep because it increases that drive. You put them on low dose Diamox or Neptazane and it increases that drive for respiration. Makes it little harder in terms of getting the CO_2 out of the system, but it pushes a little bit.

Inhibition of Aqueous Formation

- ❖ CA-II is present in 100-fold excess
- ❖ CA-II must be >99% inhibited
 - CA requires a complete blocking [in order for CAIs to be effective] because it is widely distributed and in high concentration throughout the body.
- ❖ CAIs must inhibit aqueous
 - Various CAIs are more effective against various CA's

These are the chemical forms of the different CAIs I presented earlier (figure 2). I think the important thing to see here, at least from my perspective, is that they have a sulfa structure. Patients who are sensitive to sulfa drugs, these are generally contraindicated. I've had patients who have said that they have sulfa allergy. They have angle closure attacks with pressures of 60. We put drops on, we used hyperosmotics and their pressure is 55. We say "well, we have given everything we can give you. Would you rather develop Stevens Johnson or die from taking a drug you are allergic to and having anaphylaxis? Would you want to try this to help you see?" I have had this situation actually occur. That's why, when I talk about allergy with patients, I will ask them what happened? "I had allergy to codeine because I threw up." That's not allergy. Did you have respiratory problems? Did you have pruritus (itching), wheals, hives, swelling (peripheral edema)? "No I threw up." That is not allergy. But if they go around thinking that it is, it can prevent them from receiving medication that they need to have. Keep that in mind.

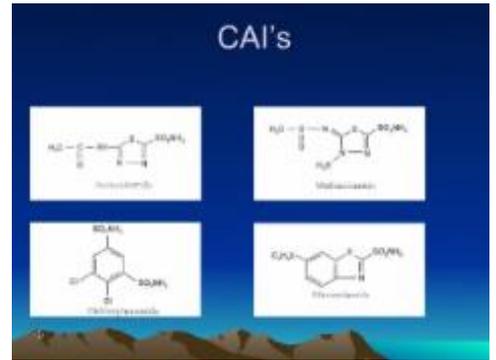


Figure 2

CAIs

- ❖ Sulfonamides
- ❖ No bacteriostatic activity

CAIs Indications

- ❖ POAG
- ❖ Secondary Glaucoma
- ❖ Acute angle closure glaucoma
- ❖ Macular edema- various forms
- ❖ Reduce aqueous production
 - Wound leaks

A patient who's had neovascular glaucoma is not a good candidate for surgical intervention because of that neovascular scarring process. You may need to use a CAI systemically [instead].

[The most common indications of CAIs are] Acute angle closure glaucoma or acute inflammatory glaucoma. Herpes zoster is the most offensive, herpes simplex is probably next in terms of producing inflammatory glaucoma. The faster you can break an attack, the better the prognosis. The longer that iris stays in contact with lens and angle, the more difficult it is going

to be reverse that.

A CAI is very effective for some forms of macular edema. The downside of treating with CAIs is that once you stop the drug, if the underlying cause for the macular edema has not been addressed, [the edema] comes back. With your angle closure, you're reducing fluid production into the eye by blocking carbonic anhydrase. You get the pressure down and then you do a laser iridectomy or you do a lens extraction. You have removed the cause for that high pressure. But if you got a patient who has chronic macular edema post operatively from vitreous prolapse or the patient has got a compromised pigment epithelium and a sick macula, you use it and it does work. But if that process that is causing it isn't intervened with and you stop it, generally it tends to come back. If you got a patient that you're trying to break the cycle, using topical drops and injections of Avastin or Kenalog for their macular edema, sometimes putting them on Diamox for short periods of time just adds a little bit more to break that cycle. You will find that in the literature.

If we can turn off the fluid production and let a little inflammation take place at the wound, it can seal [the wound leak] up. But if we got a wound leak or where fluid is actively going through a fistula, it just keeps poring through there, it's hard for that to seal off. I just don't see wound leaks that often.

CAIs Contraindications

- ❖ Na⁺/K⁺ imbalances
 - K⁺ depleting diuretics
 - Digitalis
- ❖ Kidney and liver dysfunction
- ❖ Severely compromised lung function
- ❖ Adrenal failure
- ❖ Pediatrics: safety not established
- ❖ Pregnancy
 - Teratogenic in rodents
 - No controlled human studies
- ❖ Nursing mothers
 - Small amounts secreted in milk
 - Safety in infants not established

Potassium depleting diuretics like hydrochlorothiazide would be drugs that you need to be aware of. The patient is on this drug and they've got angle closure and you want to add to that Diamox. You might [ask] "how's your blood pressure been doing?" You got a blood pressure on them, respiration and pulse are good. You go well "this is the first time I used Diamox in my practice" go ahead and put the drops in and give the doctor's office a call.

