Ocular side-effects of drugs

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The eye may manifest side-effects from a wide variety of drugs used in the treatment of diseases of all systems of the body. Some of these side-effects, though undesirable, have to be accepted as unavoidable. The discovery of serious ocular defects arising in association with the long-term use in high dosage of such drugs as the antimalarials, the phenothiazines, and the steroid hormones has indicated the need for all prescribers to be aware of the risks involved. Particularly is this so since some of the toxic effects have seriously impaired vision and proved to be irreversible. A tabulated synopsis of ocular side-effects is presented, based on the classification of drugs by their use in the treatment of diseases of the various systems of the body as given in the 1966 British National Formulary.

The many factors concerned in the production of ocular side-effects by a drug include:

1. The nature of the drug.
2. The amount of the drug consumed.
3. The route of its administration.
4. The general health of the patient, and in particular the condition under treatment.
5. The element of individual idiosyncrasy (an inherited predisposition to an abnormal reaction to a drug).
6. Other substances consumed simultaneously or within a short interval of the drug which may potentiate its toxic effects.
7. Previous exposure to the drug.

Nature of the drug
This determines the rate of its absorption into the body and its pharmacological effects on the body’s metabolism together with the mode and ease of its detoxication and excretion. The ease with which a drug passes into the general circulation and thence into the eye determines the ability of systemically administered drugs to affect the eye directly. Some drugs have been thought to produce ocular side-effects indirectly by their influence on the general circulation (e.g. amaurosis from a precipitous fall in blood pressure due to the use of detensive drugs) or the blood (e.g. intraocular haemorrhages produced by anticoagulants or drugs producing aplastic anaemia, agranulocytosis, or thrombocytopenia.

Amount of the drug
Toxic levels of drugs may be reached in some instances by high daily dosage and in others, where detoxication and excretion are slow, by prolonged consumption. The effect of dosage in ocular toxicity is well-illustrated in the case of the antimalarials. As a malaria
suppressive, dosages of chloroquine of the order of 500 mg. weekly are used and ocular complications are rare, though corneal oedema from mepacrine was first noted in such circumstances (Chamberlain and Boles, 1946; Abbey and Lawrence, 1946; Reese, 1946). In the treatment of rheumatoid arthritis, lupus erythematosus, and actinic dermatitis, doses of up to 1,000 mg. chloroquine daily are used and ocular complications have now been extensively recorded and necessitate regular ophthalmic examination of such patients.

**Route of administration**

While it is natural in dealing with this subject to think in terms of drugs administered orally or parenterally, it must not be forgotten that topical application of drugs at a distance from the eye may allow sufficient absorption to risk ocular side-effects. The danger of absorption of toxic substances applied to burns was stressed in a leading article in the *British Medical Journal* of June 3, 1967. Systemic argyrosis following the application of silver compounds to skin ulcers was noted in four of a large series of cases of argyrosis reviewed by Hill and Pillsbury (1939). A case of systemic and ocular ochronosis following the protracted application of carbolic acid to varicose ulcers (Beddard, 1910) and another of toxic amblyopia from the use of iodoform for an ulcerated carcinoma of the breast (Critchett, 1898) have been reported.

The eyes are frequently involved in the generalized sensitivity reactions occurring from the topical use of drugs, particularly the antibiotics. Conversely, Gerber (1957) reported a patient who developed generalized urticaria as well as a local allergic response after the treatment of herpetic keratitis by Gifford's iodine administered topically.

**Patients' general health and condition under treatment**

Liver and renal disease frequently affect the detoxication and excretion of drugs, allowing them to accumulate to toxic levels. In some instances, it is difficult to determine whether an ocular defect has arisen as a result of involvement with the general disease or as a toxic manifestation of a drug used in therapy. This was the cause of doubt regarding the toxicity to the optic nerve of the arsenicals, particularly tryparsamide, when used in the treatment of neurosyphilis, and of streptomycin when used in tuberculous meningitis.

**Individual idiosyncrasy**

Rosenheim (1958) classified the unwanted effects of drugs as:

1. overdosage;
2. intolerance, *i.e.* a lower threshold to the normal pharmacological action of the drug;
3. side-effects;
4. secondary effects, *i.e.* indirect consequences of the primary action of the drug;
5. idiosyncrasy, *i.e.* an inherent, qualitatively abnormal reaction to the drug;
6. hypersensitivity, *i.e.* a reaction conditioned by previous exposure to the drug.

Many of the isolated reports of ocular side-effects from drugs may well be the result of individual idiosyncrasy. However, in a few instances of drug toxicity, it has been shown that the tendency to an abnormal response to a drug or group of drugs is inherited and the
subject of pharmacogenetics is attracting increasing attention (Vogel, 1959). The
dominant inheritance of the ocular hypertensive response to topical steroids (Becker and
Hahn, 1964; Armaly, 1965, 1966; Becker, 1965; Becker and Chevrette, 1966) is an example
of ophthalmic interest. In certain individuals a lack of acetyl transferase slows the rate of
inactivation by acetylation of isoniazid, exposing these patients to a greater risk of toxic
effects, including the rare optic neuritis (Sutton and Beattie, 1955; Keeping and Searle,
This enzyme deficiency is dominantly inherited.

