AUTONOMIC NERVOUS SYSTEM AND CYCLOPLEGIC DRUGS

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This chapter includes a review of:

- Autonomic nervous system
- Cycloplegic drugs

ABBREVIATIONS

A number of accepted Latin derived names are in regular use in pharmacology. Abbreviations usually related to timing of when medicines are taken and by what route, viz., Twice a day (bis in die – b.d), OD oculus dexter – right eye, OS oculus sinister – left eye, Eye drops gtt – guttae (drops), Ante cibum (Before meals).

Table 3.1: Abbreviations

Terms	Abbreviations	Terms	Abbreviations
once-a-day	*d.i.e.o.d. (q.d.)*	twice-a-day	*b.i.d.* or *b.d.s.*
3-times-a-day	*t.i.d.* or *t.d.s.*	4-times-a-day	*q.i.d.* or *q.d.s.*
In the morning	*o.m. or a.m.*	at night (before bed)	*o.n. or h.s.*
as needed	*p.r.n.*	nothing by mouth	*n.b.m.*
before meals	*a.c.*	after meals	*p.c.*
eyedrops	*gtt*	ointment	*ung*
tablets	*tab.* or *tbl.*		
prescription-only medication	PoM or POM	Pharmacy Medicine	P (not PM)
(general) sales list	(G)SL	hospital product	HP
controlled drug	CD		

May be written in capitals, e.g. DIEOD or BID or BDS, etc

AUTONOMIC NERVOUS SYSTEM

Many ocular drugs in regular use act directly or indirectly on the autonomic nervous system. Endocrine system is based on a hormone-released system, using chemicals. The nervous system uses electrical impulses to send signals to chemically based synapses. Electrical signals are carried along axons and chemical signals occur across axons.

The nervous system and the endocrine system are the major means by which body functions are controlled and integrated.

- **Endocrine system** – hormone release- chemical
- **Nervous system** – electrical nerve fibre transmission- except at synapses- chemical neuro-mediator substance

Exocrine glands secrete products into ducts as opposed to blood e.g salivary glands. Synapses are breaks in continuity of nerve pathway. Transmission is impossible across gap. It takes place chemically. Synapses occur on swellings on nerve endings called ganglia. Preganglionic nerves leave CNS. Post-ganglionic nerves travel to the effector organ. Most involuntary structures are innervated by both structures usually displaying antagonistic effects i.e. one will stimulate and one will inhibit. The sympathetic system prepares the body for situations of stress (fright, flight or fight responses) and the parasympathetic system dominates normal sedentary life. It is responsible for smooth muscle, cardiac muscle and exocrine glands. It is the involuntary part of the nervous system. The parasympathetic and sympathetic systems have anatomical and functional differences. The major difference resides in from nerve fibres supplying skeletal tissue – synapses.

Gaps in neurones are across which electrical signals cannot travel. Signals are transported across these gaps chemically. Specific chemical agents are known as neuro-humoural transmitters, viz., Acetyl choline and noradrenaline. Many drugs will act in a way to mimic these natural transmitters to initiate or inhibit actions. Receptors using acetyl choline are known as cholinergic receptors. Receptors using noradrenaline (norepinephrine in US) are known as adrenergic.

The neuro-mediator substance crosses synaptic cleft by diffusion and activates (or inhibits) the post synaptic cell by binding to a specialised receptor molecule.

Neurotransmitter

Neurotransmitters acting in the body are of two types, viz., Acetyl choline and noradrenaline. Many drugs will act in a way to mimic these natural transmitters to initiate or inhibit actions. Receptors using acetyl choline are known as cholinergic receptors. Receptors using noradrenaline (norepinephrine in US) are known as adrenergic.

