COURSE TITLE:

DRUG-RELATED ADVERSE EFFECTS OF CLINICAL IMPORTANCE TO THE OPHTHALMOLOGIST

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Some medications are classified according to the World Health Organization's Causality Assessment of Suspected Adverse Reactions Guide. This template helps categorize medications into side effect profiles. The definitions are as follows:

- **Certain**: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

- **Probable/Likely**: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- **Possible**: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

- **Unlikely**: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

- **Conditional/Unclassified**: A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.

- **Unassessible/Unclassifiable**: A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

Topiramate - Topamax®

Primary Use: Topiramate is a novel agent used in various types of epilepsy and migraine headaches. It is used "off label" as a "magic" weight reduction medication.

Clinical Concerns: Recent case reports by Banta, et al, Rhee, et al, and Sankar, et al. have ballooned into almost 100 cases of a classic syndrome unheard of in clinical ocular toxicology.

In the Registry series:
- Patients range in age from 3 ½ to 53 years
- Ranging from 3 to 14 days after the start of oral therapy

WHO Classification:

Certain

Acute glaucoma (usually bilateral)
- Anterior chamber shallowing
- Ocular hyperemia
- Increased ocular pressure
- Mydriasis

Decreased vision
Acute myopia (up to 6-8 diopters)
Uveitis
Suprachoroidal effusions
Visual field defects – acute glaucoma
Ocular pain

Probable/Likely

Blepharospasm
Oculogyric crisis
Retinal bleeds

Possible

Blindness
Scleritis
Teratogenic – ocular malformations

Before the syndrome was recognized, the majority of cases had laser iridectomies or peripheral iridectomies. We now know this is not correct.

Suggested Treatment
1. Stop the medication
2. Hyperosmotic therapy
3. Cycloplegic
4. Topical antiglaucoma medication

Bisphosphonates
(Pamidronate, Alendronic Acid, Ibandronate, Zolendronate)

Primary Use: Pamidronate disodium (3-amino-1-hydroxy propylidene, disodium salt pentahydrate) inhibits bone resorption in the management of hypercalcemia of malignancy, osteolytic bone metastases of both breast cancer and multiple myeloma, and Paget's disease of the bone.

Clinical Importance/ Ocular Concerns: This class of medicine has been reported to cause anterior uveitis and nonspecific conjunctivitis. There are case reports of episcleritis, nerve palsy, ptosis, retrobulbar neuritis, and yellow vision. We previously reported a case of anterior scleritis and a case of posterior scleritis associated with pamidronate use, without rechallenge data. The most studied drug in this class, pamidronate, has caused seventeen cases of unilateral scleritis and one case of bilateral scleritis usually within 6 to 48 hours after intravenous use. Six patients had positive rechallenge testing with the scleritis occurring after a repeat drug exposure. Other ocular side effects with positive rechallenge data, associated with pamidronate disodium use, include: blurred vision, nonspecific conjunctivitis, ocular pain, bilateral anterior uveitis and episcleritis.

Guidelines/ Conclusions: This is the only class of drug proven to cause scleritis. Bisphosphonates can cause vision threatening diseases, which may require discontinuing the drug in some uveitis cases and, in this series, all cases of scleritis. Further guidelines are as follows:

1. If persistent decrease in vision or ocular pain occurs, the patient should see an ophthalmologist.

2. Nonspecific conjunctivitis seldom requires treatment and usually decreases in intensity or may be absent on subsequent pamidronate injections. In rare instances, a non-steroidal anti-inflammatory eye drop may be needed.

3. Bilateral anterior uveitis or rarely posterior or bilateral uveitis may occur and can vary markedly in severity. Many cases required intensive topical ocular or systemic medication. In some instances, the drug may need to be discontinued for the uveitis to resolve.

4. Episcleritis may require topical ocular medication, however pamidronate may be continued.

5. In this series, for the scleritis to resolve, even on full medical therapy, the intravenous pamidronate had to be discontinued.

