Ophthalmic drugs

Part 3 – Mydriatic drugs - which ones to use when and how they work

In the first of a two-part look at mydriatics, **Dr Michael Johnson** describes the indications for mydriasis, what drugs to use and how they work. Module C19751, one specialist point for therapeutic optometrists, one general CET point for optometrists

The pupil acts to improve optical resolution, allows for rapid control of retinal illumination, and conveys emotion in non-verbal communication. Enlargement of the pupil is termed mydriasis and a reduction in the size of the pupil is termed miosis. Physiological mydriasis occurs when the level of light is dimmed, and in reaction to stress and arousal. Miosis is a reaction to an increase in light. There are times when an optometrist wants to override the physiological control of pupil size, and this article reviews why and how this can be achieved.

When to dilate

The most common reason that an optometrist chooses to dilate the pupil is to improve the view of the internal structures of the eye posterior to the iris. Therapeutic use of mydriatics invariably makes use of chemically related cycloplegic drugs, owing to their longer duration and the sometimes useful attribute of greater action on the ciliary body. These medical indications include lessening painful muscular spasm and breaking posterior synechiae in iritis, disrupting ciliovitreal block in aqueous misdirection (malignant) glaucoma, improving access to the posterior segment in surgery, and penalisation therapy for amblyopia.

Viewing through an undilated pupil can be likened to peering through a keyhole, with the situation compounded by the miosis triggered by the high light level associated with most examination techniques. It is certainly possible to get a view through an undilated pupil in most patients, at least with one eye, but dilation always gives a better view by improving coverage, stereopsis and clarity. In particular, without dilation it is not possible to optimally visualise the peripheral retina, vitreous, or to achieve stereoscopic appreciation of the optic nerve or macula (even when it can easily be seen monocularly). It may be argued that a dilated ocular examination is an ideal that optometrists should offer all of their patients. However, it is not customary to offer dilation routinely in primary eye care sight tests within England and Wales owing to its associated inconvenience and low benefit-cost ratio for the majority of patients. A pragmatic compromise is that patients with larger benefit-cost ratios are identified and offered dilation. There is no definitive list of the patients that 'must' be dilated, and this is appropriate given that individual circumstances are by definition individual, and the opinions of clinicians along with the fashions of our profession differ with time and geography. What follows is a guide to help optometrists make better decisions (Table 1).

Risk of retinal detachment

A retinal detachment is a relatively rare event, with an annual incidence of about one in 10,000 – lifetime risk about one in 200.[1] This risk is not shared evenly, and some people are much more likely to develop a detachment. The main risk factors for retinal detachment are trauma (including surgery), and high myopia or a family history of non-trauma related retinal detachment. For comparison with population averages, the lifetime risk of someone with more than six dioptres of myopia developing a retinal detachment is about one in 20. It is my opinion that asymptomatic high myopes should be offered a dilated intraocular examination bi-annually to detect retinal breaks that could be treated before they lead to a rhegmatogenous retinal detachment, and this should be increased to annually for extreme myopes whose refraction exceeds 12 dioptres. Moreover, a dilated view of the anterior vitreous and fundus should be recommended in the strongest terms to anyone who has symptoms suggestive of a retinal detachment or its precursor, a posterior vitreous detachment. Symptoms of a posterior vitreous detachment include a sudden increase in the number of floaters, often with a large central opacity that moves with the eye, representing a Weiss ring, and flashes. A retinal detachment may also be accompanied by a black shadow that extends to the edge of vision.

TABLE 1

Indications for dilated ocular examination

Risk of retinal detachment
Flashes and floaters
Lattice degeneration
Recent blunt trauma
High myopia
Family history of retinal detachment
Post-intraocular surgery
Risk of macular disease
New distortion
AMD and reduced acuity
Numerous soft drusen
Specific conditions
Diabetes (not screened)
Uveitis
Pigmented fundus lesion
Suspected glaucoma
Suspected papilloedema
Penetrating trauma

Risk of macular disease

It is difficult to confidently assess the macula without dilation because its examination is associated with the strongest light-induced miosis. Furthermore, the most important sign in macular disease is elevation or thickening, which represents the accumulation of fluid within or under the retina, and this demands stereoscopic viewing. In my opinion, a dilated examination of the macula is indicated when there are complaints of new distortion, or reduced acuity in persons with AMD or diabetic retinopathy, or at high risk of choroidal neovascularisation due to numerous soft drusen or a history of wet AMD and not being monitored by the hospital eye service.

