

## Systemic Management of Ocular Inflammation, Allergy, Pain & Anxiety

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Ocular inflammation, allergy, pain, and anxiety share many common characteristics and therapeutic interventions. As an outcome of the allergic immune response, inflammation can be managed by intervention in the hypersensitivity process. As a major component of inflammation, pain management often involves treatment of inflammation. And with pain or its expectation comes anxiety, to which anxiolytic medications can be applied.

So they have some similarities. As a result, we can group them together and look at how the drugs intervene at the different levels to restore normal function and relieve pain and suffering.

The content of this presentation will be shared over three hours. The presentation will be loosely divided into topics:

- ❖ Management of
  - Inflammation
  - Allergy
  - Pain
  - Anxiety

### Objectives of Presentation

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

The mechanisms of action are beneficial, at least for me at a basic level, to remember what they're doing and how I apply them in patient care. We will talk about that a bit.

### Good Reference Material

We could just talk about this slide for a while because I don't remember things really well. Matter of fact, I think I forget more now more than I remember. But if you got good references available, I know there are more, you got stuff online [and] PubMed, you can really do a nice job helping yourself and also helping other clinicians. [...] The ER docs around our area that end up using us, even though we are not on staff. I'm not on staff at any hospital but I get contacted probably once a month by one of the hospitals around the area with regard to a patient that's got an eye problem or I send a patient to the ER. Photocopying a couple of pages, sending it in, faxing it in, they'll say "thanks for sending that; I haven't dealt with that kind of eye problem since I was in residency." It kind of lays out some of the testing that the patient needs to have done. So having those references at hand are beneficial. Drug-Induced Ocular Side Effects by

Fraunfelder is a good one (figure 1). There's also Differential Diagnoses by Roy which is not up here [on the slideshow] (figure 2). If you're interested in some of the references that I use, you can contact me. I'm at pcli.com and just go there. You can find where I'm at and I've got an email address. I'd be glad to respond and let you know what I use. There's a PDR that you can get for your computers. I use Epocrates. So get those reference materials. They are really beneficial.

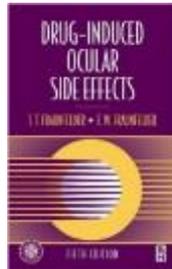


Figure 1

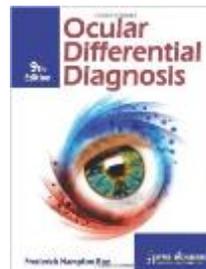


Figure 2

## Inflammation

This opening statement is very helpful to me as I think about what we do in terms of caring for patients. That is understanding what is inflammation and what is its purpose.

Physiologic process intended to protect and repair the body when threatened, injured, and or invaded by agents recognized as "foreign".

When you step back and think of it not as necessarily an enemy, but as part of what keeps people healthy, it changes your perspective and management a little bit. It also helps you when you are dealing with your patients because people [...] want to be free of pain. Patient comes in with a corneal ulcer and they are in pain. They want you to free them of pain. Maybe they come in with an abrasion that you are questioning whether or not it's an ulcer. So you decide "we're going to take care of this pain. We're going to give a bottle of alkane and a prescription for Vicodin." They come back 24 hours later and you're treating their abrasion thinking it might be an ulcer so you are treating with antibacterials or whatever antifungals if you think it's that.

The patient goes "boy Doc, I'm doing better, feeling pretty darn good [with] these medicines you gave me."

You look at their eye and you go "hmm, I don't know that it looks like it's getting all that much better." Well, we go another 24 hours.

They come back and [the patient says] "well Doc, it really got a lot better that first day, but now my vision really stinks. It's getting worse." You look and now you got increased infiltration and pus discharge. Well, what you have done is you have removed one of the indicators for you as a clinician of response to treatment and you also removed the body's ability to repair itself by the impact of anesthetics. Not that you can't in some situations utilize these agents but you need to understand the inflammatory process is intended for protection and restoration of function. Just

deciding that it's all bad is not a good thing. We'll see that when we get into some of the adverse effects of some of the non-steroidal oral medications [that] when used indiscriminately cause problems [...].

So just remember it's intended for protection and repair of the body.

Three different categories, at least at the time of my authoring of this:

- ❖ Traumatic inflammation
- ❖ Immunogenic inflammation
- ❖ Neurogenic inflammation

Corneal abrasion would be an example of [traumatic inflammation].

Immunogenic inflammation would be an invader like Staph Aureus, corneal ulcer infecting the corneal tissue so you got a foreign invader coming in.

Neurogenic inflammation would be inflammation resulting from some type of toxic binding to neurons like when you get conjunctivitis from cutting onions. You get vasodilation and burning and irritation.

The first two are the ones we run into most commonly in practice; that's trauma and immunogenic inflammation.

Inflammation can be broken down into two groups. There's a lot of different ways to break this down. This is the way that I found to be most beneficial and the way that the course is laid out. Also, Dr. Walls, how he addressed medications, it fits pretty nicely with that. If we talk about acute inflammation and chronic inflammation, their presentation and their management is fairly different with some overlap.

#### ❖ Acute inflammation

##### ➤ Characteristics

- Frequently stimulated by identifiable unsustained insult
  - You can say I got poked in the eye on Friday. I didn't keep poking myself in the eye. I got poked in the eye by my child. It happened now. It's not sustained. It's identifiable.
- Rapid onset with distinct termination
  - So with the abrasion: the eye gets red, you have pain. The tissue repairs itself and the [redness and pain] goes away. You can have a distinct time interval.
- Self-regulated process that usually abates several days to a week following triggering event
- Predominantly vascular and exudative process
  - We talk about the eye. We have vascular components but sometimes we have a [non-vascular inflammatory process like keratitis].
  - Wherever there [are] blood vessels in the vicinity, you usually get a vascular response and an exudative process.

- Symptoms and signs
  - Pain
  - Fever
  - Swelling
  - Redness
  - Dysfunction

The classic [symptoms] are the first four: pain, fever, swelling, redness. Dysfunction was added years later after these initial four characteristics of inflammation. I talked in the workshops about how in optometry, generally we were a look but don't touch profession for many years. This is where when we are talking about fever (and we check the temperature in our lab, that's great; that's important to know what core temperature is or an estimate), but for me, what's more valuable than that, is being able to touch the patient and find out is it hot, cold, or just right? If you got swelling or signs of abnormal tissue response and we are looking to find out what the state of inflammation is, is it hot? Touch it. When you touch it, does it hurt? You can see the swelling. But when you touch it, what kind of swelling do we have? Do we have pitting edema or diffuse edema? Of course, with redness, [it's a] visual observation.

Dysfunction. Of course, whatever structure is involved has the function been compromised?

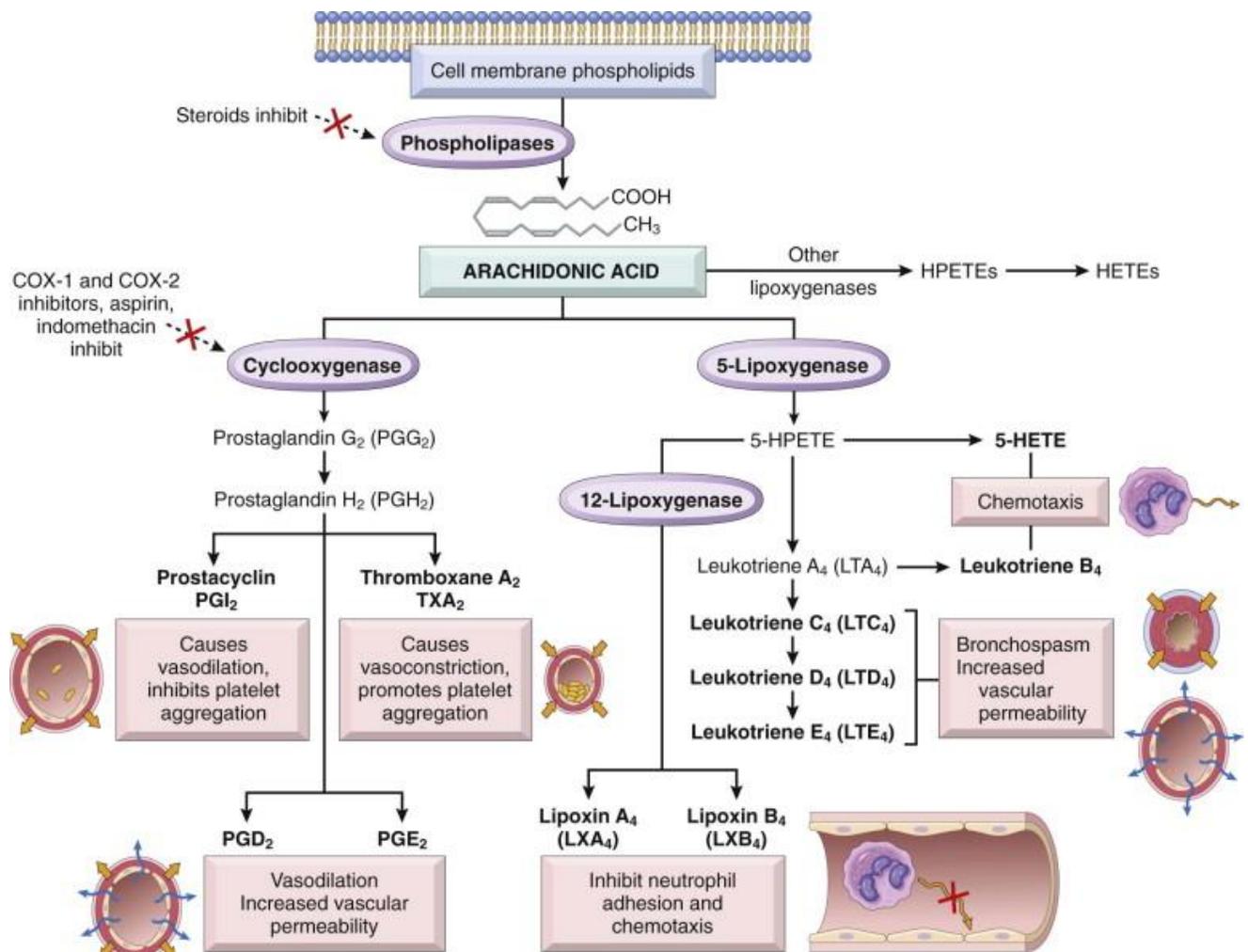


Figure 3

Photo Credit: Robbins Basic Pathology, 9th Edition by Vinay Kumar

The acute phase inflammatory response (figure 3). This gets to some of the basics of the mechanism. [...] I will do my best to explain it and keep it simple but clear. This is the foundation for the way our body responds. The body is phenomenally simple, amazing machine, but also very complex. The contrast to me is just pretty awesome. But the simple part is that our inflammatory process has harbored its energy, so to speak, in cell membranes. That's where the majority of the inflammatory response is made possible. It's made possible by phospholipids that are found in all cell membranes. When there is a trigger, one of these triggers: trauma, immunogenic response, these phospholipids will bind... say there is damage to this cell membrane here so it triggers the inflammatory process to begin. There are some enzymes, phospholipase A2 which is one of the key ones, that helps to bind these phospholipids to produce the fundamental building block of the inflammatory process: arachidonic acid. You will see, if you go online, and you study inflammation, you will see [arachidonic acid] everywhere. That is your basic foundational building block to all the chemicals that are produced and help to potentiate, or keep going, the inflammatory process. From [...] the production of the arachidonic acid, further production of chemicals comes from changing that molecule. There are two primary pathways. One is the cyclooxygenase pathway, which produces [the] prostaglandins,

prostacyclins, and thromboxanes. [Then we have the] lipoxygenase pathway which produces the leukotrienes, the heat, and we will talk a little bit about this pathway in light of the different inflammatory processes and the drugs we can use to intervene. Just keeping in mind, that again, cell membranes are where the building blocks of the inflammatory chemicals start. Some insult, some trigger, to cause that reaction to begin produces arachidonic acid; from there, the other chemical mediators are produced from different enzymes that modify that basic building block.

Are we together on that pretty well? I'm a clinician so that's an area that I have to work hard at and make sure you got it.

This is too busy [*referring to a diagram on the slideshow*]. It's in your handout, I believe. Is it printed out there, for you? [...] Basically, there are three pathways to inflammation when there is tissue damage. The three things that happen when we damage tissue, whether it's trauma or immunogenic process, is we are going to get dilation of blood vessels to move blood to the area of insult. Then we are going to get activation of white blood cells, particularly the neutrophils (that's going to be your first responders). Then you're going to get activation of the endothelium that lines the capillaries in that area. These three things, if you stop and think about what we are wanting to do. We are going to want to protect the body [because] we got an invader of some kind. Something that the body senses shouldn't be here so we want to get our defenses there. So we got to transport them [via] the bloodstream, one of the most effective or rapid response. Again for acute phasic inflammation, rapid response. Then we got to stop them there so there is some changing in the capillary beds to cause these white [blood] cells to begin to bind and to move through the cell wall. [...] The neutrophils move through the bloodstream and bind to the wall because the endothelium of the capillaries are prepared for them to stick and transfer through the wall and into the involved tissue. Then it just continues on down through the specific processes of attacking [...] but the main thing is: you got vasodilation to increase blood flow to the area and also to produce some pooling in the site. We got activation of the white blood cells and then we got preparation of the cell lining to allow those cells to move into the tissue.

### Tissue Response

This is just a histological slide showing [the] inflammatory process (figure 4) [...]. We got a capillary here with red blood cells in the central lumen. Here, we got white blood cells, neutrophils, they are the purple staining nuclei, that are lining the wall of that capillary. That's called margination. If you see a patient that has iritis and you look closely, if they have a really aggressive iritis, and you study the iris anatomy, you will be able to see this. If you don't look, it's like where's Waldo? You go past it. But if you look from one iris to the other, particularly I see it a little bit easier in a light colored iris that's got a thin stroma, you will see there's a red column with little white bands along the edge of it. You might have seen sarcoid in the retina when there's that candle wax appearance. That's white blood cells along the borders of those vessels ready to follow their brothers and sisters into the aqueous.

Then you look in the anterior chamber and you see cells and flare and all kinds of inflammatory activity. But look a little farther. It's got to be a pretty aggressive iritis and you have to a fairly clear cornea to be able to see.