WHO Classification:

Certain
Blurred Vision
Ocular Irritation
Nonspecific conjunctivitis
    Pain
    Epiphoria
    Photophobia
Anterior Uveitis (rare – posterior)
Anterior Scleritis (rare – posterior)
Episcleritis

Probable
Periocular, lid and/or orbital edema

Possible
Retrobulbar neuritis
Yellow vision
Diplopia
Cranial nerve palsy
Ptosis
Visual hallucinations

Pledgets of 10% phenylephrine

Primary Use*:* Hemostasis during LASIK procedures, potentiate pupillary dilation, lyse posterior synechiae**.**

Clinical Importance/ Ocular Interest: Previous reports have documented danger of malignant hypertension, cardiac events, and subarachnoid hemorrhage after treatment with topical 10% phenylephrine. Effects are magnified in the pediatric population. Currently, refractive surgery has brought this medicine back to the forefront of ophthalmology given its effectiveness in vasoconstricting peripheral corneal blood vessels during bleeding from LASIK procedures. Package insert instructs only one drop per eye per hour.

Guidelines*:* Avoid this medicine in pledglet form as the systemic side effects, although rare, can be severe. One-hundred serious, fatal and near fatal reports from 10% phenylephrine from the National Registry and 41 peer review papers in literature urging caution in the administration of this drug.

WHO Classification:

Certain
Hypertension

Possible
Myocardial Infarction
Subarachnoid Hemorrhage

HYDROXYCHLOROQUINE (Plaquenil)

*Note: Chloroquine no longer available except for malaria treatment, primarily military.

Primary Use
Hydroxychloroquine is used for the treatment of rheumatoid arthritis and lupus erythematosis, dermatologic conditions, and various inflammatory disorders..

Definition of Hydroxychloroquine Maculopathy
Maculopathy must be bilateral and reproducible by Amsler grid and visual field testing. Transient or unilateral defects are not sufficient reasons to implicate the drug, and are not necessarily an indication to stop therapy.

The Goal
The goal is to find early changes, i.e., relative scotomas. Patients with early paracentral relative scotomas seldom advance when the drug is discontinued. Later findings include retinal changes, color vision loss, absolute scotoma or decreased vision. Even if the drug is stopped, once these occur, changes are irreversible, and many patients may continue to lose some vision and/or peripheral fields.

Overview
How best to follow patients on hydroxychloroquine is still being developed. These thoughts are only suggestions. I recommend following the overall guidelines of the American Academy of Ophthalmology for seeing patients, i.e., age 39 and below, see at least once; ages 40-64, every 2 to 4 years, and ages 65 and over, see every 1 to 2 years. I documented in the patient=s chart that I have explained to the patient that in very rare instances, significant loss of vision can occur after only a few years of therapy, and that he or she may need to see me if any visual abnormality occurs.

Guidelines for Following Patients:

Baseline Examination
Within the first 1 to 2 years after starting this drug, a complete - dilated - ophthalmic

examination should be done, including some type of informed consent of possible permanent visual problems in rare instances. This baseline exam should include visual acuity, Amsler grids (with instructions for monthly home use), and color vision (preferably including the blue-yellow axis, such as the pseudo-isochromatic plates for color by American Optical corporation). If any abnormality of the macular area is seen, it would be ideal to obtain fundus photographs. If you have any suspicion of an ocular abnormality of any progressive type, consider a baseline Humphrey 10-2 or other automated perimetry.

Follow-up Examinations

If the patient is not obese, frail, elderly or extremely thin, or does not have significant renal or hepatic disease or macular disease of any type, and is below age 40, he or she does not need another complete exam for 2 to 4 years. They need to see you sooner if:

They experience any persistent visual symptoms
Their dosage exceeds 6.5 mg/kg

If between 40 and 64 years:

Same as above, however, need to see you every 2 to 4 years.

If age 64 and above:

Same as above, however, need to see you every 2 to 4 years.

Annual Examinations should be done if:

Over 5 years of therapy.
Obese, or lean and small - especially elderly.
Progressive macular disease of any type.
Significant renal or liver disease
Dosage exceeds 6.5 mg/kg

Follow-up Examinations

Repeat baseline examination.
Fundus photography if any macular abnormality noted.
Consider fluorescein angiography only if suspect pigmentary changes of any cause.
Automated central visual fields.
If available, but not essential, in selected cases, multifocal ERG.

