OCULAR ADVERSE EFFECTS OF SYSTEMIC DRUGS

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- Drugs acting on the nervous system
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- Drugs acting on endocrine system
- Drugs used to treat breast cancer

SYSTEMIC DRUGS

- Systemically administered drugs can reach the eye through the general systemic circulation.
    - Vice versa is also possible – ocular drugs can reach systemic circulation
- Patients must be questioned about all drugs (including those OTC medications).
- Consider – Drug, dosage and duration
    - Dose - some drugs have more than one indication and the dosage for these varies greatly
    - E.g. hydroxychlorine can be used to treat malaria and rheumatoid arthritis in different doses
    - Duration: px's can become tolerant to side effects of drugs especially if mild
    - Some side effects (SE) are cumulative and only appear after years of treatment

PATIENT VARIABILITY

- Age
    - Children's metabolism is different; e.g.aspirin is contraindicated in children as it causes Reye's syndrome, which is a disease that affects all organs of the body, but most lethally the liver and the brain. It is safe for children over the age of 12. Older people metabolize more slowly.
- Sex
    - Sex hormones affect men and women differently
- Weight
    - The fat water ratio also affects the metabolism of drugs. Weight plays a role in the fat water ratio
- General health
- Ophthalmic health
- Other medication
- Contact lenses

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ADVERSE OCULAR EFFECTS

Mildly irritating to sight threatening:

- Cyclospasm
- Cycloplegia
- Corneal changes
- Media changes
- Optic neuritis
- Retinal changes
- Reduced tolerance to contact lenses
- Cataract
- Reduced accommodation
- Mydriasis
- Increased IOP
- Retinal pathologies
- Diplopia

Many ocular changes are simply described in literature as blurred vision. Majority of mydriasis-causing drugs can enter systemic circulation and cause relaxation of ciliary muscle, e.g. atropine like drugs (repeated doses of histamine blocking drugs, and certain antidepressants Monoamine Oxydase Inhibitors (MAOI) or Selective Serotonin Reuptake Inhibitors (SSRI)).

Other ocular effects of certain drugs

- Cyclospasm: strong narcotic agents like morphine can induce pseudomyopia.
- Corneal deposits can be caused by photosensitisation due to amiodarone
- Lens: steroid induced cataract
- Optic Neuropathy (ON): Quinine
- Retinal changes: Tamoxifen
- Interference with tear film: oral contraceptives
- Diplopia: drugs for certain CNS disorders

Information

- Data sheet compendium
- MIMS (MIMS.com.au)
    - Australian website that provides a source of all the available medication in Australia and list of indications, side effects, contra-indications etc
    - list a range of adverse drug reactions
- BNF (British National Formulary)
- Can also gather data from the manufacturer regarding indications, side effects, interactions
    - Now available electronically, http://www.medicines.org.uk/emc/
- Drugs database PRO

FREQUENCY OF DRUG SIDE EFFECTS

The BNF suggests five classifications:

- Very common – Greater than 1 in 10
- Common - 1 in 100 to 1 in 10
- Uncommon – 1 in 1000 to 1 in 100
- Rare – 1 in 10,000 to 1 in 1000
- Very rare – Less than 1 in 10,000

DRUGS ACTING ON ALIMENTARY TRACT

- If drugs are administered orally, alimentary tract is the first system drugs will come in contact with.
- GIT innervated by autonomic nervous system
- Dicyclomine (Merbentyl)
- Hyoscine (Buscopan)
    - A drug that also may be used for mydriasis, available in an eye drop preparation form.
- Mydriasis and cycloplegia

> Modern drugs are designed not to be digested by the gut, however, if absorption does take place an adverse drug reaction (ADR) is possible. The gut is innervated by ANS and stimulation of parasympathetic system causes increase motility and secretions. Antispasmodics have antimuscarinic actions and reduce GIT spasms.