- Acetylcholine
  - pre and post ganglionic neurotransmitter in parasympathetic division
  - Pre-ganglionic neurotransmitter in sympathetic division
- Noradrenaline
  - Post-ganglionic neurotransmitter in sympathetic division

Subdivisions of CANS

There are two major functional subdivisions:

a. **Autonomic division –** Activities not under conscious control e.g. cardiac output, blood flow, digestion etc.
b. **Somatic division –** Non-automatic division- consciously controlled functions e.g. locomotion, posture etc. (transmitter is acetylcholine- nicotinic receptors)

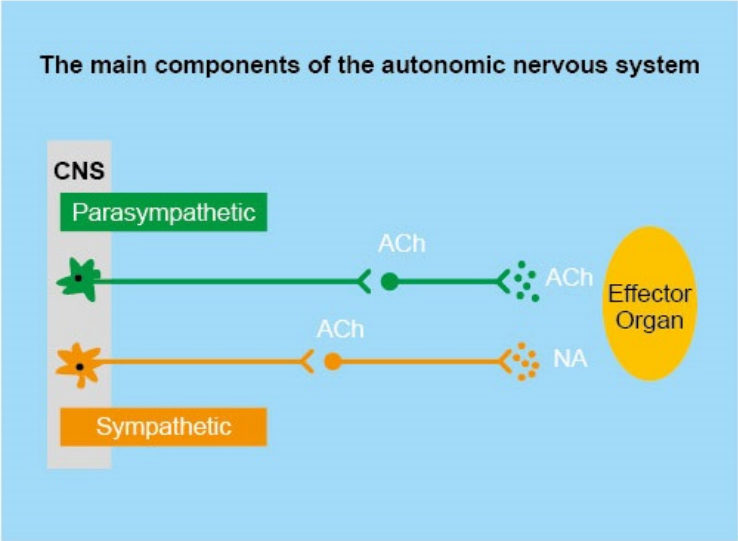

Figure 3.1 Representation of the neurotransmitters and ganglia the autonomic nervous system

ANS can be further sub-divided into:

Sympathetic division – discrete motor ganglia lying on either side of the spinal column. Pre-ganglionic axons leave CNS via thoracic and lumbar roots.

Pre-ganglionic (short) efferent fibres are cholinergic, post ganglionic (long) fibres are mainly noradrenergic.

Dopamine is released from some peripheral sympathetic fibres.

Parasympathetic Division – ganglia distributed diffusely in walls of organs innervated- pre-ganglionic fibres leave CNS via cranial nerves III, VII, IX, X and sacral spinal roots III, IV.

Pre ganglionic (long) and post ganglionic (short) efferent nerve fibres are cholinergic.

Ganglia, in which they synapse, are very close to the organs which the post ganglionic fibres innervate (effector organs). Cholinergic – use Ach.

Both sympathetic and parasympathetic neurones originate in the CNS and give off pre-ganglionic fibres that exit from brain stem or spinal cord.

Figure 3.2 shows brain stem, autonomic (parasympathetic and sympathetic) and somatic neurones (associated with innervation of skeletal muscle). Note the neurotransmitter (Ach or Noradrenaline/Norepinepherine). Ach is the neurotransmitter of all preganglionic autonomic nerve fibres, all parasympathetic post ganglionic fibres and a few post ganglionic sympathetic fibres.

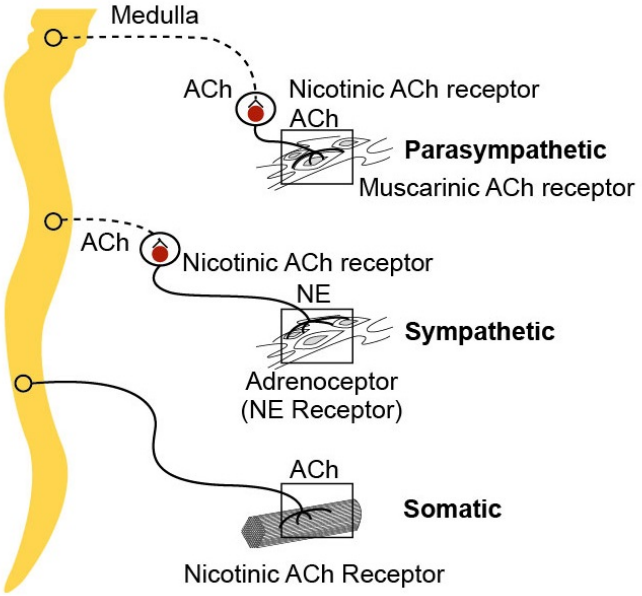

Figure 3.2 *Brain stem, autonomic (parasympathetic and sympathetic) and somatic neurones (associated with innervation of skeletal muscle)*

Cholinergic Neurones

Nerve terminals contain large quantities of small, ACh containing, membrane-bound vesicles.