"We got an angle closure on your patient. We see that they're on HCTZ and we want to give the patient 250 mg of Diamox and then 250 mg 4 times a day for the next 24 hours. Is there a problem. Do you see a problem with that?"

They are probably going to say “nope, go ahead and give it to them. Let the patient know what the possible side effects would be.”

You give them the medication and you watch for a response.

I already mentioned that Digitalis, because it's used to treat congestive heart failure and because it's got a very narrow therapeutic index. Disturbing carbonic anhydrase in an individual who's got congestive heart failure can knock their treatment out of balance. If you got that, you are going to want to communicate with their cardiologist and say “we really need to use this drug but I see that this patient is on digitalis and they got congestive heart failure. I noticed that they're having trouble breathing while they're sitting here in my chair. Their legs are a little bit swollen. I'm really not wanting to give them this drug. Our pressure is 65 and we only have one eye. The other one was lost to injury.”

I kind of throw these [examples] out because these are things I've run into. The more complex [the patient], the more you need to have a team approach. The less complex, the more you just jump right in and do what needs to happen.

Kidney and liver dysfunction. The liver is primarily responsible for break down and the kidney is responsible for excretion. You do have elimination from the body through respiration and through the intestinal tract. In general, most of your drugs are eliminated through urination and they're broken down by the liver. CAIs are not impacted by the liver. They are excreted as their structure, but they are bound heavily to protein. Drugs, in general, are carried out in the bloodstream by protein. So if you give a patient a lot of a drug that is bound by protein, and they have other drugs that are bound by proteins, now you're putting more people in the game. It's like putting more people out there on I-5 trying to get to downtown Portland. Guess what? They're not all going to get there as fast. So what does that mean? They're going to hang around longer. It's going to take longer to get the drugs out of the body. The more drugs the patient's on, you give them Diamox, though it doesn't impact the liver directly, it keeps the drug around longer. If their liver doesn't work well and they're having to break down these other drugs, they stick around longer and could be more toxic. Giving high doses of acetaminophen is hepatotoxic along with high doses of Diamox can end up [causing] problems to the liver. For Diamox, the liver is not critical to metabolism but it does play a role. The kidney is its primary mode of elimination.

The patient that has lung problems like COPD, history of asthma (even though it may be well controlled), that's the kind of person you need to be alert to.

Adrenal failure. Patients who have Addison's Disease, either from taking steroids for a long period of time or from autoimmune disease, are at higher risk because of the lack of cortisol in their system. You add the load of CAI to their system and their lethargy can go from just lethargy to seizure to and into becoming comatose. I have never treated a patient with Addison's with Diamox. I've had patients with Addison's and I've had a lot of patients who had

to stay on low dose steroid because they can't get off it because they been taking it for so long that their adrenal medulla will not produce the cortisol that they need so they always have to stay on 2.5-5.0 mg of prednisone a day.

When we have to deal with emergencies with kids, I just do not like it. Sometimes, we have to because of our setting but we work with a pediatrician or family physician on a case with a child. We are probably going to stabilize them and get them to a pediatric center, in the big city, where they know how to deal with complex child problems.

Pregnancy. Any event that you got angle closure on a pregnant patient, we are going to counsel the patient that there are no human studies. "We are going to try drops to eliminate your problem [and] try hyperosmotics because that's basically just sugar. But if that doesn't, what do you want to do? We need to get this pressure down."

Nursing mothers. We tell patients that they will need to stop [nursing] for a short time. We tell them that there's formula available. "This is going to be a short-term treatment and we counsel you to stop nursing at this point in time."