Dyde et al (2008) discussed the precautions for using Buscopan (used to treat cramping abdominal pain). They made the following recommendations to those administering Buscopan:

- Enquire whether there is an allergic history
- Ensure patient literature warns that "in the rare event that following the examination you develop painful, blurred vision in one or both eyes, you must visit the hospital immediately for assessment"
- Warn patients to expect blurred vision and not to drive until this has worn off
- Remind clinicians that special consideration needs to be given as to the method of investigating patients with cardiac instability

DRUGS ACTING ON CARDIOVASCULAR SYSTEM

- Direct pharmacological effects on ocular tissues.
- Indirect effects on blood pressure and blood flow.
    - Cardiotonic drugs
    - Diuretics
    - Anti-arrhythmic drugs
    - Beta blockers
    - Anti-hypertensives
    - Anti-coagulants

Cardiotonic Drugs

Digoxin (Lanoxin)

- Digoxin is used for treatment of various heart conditions, atrial fibrillation atrial flutter (abnormal heart rhythm), and congestive heart failure (failure of heart to pump blood around body) that cannot be controlled by other medication.

Possible side effects

- Glare (white halo)
- Changes in ERG and VF
- IOP reduced (not enough for glaucoma treatment)

- The most common side effect, generally seen at toxic levels, is blue/ green visual disturbance: Xanthopsia. Some estimates show that it affects 80% of those treated to some degree, however this is not always noticed by the patient.
- Cone dysfunction
- Can damages neural tissue
- Glare phenomenon or the snowy appearance of objects
- Blue-yellow colour vision defect due to damage to the photoreceptors

Lanatoside C (Cedilanid)

- Toxic effects on retina
- Disturbance in colour vision
- Changes in ERG and VF
- abnormal heart rhythm

Disopyramide (Rythmodan), an anti-arrhythmic drug

- Mydriasis and cycloplegia (equal to atropine)

Diuretics

- Used for excretion of water from body
- Promotes flow of urine and reduce oedema in heart failure, hypertension and renal dysfunction.
  1. Acetazolamide (carbonic anhydrase inhibitors) (Diamox)
  2. Bendroflumethazide (Aprinox)
- Slight myopia (regresses upon withdrawal of the causative drug)
- There could be a drug-induced myopia as reported in Prescrire Int. 2003 Feb;12(63):22-3
- Drug-induced myopia
- Few ocular side effects, which regress spontaneously
- Lacrimal hyposecretion leading to reduced tolerance to contact lenses
- Reduced IOP

Antiarrhythmic Drugs

- Amiodarone (Cordarone X)
- Yellow brown corneal deposits
- Castells et al 2002 – discussstudied visual changes secondary to initiation of amiodarone
- Disopyramide (Rythmodan)
- Anticholinergic action: cycloplegia and mydriasis
- If narrow angle, at risk for glaucoma
- Corneal deposits in 90% of patients who take the drug for few weeks
- Deposits will disappear after discontinuation in majority of cases
- Few cases of blurred vision

Beta Blockers

- Used to treat angina, hypertension and cardiac arrhythmias
  1. Atenolol (Tenormin)
  2. Metoprolol (Trandate)

- Majority relatively safe – side effects are mild and transient.
- Reduce IOP
- One drug Practolol (now restricted use) has been implicated in a condition called oculo-mucotaneous syndrome which affects the mucous membranes and causes very dry eye.

Anti-hypertensives

- Variety of treatments including beta blockers.
  1. Clonidine (Catapres)
     a. retinal changes
        i. Constricts retinal vessels and may cause visual loss
     b. Reduction in IOP
     c. pupillary miosis
  2. Methyldopa (Aldomet)
     a. affects anterior eye
     b. Reduction in IOP
     c. Keratoconjunctivitis sicca (Tu and Rheinstrom 2010)
  3. Hydralazine (Apresoline)
     a. Bilateral retinal vasculitis

DRUGS ACTING ON RESPIRATORY TRACT

Usually administered locally – so side effects are limited.

- Corticosteroids
- Antihistamines
- Bronchodilators

Antihistamines

- Antimuscarinic effects – slight mydriasis and cycloplegia.
- Depressed secretion of tears (contact lens wearers): e.g. Chlorpheniramine (Piriton), Terfenadine (Triludan)
- In theory patients should be screened for risk of angle closure
  - 1 in 10,000 with cyclopentolate
  - Much lower with systemic antihistamines
- Most systemically administered drugs that cause mydriasis also have the potential to interact with cilary body and cause cycloplegia
- May need to postpone refractive error assessment until patient has finished course of medication – not very practical
- Chronic alcohol abuse: reduced accommodation

The ocular anticholinergic effect of systemic antihistamines is equivocal. Brion et al (1988) examined the anticholinergic effect of two antihistamines, terfenadine and mequitazine in eight subjects and observed no significant difference in pupil diameter measurements. A similar study that used terfenadine, astemizole and triprolidine also demonstrated no changes in pupil diameter (Nicholson et al 1982). In contrast, significantly increased mydriasis was observed when 0.3% pheniramine (antihistamine) and tetrahydrozoline (ocular

decongentant) were used in combination (Gelmi and Ceccuzzi 1994). Animal studies have also demonstrated increased anticholinergic effects including mydriasis with antihistamines (Cardelus et al 1999).

