Anisocoria in unilateral ophthalmic disease

Russell V Pearson, Geoffrey E Rose

Abstract
Pupillary diameters in the affected and unaffected eyes of 327 patients with unilocular red eye were assessed during fixation of a distant target. The mean pupillary diameters were similar in the unaffected eyes in each of eight diagnostic groups, but were significantly different (F=3.84, p<0.001) in the diseased eyes. With corneal abrasions (p<0.001), marginal keratitis (p<0.05), and acute anterior uveitis (p<0.001) the mean pupillary diameter for the affected eye was significantly smaller than that of the unaffected eye. The observed differences of pupillary diameter probably reflect the role of neuronal and autocrine mechanisms in the unilateral control of pupillary size.

The ocular response to injury comprises a reduction in the blood-ocular barrier, an intraocular pressure rise, and miosis.1-4 It is probable that the changes in the blood-ocular barrier and intraocular pressure are due to concentration of prostaglandins within the eye,5-7 this being a result of both increased production within11 and decreased clearance from12 the eye. The miosis, however, is probably caused both by intraocular prostaglandin accumulation and by substance P acting on the smooth muscle of the sphincter pupillae, this neuropeptide being released from trigeminal sensory radicals within the iris.13 The stimulus for the release of substance P is probably depolarisation of afferent sensory trigeminal fibres in the cornea and other ocular structures, with the efferent path being mediated through an axonal reflex.14 Central or peripheral trigeminal denervation reduces the accumulation of substance P and the miosis in response to injury.15 Calcitonin gene-related peptide (CGRP) occurs within trigeminal nerve fibres16,17 and dilates ocular blood vessels. CGRP and substance P might act synergistically in mediation of the ocular response to injury.18,19 Miosis in an inflamed eye, as compared to the unaffected fellow eye, is generally recognised among ophthalmologists as frequently being a sign of significant ocular pathology. The actual incidence in various diseases would not, however, appear to have been recorded.

In the present report the changes of pupillary diameter are determined for various diseases causing unilocular red eye, and the changes are considered in relation to the neuronal and autocrine mechanisms affecting pupillary diameter in a single eye.

Patients and methods
The pupillary diameter of patients with unilateral red eye, attending the Accident and Emergency Department of Moorfields Eye Hospital, was assessed in a room with uniform illumination of moderate intensity (approximately 1000 lux). The patient was instructed to fixate a distant, non-accommodative target at 3 metres, and the pupillary diameters were assessed by matching with a comparative scale. The scale was held alongside the pupil, care being taken to avoid the visual axis of the patient. The scale had 'half-pupil' marks along one edge, with diameter increments of 1 mm, thereby permitting diameter estimates to 0.5 mm gradations.

After recording the assessment of pupil size, a problem orientated history and ophthalmic examination was performed. The iris colour was also recorded.

Results
Three hundred and twenty-seven patients (213 male, 114 female) were enrolled in the study. In 317 patients the condition was one of eight major diagnostic categories (Table 1), and others (6 male, 4 female) having various conditions, namely trauma (5 eyes), stromal keratitis (2 eyes), corneal abscess (1 eye), chemical injury (1 eye), and acute angle-closure glaucoma (1 eye).

There was a predominance of males over females in all diagnostic groups except episcleritis (with a similar sex incidence). Dendritic keratitis and corneal foreign bodies occurred almost exclusively in men (Table 1).

There was a significant difference between the mean ages at presentation (Table 1. One-way analysis of variance: F7,309=4.92, p<0.001). Patients with subconjunctival haemorrhage were significantly older than those in each of the other seven diagnostic groups - that is, marginal or dendritic keratitis (p<0.05), corneal foreign body, episcleritis or iritis (p<0.01), and conjunctivitis or corneal abrasion (p<0.001). Similarly, those patients with marginal keratitis were significantly older than those with conjunctivitis (p<0.01) or corneal abrasion (p<0.05), and those with iritis were significantly older than those with conjunctivitis (p<0.05).

In the group overall, the side of involvement was similar (162 right, 155 left), though there was some variability between the subgroups. Likewise, with the exception of episcleritis, the ratio of involvement of blue/grey eyes with respect to brown/green was similar in all the groups (Table 1).