ACh formed in nerve cell cytoplasm from Choline (taken up from extracellular fluid) and Acetyl Co A (synthesised in cell mitochondria) are catalysed by choline acetyltransferase.

> What actually happens at these synapses? ACh is found in nerve terminals in large quantities in membrane bound vesicles. ACh is formed in nerve cell cytoplasm from Choline. Each synaptic vesicle contains 50,000 molecules of Ach and a single motor nerve terminal contains >300,000. Active transport is used to take up Choline from extracellular fluid.

The release of ACh when there is an action potential causes an influx of Calcium ions into the nerve ending which destabilises storage vesicles and causes exocytotic expulsion into synaptic cleft.

Neurotransmitter binds and activates cholinoceptor and is eventually broken down by acetylcholinesterase molecule (AChE) to form choline (recycled) and acetate.

> Action potential: the nerve impulse arrives at synapse, depolarises terminal, increases permeability causing an inflow of calcium ions, causes liberation of ACh into synaptic cleft by exocytosis. Membrane of vesicle fuses with membrane of nerve cell allowing ACh to be released. Ach occurs in clear vesicles. Noradrenalin in granulated vesicles. AChe, acetyl choline esterase, is an enzyme present at neuromuscular junctions and red blood cells.

- Choline is taken into cell
- Enzyme choline acetyl-transferase catalyses reaction to form Ach vesicle
- An influx of Calcium during action potential causes instability of vesicle and expulsion into synaptic cleft
- Neurotransmitter binds and activates receptor
- Eventually broken down into choline again and recycled

Adrenergic Neurones

Transmitter substance (norepinephrine) is also stored in membrane bound vesicles but synthesis of catecholamines is much more complex than ACh.

> Norepinephrine and noradrenaline are the same. Noradrenaline is the neuro-humoral transmitter for the majority of post ganglionic sympathetic fibres. Adrenergic are secreted by adrenal medulla. Epinephrine, which is also secreted by the adrenal medulla, (adrenaline) is a hormone that plays a role in the body's short term-stress reaction increasing heart rate.

Secreted by adrenal medulla, norepinephrine is both a hormone and a neurotransmitter.

> The adrenal medulla is the inner part of the adrenal medulla in the adrenal gland (located near the top of the kidneys). Catecholamines are a group of chemical compounds distributed through cells in body. They can act as neurotransmitters and inhibit or excite muscles depending on site or amount e.g. noradrenaline. Noradrenaline mimics stimulation of the sympathetic system, i.e. causes vasoconstriction and increase in heart rate, blood pressure.

In noradrenergic neurones, a certain portion of norepinephrine is not stored in vesicles but exists as a protected pool in the neuronal cytoplasm- released not by action potentials, but indeed by the action of certain indirectly acting sympathomimetic drugs e.g. tyramine.

> - Slower acting than Ach
> - Chemical compound found widely in plants and animals
> - Mimics action of sympathetic system
> - In chocolate, alcohol, cheese

Several important transport mechanisms in noradrenergic nerve terminal are potential sites of drug action:

1. Terminal cell membrane: actively transports norepinephrine and similar molecules into cell cytoplasm- inhibited by cocaine/tricyclics.
2. High affinity carrier for catecholamines in wall of storage vesicles:- inhibited by the reserpine alkaloids

> Reserpine alkaloids are drugs used to treat high blood pressure. Tricyclics are antidepressants that also have an affinity for some (histamine and muscarinic) receptors.

The release of vesicular norepinephrine from nerve endings is similar to Ach, however co-transmitters are ATP, dopamine- B- hydroxylase and certain polypeptides.

Norepinephrine and epinephrine are metabolised by several enzymes- for example, high activity of Monoamine oxidase in cell terminal mitochondria.

