Posterior Segment Side Effects of Commonly used Systemic Drugs

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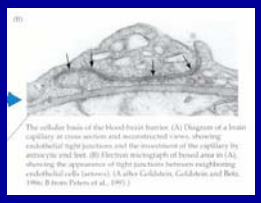
Introduction

- Many commonly used systemic medications may adversely affect visual function
- Some may be fleeting visual defects
- Others may be permanent

Introduction

- Will assume knowledge of the blood-brain barrier?



Blood-Brain Barrier

- The blood-retinal barrier prevents many systemically administered drugs from entering the eye via the circulatory system.
- Many medications that are administered systemically for non-ocular conditions may still gain access to the eye and evoke ocular toxicological complications
- The mechanisms by which these toxins exert their harmful effects on the eye are varied and in most cases remain poorly understood

So what happens?

- In man ocular toxicity associated with systemic drug therapy can result in retinal or optic nerve degeneration
- Most frequently comprises visual disturbances including:
- decreased visual acuity,
- impaired color perception,
- visual field defects,
- scotomata,
- night blindness,
- visual perseveration beyond the physiological afterimage (palinopsia),
- and illlusory movement of the physical environment (oscillopsia)

Introduction

- Drugs may affect all segments of the eye
- Today we will concentrate solely on the posterior segment!

Introduction

- You will almost certainly be aware of the commonly known side effects of such drugs as:

- Chloroquine
- Hydroxychloroquine
- Amiodarone

Introduction

- However - there are >30 classes of drugs with possible posterior segment side effects which can affect vision

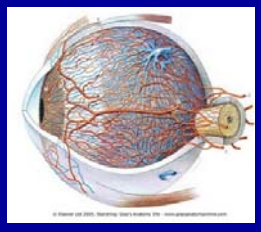
- Today we will concentrate on the most common prescription medications and a few other drugs!

How do drugs get to the eye?

- Oral/intravenous/pr routes

- Drug enters systemic circulation

- Reaches ocular tissues through both the Uveal & Retinal circulations

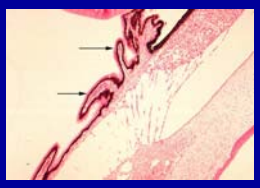


How do drugs get to the eye?

- Choroid/CB/Sclera:
- Have fenestrated walls for drug molecules to pass

- Small lipid soluble molecules pass freely into the aqueous

- May diffuse into avascular structures e.g. lens, cornea, trabecular meshwork



How do drugs get to the eye?

- Thus:
- The ability of a drug to penetrate the major barriers determines it's likelihood to affect ocular tissue and visual function

Antiarrhythmics: The Cardiac Glycosides

- E.g. Digoxin, Amiodarone
- 11-25% patients experience ocular symptoms
- Most common are changes in colour vision
- "Flickering" vision
- Initially toxicity was thought to cause retro-bulbar neuritis

Antiarrhythmics: Digoxin

- Latterly high concentrations found in retina & choroid
- The retina is now thought to be the main site of toxicity
- In particular cone dysfunction is caused by the inhibition of the enzyme Na+/K+ activated ATPase.
- Plays vital role in cone-receptor function

Antiarrhythmics: Amiodarone

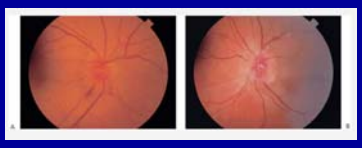
- Studies have found amiodarone in all ocular tissues
- Tendencey towards lipid storage in the cornea and lens
- Commonly causes “whorl-like” deposits on cornea
- Coloured rings around lights in 1.4%-40%

Antiarrhythmics: Amiodarone

- Dose-dependent relationship
- Reported cases of optic atrophy and pseudo-tumour cerebri : 1.3% in 8 yrs
- Usually reversible with D/C of amiodarone
- Causal relationship not well established but consider DC if not life threatening!

Amiodarone Optic Neuropathy

- Bilateral ON oedema
- RNFL haemorrhage R>L



Amiodarone Optic Neuropathy

- Amiodarone has been documented to produce disc edema in a small percentage of patients.
- It has been documented to occur with treatment from 1 to 72 months
- dosage varied from 200 to 1200 mg/day
- Presentation:
- insidious unilateral or bilateral decreased vision
- gradual progression
- associated with optic nerve edema

Amiodarone Optic Neuropathy

- The visual acuity and field loss tend to stabilize or improve following discontinuation
- The major differences between nonarteritic AION and amiodarone optic neuropathy are that the visual loss is bilateral and insidious
- the optic disc swelling persists longer with amiodarone toxicity - takes months rather than weeks to resolve.
- The mechanism of amiodarone optic neuropathy is unknown, but histology has shown primary lipidosis of the optic nerve