The average pupillary diameters in the unaffected 'white' eyes in the eight categories were not significantly different (Table 2, F7,309=1.57). In contrast, for the 'red' eyes there were significant differences between the mean diameters for the various diagnoses F7,309=3.84, p<0.001). The mean pupillary diameter for eyes with conjunctivitis (4.27 mm, 131 eyes) and iritis (3.65 mm, 44 eyes) were significantly (p<0.001) different, as were the diameters for eyes with...
Table 1. Characteristics and diagnosis for 317 patients with unilateral opthalmic disease

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients</th>
<th>Sex ratio (male/female)</th>
<th>Age (yrs) mean (SD) (range)</th>
<th>Inflamed eye (right/left)</th>
<th>Iris color (blue/brown)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subconjunctival haemorrhage</td>
<td>23</td>
<td>16/7</td>
<td>53.6 (17-9)</td>
<td>10/13</td>
<td>15/8</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>131</td>
<td>15/56</td>
<td>19 (9-84)</td>
<td>70/61</td>
<td>83/48</td>
</tr>
<tr>
<td>Episcleritis</td>
<td>13</td>
<td>6/7</td>
<td>37 (13-17)</td>
<td>97</td>
<td>1 (1.73)</td>
</tr>
<tr>
<td>Corneal foreign body</td>
<td>16</td>
<td>15/10</td>
<td>38 (10-13)</td>
<td>511</td>
<td>106/6</td>
</tr>
<tr>
<td>Corneal abrasion keratitis</td>
<td>31</td>
<td>21/10</td>
<td>44 (14-15)</td>
<td>20/11</td>
<td>19/12</td>
</tr>
<tr>
<td>Dendritic keratitis</td>
<td>8</td>
<td>8/0</td>
<td>36 (16-3)</td>
<td>1/7</td>
<td>3/5</td>
</tr>
<tr>
<td>Acute anterior uveitis</td>
<td>44</td>
<td>31/13</td>
<td>41 (16-8)</td>
<td>25/19</td>
<td>29/15</td>
</tr>
<tr>
<td>Totals</td>
<td>317</td>
<td>207/110</td>
<td>39 (4-94)</td>
<td>162/155</td>
<td>200/117</td>
</tr>
</tbody>
</table>

Table 2. Estimates of pupillary diameters in each of eight diagnostic categories of patients with unilateral inflamed ('red') eye

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients</th>
<th>'white' eye (mm)</th>
<th>'red' eye (mm)</th>
<th>Difference (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subconjunctival haemorrhage</td>
<td>23</td>
<td>3.89 (0-64)</td>
<td>3.96 (0-67)</td>
<td>-0.065 (0-23)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>131</td>
<td>4.31 (1-00)</td>
<td>4.27 (0-48)</td>
<td>-0.042 (0-26)</td>
</tr>
<tr>
<td>Episcleritis</td>
<td>13</td>
<td>3.77 (1-11)</td>
<td>3.77 (1-11)</td>
<td>0</td>
</tr>
<tr>
<td>Corneal foreign body</td>
<td>16</td>
<td>3.75 (0-97)</td>
<td>3.63 (0-92)</td>
<td>0.125 (0-34)</td>
</tr>
<tr>
<td>Corneal abrasion keratitis</td>
<td>51</td>
<td>4.08 (1-14)</td>
<td>3.74 (1-05)</td>
<td>0.34</td>
</tr>
<tr>
<td>Marginal keratitis</td>
<td>31</td>
<td>4.10 (1-29)</td>
<td>3.89 (1-22)</td>
<td>0.22</td>
</tr>
<tr>
<td>Dendritic keratitis</td>
<td>8</td>
<td>3.75 (0-76)</td>
<td>3.25 (0-89)</td>
<td>0.50 (0-66)</td>
</tr>
<tr>
<td>Acute anterior uveitis</td>
<td>44</td>
<td>4.10 (0-87)</td>
<td>3.65 (0-84)</td>
<td>0.45 (0-62)</td>
</tr>
</tbody>
</table>

*Mean (standard deviation).