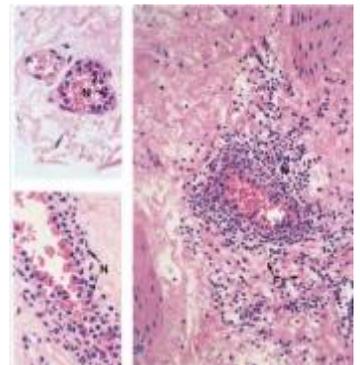


Figure 4

Magnification question. Probably 25x. But if you see it, you can go up to 40. [...] You get focused where you are at and kick it up. You're not going to see it moving. You are going to see a beard of whiteness along the border of these vessels. As the inflammation responds to treatment, [it] starts to go away.

Now, of course, in the iritis case, when they take the next step from margination: instead of moving into the tissue, they move across the capillary wall into [...] the anterior chamber.

Here is your capillary with your corpuscles here with the center lumen (figure 4). You can see all these polymorphs out into the tissue and this stringy stranded like material is fibrin in the tissue.

We look for cellular response and inflammation such as in an iritis, we look for cells, what the groupings of the cells are, sizes, colors. Is there a pigment cell along with white cells, [are] there red cells? But we also look for flare. Flare is just that increase in light scatter due to the protein that is released either in the aqueous, or the vitreous. But if you get really bad [inflammation], you'll get fibrin formation. If you [have] seen a patient with a pretty nasty iritis, you'll see that they will get that spider web start forming. [That's] really cool because that just doesn't happen for fun. It's happening because the inflammation is so intense that the eye is wanting to move to get white [blood] cells as rapidly distributed as possible. That actually is a highway, it's a network. The fibrin is attached and exuded from the capillaries on the iris. The white [blood] cells just march right out. If you look on them, you will actually see white [blood] cells on the fibrin. Same thing when you look in the vitreous cavity when you have patients with vitritis. One of the things I look for to see if I have active vitritis vs old, is I look at free and fixed cells. In an eye that's got active vitritis, you [...] look in the lacunae, those water pockets, you will see tumbling cells just like you see in the anterior chamber. But when they're quiet, maybe [there is] a history of posterior uveitis and they're quiet, there isn't any of that. Maybe there is just very little in the fluid tumbling. You will see it attached to the vitreous because those old cells have been there and they don't always go away. In the case of solid tissue, the fibrin is deposited into the dermis or the skin. If it's a serious enough inflammation, it's going to end up leaving behind scar tissue. That fibrin is going to produce a permanent tissue change. This is just showing that the cell is moving through the wall but not yet disseminated out into the tissue (figure 4).

That's showing the basics of vasodilation, the white cell response activation, and the endothelial cell changes in the capillaries to allow these cells to migrate out into tissues.

#### ❖ Chronic inflammation

- Characteristics
- Tissue response to sustained insult
- OR
- Failed termination of acute inflammation: Tissue fails to overcome acute insult
- OR
- Hypersensitivity immune response
- More difficult to identify cause
- Slow onset with persistent course
- Chronic tissue destruction and repair

Chronic inflammation is different. [It's] tissue response to sustained insult or failed termination of acute inflammation. So the person who is the fisher. They always come back and their eyes are red. You can't figure out why. They got mucus strands everywhere. You start noticing that some eyelashes are missing, particularly on the dominant side. That's the side that is always red. You look and there's staining of the conjunctiva in the fornix. Maybe even more than in the cornea. The other side isn't all that bad. You step out of the room to go do something else and you come back and peek in, you see this [...] the fishing syndrome. They feel like something is there so they continue to perpetuate the acute response whenever that happens somewhere in the past or it could be that it's psychological. Some people, fishing syndrome, is not just due to irritation but there is something there and they keep digging at it so it [...] the acute insult is not terminated. It's not easily identified because there's this chronic irritation. That's characteristic of chronic inflammation. It's either continued, sustained, or it's an acute response that fails to overcome that insult.

Hypersensitivity immune responses. We'll be looking at that in more detail when we get to allergy. More difficult to identify the cause for chronic inflammation. It's a slow onset with persistent course and there's chronic tissue destruction and repair. That's one of the characteristics of chronic inflammation is that tissue breaks down, it tries to repair, then it breaks down, then it tries to repair again; it's just this chronic cycle. That's one of the reasons why it's difficult to manage. Dr. Walls was mentioning that with chronic pain, which can occur as a result of chronic inflammation, it's really challenging to manage. Thankfully, most of what we all deal with is acute inflammatory [processes] which [are] going to stop. Our job is to just help it stop in an effective fashion where the patient ends up with as little permanent damage and restoration of function [...] as quickly as possible.

Chronic inflammation. This is a little cartoon showing tissue damage and necrosis leading to the acute inflammation. Then [...] you can get abscess formation where the insult walls itself off, trying to protect itself from the body's attack on it. By walling itself off, you can't terminate the inflammatory process. It's kind of like [...] when that patient gets that internal hordeolum and it doesn't spontaneously drain [...], then it ends up converting to chronic inflammation and we get a chalazion. So it's that acute inflammatory process that's shifting over to an abscess, converting over to a granulomatous chronic inflammation. Then the other responses with the tissue damage is that you can have resolution [...]. The inflammation goes away with no real evidence that it was ever present. A very light abrasion of the cornea. Patient reports "yeah, I got my eye scratched four years ago and I was really light sensitive. They gave me drops". When you look, you see nothing. The cornea just looks pristine because it healed through resolution. There was no permanent impact of that inflammation; or healing by repair, meaning that the tissue gets modified. You have that abrasion that just smacks the stroma a little bit. You get a little bit of infiltration, a little bit of fibrosis so there's a faint scar there. But still, pretty good response or [you get] chronic inflammation that doesn't go away. It just continues. Recurrent erosion that just goes on for weeks, for months. You are trying to do everything you can to get that process to stop.

This cartoon is in your talk because I put it in a number of years ago. I found it's better not to spend time on it because I have a difficult time being able to explain it. Basically, it talks about

the response of chronic inflammation in tissue versus in the bloodstream and how that takes place over time. I just don't think it's very beneficial. It takes me a long time to go through it.

❖ In general

- Acute inflammation is
  - Of short time course with rapid response to insult and similar through slower resolution
  - Less challenging to describe, assess and manage to resolution
- Chronic inflammation is
  - Of long time course, sometimes indefinite, with definitive resolution often difficult to achieve and identify
  - More challenging to describe, assess and manage. Therapy is often directed at control versus resolution

Chronic inflammation is sometimes indefinite and it goes on and on like in rheumatoid arthritis. The patient that has an immune complex response that [...] the body can't eliminate. It doesn't ever stop.

Therapy is often directed at control versus resolution. That last sentence is, I think, valuable. I don't know how I would ever ask a question about that. But I think it's valuable. When [I'm] managing patients, as to make a decision with the working diagnosis [I] got, am I going to be able to assist the patient in resolution so that they are going to get better and never have any evidence that they had a problem or am I going to be able to help this patient go through repair and clear this problem up? But they're probably going to be left with some permanent effects or is it going to be chronic? In other words, there isn't a cure for it. When you look at your patients, when you are managing them, that can be helpful in [...] [adjusting] patient expectation. I try to let patients know, when I know that something is going in a given direction, it's getting worse, it's getting better, I try to let them know. I adjust it based on personality and how I think it will impact their management. In general, I want them to be aware of what I'm aware of. If you have a patient that comes in and you diagnose them with glaucoma, you got to let them know that we don't have a cure for this. This is something you got and the damage that you have already, we can't get back. Maybe in the future, but right now, we don't have a way to regenerate cranial nerves. But, there's good news. We have lots better ways to control it than we used to. So that's a whole different mindset than treating a patient for a corneal abrasion that you know is going to clear up and they necessarily don't ever have to have again. Be thinking about that when you're managing your patients. In chronic inflammation, often times the direction of therapy is to control it, but not to bring it to resolution. That's why it's difficult to manage chronic inflammation and not necessarily fun.

[I will] give you an example. Patients who have recurrent graft rejection; what a pain. They also have steroid ocular hypertension and their graft was for herpes. You put them on steroid, so much steroid [their immune suppression goes out] so their graft rejection is stopped and then the pressure goes up to 35. Then you put them on Betoptic and Brimonidine. Then they develop [an] allergic response to the brimonidine so you back off of that. Then maybe you go with Diamox while they're on steroid every two hours while they are having a graft rejection. Then you back off on the steroid and you put them on acyclovir to help them not have recurrent herpes because it's going to be ongoing. It doesn't go away. When we do a corneal transplant, we let [the patient]

know you have a lifelong risk of having your body recognize this and attacking. The longer that you have it, the less likely you are to have a problem, barring any changes in your general health. But that's a chronic condition that they need to be aware of. If not, "oh yeah, I see great" and they don't ever go back to see their doctor until their eye gets red and they can't see. That's [...] an example where chronic inflammation is a pain (excuse the bad pun) to manage in the optometric practice. [I would] much rather deal with an abrasion [and get it] cleared up and [the patient] feeling good.

### Anti-Inflammatory Intervention

- ❖ Search for and describe the etiology of inflammation
- ❖ Pursue a comprehensive health Hx (HHx)
- ❖ Incorporate comprehensive medication history, including allergy
- ❖ When prescribing systemic medication: the old, the young, the fat, the thin, and the medically complex require greater attention to HPI (health and present illness) & HHx (health history)

When we look at intervention with any our drugs, these categories are good to keep in mind. We already talked about it a bit. Maybe this would have been more appropriate earlier in your course. [The organ systems}: heart, lungs, liver, pancreas, kidney, bone marrow (figure 5). The big ones for us [...] are the things that are impacted, in terms of a dynamic nature, are elimination of the drugs. The drugs are eliminated by respiration; they're blown off in our respiration. They are metabolized in the liver and excreted in the kidney. This diagram doesn't have the intestines highlighted but also, we have drug excretion in the feces. If we think about patients who we are giving drugs to, we need to be thinking about these different organ systems.

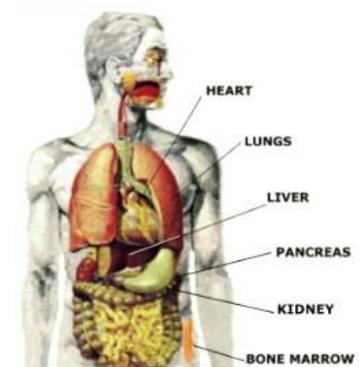


Figure 5

Search for and describe the etiology of inflammation. That's important to remember. When you are dealing with a patient that comes in with some form of inflammation, pain, fever, dysfunction, swelling, redness. [You say] "what's causing the problem?". You may not know right away before you have to start treatment but you always have to be revisiting it. Why do I have inflammation? Why is it responding the way it is? Why isn't it going away or why is it behaving in this fashion? Always try to discover the etiology of the inflammation.

Those are important things to remember.

An example. I was leaving town for something, I can't remember exactly what it was. My wife developed a sinusitis [...] I can't really remember exactly the etiology of her problem. But I really remember what happened after the fact. She was developing sinusitis and at the office, we had Keflex and Cipro. She had Keflex before in the past. I want to use a different drug for this because I don't want to keep using the same thing. I got her some Cipro and she started on that. Three days later, I got a call from her and she just says "something is not right. I'm in bad shape."

"What's going on?"

She says "I'm living in the bathroom. I can't keep a stool. I'm cramping and I'm in pain."

I go "hmm, that's not good. How are your sinuses doing?"

She says "I don't even know whether they exist right now."

I said "well stop the Cipro and I will call Chuck." Chuck is a family physician, a very good friend of mine. [...] I provided my wife the opportunity to develop clostridium difficile because the antibiotic, Cipro, that I gave her modified her intestinal flora. She got an overgrowth of clostridium which produced GI distress with bad diarrhea and really screwed her up for months. She had to get the stuff that you take to repopulate the intestines. Needless to say, my wife didn't have an allergic reaction to Cipro. But on her records, [it says that my wife] does not receive Ciprofloxacin systemically or at least orally. She probably would be okay with taking it IV, but not through the gut. Cipro is a little bit more prone to doing that. I did not know that before I did that. Now I know it. It's just an example [...] she's a young pretty healthy lady and I can't imagine if I'd given that to somebody who had ulcerative colitis. I started to treat them for preseptal cellulitis with Cipro. It could happen. I don't go to Cipro as a first-line with that kind of condition. I like to go with Dicloxacillin for that. That's the patient. They got GI, they got weird stomach problems, they got weird skin problems like atopic dermatitis. You know what? This patient needs this medication for this eye-related problem. But I need some help because I don't manage systemic stuff all the time. Tell me what you think, Dr. Jones, Dr. Smith. That's an example of the importance of understanding or being aware of those organ systems as we manage patients with systemic drugs.

I hope the volume is working on this. I've gotten probably the most positive comments in this lecture about this slide. Part of it is because I don't talk to you while the slide is going. The other part is I think it reflects for us some of the things we may not be aware of when we are in the classroom [or] in our clinical practice about how medical management of patients is far more than just you, your patient, and your office. The main barrier to effective therapy is non-compliance. It's a big issue. This is a video clip of my father that I took, not for the purpose of this lecture, I just set up the camera because I wanted to get some recordings of him and he grabbed out some stuff. Hopefully, it will run and you will get to see and hear.

Due technical difficulties the video does not play

We can come back to it later and it still will be appropriate. I need to keep moving. We can come back to it in a minute.