CAIs-Side Effects

- ❖ Death
 - Steven's- Johnsons syndrome (SJS), toxic epidermal necrolysis, fulminant hepatic necrosis
 - Aplastic anemia, agranulocytosis, others
 - Dose related or idiosyncratic
 - 2/3 occur within 6 months
 - Anemia, fatigue, infections, bruising
 - Routine blood testing ????
- ❖ Concomitant use of high dose ASA
 - Anorexia, lethargy, coma, death
- ❖ Paresthesias: unknown cause
- ❖ Malaise complex
 - Unwellness
 - Weight loss
 - Depression
 - Decreased libido
- ❖ Metallic taste: carbonated beverages
- ❖ GI distress
 - Cramping, heartburn, nausea, diarrhea
- ❖ Induced myopia
 - Lens swelling (?)
- ❖ Frequency of urination: diuretic
- ❖ Kidney stones
 - Alkalinization of the urine
 - Depletion of urinary citrate and magnesium
 - Calcium oxalate stones: 50% recurrence

➤ Acute renal failure from tubular obstruction

Death: that's a disconcerting side effect. We've talked about how these things can happen. I have been involved in patients, who in spite of counseling, get out of whack with chronic therapy. If you hit these people too hard and they got multiple system diseases, they can die from the use of CAI.

SJS: almost every drug that you can give a person can produce an immune response, a hypersensitivity response that results in SJS. It does happen. That's why it's important on the allergy thing to be sure, when the patient is told that they have allergy, that they [really] do have [the] allergy.

These are things (SJS and aplastic anemia) that generally you are not going to know in advance. It's something that the patient is going to be treated and then they develop it.

Routine blood testing: Back when the use of chronic CAI was a little more common, we used to get patients tested a couple times a year to be sure that their electrolytes weren't getting out of balance. You would get a metabolic panel just to make sure that they weren't getting out of balance on their potassium, chloride. Now, since we don't have many patients on that, it's really questionable. If they eat a banana a day or take a potassium supplement, they're probably not going to get into trouble.

Aspirin can add a respiratory load. They are patients who are sensitive to aspirin from a respiratory standpoint. They have aspirin allergy; they take aspirin and it causes bronchiole constriction and they have aspirin-related asthma. Keep in mind that high dose aspirin can add a load to respiration. We think of our mountain climbers who take Diamox to get ready for the mountain climb, adding a load to respiration. The two together, double the [effect]. Over three grams a day is considered high dose ASA. I like to see patients under a gram of day of aspirin. If the patient has got ringing in their ears, ask them how much are they taking? If they tell you, I'm taking 20 a day. They're probably on too much aspirin.

Paresthesias: the tingling that patients have around the mouth and the extremities, fingers, and feet. It's not fully understood. It probably has to do with the impact to nerves that the CAI is disturbing that electrolyte balance. It's probably producing some type of abnormal nerve conduction that gives people that tingling.

Malaise complex: When you get Diamox in the pharmaceutical sized bottles, it comes with a gray label, sometimes with a gray top. I think they did that because that's just how it makes people feel. They may not feel it when they're taking it but when they get off it. [They might say] "man that stuff was nasty. My energy is back." If they're on it long enough, they will start to feel [as if] life is not good. They can have weight loss and depression. That patient that is on amitriptyline, maybe they've had herpes zoster uveitic glaucoma. They come in with a high pressure which we need to get down. You put them on Diamox, all of a sudden they crash. Their depression gets uncontrolled.

Metallic taste of carbonated beverages; important to remember and important to share with your patients. You give them this drug and they're going to go out and have a soda or a beer. They're going to say "this tastes crappy, this is horrible. What happened?"

With any drug you give a patient, I tell them "if you have any systemic problems particularly with problems of elimination: diarrhea, constipation, vomiting, you need to let us know right away and call right away." I give a general description of the places where systemic effects occur.

Induced myopia: lens swelling. It's been documented that these drugs can change refraction.

For patients who have renal stones, they know that they don't want to have it again. If you put a patient on Diamox or Neptazane, even for a short period of time, you could help precipitate stones again. If a patient has kidney stones, they need to hydrate. Try to [discontinue the drug] as soon as possible. Obviously, if a patient has acute renal failure from tubular obstruction, you're giving a drug that's going to put a load on the kidney. If the kidney is not working, you're going to get into trouble. That's the primary way that these drugs are eliminated, through the kidney and urination.

Dosage and Administration

❖ Acetazolamide

- Diamox® (generic available)
- 125 mg tabs, 250 mg tabs, 500 mg Sequels®
 - Sequels® have delayed onset
 - Fewer GI symptoms with the Sequels®
- Dose: 375-1000 mg per day in divided dose
- IV: 250-500 mg q 4-6 hours
 - Very rapid onset

❖ Methazolamide

- Neptazane® (generic available)
- 25 mg tab, 50 mg tab
- The good thing about Neptazane is if you have a patient where therapy fails with acetazolamide and they need to be on a drug, this can work very nicely. It may not work and lower the pressure as much, but how much do you need to lower the pressure?