CNS Drugs

- Antipsychotics *
- Anti-epileptics *
- Anti-parkinsonian drugs
- General anaesthetics
- Anti-emetics
- Central analgesics

CNS Drugs: Antipsychotics

- Phenothiazines cause most ocular side effects
- Most common is Thioridazine
- Not widely prescribed but many older patients still on this drug
- Used since 1950's - initially at very high doses - several grams per day

CNS Drugs: Antipsychotics

- After 2 weeks of therapy the following have been reported
- Blurring
- Nyctalopia
- Brownish discolouration
- Much lower doses used nowadays!

CNS Drugs: Antipsychotics

- Characteristic changes were noticed:
- Pigment granularity posteriorly
- Increasing coarseness over time
- Later stage showed GA and loss of chorio-capillaris over time
- Often recovered if withdrawn early

Advanced GA in Thioridazine Retinopathy

CNS Drugs: Antipsychotics Chlorpromazine

- Used for schizophrenia
- Usual dose 75-00mg daily
- Retinotoxicity characterized by non specific pigment granularity & pigment clumping

Typical salt & pepper maculopathy

Anti-epileptic Drugs

- Phenytoin
- Carbamazepine
- Ethosuximide
- Valproic Acid
- Levetiracetam
- Vigabatrin
- Oxcarbazepine
- Felbamate
- Lamotrigine

Anti-epileptic Drugs

- Phenytoin/Carbamazepine:
- Commonly cause colour vison defects
- Usually blue-yellow axis (FM100 Hue)
- Usually reversible on DC the drug

Anti-epileptic Drugs: Vigabatrin

- Inhibits brain GABA
- Ample evidence that it can cause retinopathy and neuropathy
- Commonly in children
- VF constriction well documented & bilateral
- 30-50% of patients - months to years after starting Rx.

Anti-epileptic Drugs: Vigabatrin

- *Arch Dis Child* 2001;**85**:469-473 doi:10.1136/adc.85.6.469
- **ArticleVigabatrin associated retinal dysfunction in children with epilepsy.**
- R Koula, A Chackoa, A Ganeshb, S Bulusuc,
- K Al Riyamid

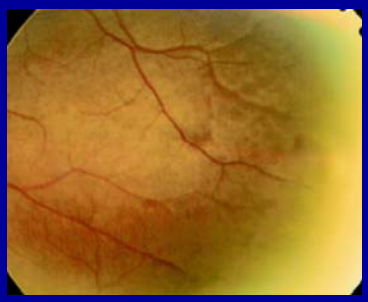
Anti-epileptic Drugs: Vigabatrin

- Of 21 children in the study - 4 developed retinopathy (19%) developed eye changes
- (retinal pigmentation, hypopigmented retinal spots, vascular sheathing, and optic atrophy).
- Visual evoked potentials were abnormal in 16 children

Anti-epileptic Drugs: Vigabatrin

- Vigabatrin causes eye damage!
- Most children with epileptic syndromes on vigabatrin cannot complain of their eye problems: 3-6 monthly ophthalmic follow up is strongly advised
- regular electroretinography,
- electro-oculography, and
- visual evoked potentials if possible

Vigabatrin Retinopathy



Anti-Cancer Drugs

- All known to cause toxic ocular side effects
- Traditional chemotherapy
- Often multiple agents
- Tamoxifen
- Interferons

Systemic chemotherapy

- Cisplatin & Etoposide
- Many cause bilateral irreversible visual loss
- VF often show bilateral central scotomata
- VEP's & ERG's used to document retinotoxicity

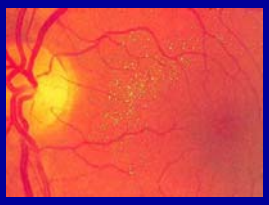
Cisplatin & Etoposide

- ERG shows:
- decreased a wave amplitude
- Absent b waves
- Autopsy shows splitting of the plexiform layer
- Retinal ischaemia has also been reported

Tamoxifen Retinopathy

- is an anti-estrogen used to treat breast carcinoma
- It has few systemic side-effects at a traditional normal dose of 20 to 40mg/day.
- Current dosages prescribed today may be even less, reducing the prevalence of side-effects.
- Vortex keratopathy and optic neuritis can rarely occur, which usually is reversible on cessation of therapy.
- Retinotoxicity presents as multiple superficial yellow crystalline ring-like deposits at the macula, that can cause visual acuity loss

Tamoxifen Retinopathy



Tamoxifen Retinopathy

Interferon Retinopathy

- Characterised by -
- retinal haemorrhages
- Cotton wool spots in posterior pole
- Visual function usually maintained
- Usually reversibe upon DC therapy
- All cancer patients on IFN need baseline + 3/12 follow up in eye dept.
- About 4% of patients

Interferon Retinopathy

Erectile Dysfunction Drugs

- All cyclicGMP phosphodiesterase inhibitors
- Viagra
- Levitra
- Cialis
- Many visual side effects
- 11% of users report visual problems!