So we look at anti-inflammatory intervention [*refer to figure 3*]. So we got some review of basic biochemistry and now we are going to look at intervening in that process. This diagram is a good diagram, but there's been some changes in the last 5-7 years with regard to the LOX or lipoxygenase pathway. I will verbally give you some input. This isn't something that you have to be able to draw or re-diagram. You will not see this diagram on an exam. It's to help us visual what we are doing when we are prescribing medication. Tissue phospholipids. Remember, that's the place where the building blocks begin. Those tissue phospholipids are formed from what we

take into our bodies. We are what we eat. These tissue phospholipids are formed from essential fatty acids, omega-3 and omega-6 are two of the big players. Interestingly enough, the chemical mediators in the protect and repair process, let's not call it inflammation, there are good chemical mediators and there are bad ones. Well that's kind of how they are categorized but they are different roles for these. The omega-6 fatty acids that form into these phospholipids produce the mediators that tend to be more involved with the good repair and protection process. While the omega-3's are more with the aggressive tissue destruction and tissue attack process. If we want to minimize inflammatory process, having more omega-6 fatty acids in our diet seems to make sense. That's where some of the things with dry eye therapy [...] we talk about having a higher level of omega-6 fatty acids than omega-3's. Diet can play a role in inflammatory intervention; probably not an acute intervention for you as a doctor. But for your patients, dry eye patients, [diet] plays a role. So that would be through diet. We also have formation of arachidonic acid from phospholipase A which is that first state and we can intervene at that level with corticosteroids. Corticosteroids intervene at the most basic level of the inflammatory chain. We go then down the inflammatory cascade. We then have release of long chain fatty acids and we go to those are formed by further breakdown of the arachidonic into prostaglandins and prostacyclins and thromboxanes by the cyclooxygenase pathway. If you listen to a commercial on a Mariner's game, although people don't watch them much anymore, you will hear about these COX inhibitors. You can interfere with the inflammatory process here at the formation of these chemical mediators: prostaglandins, thromboxanes, prostacyclins with our drugs like Motrin, Advil, Aleve, and aspirin. You notice that they aren't any over on this side for the LOX in this diagram. Part of the reason why is because when I pulled this diagram from a text, there weren't a lot of drugs available that were considered beneficial. It wasn't really well understood about intervening on the lipoxygenase side. But since that time, there have been. you do have drugs like Zileuton, which is a drug that is currently being looked at, it inhibits actually on both sides, but it has a predilection for the LOX side of the inflammatory cascade. Also, Singulair. These have been utilized in pulmonary disease: chronic obstructive pulmonary disease, asthma patients. You can intervene at these different points along the inflammatory cascade and modify the inflammatory response. You will see here in just a little bit that we have to be careful with our intervention because we can knock things out of whack and create problems. That's the beauty of acute management. Acute management is generally short; people can tolerate screwing them up for a short period of time, but when you start extending treatment, that's when we tend to run into more problems. If I got a patient that's staying on a drug longer than I'm comfortable, I have to step back and say "wait a minute, what's the chronic treatment going to be doing?" I'm talking to the patient how I'm doing with that.

Now you get a whole listing of drugs because it's required to have some drugs in the talk. I preface this section with the statement that I made earlier. We got references for these. So having to remember a specific drug to me really has no value. Remembering classes and what they do, like Dr. Walls talked about the other day acetaminophen only works on pain and it works centrally. That's an important thing to do. You are probably not going to use acetaminophen to treat a patient that has an inflammatory condition unless there's pain that you want to control. It's not going to work on the inflammation. In turn, if you want to treat somebody that you want to deal with local inflammation, then you are going to want to use a drug that acts on these mediators where the damage is.

## Salicylates (Aspirin being an example of that)

### ❖ Pharmacokinetics

#### ➤ Oral ingestion

- Rapid absorption and distribution
- Extensively bound to plasma protein
  - Remember I mentioned that Diamox/Acetazolamide is 95% bound by plasma proteins. Aspirin is extensively bound. The two together can create challenges with pulmonary function. It keeps it around the system and it also puts a load on the breathing
- Peak blood concentration 1 to 2 hours
- Metabolism by liver
- Excretion by kidney
- Half-life: pro-drugs hydrolyzed in minutes to a few hours, Salicylates 6 to 20 hours.
  - For the category of Salicylates, the half-life can vary from 6-20 hours.
  - If you look under Salicylates, Aspirin being an example, there are a wide range of drugs available. Short acting and long acting. So if you are going to use something be familiar with it. If you're not, or the patient comes in with something you're not familiar with, look it up. Find out what are the pharmacokinetics of that drug.

### ❖ Aspirin (acetylsalicylate)

- 81-650 mg q4h not to exceed 4 g/day
  - My level of comfort is 3g/day. If I'm prescribing more than that, then I shouldn't be prescribing it. It's something I'm not comfortable with.
- Generally, not for pediatric use: risk for Reyes Syndrome
- Metabolized in gut, plasma, & liver half-life 15 minutes to 2 hours
  - Aspirin is a rapidly absorbed and a rapidly metabolized and excreted drug. So it has to be used more frequently. Of course, that's using a regular tablet as opposed to an extended release. But it also gets it out of your system faster.
- Excreted in urine

### ❖ Dolobid (diflusal): Dolobid is no longer available in the United States. The generic which happens a lot of times. A drug comes out like Zalatan and then they lose their patent and all of a sudden "we don't make any money making this" so all of a sudden you just got Latanaprost generic. It's available but it's not available as Dolobid. This is a longer acting drug than Aspirin

- 250-500 mg Q12h not to exceed 1500 mg/day
  - It can be dosed less frequently [than Aspirin]
- Metabolized in liver with a half-life of 8 to 12 hours
- Excreted in feces and urine

### ❖ Specific mechanism unknown

- Anti-inflammation, anti-pyretic (heat reducing), anti-coagulation, analgesic

### ❖ Inhibits Prostaglandins

Dr. Walls mentioned that the non-steroidals, which salicylates are part of that family. Salicylates are kind of a unique part of that family because of their other effects, it has anti-inflammatory effect at the site of the inflammatory activity but it also has some central analgesic effect as well.

So it kind of has a dual action. I always tend to think more of the inflammatory side. One of the things to keep in mind also is that it has anti-coagulative effect that can be both beneficial and it can be a problem. Patients that are on lots of aspirin, I mentioned the patient that I saw with the retinal hemorrhaging, if you're taking too much, you can end up causing hemorrhage because of the inability to have normal platelet activity. It inhibits prostaglandins, the exact mechanism is still not fully understood. So the salicylates are prostaglandin inhibitors but they are kind of in a unique class so they aren't always considered with the ibuprofens and so on because it does have a greater anti-coagulation impact and platelet impact than do the other non-steroidals.

## Salicylates

### ❖ Caution

- Aspirin Allergy
  - Asthma
    - That's why your allergy history is important. If your patient has this, they are generally going to know it. Hopefully, you're not the one that prescribes it to discover it for the first time.
- Severe pulmonary disease: added load for respiration
- Compromised renal and or hepatic function
  - Because it's excreted by the kidneys and it's metabolized by the liver
- Congestive heart failure
- Concurrent steroid or NSAID use
  - That is something we see in our practices; we are more aware of it now than in the past as we have done more primary care. Patients are coming in on a number of drugs that maybe have an overlap of an effect. One of the areas we are seeing it is in the anticoagulants. Patients are coming in; they've had strokes [...] so the patients are on Plavix and an aspirin. Or Coumadin and an aspirin or Ticlid. We're thinking we need to prescribe them a systemic steroid. Now they are on Plavix, aspirin, and a systemic steroid. Those all together have a pretty major impact on platelet function. If you need to do that, maybe we need to stop the aspirin while the patient is on the steroid systemically. Do I really know how to do that? No. I'm going to get on the phone and talk to somebody who does and say, "here's what we need to. How do we get it done?"
- Hx of GI bleeding
- Hx of concurrent prescription anticoagulants
  - Plavix
  - Coumadin
  - Ticlid
- Tinnitus (ringing of the ears) implicates overdose

## Salicylates

### ❖ Ophthalmic Indications

- Retinal vascular occlusive disease
  - BRVO
  - CRVO
  - Diabetic retinopathy
  - Amaurosis Fugax

Once a patient has a BRVO present for 4-6 weeks; they are starting to go into their repair process, I will have a patient begin to use low-dose aspirin. The process of the occlusion occurs, in part, due to turbulence [...] the crossings, where the arterioles impinge on the veins and the blood is not getting through. So you get this backup. Once they start forming shunt vessels around that, I don't want it to happen somewhere else or maybe have a CRVO happen.

### CRVO

Once the acute episode is over, we don't want to encourage hemorrhage while the patient is actively having inflammation from this insult, but once they've been repaired, there's a reason why they had that blockage. Low-dose aspirin is beneficial in that case. CRVO might be an implication of an amaurosis fugax or transient vision loss. Giving aspirin immediately in the office is indicated. So if a patient comes in and [they say] "my vision went out an hour ago. It's kind of gray and fuzzy". You look in and you see emboli in circulation. I'm giving that patient some aspirin. I'm communicating with their physician as well but that rapid onset of aspirin can help decrease the likelihood of having further blockage and help to break that attack.

Diabetic retinopathy. It's interesting. There was a study that just came out that patients that are treated with low-dose aspirin that are diabetic [...] we are questioning whether that is really appropriate. I read it just before I came down here. I can't remember the specific citation. So I don't know about that one anymore.

*Question from audience:* what dosage would you give for BRVO?

*Answer:* 81 milligrams. Just low-dose is what I would do. The idea being [is to] reduce platelet aggregation a bit so we are not building up a thrombus at crossing areas.

In terms of the aspirin, if I had a patient come in, I probably would give them 2 325 mg tablets if they were in an acute episode. If they had an amaurosis episode and they came in ... I had this happen just recently. I had a lady in for post-op care. She had been to another practitioner, not an optometric practice, she had shared that her vision had blurred with that practice. She was in for cataract surgery on the eye that she wasn't having problems. But in the course of the history, I said "How are things doing? How is your other eye doing? I haven't seen you before for the other eye." One of my colleagues had.

She said "well my vision blurred out in this eye. I went in and saw this doctor and they said 'it was eye migraine or something'."

I said "oh okay, you have a history of migraine?"

"Yeah, I've had migraines in the past."

This is like a 65-year-old patient.

"Well tell me about what happened?"

She says, "my vision kind of just went gray and cloudy for about 30 minutes."

"Just the whole thing or did it start in a spot?"

"No it just completely went gray. I couldn't see anything and then it just kind of slowly came back."

That's not ophthalmic migraine. I have ophthalmic migraines myself and I've had patients who have it. It doesn't present that way. It presents segmentally and it distorts things but it doesn't cause things to go completely out, at least in my experience. We ended up getting her worked up and she had some occlusive disease on that side.

Just listen to the patient. If I have a patient that has amaurosis, I'm going to contact their physician and say "I'm suspicious that we are having emboli from somewhere (the heart, some of the big vessels going up to the eye) and I think we need to get this patient on some aspirin and then they need to get a workup. Get a carotid study and a heart echo." That type of thing.

I've had a number of patients over the years where we discovered patients having occlusive disease and by placing them on that aspirin, you may be avoiding them having an absolute arterial occlusion.

Aspirin has got very specific applications to eye care that I think are very beneficial. I don't know what to tell you at this point in time about the diabetic retinopathy. I don't think you need to worry about that at this point in time. You might just do a little bit more looking in the literature, talking with your physicians around your area about what they are doing with their diabetics. I'm going to go back home and do a little bit of that myself.

*Question:* would you recommend that work-up if the patient has already had one episode of that?

*Answer:* it's going to depend on what I discover as I do further evaluation. I'm going to auscultate [and palpate] the carotids. I'm going to look at their medical history and see what that's been like. I might go ahead and get a visual field to see if there has been any [...] In the meantime though, probably get them on some aspirin with their personal physician and then make the decision based on what I'm hearing coming out of the patient. [For a] single episode, if I'm hearing something or feeling some asymmetry, absolutely, I'm going to get them a carotid study. I'm also going to do gross ophthalmic dynamometry where you can use a suction cup to change the pressure in the globe and observe the effects on the circulation at the optic nerve head. You can also use a plunging device. I worked with a retinologist for a number of years that said "you know, when you have these patients that they look bad, their circulation is really asymmetric or they got some neovascularization in one eye, you think it's diabetic. Maybe not. Maybe it's ischemic. You just push on the globe." So I will put my lens up there and push. I will watch how much pressure it takes me to [...] produce pulsation of the central retinal artery and then collapse and just look at the whole tree. If I just touch the eye and I'm getting pulsation on one side, I'm having to just drive my fingers through the orbit on the other side, something is not right. If I palpate and I'm getting a real strong pulse on one side, and I can't find it on the other side. It may be their first episode but there are these other findings that are telling me something is not right

here. I'm going to be more aggressive in that case than the other. Whether I do it or not, usually in our office, what we do is we always call the patient's O.D. if they been referred into us and say "what would you like us to do?" If they are from a physician, like a family doc or internist, then we will contact their office "what do you want to do? This is what the patient's got. What would you like to do?" A lot of times they say, "you do it. I'm too busy. Just copy me with the results." Long answer to a short question which is a bad answer. It varies. But I hear transient obscurations of vision, I'm paying attention because blindness from central artery occlusion is not enjoyable thing to deal with a patient. There's really no way to get it back.

*Question from audience:* Were you saying that asthmatics have a higher incidence of aspirin allergy?

*Answer:* I don't know [if] I can say that from my own knowledge. I just know that in the literature one of the concerns is for asthmatics to be alert to that possibility of aspirin allergy. [...] That's a textbook kind of answer to your question. Good question, not such a great answer.

NSAIDs: aspirin falls within that but it's kind of its own group, the salicylates so we break it out.

#### Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

- ❖ All classes have some degree of following action
  - Anti-inflammation
  - Anti-pyretic (inhibit fever)
  - Analgesic (inhibits perception of pain)
- ❖ Seven sub-classes
  - Fenamates (eg. Ponstel)
  - Indoles (eg. Indocin)
  - Pyrazolones (eg. Butazolidin)
  - Propionates (eg. Advil)
  - Phenylacetates (eg. Voltaren)
  - Oxicams (eg. Feldene)

Ones that we are most familiar with are the propionates, the phenylacetates. The Advil and Voltaren. Voltaren comes as both as a pill and as an eye drop. The eye drops, probably, are what we are most familiar with. Indocin, the Indoles, which are a bit more effective and we use for more aggressive ocular inflammation. The other ones, I see patients have them, they're taking them like Feldene for some of the arthritides and so on, but I have not used them so I can't comment to them.

## Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

❖ NSAIDs turn down the cyclooxygenase (COX) “valve” reducing prostaglandins & thromboxane (figure 6)

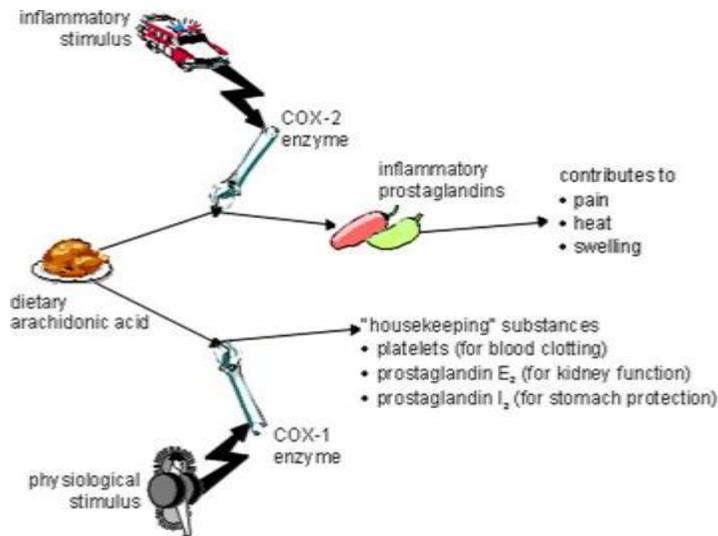


Figure 6

How do they work? Again, looking at the inflammatory cascade process, the non-steroidal drugs, they act to turn down the cyclooxygenase valve. There are selective NSAIDs and non-selective. The non-selective ones block both sides of the COX pathway. Kind of like how we talk about selective and non-selective beta-blockers. We got Timolol that's non-selective; it affects both respiratory and cardiac function. Then we have Betaxolol which is supposed to spare relatively the pulmonary side of things. We kind of have the same analogy here with the NSAIDs that block the cyclooxygenase pathway. We have ones that do both and then we have ones that are selective. The COX-2 side of the inflammatory [cascade] is considered the bad side, if there is such a thing. It's the side of the inflammatory cascade that produces the inflammatory mediators, the prostaglandins [and] the thromboxanes that produce pain, heat, swelling, contribute to the scar tissue formation that occurs with the inflammatory process. Then there's the COX-1 pathway which is considered the good side. It's more involved with cleaning up after all the bad stuff is done. It impacts platelets, slow [and] long-term repair process. You can intervene with both of these with a non-selective or you can selectively intervene at just the COX-2 area which has got the most destructive side of the inflammatory process. We are going to see here in just a minute that doing this non-selectively and very aggressively can lead to problems because of imbalance in the inflammatory process.

## Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

### ❖ Pharmacokinetics

- Oral ingestion
  - Rapid absorption and distribution
  - Extensively bound to plasma protein
  - Peak blood concentration 1 to 2 hours
  - Metabolism by liver
  - Excretion by kidney
  - Half-life: a couple hours to a couple days

The length of the activity is engineered into the drug. There are some that are fast-acting and clear quickly. There are others that are slow-acting like Aleve, which you take on a 12-hour basis is retained in the system longer as opposed to ibuprofen or Advil which is eliminated more quickly. I'm not the world's best on that when I do it. I look it up and see what it is that's going on and I'm familiar with a few drugs that I use.

## Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

### ❖ Systemic complications

- Gastrointestinal insult
  - Nausea
  - Cramping
  - Ulceration
  - Hemorrhage
  - Perforation
- Allergic reaction
  - Asthma
  - Dermatitis
- Reduced clotting
- Renal and/or cardiac dysfunction

Disturbing the housekeeping side, that COX1 side with these NSAIDs can end up leading to breaking down of the gastric mucosa. With long term treatment or say a patient who's had previous treatment and had ulceration, had gastric problems. You re-institute a drug, they're a little bit more prone to having these things happen as an adverse effect.

There is a reduced clotting effect but not as much as an impact as the salicylates.

The kidneys are very dependent on prostaglandins for normal function. Because the NSAIDs are eliminated by the kidney, you put bunch of that in the system to work on the eye, it's going to get down and be eliminated by the kidney and it will have an impact. I had a patient once that had [...] chronic cystoid macular edema. We used drops, this was back before we had injectables that work so nicely. I put him on ibuprofen. I put him on 800 mg four times a day (about four times over the over-the-counter dosing). At least I did something right. I told him "if you have any problems, GI distress, problems with elimination, please stop the medicine and call".

Two days later, he called up and said “last night I could not sleep. My back was hurting so bad. It was just horrible.”

I said “hmm, okay. Good, you stopped the drug.” Within 12 hours, he was feeling better and he was urinating properly. He was having kidney problems from overdose. For him, it was too much ibuprofen.

We can't always know these things in advance, but as Dr. Walls mentioned, counsel the patient on what to watch for and what to do. If they are having any change in the way their body is working, particularly issues of elimination [or] pain, you say “stop it and call.”

With regards to the renal function, that's the area that tends to be more affected than liver, at least in my experience.

### Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

#### ❖ Ocular Indications

- Topically recalcitrant episcleritis
- Topically recalcitrant uveitis (HLA B27)
- Topically recalcitrant cystoid macular edema
- Scleritis
- Amaurosis Fugax (ASA)
- Retinal vaso-occlusive disease (ASA)

There will be a case in the presentation. Patients who have episcleritis; it can be actually painful, contrary to what sometimes is reported in the literature. It's not very common but it does present and it can be very effective to use oral non-steroidals.

Recalcitrant uveitis particularly, the HLA associated ones like ankylosing [are where NSAIDs] can be helpful.

Cystoid macular edema. We already talked about that. It is effective but it also can have its downsides.

Scleritis: Indocin is the non-steroidal of choice with scleritis.

I already mentioned the aspirin use for amaurosis and vaso-occlusive disease

This right here is a good thing to keep in mind for your practice and later on. This has some practical application as opposed to the diagrams we went through before. This is a good place to review before you go back to your practice

### Corticosteroid (steroid) anti-inflammatory drugs

- ❖ Agents have varying degrees of following action
  - Anti-inflammation
  - Anti-pyretic (inhibit fever)
  - Analgesic (inhibit perception of pain, *pop*)
- ❖ Oral steroids must be completed or interrupted by day 7 unless consultation with MD or DO is obtained in the state of Oregon

Most of the time, if I'm dealing with a patient on oral steroids, their PCP is already involved. I think it's a great therapy when it's needed but when I'm going to place a patient on oral steroids, I'm generally not going to carry that on my shoulders alone because they can have serious problems. They're very effective at producing good results and also adverse drug reactions.

### Corticosteroid (steroid) anti-inflammatory drugs

- ❖ Corticosteroids are naturally occurring products of adrenal conversion of cholesterol
  - Cortisol
    - Mean daily production 20-30 mg, peak in the AM
    - Stress induced peak production up to 10x average
  - Cortisone
  - Corticosterone
  - Aldosterone

It is something we naturally have in our body. we produce cortisol 20-30 mg a day; it peaks in the morning. You will hear patients who are placed on steroids by their personal physicians [is that] they take their steroids in the morning. Cortisone, corticosterone, aldosterone are all endogenous, or naturally occurring, corticosteroids in the body.

### Corticosteroid (steroid) anti-inflammatory drugs

- ❖ Synthetic corticosteroids are capable of dramatic upregulation of bioactivity normally modulated by natural corticosteroids
  - Hydrocortisone
  - Prednisone
  - Triamcinolone
  - 6 Methyl Prednisone
  - Dexamethasone

[The above listed steroids] are examples of some steroids that application in eye care

We can intervene in the process by producing synthetic steroids and giving them to patients as an exogenous source. [...] Whatever our natural corticosteroids do in our body, we give synthetics, it's going to upregulate that activity.

## Glucocorticoid (steroid) anti-inflammatory drugs

❖ Corticosteroids mediate inflammation at the intracellular level (figure 7)

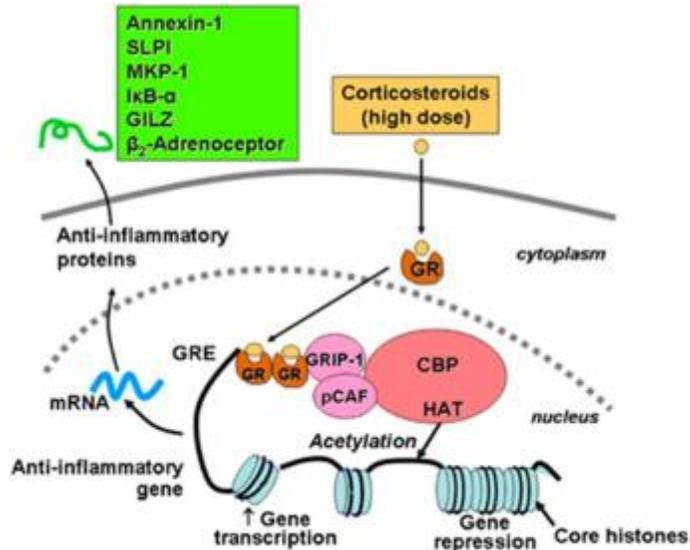


Figure 7

I think this is valuable, at least it is for me in terms of looking at steroids. They fall in their own special class. I think this diagram helps to explain why they do (figure 7). Corticosteroids mediate inflammation at the intracellular level. So they penetrate cells and go into the machinery and actually change the proteins that are produced by the cells before they exit the cell and into the tissues. Where our other drugs are modifying these chemical mediators after they have been produced. That helps me to understand why they are so dramatic in their effect. They go right to the base level of the development of arachidonic acid. They slow or stop that process. But in turn they also have a lot of other effects as well. They can be very dramatic. Corticosteroids mediate inflammation at the intracellular level where most of our other anti-inflammatories are dealing with it on the membrane level or on the extracellular level.

We take a look again at this cartoon. We got tissue or cell damage to the cell. Corticosteroids inhibit the formation of arachidonic acid while the other drugs inhibit further downline. We have dual pathway inhibitors like Zileuton and Singulair. Then we have the single pathway inhibitors which are just the COX inhibitors and then those can be broken down even further into COX-1 and COX-2.

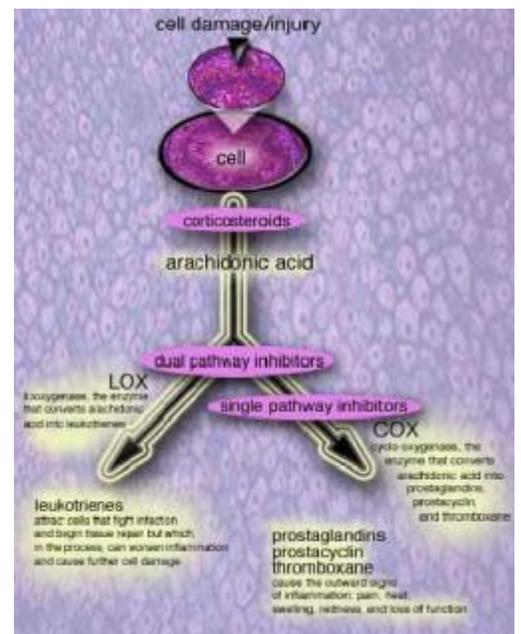


Figure 8: corticosteroids inhibit the release of arachidonic acid by blocking the action of phospholipase A

## Glucocorticoid (steroid) anti-inflammatory drugs

### ❖ Pharmacokinetics

- Oral ingestion and injection
  - 90% reversibly bound to serum protein to carry it around the body
  - Biological half-life from 8 hours to 3 days so it's kept around bit longer
  - Biotransformation by the liver modifies the majority of drug
  - Excretion is via the kidney for up to 3 days after ingestion

### ❖ Systemic complications

- Adrenal suppression
  - Mismanaged care can be fatal
- Immunosuppression
  - High dose
  - Chronic treatment
- Gastrointestinal
  - Ulceration
  - Hypokalemia

Our natural occurring steroids are produced by the adrenal medulla. A gland that sits on top of the kidney. We need to have that for sugar regulation, for cardiac function. We put this in by injection or by pill, and the body says, "okay, we got enough. you just put it in here" so the adrenal medulla reduces its output. There is the pituitary three-point triad where we get that feedback mechanism that tells our body we need more corticosteroid or we need to downregulate it, we need to have less. When we start putting the drug into the system we start monkeying with that feedback loop. Patients that are on steroids for an extended period of time, the adrenal medulla can become permanently impacted and not produce the corticosteroids that we need to live. Probably all of us have seen a patient who's on low dose steroid; 2.5 mg of prednisone, 5 mg prednisone, 1 mg of dexamethasone once a day because they have not been able to get off because they were treated for some immune disease. You go "wait a minute!" They got rheumatoid arthritis and they're on 1 mg of dexamethasone. "Come on, that's not treating." No, it isn't treating their rheumatoid arthritis. It's that they were on much higher doses during acute episodes [...] and for longer periods of time, they can't get off the drug because they need to have it for their body to function. If they don't get it, then they end up with an induced Addison's disease and it can be fatal. Dr. Ford shared one time that he had a patient on long term topical prednisolone drops and the patient suddenly stopped. [The patient] ended up having an Addisonian crisis from drops. I've never seen that but he shared that one time in a talk. I guess patients can whiff a little peanut butter and go into anaphylaxis and I can eat three sandwiches and have no problem. They're probably those people that are really sensitive. Keep that in mind: immunosuppression with high doses and chronic treatment.

If you look at the literature, as you institute a steroid into the system, initially it has an anti-inflammatory effect. As you increase the dose, frequency, and concentration, you'll eventually go from anti-inflammatory to immune suppression. Each drug has its own profile. That's why when I have a patient with a graft rejection that comes in, they're getting four drops an hour of prednisolone acetate because we are trying to do immune suppression, not anti-inflammation.

This is an immune attack on the corneal tissue as opposed to a patient that gets a drop morning and evening [...] like Lotemax for seasonal allergy anti-inflammatory.

Gastrointestinal problems: ulceration and hypokalemia or decreased potassium. Like with the non-steroidals and the salicylates, long term use of steroids can impact that housekeeping activity that needs to take place from the prostaglandins, the leukotrienes in the gastrointestinal system and they can end up with ulceration from those drugs.

### Glucocorticoid (steroid) anti-inflammatory drugs

#### ❖ Systemic complications

- Metabolic
  - Hyperglycemia
- Congestive heart failure
- Hypertensive
- Allergic reaction
- Psychosis
- Papilledema

Patients who are placed on steroids systemically, it's going to mess with their [sugar levels]. Patients who are placed on them topically: it will mess with their sugars. I've had patients who [...] are diabetic and going to have an eye surgery and they're going to be on steroids, I talk to them [and say] "how's your sugar been controlled? How's your A1C?" They go "what's A1C? what's a sugar?" You go "okay, we got a problem here." But they say "my A1C was 6.5, they checked me every three months for the last year and I checked my sugar this morning and evening and I'm running between 100-110." They're probably not going to have problems with the drops. But if I had someone that says "we've been working hard at this. I'm at 150 and I'm doing really good and my A1C is 8.2" and they're on a number of drugs, I'm going to say "this drop can whack your sugar control. So be alert to it." I don't know how many times I've had patients go "you're right, my sugars were up about 50 points this week" and that's just with topical Pred Acetate.

So again it's not that it's an issue. They're on the drop for [...] a week, ten days, sugars up a little bit for a little while but being aware of that's important. If you need to put them on systemics like that patient with Graves' ophthalmopathy, and their vision is dropping, because their globe and nerves being squeezed in the orbit. You've done your neurological [assessment] and you've seen "golly, this eye is not moving anywhere, it's sticking out. They get put on high dose prednisone to treat that, that is a challenge. I'm not going to treat that patient independently. That's going to be with an internist, family physician. [I'm going to say] "this is not going to be fun" but this eye can go blind and the treatment is systemic corticosteroids. Hyperglycemia: be alert to that with patients who are being treated with steroids. The more steroid they're on, the more compromised their sugar control is naturally. The more that's going to be a problem.