Chloroquine - Perform same tests as above. See at least annually if dosage is less than 3.0 mg/kg of ideal body weight. See every 6 months if dosage greater than 3.0 mg/kg body weight, if short/obese/or have renal and/or liver impairment.

Caution

To date, there is no data to show hydroxychloroquine toxicity worsening pre-existing macular degeneration. Common sense in a litigious society which has to find blame somewhere may

make informed consent and explanation of risk/benefit ratios necessary on an individualized basis.

Comments
Greatest at-risk group are: 1) Patients on the drug over 7 years; 2) Patients with renal or liver disease - drug metabolized via the kidney and liver, therefore damage to these organs may increase drug blood levels; 3) Elderly, thin patients - may be overdosed; and 4) Obese patients - dosage based on body weight. Hydroxychloroquine primarily absorbed by cellular tissue. Adipose tissue is relatively acellular so obese patients may be overdosed.

Hydroxychloroquine crystals have been found in the tear film which may aggravate sicca or contact lens wearers.

If hydroxychloroquine caused skin, eyelid, corneal or hair changes - suspect retinal changes.

A recent preliminary paper by Shroyer, et al. suggest that individuals with an ABCR mutation (Stargadt disease) may be predisposed to develop retinal toxicity when exposed to chloroquine/hydroxychloroquine.

Note: The American Academy of Ophthalmology has a committee working on guidelines for hydroxychloroquine which should be released soon.

MARIJUANA

Strong patient advocacy group forced national government to form commission to study research data.

What do we know?
Industry tried to purify and isolate the cannabinols to localize pressure-lowering agents. Unsuccessful because other products are better, problems getting the drug into the eye, and cannabinols which lower IOP also cause the CNS high.

Smoking marijuana can lower IOP an average of 25%.

Effect only lasts 3-4 hours.

Synthetic cannabinoids or marijuana orally have same pressure-lowering effect, but still only 3-4 hour ocular effect on IOP.

Side effects of glaucoma patients smoking marijuana include reduced BP, psychotrophic changes, hypertension, palpitations, anxiety, tachycardia.

Conclusion
Not impressive drug to treat glaucoma

Too short acting

Better drugs available

Since may have neuroprotective effects, some are pushing for more research on this agent.

Strong pressure for use by certain advocacy groups

AMIODARONE (Cordone)

Primary Use: Primarily used in the treatment of various cardiac arrhythmia.

Recent $22.3 million settlement for possible amiodarone-induced optic neuropathy occurred in Portland, Oregon. Patients receiving amiodarone often carry risk factors for developing nonarteritic ischemic optic neuropathy (NAION) which has signs and symptoms very similar to that of amiodarone neuropathy. Until 1997, optic neuropathy was not listed as a possible side effect of amiodarone in the United State=s package insert. It was, however, listed in Canada, which was, in part, the basis of the lawsuit in Oregon. There are at least 6 other lawsuits in progress, in the last year, that we are aware of.

Known Ocular Side Effects
Corneal deposits (100%) - may interfere with vision, especially with night driving
Color vision defects
Photosensitizing drug - eyelids and conjunctiva (yellow-brown, gray-blue) discoloration
Cataracts - anterior subcapsular, seldom interfere with vision

Guidelines for Following Patients :

1. Baseline ophthalmic exam
2. See every 6 months (controversial)
3. Any visual disturbance, patient to see ophthalmologist promptly.

Since it may be impossible to distinguish nonarteritic anterior ischemic optic neuropathy (NAION) from amiodarone neuropathy in many cases, the following table may be helpful. Many of these patients may already have a compromised optic nerve due to vascular disease, and the amiodarone deposition in the axons further impedes neural function, causing vision loss.

	AMIODARONE-INDUCED OPTIC NEUROPATHY	NONARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY
Onset of Visual Loss	Insidious (Months)	Rapid (Days to Weeks)
Degree of Visual Loss	20/20-20/200	20/20-NLP
Resolution of Disc Edema	Months	Weeks
Ocular Involvement	sually Simultaneous within weeks	Rarely Simultaneous

Cause of amiodarone neuropathy unknown, but may be due to selective accumulation of intracytoplasmic or its by-product inclusions (primary lipidosis)in optic nerve axons which may mechanically or biochemically decrease axoplasmic flow.