❖ Dichlorphenamide

- Daranide®
- 50 mg tabs
- 50-150 mg per day in divided dose

Prescribing Tips

- ❖ Side effects are dose related
 - Start with a low dose if that's appropriate for chronic treatment
 - If you're dealing with an angle closure, you're probably going to want to use maximum dose for the person's size to rapidly reducing the pressure
- ❖ Partially additive to other glaucoma meds
 - Except topical CAIs
- ❖ Different individuals respond to different CAIs differently
 - Effectiveness
 - Side effects
- ❖ Side effects can decimate compliance
- ❖ Side effects may be lessened by
 - Taking with meals
 - Taking sodium bicarbonate or sodium acetate

Comparisons

- ❖ Acetazolamide
 - Indications
 - Glaucomas
 - Edema from CHF (congestive heart failure)
 - Petit mal, un-localized seizures
 - Acute mountain/altitude sickness
 - Primarily excreted by the kidneys
 - Use with caution with reduced kidney function
 - Onset
 - Tablets: 1 hour
 - Sequels®: 2 hours
 - IV: 3 minutes
 - Peak
 - Tablets: 2-4 hours
 - Sequels®: 4-6 hours
 - IV: 15 minutes
 - Response: 30% reduction in IOP
 - 30% is a reasonable average but I've seen it 50% in emergent cases
- ❖ Methazolamide
 - 60% bound to plasma vs 95% for acetazolamide
 - Plasma $\frac{1}{2}$ life = 15 hours vs 4 hours for acetazolamide
 - Onset: 2 hours
 - Peak: 4-6 hours
 - Greater lipid solubility
 - Absorbs better
 - Lower dose
 - Less likely to affect kidney CA
 - Less systemic acidosis

- Less side effects (?)
- More variable response
- Less effective vs acetazolamide (?)
- ❖ Dichlorphenamide
 - Onset: 45 minutes
 - Peak: 2 hours
 - Similar or slightly less effective than other CAIs
 - Similar or slightly worse side effects than other CAIs

Systemic vs Topical CAIs

- ❖ Systemic agents are more effective
- ❖ No additivity between systemic and topicals
- ❖ Classical side effects are rare with topicals
- ❖ Allergic and idiosyncratic reactions are still possible
- ❖ Safety of topicals in pregnancy and pediatrics has not been established
- ❖ ½ life of topical dorzolamide is 147 days

I haven't seen any added benefit in using a systemic and topical CAI together

If you're wanting to see how a patient tolerates a CAI, in terms of POAG, put them on a topical first.

Hyperosmotics Agents

- ❖ Draw fluids from the eye through the vascular system
 - Retinal circulation
 - Choroid
 - Iris/ciliary body circulation
- ❖ Increased serum osmolality
 - Rapid but transient
 - Water follows the osmotic gradient
 - Reduced IOP is from reduced vitreous volume
 - (Reduced vitreous allows opening of the angle)
- ❖ I only use these drugs for emergent treatment. I've never treated a patient chronically with hyperosmotics

Factors Affecting Hyperosmotics

- ❖ Dose and rate of administration
- ❖ Rate of removal from circulation
- ❖ Distribution in all body fluids
- ❖ Rate and degree of penetration into the eye

When we give hyperosmotics to patients, generally it's half a bottle of 220 mg of glycerin in a cup and we put some flavor stuff in it like apple juice, give them a straw, hold their nose, and say "try to suck it down as quickly as you can. Try to keep it moving." Once it hits the stomach,

if they nurse on it, they will probably end up nauseated and they will probably want to vomit. Then it's not going to work. So you want to get it down; a straw works well. It's nice to have your Diamox on board before you give them this. If you give it to them right away and they puke, then they may have tossed a bit of the Diamox out so you might have to re-dose them.

It's very rapid in terms of its activity; within 30 minutes of ingestion, we are going to see pressure reduce on these patients.

The way I remember it is for an adult of normal weight and size, it's about half a bottle. But if we have a little person, we will ask them how much they weigh? I then go to Epocrates, punch in the numbers, and say "she gets a third of the bottle."