Congestive heart failure: these mediators are important to normal cardiac function.

High blood pressure: patients who are on chronic high dose steroids will end up developing hypertension

They can have allergic reactions. I had a tough time buying into. It's like a lot of things. You have to have it happen to you once first. I say "this is what we use to treat allergy. This blocks the inflammatory process. How can this be?" I had a patient told me she says "I'm allergic to corticosteroids" [... I say] "yeah right, we'll be fine. we are using eyedrops here." Sure enough, I put her on it and her eye got red. She developed erythema of the lids and she was not happy with me at all. Thankfully, we got it cleared up. We shifted to a non-steroidal and we went with systemic non-steroidal and cold compresses. When we did her second eye, she did not get any steroids. It was all Voltaren, I think it was what we were using at the time. I've seen it happen.

Psychosis: important to remember. It can happen as short as 24-48 hours. If we get the video later on of my dad, I got a call in the middle of the night in his last 2-3 weeks of life from my sister who is very upset with me because I had said something to my dad that had made him upset. Because he woke up in the middle of the night. He was ripping up his IVs and he was screaming at everybody. I said "I don't know what I said to him. Can I talk to the doc?" We were taking turns, rotating being present. So we were talking and because I was his healthcare manager, I said "how long has it been now since you had him on 120 mg of prednisone?"

"We started that two days ago."

I said "maybe we should cut that down a little bit if that's possible. How's his lung function doing?" because he had pneumonia. They were trying to keep him from drowning. They cut it way down to 40 mg. The next night he slept pretty well. I don't think I said anything to him but what he had was he was developing psychosis from the high dose steroids. [This] is very real. So patients who have arteritis and have lost vision, those are the patients we are going to see that need high dose steroids. Being alert and realizing "you may have weird dreams, you may not sleep well. You may feel agitated." Okay, [the family should be] alert to that. Remember, it can definitely alter our cognitive function with high dose steroids.

Papilledema: interestingly enough. The treatment for papilledema is steroids in many cases and the cause of papilledema is steroids. It's interesting. It's kind of like papilledema is glaucoma of the brain. In some cases, steroids are helpful in the treatment of glaucoma but in other cases, using chronic steroids cause increased pressure. When you stop the systemic steroids, generally the intracranial hypertension will reduce and the papilledema will resolve. [...] It's similar to when we see ocular hypertension from steroids. We get intracranial hypertension that can produce papilledema.

#### Glucocorticoid (steroid) anti-inflammatory drugs

##### ❖ Adverse effects

- Nausea vomiting dyspepsia reduced appetite
- Headache dizziness mood swings anxiety
- Insomnia
- Fat distribution (cushinoid appearance)
  - Humpback

- Full face
- Skin conditions with chronic use
  - Ecchymosis
  - Atrophy of the skin
  - Reduced wound healing

Re: fat distribution (cushinoid appearance)

We are probably not going to be treating these patients but we are going to see them in our offices. We probably already have. Those patients have that cushinoid appearance because they're on chronic on-going steroid treatment.

Reduced wound healing is an important thing if your patient is on steroids for systemic conditions. Just ask them "how do you heal?"

"Oh I heal pretty well doc" or "no see over here", they pull up their sleeve, "I bumped my elbow a week ago. See this? I have trouble healing." Okay. Maybe we are going to adjust our topical anti-inflammatory therapy. You are getting enough in your pill. Maybe we don't need to use a whole bunch in terms of eye drops. That is real.

With the skin application with creams and so on, you can get thinning of the skin and breakdown from chronic steroid use.

Glucocorticoid (steroid) anti-inflammatory drugs

❖ Ocular indications

- Uveitis not responding to topical therapy
- Posterior uveitis and/or chorioretinitis because you can deliver the medication [via] topical route effectively
- Orbital pseudotumor
  - That's that diagnosis of exclusion meaning you've looked at everything else. You got inflammation of the orbit. It's not infectious. You don't have any associated systemic conditions but it's there so they call it orbital pseudotumor.
- Graves orbitopathy

Probably a number of these cases are related to herpes. It's just hard to identify in the presentation

Another slide, valuable for you to remember. I've used oral steroids in some patients. I don't do it independently. Most commonly in our practice, it's with arteritic ischemic optic neuropathy. Patient gets sent into us because they've had a sudden loss of vision in one eye. We get them right out to the lab, get a sed rate [and] C reactive protein are elevated. We get them started, with their personal physician, on systemic steroids.

Glucocorticoid (steroid) anti-inflammatory drugs

❖ Ocular indications

- Acute ocular allergic response
  - Severe or not resolving with topical therapy

- Scleritis- note subconjunctival injections are contraindicated
- Temporal arteritis/arteritic anterior ischemic optic neuropathy (AAION)
- Optic neuritis (initiate IV, transitions & taper PO)
- Graft rejection

### Acute ocular allergic response

Sometimes you will have a patient who lives in an area that they have something they are really sensitive to [...] and they just really blow up, badly. You try to use some drops, some oral antihistamines and it's just not clearing. A Medrol dose pack can work very nicely for those patients. It's a set utilization. They get the pack and they take six pills the first day, then five, then four, and it just takes them right down. I've had that happen in some cases. Usually I'm coordinating with their personal physician to manage that.

Subconjunctival injections are contraindicated in scleritis and the reason for that is because kind of getting back to what we were talking about the adverse effects of steroids with regard to ocular hypertension and protein precipitation. When you have real aggressive inflammation and you get a lot of protein into the area, that produces fibrin to help fight off this attack that's coming to the body. But it's not coming outside the body. In the case of scleritis, it's the body attacking itself. Well you go ahead and put a big bolus of steroid right in that area, all those blood vessels that are thick with protein get a big dose of steroid right there. It all binds and then consolidates and then you just close off the blood vessels. You end up getting an ischemic melt. That's why in scleritis, you don't have a lot of circulation to the sclera. You want to use [...] an oral. I don't think most of us are going to be doing that in our practice anyway.

Temporal arteritis. We already talked about that. That's probably one of the more common presentations of it. What's neat about that is you can really make a huge difference by making the correct diagnosis, by getting a simple lab test. You help a patient from being bilaterally blind. In the case of arteritic related AION, the risk for second eye involvement without treatment for the first several weeks is very high. I don't remember the number, sorry. But it's really high. I have to go look at my references to remember exactly. It's like 50% within the first few weeks.

The optic neuritis is a little more complex because of the optic neuritis treatment trial. If you are going to treat a patient with optic neuritis, you don't know that it's non-multiple sclerotic or non-demyelinating disease, you have to treat them IV. Otherwise, you can perpetuate the problem and increase the risk for developing actual manifestation of multiple sclerosis down the road. So if you got optic neuritis and you're not sure what you're dealing with and you want to treat them, you got to treat them with IV methylprednisone. But if you get a head scan and the rest of their findings are negative for multiple sclerosis but say you see nodules in their lungs so it's sarcoid related optic neuritis. Then treating them with oral steroids is very important and valuable. I will show you a case here of that a little later on.

Graft rejection: I generally don't use oral steroids for graft rejection. We try to always get it delivered by drops because it's the most effective for corneal graft rejection. But sometimes, you may situation where the patient can't get drops in or their caregiver can't deliver that, the patient has to take pills because they can't put drops in their eyes. Do you want to hospitalize them to

have them do that? There might be a situation with graft rejection using orals would be very appropriate. We generally treat them with topical drops.

#### Glucocorticoid (steroid) anti-inflammatory drugs

- ❖ Prednisone
  - Adult up to 120 mg QD
  - Child 0.05 to 2 mg/kg/day
- ❖ Dexamethasone
  - Adult up to 9 mg QD
  - Child up to 0.3 mg/kg/day
  - Injection- 4 mg/cc up to 0.5 cc SCI (sub-conjunctival injection)
- ❖ Triamcinolone (Kenalog)
  - Adult up to 50 mg QD
  - Child not advised for under 12 years
  - Injection- 40 mg/cc up to 0.5 cc SCI
- ❖ Nasal inhaler
  - Flonase & Beconase
    - 2 sprays/nostril/day

The question is “how would I decide what dose I would use.” If I was dealing with a patient that was about my size and weight, I would just go to 100-120 milligrams of steroid and I would do it [...] based on the presentation, how nasty the inflammation was. What the risk was. If it was arteritis, I'm going to hit them [...] with 100-120 milligrams. If it's a smaller lady, I'm probably going to go “hmm, I don't think you should have that much. Matter of fact, let's look and see at what it says mg/kg in my Wills Eye Manual and let me talk to the patient's physician. I got this patient with a blind right eye from AION. I'm getting lab work done because I think it's arteritic. She's having tenderness of the scalp and I think we need to get this started right away. I'm thinking about this much. Do you think she can tolerate that?” and then we go with it.

#### Question from audience

Would I ever use oral prednisolone for recalcitrant episcleritis? Not my first [choice]. I would try a non-steroidal first. If I've got posterior involvement [related uveitis], I'm usually doing that in concert with the retinal specialist. I'm usually helping out with co-management. It just seems like there's one person doing this.

I appreciate the comments and input. I learn a lot from people who come to these talks. I got someone to help correct me that I was stating adrenal medulla when I should have been stating adrenal cortex for the source of our endogenous cortisols.

#### Allergy (allos; *other ergon action*)

- ❖ An exaggerated response of the immune system to substances recognized by the body, as foreign (Immune hypersensitivity)
- ❖ Frequently characterized by inflammation
- ❖ Phrase “coined” by pediatrician Clemens von Piquet in 1906

### Types of Hypersensitivity (allergy)

- ❖ Type I: immediate, anaphylaxis
- ❖ Type II: Cytotoxic
- ❖ Type III: Immune Complex
- ❖ Type IV: Delayed, cell mediated

Type 1, the immediate anaphylactic type of response. That's what we see most commonly in our patients with hay fever, conjunctivitis.

Cytotoxic, where there's antigens that bind or are precipitated in cells. Cyto-in tissue, cytotoxic responses, we will see that with corneal graft rejection in its early phases.

Immune complex, where you have antibodies binding with antigens and then they circulate through the body and deposit in joints and they cause chronic allergy response.

Finally number four which is again where we deal with the most commonly with is delayed, cell mediated allergy seen with chronic drug use particularly topical agents that we use in eye care like glaucoma drugs, for example.

We will be emphasizing the first type of allergy and the fourth. The intermediate ones don't have much application in eye care and generally are more requiring systemic management by other providers.

### Type I hypersensitivity (atopy)

- ❖ Immediate reaction; if it goes unchecked, leads to anaphylaxis
  - Inciting agent (allergen) adheres to a pair of IgE immunoglobulins which are surface bound to a mast cell or basophil stimulating degranulation and release of histamine and other mediators
    - Hay fever
    - Insect stings
    - Rapid onset drug reaction
      - Penicillin
      - ASA
      - Protein drugs (heparin, insulin, etc)

Histamine is a powerful vasodilator. We will see a lot of fluid accumulation in the tissues involved in the allergic response due to the impacts of histamine.

### Type I hypersensitivity (atopy)

- ❖ Histamine is the primary mediator of type I allergy
- ❖ Histamine is found in high concentration in “linings” and “coverings” of the body
  - Stomach
  - Duodenum
  - Bronchial & nasal mucosa
  - Conjunctiva & episclera
  - Skin
- ❖ Histamine resides in mast cells (tissue) & basophils (blood)
- ❖ Histamine binds with 3 receptor types
  - H1 found in:
    - Smooth muscle of bronchi
    - Blood vessels
    - Intestinal mucosa
    - Oral, nasal, and ocular mucosa
  - H2 found in:
    - Gastric parietal cells
    - Heart
    - Pulmonary vessels
    - Immune cells
  - H3
    - Recently described

The H1 receptors is the area we are dealing with when we are dealing with our ocular allergic responses. H2 receptors tend to be more dealing with gastric intestinal issues and patients will be placed on H2 blockers for that. We are looking primarily at H1 intervention. H3 [has been] recently described. It's not all that recent anymore because it's been a few years since the course was first developed. Their role is still not well defined. It doesn't really have the role for us that the H1 receptors do.

### Type I hypersensitivity (atopy)

- ❖ Histamine bioactivity
  - Dilation of small pre-capillary vessels
  - Capillary dilation and increased permeability
  - Constriction of larger venules
  - Direct action of immune cells
  - Resulting inflammatory signs
    - Skin flushing
    - Fluid production & edema
    - Itching

You got venules that return flow and capillaries at the site of activity. You dilate the larger arterioles so you get blood to the area and then you stop it by constricting the venules. You want to get it there and you want it to take its effect. Wait a minute, want to? In some cases, inflammation is good, but sometimes the body gets fooled or gets overresponsive to something it shouldn't, but the mechanism is still intended to be protective against an attack or insult from an

outside foreign substance. As a result, you get skin flushing, fluid production & edema, and itching is hallmark of histamine release.

### Type I hypersensitivity (atopy)

- ❖ Histamine bioactivity
  - Cardiac
    - Decreased blood pressure
    - Increased heart rate
    - Increased strength of contraction
  - Pulmonary
    - Bronchiole constriction H1
    - Bronchiole relaxation H2

In these patients that go into anaphylaxis, you will get a tachycardic pulse rate contrary to patients who have vasovagal where they tend to become bradycardic and the strength of contraction goes up. The heart is speeding more rapidly but the blood pressure decreases because you got this massive vasodilation of the circulatory system. For the pulmonary system, the H1 histamine cause constriction while the H2 cause relaxation. This is a little curious to me. I was listening to one of our other lectures and they were talking about giving a patient both H1 and H2 blockers when they were going into anaphylaxis and it seems a little counterintuitive when the H2 blockers involve bronchiole relaxation but nonetheless. The primary site of intervention for anaphylaxis is the H1 receptors to keep the patient from having that constriction of airway.

### Type I hypersensitivity (atopy)

- ❖ Histamine bioactivity
  - Gastric
    - Increased acid production
  - Neurologic
    - Cholinergic (“pilocarpine like”)

When you block it, you have an anti-cholinergic like effect. With our patients that we put on anti-histamines, that anti-cholinergic effect tends to decrease lacrimation and it can also have some effects on impairing accommodative function, but the main thing is that dry eye can be aggravated by the anti-histamines.