Resultant optic nerve head edema may persist as long as transport is inhibited, i.e., as long as several months following discontinuation of amiodarone which has up to a 100 day half-life, while with NAION, edema resolves much more rapidly.

No reported cases of amiodarone neuropathy causing NLP.

Degree of amiodarone neuropathy may not be equal in each eye for a few months, but usually will be if the drug is continued.

Stopping the drug, in consultation with the cardiologist, at the first signs of optic nerve involvement must be considered unless very confident of the diagnosis of NAION.

TAMOXIFEN (Nolvadex)

Primary Use

For metastatic breast cancer, pancreatic cancer and malignant melanoma. Being used worldwide for long-term therapy as a prophylaxis in patients with strong family history of breast cancer. Expect to see more patients on long-term tamoxifen for follow-up ocular examinations.

Clinical Concern

Minimal data on long-term exposure (4-5+ years) with a drug with documented significant ocular side effects, so this data is preliminary. However, unpublished data from great Britain

suggests that this drug is safe at low dosages over a 5 year period. However a series from Beirut, Lebanon, (Seoud, et al.) disagrees with this and feels mandatory annual ocular examinations are essential.

Known Side Effects
Posterior subcapsular cataracts
Decreased color perception
Decreased vision
Retina or macula - refractile bodies, edema, degeneration, pigmentary changes and hemorrhages
Visual fields - constriction, scotomas
Papilledema
Optic neuritis
Corneal deposits
ERG changes

Guidelines for following patients: (modified after Gorin)

1. Baseline ophthalmic examination within the first year of starting tamoxifen. This should include slit lamp biomicroscopy of the anterior and posterior segments in combination with an indirect ophthalmoscope or contact lens. Baseline color vision testing is important.
2. In keeping with the American Academy of Ophthalmology=s current recommendations, in normal adults, do a complete eye examination at least every 2 years. Any persistent ocular symptoms in a patient taking this drug, regardless of the dosage, require an ophthalmic examination.
3. More frequent examinations if ocular symptoms occur.
4. The discovery of a limited number of intraretinal crystals in the absence of macular edema or visual impairment does not seem to warrant discontinuation of the drug.
5. Consultation with the oncologist is essential if significant ocular findings occur.
6. Presence of age-related maculopathy is not a contraindication to the use of tamoxifen. However, informed consent may be advisable in our litigious society.
7. Presence of posterior subcapsular cataracts is not an indication to stop the drug since the condition usually progresses even if the drug is discontinued.
8. Significant color loss may be a valid reason to consider discontinuing the drug. Gorin recommends considering stopping the drug for 3 months (in patients on prophylactic therapy), and retest. If the color vision returns to normal, restart the drug and retest in 3 months. If, at anytime, there is no recovery after stopping the drug, or continued progression, then one may need to consult the oncologist and re-evaluate the risk/benefit.

Comments
Incidence of ocular toxicity reported in the literature to be from 1.5 to12%, however incidence requiring stopping the drug due to an ocular complication is less than 1%.

Indications for stopping the drug require consultation with the oncologist since many variables. Decreasing the dosage may be an option if frequent ophthalmic observations are performed. Indications to stop the drug include:
- macular edema

- decreased vision (with or without refractile bodies or pigmentary change)
- optic neuritis
- decreased color vision

Retinal crystals, per se, not an indication to stop the drug.

Retinal changes can occur even at 20 mg dosage levels.

Optic neuritis has been reported at total dosage of only 2-3 grams.

ISOTRETINOIN (Accutane)

Primary Use: Cystic acne, psoriasis and various skin disorders.

Clinical Importance
The drug competes with binding sites with retinoic acid and retinol in the retina. Isotretinoin can cause decreased dark adaptation. However, only recent data suggests the probability of rare cases of permanent night blindness. Therefore, the PDR in the year 2001 will list a warning about this in the package insert.
This drug can cause meibomitis, blepharitis, atrophy of the meibomian gland (in animals - complete destruction), often with increased staphylococcus disease. Any or all of these may decrease tear film break-up time and increase tear osmolality. Therefore, isotretinoin probably can cause a permanent Aevaporative@ form of sicca.