Erectile Dysfunction Drugs

- Well tolerated treatment for ED
- Enhance the effect of NO by inhibition of PDE-5 which is responsible for degrading cAMP in corpus cavernosum
- Inc NO and Inc cAMP causes sm muscle relaxation - and thus ingress of blood!

Erectile Dysfunction Drugs

- These drugs show high affinity for PDE-5 however there is some affinity for PDE-6 found in the retina.
- Inhibition of PDE-6 may provide the basis for ocular side effects

Erectile Dysfunction Drugs: Symptoms

- Mild/transient dose related impairment of colour vision
- Peaks at peak plasma concentration
- Other ADR's: NAION & RVO
- Use with caution in RP

Erectile Dysfunction Drugs

- NAION & PDE-5 drugs controversial
- ? Exacerbate nocturnal hypotension
- Most important feature in development of NAION
- May be exacerbated in over-treatment of NAION

Erectile Dysfunction Drugs

- Risk Factors for NAION
- > 50 y old
- CV disease
- Increased lipids
- Diabetes
- Small CDR
- Sleep apnoea

Erectile Dysfunction Drugs

- No compelling evidence to discourage use but use with care in high risk patients!
- Use with caution in RP - some forms of which have genetic disorder of PDE's
- Patients often do not volunteer use of PDE-5 drugs - ask!

Erectile Dysfunction Drugs: Most Common Side Effects

- Most common: cyanopsia
- Others:
- NAION
- Macular oedema
- Increased light sensitivity
- Recent small study gave daily 100mg doses for 6 months. No change in VF, ERG or VEP!
- Very reassuring!

Anti-TB agents

- Ethambutol**
- Rifampicin
- Isoniazid
- Pyrazinamide
- Streptomycin

Anti-TB agents: Ethambutol

- **Ethambutol** Optic neuritis is the most important potential side-effect of ethambutol HCL.
- It is rare in patients prescribed standard doses.
- Retrobulbar neuritis is the most common with involvement of either:
- axial fibres
- less commonly periaxial fibres.

- The exact mechanism of this ocular neurotoxic effect has not been identified.
- Animal studies have demonstrated ethambutol toxicity in the retinal ganglion neurons of rodents.
- One of the principal theories for its toxicity has been the zinc-chelating effect of ethambutol and its metabolite

Anti-TB agents: Ethambutol

- **Clinical presentation**
- The onset of ocular symptoms is usually delayed and may occur months following commencement of therapy.
- Days to months
- ethambutol-related retrobulbar neuritis varies between:
- 18% in patients receiving more than 35 mg/kg per day,
- 5% to 6% with 25 mg/kg per day, and less than
- 1% with 15 mg/kg per day of ethambutol HCL for more than 2 months
- No safe dose of ethambutol has been reported

Isoniazid & Rifampicin

- Can also cause optic neuropathy
- Few cases reported than for Ethambutol
- Patients often on Multi Drug Treatment
- Often difficult to work out causative agent!

Anti-TB agents: Ethambutol

- Toxicity observed at doses as low as 12.3 mg/kg per day
- Patients may complain of bilateral progressive painless blurring of vision
- decreased colour perception.
- Central vision is most commonly affected,
- other visual field loss has also been described
- Visual acuity drop varies greatly from nil or minimal reduction to no light perception.
- Central scotoma is the most common visual field defect
- Bi-temporal defects or peripheral field constriction have been reported
- largely reversible on drug withdrawal although this has been recently challenged

Aminoquinolones

Anti-malarials

Also used for connective tissue diseases e.g.

Rheumatoid arthritis

Systemic lupus erythematosus

Cutaneous lupus

Aminoquinolones

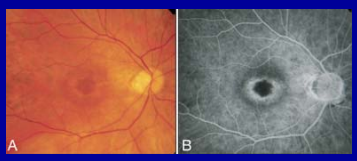
- Initially used for malaria
- Latterly for connective tissue diseases
- Chloroquine now rarely used
- Hydroxyxhloroquine most common
- High affinity for pigmented structures in the eye e.g. Ganglion cells, RPE

Aminoquinolones

- Clinical Picture:
- Fundus may be entirely normal
- Scotomas present
- Blunting of foveal reflex
- Later - central irregular pigmentation surrounded by concentric zone of depigmentation: classic Bull's Eye Maculopathy!