Specific conditions

There are some specific conditions or clinical scenarios that warrant dilation.

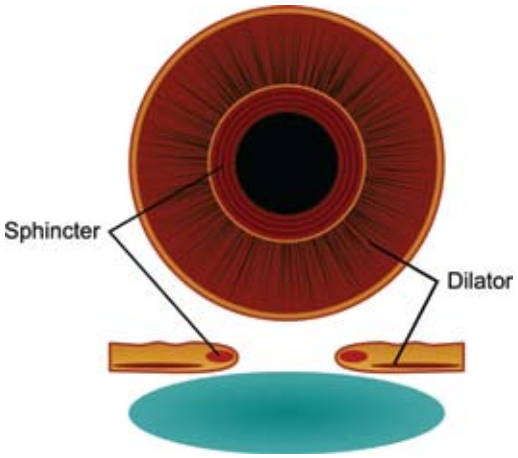

Figure 1 Iris muscles

Most diabetics have a retinal photograph taken annually, but in the rare instance that this is not being done then these patients should be dilated. In patients with suspected uveitis dilation helps better identify small numbers of cells or flare in the anterior chamber due to the enhanced contrast with the black pupil, and allows for better examination for cells within the vitreous; furthermore, dilation (and often cycloplegia) is used therapeutically in these patients to lessen painful spasm of the iris and break posterior synechiae. Dilation is essential for good stereopsis, even when a good monocular view is possible, and so is indicated when assessing possible elevation of pigmented fundal lesions or borders of the optic nerve when malignancy or papilloedema are suspected, and the cupping of the optic nerve when an optic neuropathy such as glaucoma is suspected. Additionally, although rare for optometrists in primary care, any patient presenting with a recent history of high speed impact injury to the eye, especially when working metal and in the presence of a corneal scar, requires dilation to more confidently exclude a penetrating foreign body that can self-seal its entry wound. Indeed, owing to the sometimes dire risk of the often delayed consequences of not finding a ferrous intraocular foreign body these patients usually go on to have an X-ray. Finally, many imaging technologies get better pictures when the pupil is dilated, and this is particularly the case in older persons with senile miosis and cataract.

MYDRIATIC DRUGS

Mechanisms of action

The size of the pupil is governed by the interplay of the sphincter and dilator muscles within the iris (Figure 1). The sphincter muscle is about 1mm wide and runs circumferentially around the pupil margin. It has a parasympathetic nerve supply that originates from the Edinger Westphal nucleus and arrives at the eye via the oculomotor nerve, ciliary ganglion and short ciliary nerves. The dilator muscle is composed of radial fibres, like spokes of a wheel, that converge from the circumference of the iris toward the centre and blend with fibres of the sphincter muscle near the pupil margin. It is controlled by the sympathetic nervous system with a nerve pathway that originates in the hypothalamus, loops down to the cervical portion of the spine and then travels upward towards the eye via the carotid plexus, cavernous sinus and the long ciliary nerves.

Mydriatics can work on either end of the push-pull system controlling pupil size, namely by preventing contracture of the iris sphincter muscle, or augmenting the contraction of the iris dilator muscle. It should also be appreciated that the tone of the ciliary body is also controlled by cholinergic nerves, and so anticholinergic mydriatics have a spill-over of effect on accommodation. Indeed, mydriatic and cycloplegic drugs that act on cholinergic nerves differ in their strength, rather than in their pharmacological mechanism of action. Cycloplegic drugs always cause pupil dilation in addition to their effect on the ciliary body, whereas drugs marketed as mydriatics are less potent and so have reduced effect on accommodative function.

Natural alkaloids

The first mydriatics were plants such as mandrake, which was used (and abused) by many ancient civilisations, including the Hebrews, Greeks and Romans. This perennial herb is a narcotic and so serves to dull the perception of pain through central mechanisms. In ocular inflammation it also lessens pain caused by iris spasm as a result of the anticholinergic effect from its high alkaloid content. In addition to pain relief, the Greeks and Romans made use of the dilating properties of mandrake to improve access to the cataractous lens in couching operations, and to simulate the pupil signalling of sexual arousal in courtship and religious ceremonies.