Isotretinoin is secreted in the tears, causing an irritative conjunctivitis, superficial punctate keratitis, drug deposits in the superficial cornea, and decreased tolerance for contact lens wear.

Some sicca patients are made worse, or latent sicca becomes manifest.

This photosensitizer can cause or significantly aggravate existing lid disease, especially blepharitis.

Other known side effects include: acute myopia, papilledema secondary to pseudotumor cerebri and optic neuritis.

American Journal of Ophthalmology (Fraunfelder, et al) - Isotretinoin can also cause reversible color vision defects.

Guidelines for following patients:
Specific guidelines are difficult since patients are on various dosages and treatment schedules.
These recommendations are only intended to be a guide. A baseline ocular examination is seldom indicated except to find ocular pathology so that the drug may not be unjustly implicated.

If a patient is sent to you prior to starting this drug:
Question or test as to decreased dark adaptation, color vision, and ocular sicca.

Consider discontinuing or delaying the fitting of contact lenses.

Suggest they see you as soon as possible if any significant ocular signs or symptoms occur, especially decreased vision, headaches, or transient visual obscurations.

Explain risk/benefit ratios to patients with:

a Retinitis pigmentosa;
b. Severe or chronic blepharoconjunctivitis;
c. Significant tear film abnormalities;
d. Pre-existing night blindness.

$ In patients with significant anterior segment disease, consider ultraviolet (UV) blocking lenses, since this drug is a photosensitizing agent.

If a patient is already on isotretinoin:
Question as to the onset of decreased vision, night blindness, keratitis sicca, decreased color vision, headaches or transient visual obscurations. If progressive or persistent, consider discontinuing the drug. Since most cases are transitory, these are not necessarily an indication for discontinuing the drug. However, if they persist, closer monitoring and further testing are recommended. Counsel patient on the benefits and risks of continuing isotretinoin therapy.

Consider testing for ocular sicca, color vision.

View the optic nerve for signs of edema.

Discontinue the drug if any of the following occurs and obtain informed consent if restarted:

a. Pseudotumor cerebri
b. Optic neuritis
c Night blindness
d Decreased color vision
e. Significant ocular sicca

$ If patients are on multiple cycles of this drug, we recommend at the minimum an annual ocular examination with emphasis on dark adaptation, color vision, ocular sicca and viewing the optic disc for any signs of papilledema.

Note: Permanent night blindness, permanent sicca, and transitory loss of color vision only occur in patients on long-term, chronic therapy, and are indeed rare events (Fraunfelder, et al.)

SILDENAFIL(Viagra7)

Primary Use: For management of erectile dysfunction.

Clinical Importance - minimal
Ocular side effects are uncommon, dosage dependent and thus far all have been fully reversible.

Reported Side Effects:

Changes in color perception
Objects have colored tinges - usually blue or blue/green, maybe pink or yellow
Diminished color vision (Farnsworth-Munsell 100 Hue Test)
Dark colors appear darker

Blurred vision
Central haze
Transitory decreased vision
Changes in light perception
Increased perception of brightness
Flashing lights - especially when blinking

ERG changes
At 4 times recommended dose (200mg), minimal changes in b2 wave amplitude, both in phototopic and scotopic conditions. Less than 10% decrease in photopic implicit times in a- and b-wave. No lasting changes found.

Conjunctiva
Hyperemia
Subconjunctival hemorrhages - not proven drug related
Ocular pain
Photophobia.

Mydriasis - Probably not drug related

The above ocular side effects are dose dependent and occur at the following incidence:

50mg	3%
100mg	10%
200mg	40-50%

Incidence - Same all ages

Ocular side effects directly proportional to blood drug levels.
The side effects based on dosage start at 15-30 minutes, and usually peak 1 hour after ingestion of drug.

50 mg	gone 1 hour
100 mg	gone 2 hours
200 mg	gone 4-6 hours

Drug half-life is 4 hours

Ischemic Optic Neuropathy - Retinal Vascular Occlusion
Less than 10 cases of AION and __ cases of retinal vascular occlusions have been reported, and its difficult to tell if it is drug induced.