Table 3. The incidence of anisocoria in each diagnosis and the frequency of anisocoria in which the pupil is smaller on the affected ('red') side

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients with anisocoria (blue/brown)</th>
<th>Number with red eye smaller anisocoria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subconjunctival haemorrhage</td>
<td>2 (9%) (1/1)</td>
<td>0/2</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>14 (11%) (7/7)</td>
<td>11/14</td>
</tr>
<tr>
<td>Episcleritis</td>
<td>0 (0%) (0/0)</td>
<td>0/0</td>
</tr>
<tr>
<td>Corneal foreign body</td>
<td>5 (31%) (5/2)</td>
<td>4/5</td>
</tr>
<tr>
<td>Corneal abrasion keratitis</td>
<td>21 (41%) (14/7)</td>
<td>20/21</td>
</tr>
<tr>
<td>Marginal keratitis</td>
<td>10 (32%) (3/1)</td>
<td>9/10</td>
</tr>
<tr>
<td>Dendritic keratitis</td>
<td>4 (30%) (3/1)</td>
<td>4/4</td>
</tr>
<tr>
<td>Acute anterior uveitis</td>
<td>24 (55%) (20/4)</td>
<td>22/24</td>
</tr>
</tbody>
</table>

**All eyes** | **Blue eyes** | **Bromen eyes** | **Significance (p)**
--- | --- | --- | ---
--- | --- | --- | ---
--- | --- | --- | ---
0/2 | 0 | 0 | 0.48
11/14 | 6 | 5 | 0.06
0 | 0 | 0 | ---
4/5 | 3 | 1 | 0.37
20/21 | 13 | 7 | <0.0001
9/10 | 6 | 3 | <0.03
4/4 | 3 | 1 | 0.13
22/24 | 19 | 3 | <0.0002

Two-tail probability of drawing observed overall incidence (t) of 'red eye smaller' anisocoria.

Discussion

In the present investigation a relative miosis, significant in both degree and incidence, was present in eyes with corneal abrasion, marginal keratitis, and acute anterior uveitis. This possibly reflects the mechanisms involved in the ocular response to injury.

Corneal abrasion is associated with marked stimulation of afferent fibres of the trigeminal nerve, manifest clinically as extreme pain. In these eyes it is probable that the miosis is mediated through a trigeminal axon reflex, with release of substance P (and possibly CGRP) at nerve fibres on the sphincter pupillae.

With acute anterior uveitis the miosis is probably due to an accumulation of prostaglandins and other autacoids within the inflamed eye.17,18 The presence of pain with acute anterior uveitis might, however, imply a partial mediation through trigeminal axon reflexes. Similarly, the miosis of marginal keratitis is probably induced by both neuronal and autacoid mechanisms, marginal keratitis being an immune process occurring at a site rich in trigeminal sensory innervation.

Subconjunctival haemorrhage, conjunctivitis, and episcleritis did not cause a significant miosis in the present investigation, perhaps because these diseases occur in tissues remote from the anterior chamber of the eye and in tissues with relatively poor trigeminal innervation.

The absence of significant miosis with corneal foreign bodies or dendritic keratitis (Tables 2 and 3) would appear to be enigmatic, these lesions arising in tissues with considerable trigeminal innervation. However, although a corneal foreign body disrupts corneal (trigeminal) nerves, this occurs over a very much frequency of anisocoria in blue/grey eyes as compared with brown/green eyes with the same diagnosis ranged from 1-0 for subconjunctival haemorrhage or conjunctivitis to 5-0 for iritis (Table 3). This contrasts with an iris colour frequency-ratio of 1-71 for blue/grey eyes with respect to brown/green eyes.

In the 80 eyes with anisocoria, 'red eye smaller' anisocoria occurred in 70 eyes, and the proportion was similar in the two groups of iris colouration (for each of the diagnoses – Table 3). The incidence of 'red eye smaller' anisocoria, without respect to iris colour, ranged from 0% (with subconjunctival haemorrhage) to greater than 90% (marginal keratitis, iritis, corneal abrasion, or dendritic ulceration). The prob-
smaller area than that with most corneal abrasions. Moreover, whereas an abrasion exposes nerve endings, those under a foreign body are not exposed to the external environment. The relatively painless nature of corneal foreign bodies, as compared with abrasions, is compatible with a reduced trigeminal afferent stimulation. The lack of a significant miosis with herpetic dendritic keratitis is probably due to insufficient numbers in this group (eight cases). It is possible, however, that both the absence of intraocular inflammation and a malfunctioning of virus affected trigeminal neurons might reduce the incidence of miosis in such eyes.

To elucidate further the mechanisms causing miosis in ocular disease it would be of particular interest to ascertain whether blockage of the trigeminal afferent response with topical anaesthesia reduces or prevents the miosis in, for example, patients with corneal abrasion. Similarly, the use of antagonists to prostaglandin synthesis might prevent the miosis associated with marginal keratitis or acute anterior uveitis, this reflecting a role for autacoids in these diseases.

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