The vogue of mydriatics in Greece and Rome was lost during the succeeding centuries. It was only towards the end of the 18th century that the mydriatic effect of the herb belladonna, more commonly known as deadly nightshade due to its lethal effect as a poison, was recognised by the medical establishment, which subsequently led to the isolation of atropine. As an aside, the name belladonna, meaning 'beautiful lady', comes from the first use of the plant leaves to dilate women's pupils to make them appear more amorous. Also, it has been argued that the alkaloids produced by this genus of plants have evolved to poison unwanted insects tempted to feast on their foliage in a manner analogous to chemical warfare.

Atropine is an anticholinergic drug, which means that it acts to frustrate cholinergic nerves (those using catecholamine such as acetycholine as neurotransmitters) that form part of the parasympathetic nervous system. The drug binds to cholinergic receptors on the sphincter (and the ciliary body) where it shields them from acetycholine and prevents it from triggering muscular contraction. In essence, anticholinergic drugs cover the ears of the iris sphincter so it cannot hear the nerves shouting. The effect is pupil dilation, and importantly, an abolition of the normal light reflex. Atropine also causes pronounced cycloplegia.

Tropicamide

The natural alkaloid atropine was used for many years in ophthalmology, but clinicians, and especially patients, were inconvenienced by its long half-life that meant its dilation and cycloplegic effects persisted for many days, perhaps for as long as a week. This prompted the development of a short-acting alternative, and the fruit of this labour was a synthetic compound that answered many of the practical failings of atropine. The synthetic derivative was named tropicamide, which produces dilation quicker and has a much shorter duration. As an added benefit, it does not cross the blood-brain barrier, and so in contrast to atropine there is no risk of central nervous system dysfunction that can lead to amnesia, confusion and excitation. Tropicamide gives good dilation in about 20min, and this rapid action is the result of a relatively low PKα of 5.4 (versus 9.8 for atropine), which means that its penetration across the lipid membrane of the corneal epithelium is enhanced by the low proportion of the drug in ionised form at physiological pH (about 2.3 per cent). Dilation begins to diminish after 2hrs and pupil size has typically returned to its habitual level after 4-6hrs. The cycloplegic effect of tropicamide is generally only noticed by early incipient presbyopes, especially those with uncorrected hypermetropia, and early presbyopes who have little accommodative reserve and incomplete near correction.

Tropicamide is available in 0.5 per cent and 1 per cent concentrations in both preserved multiuse bottles and more popularly as non-preserved single-use ▶

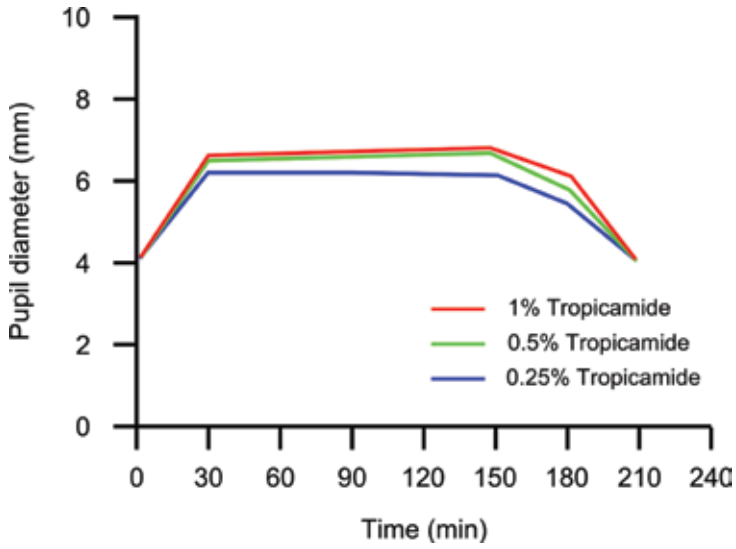

Figure 2 The dilated pupil size is similar for 0.25 per cent, 0.5 per cent and 1 per cent Tropicamide – adapted from Marchini *et al*, 2003[2]

Minims. The 0.5 per cent formulation is already towards the top of the sigmoidal dose-response curve for this drug, and so doubling the strength only leads to a marginal increase in dilation, but is associated with the drawbacks of a more pronounced cycloplegic effect and a longer recovery period (Figure 2).