> ATP also causes transmission at synapses. Co-transmitters enhance transmission across a synapse. Monoamine oxidase breaks down neurotransmitter substances. It is found in outer membrane of mitochondria. Enzymes are used to dispose of the neurotransmitter once the transmission across synapse is complete.

Termination of transmission of catecholamine results from several processes:

- Simple diffusion away from receptor site
- Metabolism in plasma / liver
- Re-uptake into nerve terminal (uptake I)
- Re-uptake into perisynaptic glia or smooth muscle cells (re-uptake II)

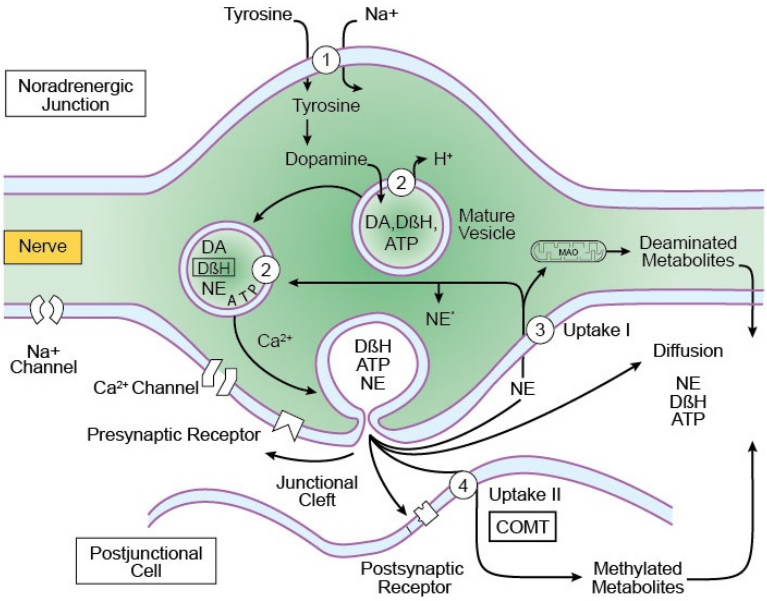

Figure 3.3 Formation of noradrenaline. Formation and release of noradrenaline takes place at the synapse. It is formed in vesicles in a similar way to Ach.

Receptors

- **Cholinoreceptors:** Muscarinic/ Nicotinic
- **Adrenoceptors:** Alpha 1 or 2, Beta 1 or 2 and Dopamine

> Cholinergic receptors can be stimulated by nicotine (tobacco) or muscarine (found in poisonous toadstool). Muscarinic receptors are found on receptor cells of effector organ. Nicotinic receptors are at autonomic synapses and skeletal muscle. Adrenoceptors refers to those receptors for which: noradrenaline, adrenaline and dopamine can act as neurotransmitters. Noradrenaline is the most potent. Receptors on smooth muscle can be termed alpha – excitation, beta- inhibition. Exceptions to these rules: intestine – inhibitory A and B.

Table 3.2: Autonomic receptor types

Name	Typical locations
Cholinoceptors Muscarinic	Parasympathetic effector cells: smooth muscle, cardiac muscle, exocrine glands; brain
Nicotinic	Autonomic ganglia, skeletal muscle neuromuscular end-plate, spinal cord
Adrenoceptors $Alpha_1$	Post-synaptic effector cells, especially smooth muscle
$Alpha_2$	Pre-synaptic adrenergic nerve terminals, platelets, lipocytes, smooth-muscle
$Beta_1$	Post-synaptic effector cells, especially heart; lipocytes, brain, pre-synaptic nor-adrenergic nerve terminals
$Beta_2$	Post-synaptic effector cells, especially smooth muscle
Dopamine	Brain and post-synaptic effectors, especially vascular smooth muscle of the splanchnic and renal vascular beds. Pre-synaptic receptors on nerve terminals, especially in the heart, vessels, and gastrointestinal system

Source: *Hopkins G, Pearson R. O'Connor Davies Ophthalmic Drugs - 4th edition 1996. Butterworth Heinemann.*

Adrenoceptors are further divided into A1 A2 and B1 B2 based on molecular mode of action.