Oral Agents

❖ Glycerol

- Osmoglyn®
- 50% solution
- 1.0-1.5 gm/kg (1 gm = 1.6 mL of 50% solution)
- Onset: 10-30 minutes
- Peak: 45 minutes – 2 hours
- Rapidly metabolized to glucose
- Not excreted by the kidneys

❖ Isosorbide

- Ismotiv® (no longer available)
- 45% solution
- 1.5 gm/kg (1gm = 2.2 mL of 45% solution)
- Is not metabolized to sugar so good for diabetic patients
- Excreted by the kidneys

❖ Ethanol

- Widely available!
- 80-100 proof
- 1-2 mL/kg
- Enters the eye, reducing the osmotic gradient
- Distributed to total body water
- Acute alcohol toxicity, nausea, vomiting

IV Agents

❖ Urea

- Ureophil®
- 30% solution
- 2-7 mL/kg
- Onset: 15-30 minutes
- Peak: 60 minutes
- Distributed to total body water, enters the eye
- Unstable: mix and use fresh

- Extravasation is painful
- ❖ Mannitol
 - Osmitol®
 - 20% solution
 - 2.5-7.5 mg/kg (175-525 mL in 70 kg person)
 - Onset: 10-30 minutes
 - Peak: 30-60 minutes
 - Remains extracellular, does not penetrate eye
 - Excreted unmetabolized by the kidneys
- ❖ Indications
 - Rapid but transient reduction of IOP
 - Acute angle closure glaucoma
 - Ciliary block (malignant) glaucoma
 - Preop surgery to reduce vitreous volume

Ciliary block (malignant) glaucoma is not very common, but it looks a lot like angle closure glaucoma. It is a form of angle closure glaucoma. With our typical, more common, angle closure glaucoma, we get a barrier at the level of the pupil between the posterior and anterior chamber. Fluid can't get through; the iris is stuck to the lens. The iris gets pushed forward and blocks off the angle. If you look at those patients with a slit lamp, what you see is you see this pupil that's back and this bowed iris up towards the cornea [...] like a convex appearance of the iris. This is nice when you are going to do a laser treatment because it's right up there where you can get at it. When you have a patient with malignant glaucoma, what you see is that the iris isn't really curved, it's just right up in your face. The lens and ciliary body have all translated forward because fluid is running into the vitreous cavity instead of the posterior chamber and pushing the lens-zonule complex forward. So you have this pupil right up against the cornea. You have an angle closure but it's because everything has moved forward because fluid is going into the back behind the lens instead of the posterior chamber where it's supposed to be. What would be good is if we can suck fluid out of the vitreous; it's good for both (angle closure and malignant glaucoma) types of patients. We pull fluid out the vitreous and into the choroid and it lets that settle back. If the pupil and the lens are right up behind the cornea, "wait a minute, it should be back. The iris should be bowed." It would be appropriate for the use of hyperosmotics in these patients that have malignant glaucoma.

Hyperosmotics – Side Effects and Contraindication

- ❖ Nausea (especially oral agents)
- ❖ Headache/back pain – CNS dehydration
- ❖ Diuresis
 - Awkward during surgery
 - Urinary retention – prostatic hypertrophy
- ❖ Circulatory overload
 - Compromised renal or cardiac function
- ❖ Use with caution in renal failure
 - Circulatory overload

- Prolonged hyperosmotic state
- Profound hyponatremia
 - Lethargy, obtundation, seizures, coma
- Potassium depletion
- Mannitol toxicity may require dialysis

General Observations

- ❖ Reduce intake of other fluids
- ❖ Oral agent: slower onset, less effective vs IV
- ❖ May need anti-emetic agents also

Retrobulbar Alcohol

- ❖ Alcohol denatures proteins – destroys nerve fibers
- ❖ Used in blind painful eyes to preserve globe but relieve the pain
- ❖ Technique
 - Inject long acting anesthetic (Marcaine®)
 - Leave needle, remove syringe
 - Inject absolute alcohol
 - Leave needle, remove syringe
 - Inject anesthetic along needle tract

Patients who end up having a blind painful glaucomatous eye (high pressures, corneal decompensations) and they don't want to have the eye removed or they are not a good surgical candidate to have their eye removed, you can control their glaucoma (which is primarily a painful process) by doing an alcohol block which denatures or destroys nerve fibers.