### Type I hypersensitivity (atopy)

- ❖ Ocular and related disease
  - Blepharitis, keratoconjunctivitis
    - Lid swelling (angioedema)
    - Itching (pruritis)
    - Tearing comes with the histamine stimulating that parasympathetic activity
    - Chemosis
    - Erythema
    - Papillary reaction
  - Food & drug induced anaphylaxis
    - Disseminated angioedema and pitting edema (swelling)

- Disseminated erythema of skin (redness)
- Disseminated urticarial (infiltration of skin)
- Bronchoconstriction
- Generalized vasodilation and increased permeability
- Cardiac hypotension (because of the massive vasodilation throughout the body) & arrhythmia
- Respiratory distress (due to the pulmonary constriction)
- Pruritis (itching)

When I opened up the talk, I mentioned that the original writings on allergy talked about other reaction or strange reaction. Allergy is quite idiosyncratic in both my experience and also in the literature. I have two children who are atopic. One, she has pretty significant eczema, a little bit of atopic dermatitis. The other, young lad, not young anymore, he's 23 now, he doesn't have any obvious systemic disease process but I have treated them at different times. They've been treated different times throughout their life and my daughter is very sensitive to sulfa and my son is sensitive to cephalosporin.

A brief story. My daughter had gotten an ear infection and they put her on a sulfa drug and my wife called me at the county clinic I working at. She said, "Bailey's walking funny, she's waddling around and she umm, she kind of looks like the little girl on Willy Wonka and the Chocolate Factory."

I just said "go get some of the diphenhydramine elixir and give her a couple of teaspoons and head to [the doctor's] office right now. Is she able to breath?"

"Oh yeah, she's laughing [...] but her knees are just all swollen and look funny."

She was having a reaction to the sulfa so my daughter is sensitive to sulfa. She also has this [on her] allergy history.

My son was given some Cefzil and I used him in some pictures. I don't think he's in this lecture but he developed some nice big wheels all over his body so I got some pictures of that before. He didn't have any respiratory or swelling problems in terms of he didn't go as far into the allergic response as my daughter did. So several years later, he had an ear infection, and his bright father said, "we got some Keflex here at the office. It's going to be dated here shortly so let's go ahead and give him that." After four days of giving him that, I stop and thought "why did I do that?" I'm giving him a drug from the same class that he's already allergic to. I looked and no reaction. We talk about cross-reactivity for drug sensitivity. Penicillin and cephalosporins, it's there [at about] 30% rate. Even a given individual at a different point in life may not respond to the antigen, to the allergen that comes into their system because it is a strange reaction. It's not necessarily dose-dependent, small amounts can trigger big responses; other times, patients will take whatever it is or be exposed to whatever it is and not have a problem at all. Hypersensitivity reactions are strange and they don't always manifest. The more of these that are presenting, the more serious the problem.

### Type I Intervention (atopy)

#### ❖ Eliminate allergen

- Cats
- Facial products
- Filters to filter out air
- Flooring
  - Hard floorings are better than carpeted floorings that catch allergens
- Frames
  - some patients are sensitive to materials and you guys are very familiar with that

I had a patient who we saw for ocular surface disease. He had multiple corneal infections, staph, strep, bilaterally. At one point, he was bilaterally blind, he's had bilateral corneal transplants. He has atopic dermatitis and he had very bad atopic dermatitis. His whole body was just falling apart. I got him sent over to the university to get his atopic dermatitis under control. He was on immunosuppressants systemically. To make a long story fairly short, he developed cancer. Went out and had a lung removed because he was a smoker. He was semi-comatose, semi-conscious for two months in the hospital. He couldn't smoke. When we got out, they told him "you got one lung left and it's not that great" so he quit smoking. Guess what? His skin, his eyes, it was dramatic. He's no longer on Imuran, his dry eye, his tear quality has improved dramatically. There's tons of people who are smokers that don't have that, but this guy's immunity along with his smoking really was a key trigger there. I would not have guessed that it would not have been that dramatic but it took him getting a lung out, being in the hospital and finally stopping it. Elimination of the allergen is our number one goal when we are dealing with type 1 intervention. Then we are trying to control symptoms.

### Type I Intervention (atopy)

#### ❖ Histamine blockade

- Antihistamine agents compete for receptors reducing action of histamine
  - H1 antagonists effective at blocking atopic immune reaction
  - H2 antagonists effective in treatment of gastritis and ulcer related hyper pepsia
  - Exhibits mild variable degree anticholinergic activity
    - Reduced lacrimation
    - Mydriasis
    - Reduced accommodation

When we give antihistamines, they have to have an opportunity to grab a hold of the receptors. If there's a histamine molecule binding to a receptor, the anti-histamine isn't going to have an impact on that until that's released. Antihistamines stop the potentiation, the on-going process, but they don't "reverse" it. Steroids can get it and actually begin to stop the inflammatory mediators. Antihistamines block the signal that cause the reaction to continue. Antihistamines stop the on-going process but they don't get in and actually impact the inflammatory cascade.

Patients who are on medications that reduce lacrimation and then they get added an antihistamine to their regimen can tip them over the edge. One of the fascinating things I do in medical eye practice is that I run into these patients that have weird problems and people say "I don't have time for this." Send them to Dr. Urness, he's got all kinds of time. He just sits over at PCLI and

goes on the internet and looks up things. But you look at their medical history and all of a sudden, you see them they are on all these cycloplegic drugs and cycloplegic medications just in general have an impact at reducing our lacrimation.

So you have these patients on three of them and their eyes are just beat red and they're having all kinds of problems. Then they get put on an antihistamine because they're itching and they get worse. You start going "wow, look at all these medications that impair lacrimal function" and then talk to their physician "we need to cut some of these out."

"Well they're crazy."

Yeah well, they're going to be crazy and blind because we got an infection going here and you start cutting it back and some adjustments, all of a sudden we tipped the balance back to where their lacrimal function is sufficient to keep their eyes comfortable. It was done by a doctor giving the patients stuff, too much stuff. So antihistamines impair lacrimation and again that's something to keep in mind as we're treating patients with ocular conditions with antihistamines.

### Type I Intervention (atopy)

#### ❖ Histamine blockade

- Toxicity possible with high dose
  - This is going to be in a patient that would overdosing and taking this chronically in most cases.
- Does not impact manifest reaction, but inhibits continued allergic stimulation

### Non-topical Antihistamine Drugs

#### ❖ First generation sedating antihistamines (old, inexpensive, available OTC)

- Diphenhydramine (Benedryl)
  - Adult: 25-50 mg po q 4-6h, 12.5/5ml IV or IM
    - Maximum 300 mg/24h
  - Child: half adult dose
- Brompheniramine (Dimetapp)
  - Adult: 4 mg po q 4-6h, 2mg/5ml IV, IM or SC
  - Child: half adult dosing down to age 6 years
- Chlorpheniramine (Chlor-trimeton)
  - See Brompheniramine
  - Sustained release adult: 8mg po q12h

What I can say about this whole category and sum it up really quick is that first generation crosses the blood brain barrier more effectively and binds to GABA receptors which contributes to the sedation effect that we get. That's why these first generation drugs, Chlorpheniramine (Chlor-trimeton), Diphenhydramine (Benedryl), are effective in putting people to sleep as well as impacting type I allergy. Obviously, if a person has had an allergy response and they need to be driving somewhere or be alert for their exam on Wednesday, probably the first generation are not the best choice. Probably better to go to some of the second generation. Why do the second and third generation not cause much drowsiness. Their structure is such that they don't cross the blood brain barrier as well so they don't get the central nervous system effect. Here's some

examples. You don't need to memorize these. These are just for completeness of the talk. They're Diphenhydramine Benedryl, Brompheniramine (Dimetapp) Chlorpheniramine (Chlor-trimeton).

### Non-topical Antihistamine Drugs

- ❖ Second generation non-sedating antihistamines (newer, more expensive, larger molecule impaired blood brain diffusion)
  - Loratadine (Claritin)
    - Adult: 10 mg po qd
    - Child: half adult dosing down to age 2 years
  - Cetirizine (Zyrtec)
    - Adult: 5-10 mg po qd
    - Child: half adult dose down to 6 years, quarter dose to 6 months

They're more expensive. I took a look at the other night. I stopped over at the store to pick up some stuff for my mother-in-law. I was looking at the same dosing; it's about double the cost if you look at Benadryl and then Zyrtec. It's 5-6 dollars a package [for Benadryl] and then you look at Zyrtec and it's like 12-13 [dollars]. Roughly about double for the non-sedating ones.

### Non-topical Antihistamine Drugs

- ❖ Third generation non-sedating antihistamines (newer, more expensive, metabolites of second generation)
  - Fenofexadine (Allegra, Allegra D)
    - Adult: 60 mg po q12h
    - Child: half adult dose down to 6 years, quarter dose to 6 months
  - Desloratadine (Clarinx)
    - Adult: 5 mg po qd
    - Child: half adult dosing down to age 5 years, 1/5 dose to 6 months
  - Levocetirizine (Xyzal) recent FDA approval
    - Adults: 5 mg po qd
    - Child: half adult dosing down to age 6 years

Third generations which are generally pro-drugs of the second-generations. Allegra, Clarinx, Xyzal that recent FDA approval was actually last year so it's been out for a while. It's more commonly used in Europe, is my understanding. Although I did see this at the pharmacy at Safeway.

### NSAIDS immune-modulation in Allergy

- ❖ Inhibition of prostaglandins reduces mast cell release of histamine
- ❖ Inhibit other COX mediators of inflammation serving to accelerate resolution of manifest inflammatory response

The antihistamines, they're competing with histamine, the primary culprit in the inflammatory response of allergy. The non-steroidals are going to be intervening at the level of those chemical mediators that potentiate the inflammation which we already talked about a bit. Inhibition of prostaglandins reduces mast cell release of histamine. We can start attacking there to reduce the histamine in the system and it will also accelerate the manifest inflammatory response. It will

help to actually clear the response where the antihistamines merely block the potentiation of the response.

### Steroid Drug Modulation of Allergic Immune Response

- ❖ Steroid immune modulation
  - Inhibition of prostaglandins reduces mast cell release of histamine
  - Blockade of all arachidonic acid derived inflammatory mediators directly reduces manifest atopic inflammation
    - That's why you see such a dramatic effect with steroids in treating allergy

### Type II Hypersensitivity

- ❖ Type II: Cytotoxic reaction
  - Inciting antigen is bound to cell to which IgG or IgM attaches triggering complement cascade &/or antibody dependent cell mediated reaction leading cell lysis
    - Graft rejection
    - Drug induced hemolytic anemia
    - Autoimmune disease
      - Graves
      - Myasthenia Gravis

All I'm going to mention here is that in eye care, where we see it in the initial phases of corneal graft rejection or allograft rejection elsewhere on the eye. Say for instance, you had a cardiac graft placed on the outside of the globe, you might have rejection. Also we may see it in conditions such as Graves' Disease or Myasthenia Gravis where we get autoimmune complexes present in extraocular muscles and affecting nerve tissue in Graves' Disease and Myasthenia Gravis.

### Type II Intervention

- ❖ Type II: Acute corneal allograft rejection
  - Primary management, high dose topical prednisolone acetate 1%
    - Loading dose 5-10 drops first hour
    - 1-2 drops every 15 minutes first half day, then q1h
    - May require drops during sleep first 72 hours
  - Supplemental management
    - Subconjunctival triamcinolone injection
      - 0.1 to 0.5 cc SCI
- ❖ We are not going to spend any time talking about managing that

### Type III Hypersensitivity

- ❖ Type III: Immune complex reaction
  - Inciting antigen is bound to circulating blood cell immunoglobulin (IgG or IgM) complex which subsequently migrates to tissue triggering complement cascade resulting in immunologic inflammation
    - Serum sickness
    - Rheumatic disease
    - Lupus

We may see patients that have inflammatory diseases like scleritis or vasculitis of the eye related to lupus and that would be a type III hypersensitivity reaction.

#### Type II Intervention & III Intervention

- ❖ Types II & III Recommend co-management with subspecialists experienced in immunology of eye and systemic disease

When you get these patients, I mean I just don't deal with this regularly enough that I'm going to manage these patients independently. I had a lady with autoimmune retinopathy, she had pan uveitis and glaucoma. She had inflammation of the entire uvea, cells in the vitreous, cells in the front of the eye and she had glaucoma. She got sent into us because no one else wanted to take care of her anymore. I didn't necessarily want to either so I said "we need to go down to Portland and see Dr. Suler because this is outside of me." But I will help because she has to take the train to go to Portland and she has get a friend to go with her. She does it to please me and she just recently went down. We're dealing with a complex abnormal hypersensitivity response that they don't really fully understand, but she has antigens in the retina. They did some bloodwork and genetic typing stuff, it's beyond me to come up with this autoimmune retinopathy. When we get these folks in these categories, even the greatest patients, I'm working with other specialists in managing them. You're dealing with exposure keratopathy in all the patients or double vision, helping with prism correction, that kind of thing. But continue to communicate with their physicians.

#### Type IV Hypersensitivity

- ❖ Type IV: Delayed reaction, cell mediated
  - Antigen attaches to macrophage or dendritic cell (antigen presenting cell =APC)
  - APC sensitizes T-lymphocyte leading to production and release of lymphokines which mediate the immune/allergic response
    - Chronic drug exposure
      - Brimonidine (for glaucoma management)
      - Atropine (for chronic cycloplegia and dilation)
    - Contact dermatitis
    - Chronic graft rejection

The take home message is that you expose the body to something chronically and eventually the immune system can recognize that as something as unwanted and you'll get this specific type of immune response.

The acute graft rejection is a type II reaction. Patients with chronic corneal graft rejection, it's more of a type IV.

The big ones to remember is the drug exposure that we prescribe to patients. If you start seeing that red eye and you see that gelatinous conjunctiva and they're having itchy eyelids and leathery skin right were the drops are coming out, you need to be thinking "Ah, maybe I have a type IV hypersensitivity reaction."

What's our number one approach to treatment? Eliminate the allergen if possible.

#### Type IV Intervention

- ❖ Eliminate contact with allergen
  - Medication
  - Skin preparation
  - Occupational chemicals
- ❖ Suppress immune response

So that's it for allergy. Antihistamines are a major systemic medication used in the intervention for allergy and then the steroidal and non-steroidal medications. With steroids having its place, it's going to be for the more aggressive inflammatory problems. Try to use the less risky drugs first if that will be successful in controlling the patient's presentation.