Table 3.3: Direct effects of autonomic nerve activity on some organ systems

Organs		Effect of			
		Sympathetic		Parasympathetic	
		Action	Receptor	Action	Receptor
Eye					
Iris	Radial muscle	Contracts	α	…	…
	Circular muscle	…	…	Contracts	M
Ciliary muscle		(Relaxes)	β	Contracts	M
Heart					
Sinoatrial node		Accelerates	β_1	Decelerates	M
Ectopic pacemakers		Accelerates	β_1	…	…
Contractility		Increases	β_1	Decreases	M
Vascular smooth muscle					
Skin, splanchnic vessels		Contracts	α	…	M†
Skeletal muscle vessels		Relaxes	β_2	…	…
		(Contracts)	α	…	…
		Relaxes	M§	…	…
Bronchiolar smooth muscle		Relaxes	β_2	Contracts	M
Gastrointestinal tract					
Smooth muscles	Walls	Relaxes	β_2	Contracts	M
	Sphincters	Contracts	α	Relaxes	M
Secretion		…	…	Increases	M
Myenteric plexus		Inhibits	α	…	…
Genitourinary smooth muscle					
Bladder wall		Relaxes	β_2	Contracts	M
Sphincter		Contracts	α	Relaxes	M
Uterus, pregnant		Relaxes	β_2	…	…
		Contracts	α	…	…
Penis, seminal vesicle		Ejaculation	α	Erection	M
Skin					
Pilomotor smooth muscle		Contracts	α	…	…
Sweat glands	Thermoregulatory	Increases	M	…	…
	Apocrine (stress)	Increases	α	…	…
Metabolic functions					
Liver		Gluconeogenesis	α / β_2**	…	…
Liver		Glycogenolysis	α / β_2	…	…
Fat cells		Lipolysis	α_2, β_1††	…	…

From O'Connor, Davies Ophthalmic Drugs. Hopkins and Pearson. Chapter:general pharmacological principles. Different effects of autonomic nervous system acting on different organs.

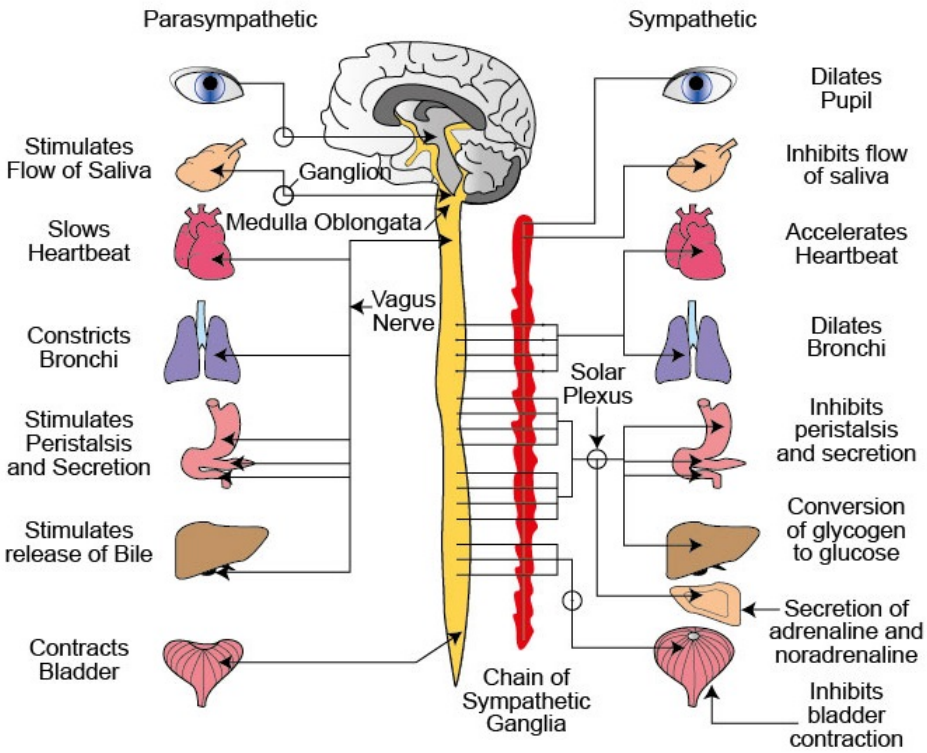

Figure 3.4 Parasympathetic and sympathetic nervous system

Effects of Autonomic Innervation of Eye

Table 3.4: Adrenergic and cholinergic of intra-ocular muscles

	Adrenergic	**Cholinergic**
Iris radial muscle	Contracts (alpha)	
Iris circular muscle		Contracts (m)
Iris ciliary muscle	Relaxes (beta)	Contracts (m)