What's done to give a patient alcohol block for this purpose is to inject long acting anesthetic into the orbit. You do it in the [same] way as a patient would get a block to have eye surgery of any kind. They're going to get an injection, usually from the inferior aspect, below the globe, into the orbit. The syringe is then removed and the needle is left in place. An injection of absolute alcohol is given with a second syringe that's applied to the needle. This is recapping. I guess it's an acceptable form of recapping since you can't get hit by the end of the needle. Then the anesthetic is re-injected along the needle track. That will give the patient relief for 6-12 months. Multiple injections will sometimes end up producing a permanent reduction in pain. Unfortunately, when these patients have this, it also impacts their sensory nerves and they can end up getting corneal erosions because of being neurotrophic. Alcohol blocks are not done very much anymore. Generally, what's being done is that patients are being enucleated if they can't have their pain controlled with oral chronic pain management.

Marijuana

- ❖ Lowers IOP in 60% of users
- ❖ Average IOP lowering: 25%
- ❖ Range of IOP lowering (-45% to +5%)
- ❖ Peak Effect: 90 minutes

- ❖ Duration: 3 hours
- ❖ Ocular Side Effects
 - Hyperemia
 - Decreased lacrimation (≈50%)
 - Diplopia
 - Decreased accommodation
 - Photophobia
 - Nystagmus
 - Blepharospasm
- ❖ Systemic Side Effects
 - Euphoria
 - Tachycardia
 - Orthostatic hypotension
 - Reduced cognitive abilities
 - Toxic pulmonary effects (worse than tobacco)
 - Effect on virtually all organ systems
 - Various hormonal changes
- ❖ Cannot separate the IOP lowering from the side effects
- ❖ No studies in the long term effectiveness
 - Toxic effects offset IOP lower effect (?)
 - Must be used 8 times per day
 - How would compliance with other meds be affected if you're up every 3 hours to make sure you're taking it.
- ❖ Federal Law
 - Schedule I controlled substance
 - Physicians cannot prescribe Schedule I drugs
- ❖ Summary
 - When "all" other conventional forms of treatment have failed, marijuana would not likely help
 - I'd rather be blind with my "faculties" intact, than seeing without sensibilities

That means you got be utilizing the medication about 8 times a day. It's really not a good choice, regardless of the carcinogenic effects of smoking marijuana. Even if you did by pill or some other oral route, it doesn't have the duration of action to be really a practical use. This hopefully will be helpful when you run into patients; just say "this is not a good treatment for your glaucoma. They're are much better drugs."

Marijuana is a controlled substance so from a federal standpoint, you do put your DEA privileges as risk. I know in Oregon that they do have some ability to indicate that a patient can use marijuana for medicinal purposes. If you're involved in with it, you're putting yourself at risk. Is it really beneficial to the patient in the practice of optometry? I just don't see that there is.

Ginkgo Biloba Extract (GBE)

- ❖ From the ancient Maidenhair Tree
- ❖ Nutritional supplement
 - Cerebrovascular disease
 - Peripheral vascular disease
 - Dementia
 - Tinnitus
 - Bronchoconstriction
 - Sexual dysfunction
- ❖ Effects
 - Reduces glutathione, increased glutathione reductase
 - Antioxidant
 - Inhibits platelet activating factor (PAF)
 - A number of measurable physiological functions improved with ↓ PAF
 - ↑ cerebral and peripheral blood flow
 - Decreased blood viscosity
 - Increased erythrocyte deformability
 - Inhibition of thrombus formation
 - Resulting in (neurological) performance improvement
 - Neuroprotection
- ❖ GBE in Glaucoma
 - Improved blood flow
 - Antioxidant
 - Neuroprotection
 - No controlled studies
 - Questionable use in low tension glaucoma

Systemic Agents – Summary

- ❖ Highly effective in lowering IOP
- ❖ Significant side effects limit their usefulness
- ❖ Usually more of a last resort
 - Weight the risks and benefits
 - Balance these agents against other options
- ❖ Always consider the **Quality of Life**

Case 1

- ❖ 52-year-old white male with past history of occasional ache in right eye, but today ache became painful and vision is blurred
- ❖ Habitual Rx:
 - OD +4.25 -0.75 x 090 20/70
 - OS +3.00 -1.00 x 090 20/20
- ❖ Biomicroscopy

- 2+ injection OD
- 2+ to 3+ corneal epithelial edema OD
- Gonioscopy: No structures seen OD, slit view OS
- Tonometry: OD 52 OS 22
- MHx
 - Elevated lipids x 5 years, Tx with Crestor
 - NKMA (no known medical allergies)
- ❖ Assessment: acute angle closure glaucoma
- ❖ Treatment
 - Drops: everything, including pilocarpine
 - Systemic
 - Oral CAI
 - Tablet vs Sequel (tablet preferred)
 - IV CAI: very rapid onset
 - Oral hyperosmotic
 - Nausea
 - IV hyperosmotic
 - This is the order I would treat. I'm going to the Diamox 20-30 minutes to work before I give them the glycerol
 - Iridectomy (LPI): ASAP!