Contraindicated or use extreme caution in patients with:
Retinitis pigmentosa
Congenital stationary night blindness
Deficiency or mutation of photoreceptor cGMP PDF

Informed consent advised; no data to prove it is harmful, but it theoretically could be.

Ocular Interest:

The reason for ocular interest is that the action of sildenafil citrate as a selective inhibitor for PDE-5, probably also affects PDE-6, which is found in the retina. It is believed that PDE-6 is involved in light excitation of visual cells to generate an electrical impulse. Sildenafil action on PDE-5 is 10 times stronger than on PDE-6. The transitory retinal effects are probably due to the drug=s effect on PDE-6 by interference of chemical regulators of cyclic GMP in the photo transduction pathway.

I would not be surprised to see an increased incidence of vascular ocular bleeds, i.e., subconjunctival or retinal hemorrhages secondary to sudden rises of blood pressure in the elderly. This is probably not a direct drug effect, rather secondary to increased blood pressure and heart rate secondary to sexual arousal.

CARBONIC ANHYDRASE INHIBITORS (CAI) (acetazolamide -Diamox7; dichlorphenamide - Daranide7; methazolamide - Glauctabs7, Neptazane7)

Oral CAI

Oral sales are still significant, in part due to increased short-term use in cataract surgery, prevention of air hunger in mountain climbers, in selected cases of macular edema and refractory glaucoma.

CAI may significantly increase respiratory distress of chronic lung disease patients.
Causes osteomalacia in patients on anti-convulsive medication.

Patients on high doses of aspirin plus CAI can cause aspirin-induced CNS toxicity.
Can cause metabolic acidosis and coma especially in patients with renal insufficiency or

diabetics with nephropathy.

Patients with cirrhosis can get ammonia poisoning.

Can cause hypo-potassium symptoms, especially in patients already on potassium depletion agents.

Stevens- Johnson syndrome - Japanese appear to be more susceptible.

Concomitant use of CAI may increase five-fold trough blood levels of cyclosporine with pronounced nephro and neurotoxicity.

(Editorial - American Journal of Ophthalmology (Fraunfelder and Bagby) - modified partial report here)

Nature of Aplastic Anemia Associated with CAI

The causes of aplastic anemia and other dyscrasias associated with CAI are unknown. Direct stem cell toxicity is possible, especially in the appropriate genetic context. Stem cells can be constitutively sensitive to chemical and biological agents in certain rare hereditary syndromes such as Fanconi anemia or alternatively may be sensitive to specific drugs and metabolites because of inherited defects in drug metabolism. No clear evidence of the latter has been developed to date. It is more likely that one of the major factors in drug induced bone marrow injury is T-cell mediated progenitor cell cytotoxicity. It has been recognized for quite some time that bone marrow T-lymphocytes are capable of markedly suppressing proliferation of one or more blood cell lineage. The CAI are one of the few sulfa derivatives that are used for long periods of time and may be, for that reason, more apt to be immunogenic. Of interest is the report of methazolamide-associated aplastic anemia associated with platelet antibodies. Indeed, more cases have been reported to the National Registry of Drug-Induced Ocular Side Effects (National Registry) during the past 10 years of methazolamide-associated hematopoietic toxicity than with any other CAI. We recognize, however, that this may be due to increased use or a bias of ascertainment (e.g. ophthalmologists are more likely to report such adverse responses with a relatively newer drug).

Incidence of Aplastic Anemia

A Swedish national commission consisting of multiple different clinical specialists reviewed complete medical records of aplastic anemia associated with acetazolamide usage from 1972 to 1988. This study excluded over half of the cases because of incomplete data and because some patients had been taking other drugs known to cause blood dyscrasias. The study had known numerators and denominators. The findings of this group demonstrated a 10-25 fold increased rate of aplastic anemia in CAI treated patients. The commission concluded that AThe estimated risk provides strong evidence that acetazolamide treatment is associated with a substantial increase in the risk of developing aplastic anemia.@

In addition to aplastic anemia, CAI are implicated in other blood dyscrasias, most of which are reversible if the drug is discontinued. In fact, the percentage rate of aplastic

anemia compared to the total number of reported blood dyscrasias in the Swedish study was 42%, the World Health Organization (WHO) data 66%, and the National Registry was 52%.
To date, the National Registry is not aware of any blood dyscrasias associated with topical ocular CAI.