Adrenergic and cholinergic effects of the eye: anti-cholinergic drugs cause cycloplegia.

Table 3.5: Ocular effects of drugs modulating cholinergic transmission

Site	Cholinergic effect	Cholinergic blocking effect
Lids	lid elevation	(upper lid) close
Lids (orbicularis)	(reflex closing)	opening (relax; relief of blepharoplasm)
Conjunctival veins	dilation	constriction?
Anterior uvea veins	dilation	constriction
Lacrimal acini	increased secretion (lacrimation)	decreased secretion
Iris sphincter	contraction (closing, miosis)	relaxation (opening, mydriasis)
Ciliary body	contraction (myopia)	relaxation (cycloplegia)
Ciliary epithelium	decreased secretion?	no effect?

Doughty M. 2006. Drugs, Medications and the Eye. 14th Edition.

Table 3.5: Ocular effects of drugs modulating adrenergic transmission

Part of eye	Adrenergic effect	Type	Adrenergic blocking effect
EOM's	contraction	?	relaxation
Lacrimal glands	increased secretion	beta?	decreased secretion
Eyelids (Muellers)	lid elevation	$alpha_1$	(upper lid) close
Conjunctiva	vasoconstriction	$alpha_1$	vasodilation
Anterior uvea	vasodilation	$alpha_2$	no effect?
Iris dilator muscle	contraction (open)	$alpha_1$	relaxation (close)
Ciliary body muscles	relaxation	$alpha_1$ beta	contraction
Ciliary epithelium	decreased secretion (long term effect)	beta	decreased secretion

Effect noted with a '?' indicate that, clinically, little or no effect has been reported.

Ciliary bodies are smooth muscle of the autonomic nervous system. They are innervated by the parasympathetic nervous system. They use cholinergic receptors. Cholinergic blocking drugs block action of ACh at the synapses. They prevent contraction at the ciliary body, therefore pupils dilate.

CYCLOPLEGICS

Paralyse ciliary muscle by blocking muscarinic receptors normally stimulated by release of Acetylcholine from nerve endings of the parasympathetic system at muscle end plates (ciliary muscle).

> Since the parasympathetic system also innervates the pupil sphincter muscle, cycloplegia must be accompanied by mydriasis. Anti-cholinergics- (anti-muscarinics) action takes place.

Cycloplegics are used to prevent or reduce accommodation during refraction, due to which latent refractive errors become manifest.

Under cycloplegia, full static refraction can be estimated without interference from tonic fluctuating contraction of ciliary muscle.

Uses of cycloplegics

- Children with constant/ intermittent esotropia
- Children / young adults where latent refractive error suspected
- When ret suggests accommodation is fluctuating
- Variable subjective findings, accommodation spasm, insufficiency etc.
- Retinoscopy findings differ significantly from subjective
- Accommodative insufficiency/ accommodative fatigue/ spasm of accommodation etc.
- Retinoscopy along visual axis difficult due to lack of cooperation/ communication difficulties etc.