Aminoquinolones

- Classic
- Bulls Eye Maculopathy
- Most reports of toxicity with Chloroquine



Hydroxychloroquine

- RCOphth Guidelines
- Baseline Exam
- VA
- VF
- Amsler
- HVF 10-2
- Ishihara

Quinine

- Quinine is an antimalarial associated with a distinct toxicity from that of chloroquine and hydroxychloroquine: 8g can be fatal!
- Symptoms: headache, nausea, vomiting, tremor, hypotension, and loss of consciousness and is associated with profound vision loss, which may be irreversible.
- There is mild retinal edema and venous dilation in the acute phase.
- Over several weeks, arteriolar attenuation and optic atrophy develop.
- Hemodialysis may be beneficial in the treatment of an overdose. Visual outcomes, however, are extremely variable.
- Even with recovery of central visual acuity, peripheral fields may remain constricted

Quinine OD

- Acute presentation: NPL either eye
- Pupils: dilated/Unresponsive
- Ophthalmoscopy: Normal to gross disc pallor
- Aetiology: toxic to photoreceptors and ganglion cells

Diabetic Drugs

- Rosiglitazone
- thiazolidinediones (glitazones)
- Currently controversial - ? Soon to be withdrawn
- Associated with CSMO - appears to be only Glitazone with this S/E
- Ask ALL diabetics what Rx they are on

Oral Contraceptives

- Optic neuritis
- IIH
- Increased platelet aggregation - retinal thrombosis
- Relative risk 2.0 to 2.4

Intravenous drug use

- Talc retinopathy
- Common in IVDU
- Crush tablets - commonly Ritalin/Cocaine other narcotics
- Mix with water - then inject!

Talc Retinopathy

- Talc particles enter the circulation and embolize in various tissues.
- Most parts of bloodstream including the retina will be infused with the talc deposits over a long period of time of injections
- Talc maculopathy appears as multiple tiny, yellow-white, glistening particles scattered throughout posterior poles of both eyes

Talc Retinopathy

- The talc is more numerous in the capillary bed and small arterioles of peri-macular area.
- Some patients can get macular edema, venous engorgement, punctate and flame hemorrhages, and arterial occlusion associated with the talc emboli.
- Talc retinal granulomas and neovascularization can also rarely occur.

Talc Retinopathy

Oral Retinoids

- Isotretinoin (13-cis retinoic acid) (Roaccutane)
- Cystic acne drug
- Most common eye s/e is ocular surface disease
- Some evidence of retinotoxicity causing nyctalopia and reversible reduction of colour vision

Oral Retinoids

- **Signs**: impairment o dark adaptation
- May be associated with abnormal ERG
- Usually resolves within months
- Aetiology: ? Incorporation into rod photoreceptor element during turnover processes of outer disc segment shedding & renewal

Oral Retinoids

- Management: careful monitoring for changes in night vision
- If found: VF, ERG, Dark Adaptation
- If abnormal drug should be withdrawn
- Also watch for dry eye & BIH!

Herbal Medication & OTC's

- Don't forget OTC's, Vitamin Supplements, Herbal Remedies!
- Many reported side effects from the above - most common

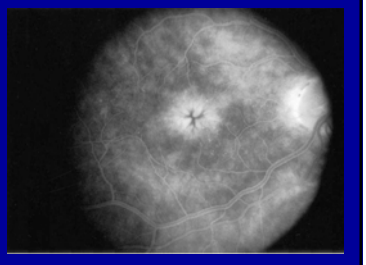
Herbal Medication

TABLE 3. World Health Organization (WHO) Classification of Ocular Side Effects Associated With Herbal Medicines and Nutritional Supplements

Drug	Ocular Reaction	WHO Classification
Canthaxanthine	Crystalline retinopathy	Certain
Chamomile	Conjunctivitis	Probable (when applied topically)
Datura	Mydriasis	Certain
Echinacea	Conjunctivitis	Possible
Ginkgo biloba	Retinal hemorrhage	Probable
	Hyphema	Possible
	Retrobulbar hemorrhage	Possible
Licorice	Abnormal vision	Possible (in large doses)
Niacin	Cystoid macular edema	Certain
	Blurred vision	Probable
Vitamin A	Intracranial hypertension	Certain (in large doses)