Bronchodilators

- Sympathomimetics used in common cold remedies
- Bronchoconstriction is caused by parasympathetic stimulation of the nervous system.
- Treatment uses antimuscarinic drugs or sympathomimetics.
- Slight mydriasis e.g. Ephedrine, Pseudoephedrine (Sudafed), Salbutomol (Ventolin).
- Large doses of ephedrine may cause visual hallucinations
- Sympathomimetics: increase cardiac output, dilate bronchioles, constriction of blood vessels

DRUGS ACTING ON THE NERVOUS SYSTEM

- Ocular tissue (neural) is likely to be affected
- Affect brain centres responsible for ocular motor control
  1. Hypnotics and sedatives
  2. Anti-Parkinson agents
  3. Anti-psychotics agents
  4. Anxiolytic agents
  5. Anticonvulsants
  6. Antidepressants
  7. Anti-nausea agents
  8. Analgesics
  9. Drugs used for migraine

Hypnotics and Sedatives

- Drugs to treat insomnia e.g. Amylobarbitone (Amytal), Temazepam (Normison), Nitrazepam (Mogadon).
- If used for short term, few side effects. Habitual users of barbiturates experience extra-ocular muscle problems resulting in reduced convergence or nystagmus.
- Induced ptosis

Barbiturates

- These are drugs that act as central nervous system depressants, with a wide spectrum of effects, from mild sedation to anesthesia which can become addicitve. Some are also used as anticonvulsants.
- Barbituates replaced largely by Benzodiazepines (Nitrazepam):
- Side effects include:
  1. Blurred vision
  2. Loss of accommodation or abnormal extraocular muscles
  3. Abnormal blinking
  4. Dysfunction of EOMs
  5. Barbituates and benzo can cause ptosis
  6. Doses of alcohol above the legal limit for driving can affect the EOM's and interefere with binocular vision

Anti-Parkinson Agents

- Antimuscarinic drugs and dopaminergic drugs e.g. Amantadine (Symmetrel), Benzhexol (Artane), Levadopa (Larodopa)
- Either increase levels of dopamine or act directly with dopamine receptors
  1. Amantadine – few side effects except visual hallucinations
  2. Benzhexol – antimuscarinic effects: reduced accommodation and mydriasis and potential angle closure
  3. Levadopa – Intense blepharospasm and involuntary eye movements.

Antipsychotic Agents

- Used for conditions such as schizophrenia and anxiety. e.g. Chloropromazine (Largatcil), Haloperidol (Serenace)
- Short term results in few ADR's
- Increased effect with duration of use
- Chloropromazine in chronic therapy produces pigmentary deposits in the eye: first lens surface, pupillary area, Descemet's membrane
  1. Skin pigmentation
  2. Corneal deposits in 15%
  3. Deposits do not interfere with vision until advanced
- Haloperidol – antimuscarinic effects: mydriasis and cycloplegia
- Chlorpromazine – yellow brown deposits beneath the anterior lens capsule

Anxiolytic (anti-anxiety) agents

- Minor tranquilizers
- Largest group is the benzodiazepines
- Few ocular adverse effects, which are reversible

Benzodiazepines

- They are one of the most widely prescribed group of drugs
- Intended for short term use but may be used chronically
- Decreased accommodation and reduction in corneal reflex may occur
- Allergic reaction to these drugs
- Allergic conjunctivitis or problems with CLs

Anticonvulsants

- Treatment for epilepsy. e.g. Carbemazapine (Tegretol), Vigabatrin (Sabril)
- Abnormal eye movements and blinking disturbances.
- Nystagmus and diplopia if overdose which will regress if dosage reduced
- Blurred vision.
- Vigabatrin – visual field defects.
- Hadjikoutis et al (2005)