Characteristics of an Ideal Cycloplegic

1. Quick in onset of action
2. Adequate depth of cycloplegia
3. Adequate duration
4. No mydriasis
5. No other pharmacological effect
6. No local toxicity
7. No systemic activity
8. Stable
9. Single use presentation
10. No adverse effects or stinging

Table 3.6: Cycloplegics

Official name	Trade name	Strengths % w/v	Single dose?	Cycloplegic onset	Cycloplegic duration	Residual accommodation	Adverse effects
Atropine sulphate	–	1.0	Yes	36 hr	Up to 7 days	Nil	Allergic reactions, genral CNS side effects
Cyclopentolate hydrochloride	Mydrilate	0.5 – 1.0	Yes	60 min	24 hr	1.00 D	Hallucinations, CNS side effects

Homatropine hydrochloride	–	1.0	2% only	90 min	24 hr	1.00 D	As for atropine
Tropicamide	Mydriacil	1.0	Yes	30 min	6 hr	2.00 D	Occasional hallucinations

Source: *Hopkins G, Pearson R. O'Connor Davies Ophthalmic Drugs - 4th edition 1996. Butterworth Heinemann.*

Contra-indications

- Narrow angle glaucoma
- Dislocation/ subluxation of crystalline lens
- History of sensitivity

> If lens is unstable or there is a previous history of Marfans, cycloplegics cause interference with the ciliary body and zonules and may displace the lens.

Cautions

- If on concurrent medication affecting pupil /ciliary body- duration of action may be prolonged
- Any history of CNS disorders can precipitate immediate (within 5-10 mins) CNS based reaction
- People with Down syndrome (DS)
    - People with DS are at a greater risk of angle closure due to anatomical differences.

- Cyclopentolate 0.5% or 1% is agent of choice normally
    - Available as 2% in US
- Atropine 1% drops or ointment may however be used in young children
    - Still considered by some as drug of choice in under 4 years old
- Cycloplegics are available as minims or multi-dose bottles
    - Minims are preservative free
    - Multi dose – often use benzalkonium chloride as a preservative.
- Cycloplegics cause a stinging sensation, so often a topical anaesthetic is used before instillation
- Should be stored in a cool place (not refrigerated)

Dosage and recovery

- One drop of 1% or two drops of 0.5% (interval of 5-10 mins).
- Accommodation <2D at 30 mins.
- Recovery slow: accommodation returns after 4-8 hours but full recovery up to 12-24 hours. Pupil dilation for a further 12-24 hours
- Increased pigmentation: slower onset and recovery

ATROPINE

Atropine has a slow onset of action and ointment is generally given to parents of child prior to refraction.- Ointment is generally applied in the morning and evening for 2 days prior to the appointment and then again that morning. The effects may take 1 week to wear off. Ensure parents return any unused medication.

- POM Minims: Atropine Sulphate 1% eye drops.

- Multiuse bottles (10ml) of 0.5% and 1% POM.
- Atropine ointment 1% 3g tube.
- Preservative: benzalkonium chloride

- For diagnostic use: drops used one or two drops morning and evening for two days prior to eye examination
- Recovery – up to one week

Contraindications

- Known hypersensitivity
- Angle closure glaucoma
- Subluxated lenses

Systemic overdose

- Dry mouth
- Reduced sweating
- Feeling hot and flushed
- Increased pulse
- Reduced GI tract motility

Effects of overdose are self limiting – will subside as drug is eliminated from body.

Cautions

- Concurrent atropine like therapy e.g. Travel sick medication (hyoscine), anti-diarrheals (diphenoxylate) .
- Cholinergic blocking drugs- Noctural enuresis medication (Oxybutynin).

Toxic Effects of Atropine

- Blind as a bat
    - Accommodation
- Dry as a bone
    - Hyoscine inhibition of sweat glands and salivary glands
- Red as a beetroot
    - Dilation of skin blood vessels to compensate for inhibition of sweat glands
- Mad as a hatter
    - CNS effects – confusion, difficulty in speaking, hallucinations and ataxia

Alternative cycloplegics

- Homatropine (1%, 2%) is alternative cycloplegic where there is hypersensitiviy to cyclopentolate.
- Less painful on instillation but causes temporary marked vasodilation of conjunctiva.
- Also Tropicamide and Hyoscine
    - Tropicamide (only older adults)
    - Hyoscine (not usual)

REFERENCES

- Doughty M. 2006. Drugs, Medications and the Eye. 14th Edition.
- Hopkins G, Pearson R. O'Connor Davies Ophthalmic Drugs - 4th edition 1996. Butterworth Heinemann.
- Optometrists formulary 2006 edition. The College of Optometrists Handbook.