Herbal Medication & OTC

- Niacin CMO in a patient taking 3g/day



Tobacco/Alcohol Amblyopia

- Heavy ETOH & nicotine use
- Leads to slow-progressive bilateral VF loss
- Now thought to be due to cyanide from tobacco
- ETOH directly toxic to ON
- ? Nutritional deficiencies in alcoholics

Tobacco/Alcohol Amblyopia

- Differential: very similar to LHON and Nutritional Optic Neuropathies
- Probably ETOH/Nicotine & Nutrition all linked

Tobacco/Alcohol Amblyopia

- Tobacco-alcohol amblyopia or toxic-nutritional optic neuropathy is a condition characterised by:

- papillomacular bundle damage,
- central or caecocentral scotoma
- reduction of colour vision

Tobacco/Alcohol Amblyopia

- There is consensus that nutritional deficiency has an important role as well (B12/Folate etc)
- The appearance of the optic nerve is usually normal, but peripapillary dilated vessels and haemorrhages have been described
- Testing with static perimetry often reveals central scotomas.
- Although this syndrome has been classified as optic neuropathy, the primary lesion has not actually been localised to the optic nerve
- may possibly originate in the retina, chiasm, or even the optic tracts

Tobacco/Alcohol Amblyopia

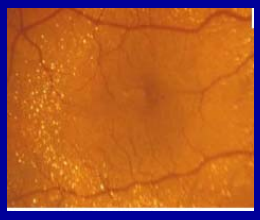
- Management:
- Avoid ETOH/Nicotine
- Check FBC, B12, Folates, red Cell indices - add Rx prn
- Correct underlying nutritional deficits
- Monitor VA, VF, Ishihara

Canthaxanthine

- Carotenoid: used as skin bronzer
- Dose related >60g total dose most patients have retinopathy
- Fundus appearance is dramatic, bilateral & distinctive

Canthaxanthin

- This appears as tiny glistening yellow dots arranged in a donut-shaped ring around both maculae.
- These deposits appear in the superficial retina (ganglion cell layer), and generally benign



NSAIDS

- Commonly used for analgesic
- Anti-pyretic
- Anti-inflammatory properties

NSAIDs

- Retinal & Optic Nerve toxicity is rare
- Most reported cases are associated with Indomethacin
- Lesions commonly show discreet pigment scattering of the RPE peri-foveally

NSAIDs

- ERG can be abnormal relative to amount of pigmentary change
- No clear dose response relationship
- When discontinued most function defects improve
- Pigmentary changes are usually irreversible

NSAIDs

- Recovery:
- May take 6-12 months post D/C Rx to see improvement in:
- VF
- Colour vision
- Dark adaptation
- VA

NSAIDs

- Pathology:
- Unsure
- Toxic effects localised to RPE
- Supported by changes in EOG & ERG in patients with Indomethacin retinopathy

Summary

Drug	Optic Nerve Change
Ethambutol	Optic neuritis
Isoniazid	Optic neuritis
Rifampin	Optic neuritis
Lithium	Papilledema
Oral contraceptives	Papilledema
Ethanol	Toxic neuropathy
Amiodarone	Papilledema
Estrogen therapy	Papilledema

Summary

TABLE 4.8 Drugs That Alter Color Perception

Drug	Color Anomaly
Digitalis glycosides	Xanthopsia
Amiodarone	Colored halos
Ethambutol	Red-green defect
Isoniazid	Red-green defect
Indomethacin	Tritan defect
Chloroquine	Tritan defect
Thioridazine	Tritan defect
LSD/mescaline/psilocybin	Variable

Summary

TABLE 4.9 Drugs That Induce Retinal Changes

Drug	Retinal Change
Phenothiazines	Pigmentary retinopathy
Chloroquine/hydroxychloroquine	Bull's-eye maculopathy
Indomethacin	Pigmentary retinopathy
Quinine	Vessel attenuation
Oral retinoids	Decreased retinal function
Antineoplastics	Whitish exudates in posterior pole
Talc	Refractile bodies in posterior pole
NSAID's	Retinal hemorrhages
Oral contraceptives	Retinal signs of vascular occlusive disease

Summary

TABLE 4.10 Differential Diagnosis of Chloroquine or Hydroxychloroquine Retinopathy

Age-related maculopathy
Best's vitelliform disease
Serous detachment of the macula
Lamellar hole of the macula
Stargardt's disease
Kuhnt-Junius macular disease
Retinitis pigmentosa
Rubella retinopathy

Remember

- Always take a drug history
- Always ask about recent changes in Rx
- What was the patient on when the symptoms started?
- Changes in dose?
- Always think about toxicity in all patients with Ca and multi-system diseases

If you have been….
Thanks for listening!