Vigabatrin (Sabril)

- Anticonvulsant
- Restriction of visual field occurred in approximately one third of patients treated, between 1 month and several years after starting treatment
    - This is worrying as used often in children
- Now must carry out visual fields testing (VEP for under 9 years old) prior to starting treatment and then again every six months
- Damage to outer segments of rods and cones and RPE
- Central VA unaffected

Antidepressants

- Tricyclic antidepressants superseded monoamine oxidase inhibitors (MAOI's).
    - MAOI largely unused due to supposed dangerous interaction with drugs and food especially cheese
    - Foods high in tyramine such as aged cheeses, processed meats, legumes, wine, beer, among others can possibly bring on a hypertensive crisis
- Used to treat depressive illnesses. Some drugs have sedative effects.
- Selective serotonin reuptake inhibitors e.g. Fluoxetine (Prozac).
- Eg. Amitriptyline (Tryptizol), Fluoxetine (Prozac), Paroxetine (Seroxat)
- All tricyclic antidepressants have anticholinergic effects
- Effects reversible
- Reduced tear flow
- CL wearers
- MAOI's interact with sympathomimetics and anticholinergics and increase effect
- Tear flow reduced
- MAOI - widening of palpebral aperture can interfere with lens wear
- Amphetamines and cocaine can also widen palpebral aperture

Anti-Nausea Agents

- Act on CNS rather than GIT.
- Used widely in chemotherapy for cancer treatment. E.g. Dolasetron (Azemet) and Ondansentron (Zofran)
- Visual disturbances

Analgesics

- Pain medication – IV morphine causes miosis
- Codeine and Tramadol
    1. Miosis
    2. Pseudomyopia
- High doses of IV morphine can lead to pinpoint pupils (<1.5mm)
- Other analgesics can produce a lesser effect
- Pseudomyopia: spasm of ciliary body
- Risk of pupil block

DRUGS USED FOR INFECTIONS

- Treatment short term. Usually only ADR's with long term treatment.
- Antibiotics
- Urinary antiseptics
- Anti-tubercular drugs
- Anti-malarials

Antibiotics

- Most widely prescribed medicines, used to treat bacterial infections.
    - Mostly treatment for a few days (except for acne)
- Groups include penicillins, cephalosporins, tetracyclines, rifamycins (rifampicin).
- Tetracyclines can cause transient myopia, colour vision defects, penetration of drug into Cerebrospinal fluid (CSF) causing diplopia.
- Secreted in tears staining CL's.
- E.g. amoxicillin, cephalexin, chlorotetracyclines
- Allergic responses
- Periocular skin and lid margin pigmentation: photosensitivity reactions

Taking rifampicin can cause certain bodily fluids, such as urine and tears, to become orange-red in color, a benign but sometimes frightening side-effect. This may permanently stain soft contact lenses. It also may be excreted in breast milk, therefore breast feeding should be avoided.

Urinary Antiseptics

- Urinary tract infections.
- E.g. Nalidixic acid (Negram)
- ADR's: ocular irritation, profuse lacrimation, colour vision disturbances, glare.
- Reversible
- Problematic for CL wearers

Antitubercular Agents

- Causative organism has slow metabolism and growth (Mycobacterium tuberculosis)
- Treatment of tuberculosis is long term e.g. Ethambutol (Myambutol), Rifampicin (Rifinah)
- Rifampicin produces a pink by-product secreted in tears and will colour soft contact lenses. It also causes conjunctivitis
- Ethambutol – optic neuritis
- Optic neuritis reversible in some cases

Antimalarials

- Prophylaxis for travellers, also used for night cramps and rheumatoid arthritis.
- E.g. Chloroquin (Avlocor), Hydroxychloroquinine (Plaquenil)
    - Used as a prophylaxis rather than treatment
    - Deposits on cornea (grey/white), aggravate existing KCS.

  - Pigmentary changes on retina – Bulls eye maculopathy.
  - Ptosis (hydroxychlorinine)
- Quinine used for night cramps and chloroquinine in rheumatoid arthritis
- Constricted VF's, ERG changes
- Quinine amblyopia direct effect on ganglion cells
- Blindness in few hours is possible with overdose

Hydroxychloroquine (Plaquenil)

Family of drugs called Aminoquinolines was initially used in prophylaxis of malaria, now used as disease modifying agent in treatment of Rheumatoid arthritis and Systemic Lupus Erythromatosus (SLE). Selective photoreceptor damage results in a characteristic fundus appearance called Bulls Eye Maculopathy, which is reversible in early stages, generally at doses greater than 400mg per day.