#### Pain

- ❖ Pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (Merskey, 1986)

I just took this. I thought it was a fairly good quote encapsulating what pain is. It's one thing we cannot measure. We can measure swelling, protein in fluid, in blood vessels serum, we can measure it in the eyes but we can't measure pain. That makes it a little more challenging to manage. Thankfully, acute pain is usually short-lived. Chronic pain is nasty stuff and probably not something we are not going to be involved in independently managing. I have a few patients that we have to manage with chronic pain but I worked with another provider that specializes in chronic pain management or a family physician.

#### Pain

- ❖ Classifications
  - Central
    - Eg pain from CVA, MS, neoplasm ect
  - Peripheral
    - Eg pain from local tissue insult (abrasion, cut)
  - Nociceptive
    - Pain perception from tissue trauma transmitted by normally functioning pain receptors
  - Neuropathic
    - Pain perception from adaption of structure and function secondary to tissue injury
  - Acute pain
  - Persistent or chronic pain

I think nociceptive, normal. Nociceptive is the normal pain response. Our nerves are working correctly. We get poked, it releases substance P and it does its thing and we should feel pain.

Then there's neuropathic pain which is abnormal pain. Pain that we shouldn't be experiencing not intended. An example of that might be the pain that we might have after herpes zoster or pain

after amputation of a limb where they get that ghost pain. It's not a normal response. It's an abnormal response or neuropathic response.

## Pain

### ❖ Mechanisms

- “The reign of pain is mainly in the brain” yet peripheral tissue insult is frequently the trigger for neural activity which produces pain
- Afferent Pathways
  - Peripheral
    - Nociceptor to C fibers to dorsal horn of cord or mid brain
    - Upregulated by thromboxane, prostaglandin, leukotriene (referred to as peripheral sensitization)
    - “wind up” results as impulse frequency exceeds 1 per 3 seconds
  - Central
    - Dorsal horn up-regulates production of substance P increasing neural activity along the spinothalamic tracts distributing pain signals to many parts of brain
      - ◆ Spinothalamic tract = discriminate pain pathway
      - ◆ Spinoreticular tract = suffering pathway
      - ◆ Dorsal columns = gut pain
      - ◆ Spinothalamic tract = emotional information from cornea, lips, tongue, genital, GI tract
- Efferent Pathways
  - Central
    - Many cortical and subcortical centers converge on dorsal horn producing efferent feedback modulation of peripheral pain stimulus
    - Dorsal horns is the location of efferent feedback modulation
    - Persistent pain stimuli trigger physiological changes converting acute pain to chronic pain

Take a look at the pain pathway. We have our receptors here and a hand is an example in the periphery. It gets stimulated, there's a substance called substance P which is released. If enough is released, you get a depolarization and the signal travels up to the spinal column or to the midbrain if it's in the head and then it travels along the spinal column or in the midbrain up to the hypothalamus up to the higher centers of the brain. You get a pain response. You insult the tissue. You depolarize the neurons. It goes up to the spinal column and it sends a message on up. Depending on what part of the body and what kind of pain receptors triggered, it's going to follow several pathways which are listed in your hand out there. The spinothalamic, spinoreticular, the dorsal column and so on. I think the thing of value is that there is a threshold that has to be exceeded. Kind of like how we look at vision. We got to enough depolarization of photoreceptors for the ganglion cell to fire and send a message. We got to get enough stimulation to that pain receptor to depolarize that cell to exceed the threshold to send that pain signal. We get that insult. It goes up. If that stimulus to that pain receptor continues, it keeps sending that afferent message. Our brains are pretty sophisticated and what it will do is that there's actually efferent pathway. A pathway from the brain back down to the spinal column and the midbrain and what it does is that it modifies that threshold. The acute pain will change. You've seen that in patients where they've had serious injury and they're having pain from it, then they get done, they

are starting to heal from it, and they don't have all that much pain. "Golly, that looks pretty nasty. How come you're not in pain?" The brain is modifying that threshold by that efferent pathway. So you have afferent peripheral pain receptors, spinal column, midbrain, Substance P is released, it goes up. Guess what some of the mediators are at the pain response that modify that pain response. Prostaglandins, prostacyclins, thromboxanes. Our drugs don't just affect pain by reducing inflammation, they actually affect the threshold for the pain response system as well. So we can intervene with regard to pain by reducing inflammation, but those same drugs are going to have an impact on the pain itself.

## Pain

- ❖ Ocular conditions causing pain
  - Trauma (including post-surgical pain management)
    - Abrasive
    - Lacertation
    - Perforation
  - Infection
    - Bacterial eyelid cellulitis
    - Fungal keratouveitis
    - Viral infection
      - Herpes Zoster Ophthalmicus (HZO)
      - Herpes Simplex
    - Orbital cellulitis
  - Non-Infection
    - Orbital cellulitis
    - Uveitis
    - Scleritis
    - Angle closure glaucoma

## Pain Intervention

- ❖ Treating ocular pain can be effectively approached with a similar strategy to that used to manage allergy
  - Take a complete medical and drug Hx
  - Aggressively seek out underlying cause
  - First Rx treatment to neutralize and eliminate underlying agent or causative process
  - Next consider case appropriate anti-inflammatory therapy
    - Primarily peripheral therapeutics is preferred, using drugs that act at the site of inflammation as opposed to just suppressing it centrally
  - Last institute non-anti-inflammatory analgesia
    - Primarily central therapeutics
    - Ex: narcotic pain medications
- ❖ God intended pain to protect us, so use a comprehensive approach to intervention
  - Don't just look at pain being bad

Don't just treat to mask [the pain]. Sometimes you can't figure that out right away. You got to deal with the pain so you do an evaluation on the patient. Say a patient comes in and they're saying "Aaahhh, my eye hurts, my eye hurts, it's terrible, I can't do anything." They got a rag on

there and you try to open it, [...], you try to look at the eye first, get an acuity first and they ain't letting you touch them. Okay well, I'm putting in a drop of anesthetic here because I got to be able to examine the eye. We are going to alleviate the pain before we really know what the cause is because we have to further evaluate them. We can't figure out what the cause is and eliminate it if we can't do an evaluation.

Getting a patient a narcotic drug that makes them say "oh yeah, there's some pain, I don't really care about it and doctor, I'm feeling great." It's hard to monitor their response to treatment that you're giving them so I tend to prefer to treat peripherally where the insult is before I do centrally. It doesn't mean that I don't do it or do both. But that's my preference.

### Ocular & Orbital Pain Intervention

- ❖ Supportive therapy more value than given credit for
  - Lubrication: preservative free tears
  - Cold compress
  - Cycloplegia
  - Bandage contact lens
- ❖ Oral medication
  - OTC: combine acetaminophen and Advil or aspirin
  - Rx: narcotic without or with non-narcotic
    - Ex: Vicodin, where you have acetaminophen along with hydrocodone

I have EMBD, both eyes. It tends to be superior but it started migrating, in my right eye, [in the] pupil zone and my acuity dropped to 20/30. I was having trouble with slit lamp exam and holding stereopsis. I finally said "scrape it." I had to debride my cornea and I'm not a contact lens wearer and never have been. It was interesting for substance P to kick up. It really helped me appreciate why patients get abraded and they don't say anything until 4-6 hours later because it takes a little time for the tissues to produce that stuff to start sending that signal "ahh, this hurts." But I said, maybe I better take my own advice so I had some non-steroidal drops and preservative free tears. I went ahead and grabbed the cold pack. I said "yeah, it doesn't feel very good but I'm going to do what I tell patients" and I kept it on there. I tell you, that cold pack and I for 48 hours were really good friends. I said "what I tell people is right. This is the best thing I'm doing." Initially it hurt to put that cold pack on [my eyes]. It's kind of like going down to the Oregon coast and getting into the water. First your feet hurt a little bit but then that cold increases the threshold for pain transmission. Cold compresses, cycloplegia, set the sphincter and ciliary body at rest and then bandage contact lenses are great for dealing with surface pain.

I don't leave a bandage contact lens on for more than a week without removal and re-application and I always soak them in an antibiotic.

### Ocular & Orbital Pain Intervention

- ❖ Cautions
  - Adverse medication response
    - Aspirin allergy, more common in asthmatics
    - Acetaminophen toxicity in hepatic dysfunction

- That's gotten more press lately. There's even some discussion about requiring to put labeling on Tylenol and the other acetaminophens about the possibility of liver damage with its overdosing.
- Ibuprofen in renal impairment
- Narcotics are addictive, they slow GI (gastrointestinal) & GU (gastrourinary) activity (constipation & urinary retention), they impair cognitive function, and depress respiration
- Compromised pulmonary, cardiac, renal, & hepatic function
- Pain medication can mask symptoms of infection

When my father was dying, it was interesting, he was placed on narcotic pain medication, but not just for pain, but also because he was dying from pulmonary disease. It decreased the body's ability to respond, pulmonary-wise so it made him more relaxed. It didn't have much distress from that.

If you put a patient on atropine and Vicodin, like for corneal transplants, pterygium, abrasions, you might do that, a bad uveitis. You're giving them a double dose of slowing the GI system down. I have run into patients that have problems with constipation. So I will tell patients if I put them on atropine and a narcotic pain medication "make sure you're getting some fruit, some fiber because this can slow you down." And if they have problems already, you look down on their medication list, some of the patients go "oh that's great. I'm so loose, maybe it will help me." You look at their history and just be aware that narcotic analgesics will slow down the GI and GU system and atropine also. It's very effective in doing that.

### Oral Analgesics

- ❖ Aspirin-ASA (Bayer, Ecotrin) 325-650 mg q4-6h
  - Do not exceed 4 gm per day
  - Produces analgesia by blocking prostaglandin synthesis (peripheral action), also has anti-inflammatory effect and impedes blood clotting
  - Has "ceiling" to analgesic effect
  - SE's include gastric upset or bleeding, possible neurotoxicity (especially CN VIII)
  - Don't use in children <18 you with recent viral infection
    - >Reye's syndrome, potentially fatal

The dosing can be a little different depending on what you're treating. That's why I'm presenting it specifically here, only ranges are of much value. You're going to look for the particular condition. We talked the other day, Dr. Saunders was giving a dosing for treating genital herpes which is different that treating ocular herpes. Because that's what's she's familiar with. We asked her afterward that's not what our stuff says about treating the eye. You need to have it in your material. You're not going to hear from me anywhere in the future "tell me how many grams of this or that" but you might hear from me "what might you need to be aware of, what kind of complications, if the patient is diabetic, what do you need to be aware of in treating their glaucoma", that type of thing.

### Oral Analgesics

- ❖ Acetaminophen-APAP (Tylenol) 325-650 mg q4-6h
  - Unknown action. Thought to produce analgesia by blocking generation of pain impulses in the CNS
  - No anti-inflammatory effect
  - Does not inhibit blood clotting or produce GI ulceration
  - Liver damage can occur in excess doses or if combined with alcohol
  - Considered safe during pregnancy (category B)

It's a good central pain controller that doesn't have the risks with the blood that it does have potential for liver toxicity. So a patient with cirrhosis or has hepatitis that has damage may want to be careful with the acetaminophen.

### Oral Analgesics

- ❖ Ibuprofen (Advil, Motrin) 200-400 mg q4-6h for pain
  - Do not exceed 1.2 g per day (OTC)
  - Anti-inflammatory dose 30-800 mg q4-6h
  - Do not exceed 3.2 gm per day (Rx)
- ❖ Naproxen (Aleve) 400 mg followed by 200 mg q8-12 h for pain
  - Do not exceed 600 gm per day (OTC)
  - Anti-inflammatory dose 250-500 bid
  - Do not exceed 1.25g per day (Rx)

One thing I will say about prescriptive vs non-prescriptive, prescriptive drugs in the same class as non-prescriptive generally are higher concentration. So it's easier to dose the patient. Prescription Ibuprofen is 800 mg; you can get it in 800 mg tablets. You can't get that over the counter. So you can have a patient take a whole wad load over the counter Advil or you can prescribe and have them take a lower dose. That's something to be aware of. I've done both. Sometimes patients don't have a prescription plan, but they got Advil at home so I will say "double the dose of your Advil and your Tylenol and we'll see you back in 48 hours." For others, [I] will prescribe.

### Oral Analgesics

- ❖ Codeine (Tylenol no. 1,2,3, or 4, Empirin No. 3,4) 15-60 mg q4-6h
  - Tylenol No. 1,2,3 or 4 = 7.5, 15, 30, or 60 mg codeine + 300 mg acetaminophen
    - Tylenol #3 most common
  - Empirin No. 3 or 4 = 30 or 60 mg codeine + 325 mg aspirin
  - Schedule III

Dr. Walls covered the narcotics, in terms of the prescribing, how to write them, the concerns about drug diversion and drug seekers. These are just lists. Tylenol No. 3 and Vicodin are the two combined narcotic/non-narcotic analgesics that I like to use, but there are others.

### Oral Analgesics

- ❖ Hydrocodone (Lortab, Vicodin, Vicoprofen) 2.5-10 mg one or two q4-6h
  - Lortab = 2.5, 5, 7.5, or 10 mg hydrocodone + 500 mg acetaminophen
  - Vicodin = 5 mg hydrocodone + 500 mg acetaminophen
  - Vicodin ES = 7.5 mg hydrocodone + 750 mg acetaminophen
  - Vicoprofen = 7.5 mg hydrocodone + 200 mg ibuprofen
  - Schedule III
- ❖ Propoxyphene (Darvocet) q4h
  - Darvocet N-50 = 50 mg propoxyphene napsylate + 325 mg acetaminophen
  - Darvocet N-100 = 100 mg propoxyphene napsylate + 650 mg acetaminophen
  - Many other combinations, generic available
  - Do not Rx for suicidal or addiction prone pts
    - Major cause of drug related deaths
  - Schedule IV
- ❖ Oxycodone (Percocet, Percodan) 5 mg q6h
  - Percocet = 5 mg oxycodone + 325 mg acetaminophen
  - Percodan = 5 mg oxycodone + 325 aspirin
  - Schedule II drug (not allowed on OD drug list)
  - Oxycodone is schedule II because it's a narcotic by itself. Therefore, it's more prone to abuse and street value because you don't have Tylenol mixed in with it or Voltaren mixed in with it, one of the other drugs that is a straight narcotic
- ❖ Neurontin (Gabapentin)
  - Treatment for HZO pain
  - 300-600 mg tid titrating low to high
  - 3600 mg/day maximum dose
  - Adjust for renal dysfunction/failure

The non-narcotic, the neuro-active pain control drugs, Neurontin is a good one, I think, to present to you. Gabapentin has a specific use in ocular care and that is treatment of post-herpetic neuralgia. I have a patient on it right now, not for herpetic neuralgia, but she's had retinal detachments, multiple surgeries, and chronic uveitis from that. She has a painful eye [with] light perception. The eye looks great because all the work was done in the back. She has chronic internal inflammation and she has pain and topical steroids don't control it. I'm working with her PCP and he has her on amitriptyline and Gabapentin and she says, "I can live life." We were debating about taking her eye out and she says "wow, since I'm taking these medications along with controlling with a low-dose steroid, it's good." She's a really attractive lady and her eye looks fine but it just doesn't see and it hurts. An example of use is post-herpetic neuralgia. I would do that with a patient's physician, I wouldn't prescribe that myself.