Onset of Aplastic Anemia

Most cases of aplastic anemia associated with CAI usage occur within the first six months peaking between two and three months. Other, non-aplastic blood dyscrasias are more variable taking weeks to many years to occur.

Treatment of Aplastic Anemia

Recent reviews of prognostic features in bone marrow transplant centers indicate clearly that earlier treatment of aplastic anemia patients is associated with a long-term outcome advantage, and blood abnormalities occur before the onset of symptoms.

Recommendations (Aalternative view@)

We believe that for patients taking longer-term oral CAI therapy, a standard CBC consisting of white blood count with differential, hemoglobin, hematocrit and platelet count should be repeated every one to two months during the first six-month period and then at six-month intervals. In addition, we believe that the patient should be instructed to contact their physician immediately if any of the following develop: persistent sore throat, fever, easy bruising, nose bleeds, fatigue, jaundice, or petechiae. Also, the drug should be discontinued and hematology consultation obtained for patients who exhibit a decline in the level of any formed blood elements during treatment. The National Registry has not received a report of blood dyscrasias with oral CAI of less than two weeks. We consider short-term CAI therapy under two weeks to be safe and should not require any screening.

In summary, although no prospective studies have been done and while no recommendations can be reasonably evidenced-based, we believe that our Aalternative views@ are reasonable, taking into account the serious nature of aplastic anemia and its more favorable prognosis when this disorder is treated early. Since aplastic anemia represents only about one-half of possible CAI blood dyscrasias, early recognition of non-aplastic anemia dyscrasias alone justifies hematologic screening.

DORZOLAMIDE (Trusopt, Topical CAI)

Primary Use

In the treatment of glaucoma it is applied as a topical ocular medication.

Reported Side Effects:

Systemic Effects

Bitter metallic-like taste (up to 1/3 of patients may increase salivation, and/or tongue and perioral numbness and edema.

Various gastrointestinal complaints such as nausea, abdominal cramping, heart burn, and upset stomach. This occurs in up to 10% of patients**.**
CNS effect rare - headaches, fatigue, insomnia, depression.

Note: The area of greatest concern is that this is a sulfonamide derivative and in skin conditioning has been shown to cross react with other sulfonamides. The first report of dorzolamide induced immune thrombocytopenia has been reported by Martin and Danese.

Recommendations for following patients:

No need to follow for blood dyscrasias with periodic blood work.

We do not feel that informed consent is necessary for systemic side effects since, to date, all are rare or reversible.

If bitter taste is a major problem, consider punctal occlusion -- but doesn=t always help.

Contraindicated to use oral and systemic CAI concomitantly.

Warn cross-reaction with other sulfonamides.

Use with caution in patients with severe kidney or liver disease.

Use with caution in patients with sulfonamide sensitivity or with a family history of blood dyscrasias.

NATIONAL REGISTRY OF DRUG-INDUCED OCULAR SIDE EFFECTS

The objectives of the Registry are:
To establish a national center where possible drug-induced ocular side effects can be accumulated.

To add to this data base the spontaneous reporting data of possible drug-induced ocular side effects collected from the Food and Drug Administration (FDA) (Rockville, MD) and the World Health Organization (WHO) (Uppsala, Sweden).

To compile the data in the world literature on reports of possible drug-induced ocular side effects in humans.

To publish some of this data every 4 to 5 years in book form.

To make available this data to physicians who feel they have a possible drug-induced ocular side effect.

You can contact us to help you with a suspected drug reaction, have access to data in the Registry or to report a case. When sending data, it would be ideal to include: name of drug, dosage, length of time on drug, suspected reaction, what happened if the drug was stopped, if rechallenged, concomitant drugs, name and address of person reporting case optional, but encouraged.

Reports can be mailed to: National Registry of Drug-Induced Ocular Side Effects
Casey Eye Institute
3375 SW Terwilliger Blvd.
Portland, OR 97201-4197

or faxed: (503) 494-4286
or website www.eyedrugregistry.com

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Bisphosphonates

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