If drugs have caused skin, eyelid, corneal (verticillata) or hair changes- may be an indicator of possible drug induced retinopathy. Since aminoquinolines are concentrated in pigmented tissue, macular changes have been thought to progress long after the drug is stopped

All patients are informed of risk of ocular side effects and usually have thorough ophthalmic examination before commencing treatment. (Best corrected VA, visual fields test, amsler grid test, colour vision test etc)

Risk is much lower with hydroxychloroquine than chloroquine.

Earliest detectable sign of toxicity is a scotoma between 5 and 10 degrees from fixation to a red pin confrontation test.

As mentioned above hydroxychloroquine also gives rise to corneal verticillata (symmetrical, bilateral greyish corneal epithelial deposits which appear in vortex fashion from a point below the pupil as a result of the carriage of the drug metabolite along the epithelial migration lines).

Toxicity related to binding of the drug to melanin (found in larger quantities in RPE).

DRUGS ACTING ON ENDOCRINE SYSTEM

- Drugs that replace or supplement natural hormones
  1. Drugs to treat diabetes
  2. Corticosteroids
  3. Oral contraceptives.

Drugs to Treat Diabetes

- Insulin or oral hypoglycaemic agents
  1. Metformin (Glucophage), Glibenclamide (Daonil), Chloropropamide (Diabinese).
  2. Chloropropamide – toxic amblyopia
  3. Overdose may cause hypoglycaemic attacks, resulting in diplopia and reduced VA
- Diabetes itself has many ocular complications.

Corticosteroids

- Replacement therapy (physiologically) or suppression of inflammation (pharmacologically).
  1. Cataract (posterior capsular)
  2. Increase in IOP

  E.g. Betamethasone (Betnelan), Cortisone (Cortelan), Prednisolone (Deltacortril).
- Rheumatoid arthritis, ulcerative colitis
- Cataract occurs after one year's treatment. 30% patients
- Topical use rarely leads to cataract
- IOP increase due to a reduction in outflow

High proportion of 1st degree relatives of glaucoma suffers exhibit a rise in intraocular pressure with administration of steroid – steroid responders.

Also main ocular side effect is development of classis posterior subcapsular cataract (in up to 50% of patients on long term steroid treatment)- causes glare especially on night driving- generally necessitates lens extraction.

Oral Contraceptives

Most common method of birth control:

- Combined pill or progesterone only
  1. Ethinyloestradiol (Microgynon)
  2. Levonorgesteral (Microval)
- Reduced tolerance to contact lenses
- Quality and quantity of tears affected

Few isolated reports of retinal vein occlusion. Millions of women have been taking the pill for many years but little information on cause and effect. No significant effects on TBUT or tear production.

Anti-inflammatory Drugs

- Alternatives to steroids. NSAIDs.
- E.g. Diclofenac (Voltarol), Ibuprofen (Brufen).
- Reduced colour vision and reduced VA (indometacin and ibuprofen)
- Retinopathy, visual field restrictions, depressed EOGs, granular appearance of fundus (Indometacin)
- Cataract and optic neuritis – linked with Naproxen.

EXAMPLE OF ADR REPORTING SYSTEM: YELLOW CARD SCHEME IN UK

The Medicines Healthcare products Regulatory Agency (MHRA) and the Commission on Human Medicines (CHM) run the UK's spontaneous adverse drug reaction (ADR) reporting scheme – which is also called the Yellow Card Scheme. This schemem receives reports of suspected adverse drug reactions (ADRs) or side effects from healthcare professionals and patients for medicines and vaccines.

The Yellow Card Scheme is the main ADR reporting scheme in the UK and was introduced in 1964. It receives about 25,000 reports of possible side effects each year.

- Any suspected reaction to ophthalmic medication is reported
    - Fatal, life threatening, disabling, incapacitating or which result in hospitalization
- Ocular adverse reaction to any therapeutic agent
    - Changes in vision, IOP changes, any change in ocular status
- Inform General Practitioner (GP)
    - The patient's GP must be informed of any suspected adverse reaction

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