Phenylephrine

Sympathomimetics acting on the adrenoreceptors of the dilator muscle within the iris lead to dilation of the pupil. Phenylephrine is a synthetic drug that is very similar to the natural neurotransmitter epinephrine, but differs in that it is more selective for alpha-selectors with reduced affinity for beta-receptors, and lasts longer because it is not broken down by the extracellular enzyme catechol-o-methyltransferase (COMT) that operates within the synapse.

Phenylephrine is available in either 2.5 per cent or 10 per cent preservative-free single-use Minims. Compared with tropicamide, dilation with phenylephrine is slightly slower with maximal dilation 45-60min after instillation, and the degree of dilation is slightly less. An important difference with tropicamide is that phenylephrine does not abolish the light reflex because it does not act on the iris sphincter. Recovery is slightly quicker with phenylephrine, with normal pupil size returning in 3-6hrs depending on the concentration used, with the effects diminishing with time due to its metabolism by the enzyme monoamine oxidase (MAO) following uptake into presynaptic nerve cells. Experiments have demonstrated that phenylephrine has no direct effect on accommodation, but some patients will experience reduced near function due to impaired visual feedback to the accommodative drive resulting from the degraded optical qualities of the eye when the pupil is dilated. Phenylephrine stings more than tropicamide, especially the stronger 10 per cent formulation, and may cause an epitheliopathy. Also, owing to a strong action on the dilator muscle, the 10 per cent formulation may cause individuals to develop transient pigment floaters in the anterior chamber that can be misinterpreted as anterior uveitis or a microscopic hyphema.

Phenylephrine eyedrops do not only affect the iris. The drug is a vasoconstrictor and so causes blanching of conjunctival blood vessels, and its use may be associated with upper lid retraction due to influence on Müller's muscle. It is particularly important to appreciate that phenylephrine has the potential for systemic side-effects. While rare, a significant elevation in blood pressure has been reported following the use of phenylephrine 10 per cent eyedrops, and so care should be taken when considering administration to the elderly, or persons known to have uncontrolled hypertension or severe cardiovascular disease. Additionally, exaggerated responses may occur due to reduced bioelimination in individuals using MAO inhibitors, such as the antidepressant phenelzine (Nardil). Drug manufacturers also note that the pressor response of adrenergic agents may be potentiated by tricyclic antidepressants, propranolol, reserpine, guanethidine, methyldopa, and atropine-like drugs.

MULTIPLE-CHOICE QUESTIONS – take part at opticianonline.net

1 Which of the following drugs is not an anticholinergic?
A Atropine
B Cyclopentolate
C Tropicamide
D Phenylephrine

2 How is phenylephrine eliminated in the eye?
A Metabolised by the liver
B Absorbed by cornea
C Oxidised by enzymes
D Diffuses into the blood

3 Which of the following drugs acts the fastest?
A Atropine
B Cyclopentolate
C Tropicamide
D Phenylephrine

4 Which of the following drugs has the least effect on accommodation?
A Tropicamide
B Cyclopentolate
C Tropicamide
D Phenylephrine

5 Which of the following drugs could raise blood pressure?
A Atropine
B Cyclopentolate
C Tropicamide
D Phenylephrine

6 Which of the following is expected to give the best dilation?
A Tropicamide 1%
B Phenylephrine 10%
C Tropicamide 1% and Cyclopentolate 1%
D Tropicamide 0.5% and Phenylephrine 2.5%

Successful participation in this module counts as one credit towards the GOC CET scheme administered by Vantage and one towards the Association of Optometrists Ireland's scheme.
The deadline for responses is September 20 2012

References

1 Mitry D *et al.* The epidemiology of rhegmatogenous retinal detachment: geographical variation and clinical associations. *Br J Ophthalmol,* 2010;94:678-84.
2 Marchini G *et al.* Comparative Study of the Effects of 2% Ibopamine, 10% Phenylephrine, and 1% Tropicamide on the Anterior Segment. *Invest Ophthalmol Vis Sci,* 2003;44:281-9.

Dr Michael Johnson is an independent prescribing optometrist who owns Johnson & Furze Optometrists, works in the Glaucoma and Accident & Emergency departments at Bristol Eye Hospital, and maintains the patient website www.eyepedia.co.uk