Case 2 (figures 3 & 4)

- ❖ 69-year-old monocular white female with longstanding Hx of POAG
 - Post cataractectomy plus trabeculectomy with delayed slow resorbing hyphema OD
 - Post pupil membranectomy OD
 - Post anterior and posterior YAG capsulotomy OD
 - Phthisis OD
- ❖ Inadequate control with maximum tolerated topical therapy
 - 0.06% Phospholine Iodide BID
 - Ocupress BID
- ❖ Systemic medication
 - Procardia: Htn, Angina
 - Atenolol: Htn, Angina
- ❖ Type IV (four) allergy
 - Brimonidine
 - Propine
- ❖ Habitual visual acuity
 - 20/20 with +0.25-0.50 x 130



Figure 3



Figure 4

- ❖ Biomicroscopy
 - Anterior seg quiet OU
 - Flat bleb? Benefit OD
 - Pseudophakia OD
 - Phthisis OD
 - Posterior seg (figure 5)
- ❖ Tonometry
 - 18 mm Hg
 - Target IOP < 16 mm Hg
- ❖ Visual field (10-2 and 30-2 of right eye) (figures 6 & 7)
- ❖ Assessment
 - Advanced POAG in monocular patient
 - Suboptimal control with moderate risk for further sight loss
- ❖ Management
 - With present meds
 - Add Diamox 500 mg sequel BID
 - Option of repeat trabeculectomy
 - Patient opts for maximum medical management
 - Counseled on ADR (adverse drug reactions)
 - Letter to PCP
- ❖ Follow-up
 - Tonometry 13.5 mmHg

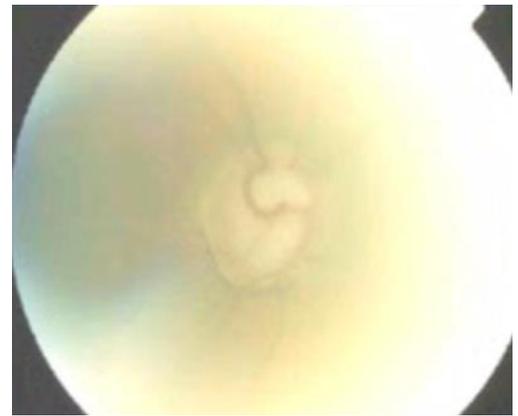


Figure 5

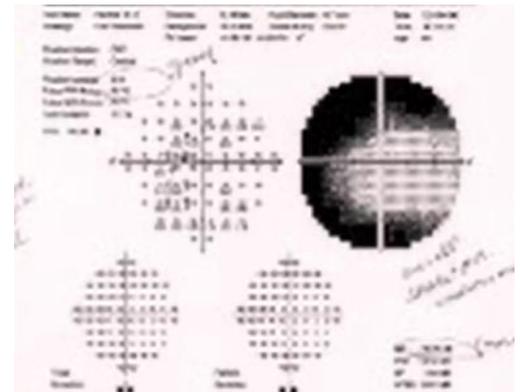


Figure 6

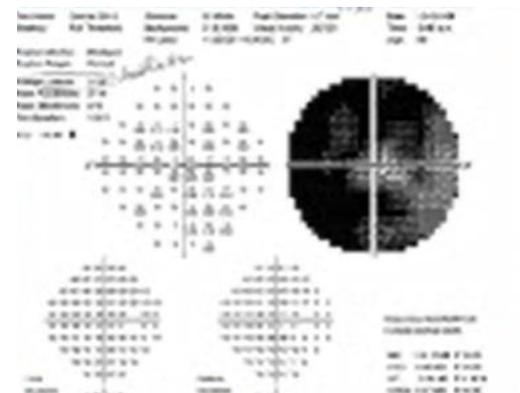


Figure 7

Thank you very much!