### Oral Anti-depressants to treat ocular pain

- ❖ Desipramine (Norpramin) 25 mg tid or 75 mg qhs
  - Maximum dosing 300 mg/day
- ❖ Amitriptyline (Elavil) 25 mg tid
  - Maximum dosing 150 mg/day
- ❖ For post-herpetic neuralgia (pain that persists after HZO lesions healed) consider these oral tri-cyclic anti-depressants (above) and analgesic (discussed earlier)

### Topical analgesic of note

- ❖ HZO dermatitis
- ❖ Capsaicin (Zostrix) cream tid-qid to affected area
  - Depletes “substance P” in sensory nerve endings
    - Thought to be primary chemomediator of pain impulses
    - May harm at first, then improves

Zostrix is painful when first applied because they already have neuropathic pain, they have abnormal pain from these damaged nerves and then you apply this Zostrix cream and it can light them up. But if they continue to take it, it depletes that Substance P, that neurotransmitter for pain, and decrease their pain response. I have not had a lot of success with patients that are on it. But occasionally, you will see that somebody does use it. More success with the systemics.

### DEA (Drug Enforcement Agency) Controlled Substances Schedules

- ❖ I- High abuse potential, no accepted medical use
  - Heroin, marijuana, LSD, illegal substances
- ❖ II- High abuse potential with severe dependence liability
  - Morphine, oxycodone, codeine, cocaine, meperidine, amphetamines, barbiturates
- ❖ III- less abuse potential than schedule II and moderate dependence liability
  - Codeine and hydrocodone combinations (Tylenol with codeine, Vicodin, etc.)
- ❖ IV- less abuse potential than schedule III and limited dependence liability
  - Propoxyphene, benzodiazepines (Valium, Xanax)
- ❖ V- limited abuse potential
  - Codeine cough syrup, antidiarrheals
- ❖ Prescribing requirements
  - Non-topical pharmaceutical certification
  - DEA licensure & number
- ❖ Prescribing practices
  - Complete written prescription
    - Patient name
    - Date
    - Medication
      - Quantity: numeric and alphabetic
      - Dosage: numeric and alphabetic direction
      - Frequency
      - Special instruction
    - Doctor name, location, signature
  - Counsel on adverse effects

### Anxiolytic/Sedative Hypnotic Drugs

- ❖ These drugs that cause progressive increase in CNS sedation, leading to hypnosis
  - Drugs that cause sedation, anxiolysis & hypnosis often differ only in dosing
    - Quantity
    - Frequency
  - Drugs vary considerably as to their pharmacokinetics and pharmacodynamics
    - how rapidly they are absorbed and how rapidly they're eliminated.
- ❖ Benzodiazepines (BZDs)
  - BZDs are commonly Rx'd for short term Tx of acute anxiety and general anxiety disorder (GAD)
  - BZDs may also be used prior to procedures
    - That's where we use them in eye care
  - BZDs reduce anxiety and encourage anterograde amnesia
    - So patients don't remember what they been through. They are able to respond and participate in a procedure, they're not completely out, but they don't remember what's happened to them if they had a deep enough dosing with the benzodiazepines.
  - BZDs used as hypnotic (induce sleep) requires careful monitoring of vital signs. Prescribers should be prepared to reverse adverse events should they occur.
    - The closer towards hypnosis, the deeper the person is taking with these anxiolytic drugs, the more critical their vital signs are going to be. If they're taking oral Valium, 2.5 mg, probably not going to be a critical issue as if they're under IV sedation.

### Anxiolytic/Sedative Hypnotic Drugs

- ❖ Benzodiazepines (BZDs)
  - Mechanism of action
    - BZDs attach to the GABA receptor in the CNS and they inhibit neurotransmission in the CNS by competition with the endogenous neuroreceptors.
    - GABA is the major inhibitory neurotransmitter in the CNS
    - BZDs indirectly up regulate the effects of GABA
    - BZDs thereby increase firings of neurons
  - Pharmacologic effects
    - Sedation
      - Difficult to spate sedation from anxiolysis
      - Tricyclic antidepressants sedate, but do not induce anxiolysis
      - Anterograde amnesia accompanies sedation from BZDs
    - Hypnosis
      - Characteristic of all sedative/hypnotics when dose is large enough
      - Goal of hypnosis: induce drowsiness to facilitate sleep
        - ◆ The sleep should be as natural as possible, not disrupting the normal stages
    - Anesthesia
      - Some agents can induce Stage III anesthesia
      - BZDs are not suitable for induction of anesthesia
    - Respiration & Cardiovascular Effects
      - At therapeutic dosing risk only for those with respiratory disease
      - Respiratory arrest due to overdose results from central action on the medullary respiratory center

- In healthy patients sedative/hypnotic dosing has no ADRs relative to cardiovascular function
- As with respiratory effects, ADR are more likely to occur in patient with concurrent heart disease (eg. Congestive heart failure CHF)
- Precautions/Contraindications
  - Hepatic disease (liver disease)
    - ◆ The patients can't metabolize the drug and eliminate it from the system. It's going to stay around longer and it's going to accumulate
  - Lactation (Diazepam)
  - Pregnancy category D: BZDs freely pass through the placenta
    - ◆ That's an issue in our clinic when we deal with patients who are going to have refractive surgery or ocular surface surgery like pterygia because if they're nursing, we don't do their procedure.
- Drug Interactions
  - Most frequent with co-administration of other CNS depressants, especially ethanol
    - ◆ If you have a patient with alcohol abuse problems and they're going in for a procedure, you're going to get additive effects of respiratory suppression and cardiac effects from combined use of ethanol or alcohol and BZDs.
- Dosing in the elderly
  - Smaller dosing
  - More susceptible to CNS depression
  - More prone to impaired daytime function
  - Memory problems
  - Most common reversible ADR is confusion due to overuse
  - Titrate carefully
- Dosing for fast action
  - Diazepam
  - Clorazepate
  - Alprazolam
- Use BZDs with shortest half-life for
  - Hepatically challenged
  - Concurrent use of drugs that impair liver function
- Adverse Drug Reactions (ADR)
  - Unwanted CNS effects are uncommon at therapeutic levels
  - Most common
    - ◆ Drowsiness
    - ◆ Sedation
    - ◆ Psychomotor impairment
    - ◆ Disinhibition
    - ◆ Ataxia
  - Check Epocrates, PDR monograph

### Case 1

- ❖ 32 yo Hispanic female with c/o enlarging irritating growth OS>OD (figure 9). Periodic redness, FB sensation and mild photophobia
- ❖ Medical Hx
  - No conditions (not pregnant)
  - Medications
    - None
    - NKMA
- ❖ Best corrected vision
  - OD +0.75-1.00 x 175 20/30
  - OS +0.25-0.50 X 180 20/25
- ❖ Biomicroscopy
  - Anterior segment
    - See photo
  - Posterior segment
    - Unremarkable
- ❖ Assessment
  - Peripheral progressive pterygium OS>OD causing symptoms [1DPO, nice staining epithelial defect (figure 10); the graft right here is nice and white because it hasn't re-perfused with new blood vessels]
- ❖ Plan
  - Pterygiumectomy with conjunctival graft OS first
- ❖ Post op medication
  - Topical
    - Quixin QID
    - Pred Forte QID (for anti-inflammatory control)
    - PF artificial tears Q1h while awake
    - Bland Unh HS
  - Oral
    - Vicodin 5/500 mg Q 6h prn for pain
    - Phenergan 12.5 mg Q 6h prn for nausea
- ❖ We talk about patients taking medications with food in their stomach. In general, that's helpful. But that's not the process that creates the nausea. It's the central acting effects of the narcotics for some people that are very effective. At least if they have food, they have something to throw up when they puke.



Figure 9



Figure 10

### Case 2

- ❖ 43 yo black female referred for evaluation of a recalcitrant painful red right eye. Initial onset 7 weeks prior. Used tears for 4 weeks without relief then saw local OD. Initial Tx Tobradex QID x 1 week. Subsequent Tx FML QID to present. APAP 500 mg po BID. Valtrex prn for cold sores, taken this week
- ❖ Medical Hx: smoker, cold sores
- ❖ Assessment

- Recalcitrant episcleritis OD (figure 11)
- ❖ Plan
  - D/C FML
  - Rx Pred Forte 1 gtt Q2h x 3 days, then QID
  - Rx ibuprofen 600 mg PO QID for 1 week
  - RTC 1 week

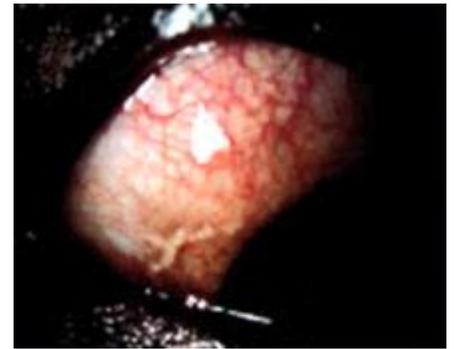


Figure 11

### Case 3

- ❖ 49 yo white male with a history of severe alternating recurrent anterior uveitis, calls reporting he believes he is having a flare up OD. The last time he was seen 3 years prior. Sight is near normal and there is only watery discharge
- ❖ Medical Hx
  - Ankylosing Spondylitis
  - No medications, NKMA
- ❖ Family Hx: strong for Rheumatic disease
- ❖ Impression: Recurrent HLA B27 Uveitis OD
- ❖ Plan: Call in Rx for Pred Forte 5 gtts loading dose then Q 30'' and meet me at the clinic in 3 hours
- ❖ On presentation patient reports 50% improvement since beginning steroid drops
- ❖ Examination confirms Recurrent Anterior Uveitis
  - Habitual VA 20/20 OD & OS
  - 1+ injection episclera greater than conjunctiva
  - Anterior chamber bears 1+ cells, 2+ flare
  - Iris pupil: round centered and sluggish
  - Lens: old iris pigment, 1NS
  - Vitreous PVD; no active cell
  - Disk shows distinct margin
  - Macula bears trace perifoveal ERM
  - Periphery is without break or inflammation
- ❖ After tapering to 1 gtt an hour at one week the patient experiences exacerbation
- ❖ Treatment is increased to 2 gtts per hour and injection (SCI) is given
  - 0.5 cc of Kenalog (40 mg/cc)
- ❖ Slow taper is being carried out currently at 5 weeks, with Pred Forte dosing at Q 2h

I could have just gone and met him at the clinic and seen what I probably knew what I was already going to see. I know what this guy's history is; let's get started. When he presented at the clinic, he said that he had a 50% improvement in the three hours since he started dosing with the drops.

This is one where we are using a combination of systemic injectables and topicals

### Case 4 (sarcoid optic neuritis)

- ❖ HPI: 58 year old white female presents with profound unilateral reduction of vision OS. Onset 5 days earlier. Vision began centrally dimming with color distortion, like looking at a video

with poor tracking. Reduction has spread to full field of view. The eye aches, but is not debilitating pain. OD is unaffected.

- ❖ LEE 1996: Optic nerve lesion unspecified OD, PVD OS
- ❖ LME 2 m pst: arrhythmia, mitral valve prolapse- Tx Tenormin & Lanoxin; peptic ulcer Tx Pepcid; Dysthyroid Tx synthroid. NKMA
- ❖ BCVA
  - OD 0/30-
  - OS CF 2'
- ❖ PHVA
  - OS 20/250
- ❖ Pupils
  - 2+ APD OS
- ❖ VF
  - See images
- ❖ Tonometry
  - OD 12 mmHg, OS 14 mmHg
- ❖ EOMs- committant XT; increased tenderness in adduction OS
- ❖ SLE
  - Trace to 1+ cells OS
  - White lesion optic nerve OD
- ❖ Assessment
  - Atypical acute onset retrobulbar neuritis OS
  - Juxtapapillary lesion unspecified OD
- ❖ Plan
  - ESR STAT
    - ESR = 2 mm/hr
  - Head MRI asap
  - Further work-up pending
  - Phone consult neurology & neuro-ophthalmology
- ❖ Diagnostic and therapeutic medical Tx
  - 1000 mg IV 6 methylprednisone x 3 days
  - Following prednisone 80 mg PO QD
- ❖ Re-evaluate 48 h
  - At 2 weeks PHVA 20/25
- ❖ Ultimate & Definitive Dx
  - Sarcoid optic neuritis OS
  - Juxtapapillary granuloma OD
- ❖ Long term medical therapy
  - Prednisone
  - Azathioprine (Immuran)

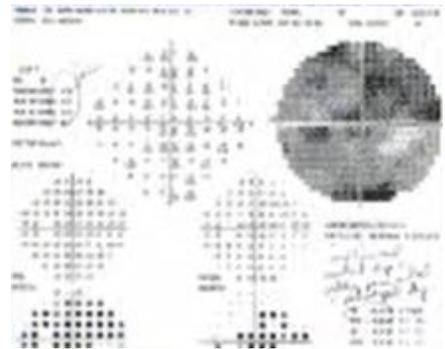


Figure 12

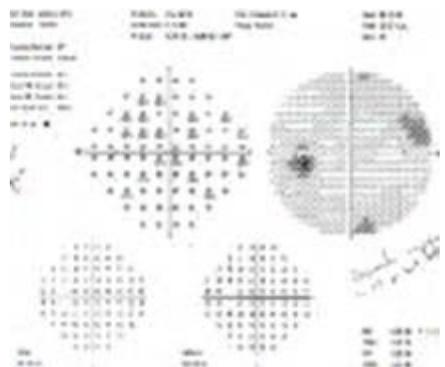


Figure 13

The picture here was her vision when she presented (figure 12). The other picture is her eye 48 hours later after she had IV methylprednisone (figure 13). It's not always safe to assume just because that a patient has optic neuritis, it's MS and they don't need specifically need treatment. An example of systemic use of steroids in ophthalmic practice. Thank you very much!