Interaction with other substances consumed at the same time
While it has been observed that the combination of some drugs tends to reduce their
therapeutic effect, in other instances full use has been made of the potentiation of their
therapeutic effect, particularly in the case of the tuberculostatic drugs. Unfortunately,
certain drugs consumed in combination with other substances have potentiated toxic
effects. An example is the potentiation of the hypertensive effects of the monoamine
oxidase inhibitors by such drugs as amphetamine and methyldopa, or by the tyramine-
containing foods such as cheese. Conversely, hypotensive effects are produced by a
combination of monoamine oxidase inhibitors with the barbiturates, phenothiazines,
thiazide diuretics, and imino-dibenzyl anti-depressants (Bouvier and Thénot, 1966;
Goodman and Gilman, 1965).

Previous exposure to the drug
The ability of non-protein drugs to act as haptens and so sensitize the patient is responsible
for much iatrogenic disease, particularly where drugs are applied topically over long
periods, and this is frequently seen in the field of ophthalmic therapeutics, e.g. sensitization
to topical atropine.

Results of present analysis of drugs in current use
These are tabulated in the Appendix (pp. 256–262); the drugs are classified according
to the system affected, and the purpose for which they are administered.

Conclusions
All physicians must be aware of the known risks to which our patients may be exposed by
the prescription of modern therapeutic agents and be constantly alert to risks as yet
undiscovered or unrecorded. The collection of data regarding such possible or actual side-
effects by a central agency is already being carried out in many countries, but the evaluation
of such data is by no means easy (Cahal, 1968). This was seen in the attempt to
correlate ocular complications arising in women taking female sex hormones as contracep-
tive pills with the drugs concerned (Walsh, Clark, Thompson, and Nicholson, 1965). We
must be careful not to condemn a drug of proven usefulness unless the evidence of drug-
induced toxicity is unequivocal or the severity of the side-effect warrants more careful
appraisal.

My thanks are due to Mr. John Foster, F.R.C.S., for stimulating my interest in this subject and for his many
helpful suggestions.
References


BECKER, B. (1965) Invest. Ophthal., 4, 198


CHAMBERLAIN, W. P., and BOLES, D. J. (1946) Arch. Ophthal. (Chicago), 35, 120


SUGGESTED FURTHER READING


## Appendix
Classification of drugs and therapeutic substances, showing purpose of administration and effects on the eyes

<table>
<thead>
<tr>
<th>Broad classification</th>
<th>Drugs groups</th>
<th>Principal general uses</th>
<th>Possible ocular side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I ALIMENTARY SYSTEM</strong></td>
<td><strong>(i) Antispasmodics</strong></td>
<td>Anticholinergic (parasympatholytic), <em>e.g.</em> Atropine</td>
<td>Peptic ulceration, Intestinal colic, Ulcerative colitis</td>
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<td></td>
<td><strong>(ii) Purgatives</strong></td>
<td>Parasympathomimetic, <em>e.g.</em> Carbachol</td>
<td>Relief of intestinal distension and evacuation of bowel, Aiding passage of ureteric calculi, Postoperative urinary retention</td>
</tr>
<tr>
<td><strong>II CARDIOVASCULAR SYSTEM</strong> (including Diuretics)</td>
<td><strong>(i) Cardiac glycosides</strong></td>
<td><em>e.g.</em> Digitalis</td>
<td>Congestive heart failure, Conversion of atrial flutter to atrial fibrillation</td>
</tr>
<tr>
<td></td>
<td><strong>(a) Antihypertensives</strong></td>
<td>(a) Ganglion blocking agents, <em>e.g.</em> Hexamethonium</td>
<td>Essential hypertension</td>
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<tr>
<td></td>
<td><strong>(b) Adrenergic drugs</strong>, <em>e.g.</em> Bretylium tosylate</td>
<td>Essential hypertension</td>
<td>Diplopia, Ptosis</td>
</tr>
</tbody>
</table>
### Ocular side-effects of drugs

#### (4) Diuretics

| (a) Thiazide diuretics, e.g. Chlorothiazide | Essential hypertension Oedematous conditions | Yellow vision (xanithopsia) Transient myopia Retinal oedema |
| (b) Carbonic anhydrase inhibitors, e.g. Acetazolamide | Epilepsy Glaucoma Congestive heart failure | Transient myopia Retinal oedema Ocular hypotony |
| (c) Frusemide (Lasix) | Essential hypertension Oedematous conditions | Altered colour vision |

#### III NERVOUS SYSTEM

### (x) Analgesics

| e.g. Morphine and Dipipanone e.g. Antipyrine | Powerful analgesia Mild analgesia and antipyresis | Miosis Urticaria of lids and keratoconjunctivitis Toxic amblyopia Toxic amblyopia ? Cortical blindness Mydriasis Conjunctivitis (allergic) Nystagmus Ocular hypotony Hallucinations |
| e.g. Salicylates | Mild analgesia (also antipyretic and antirheumatic effects) |

### (z) Hypnotics

| e.g. Barbiturates | Insomnia Anxiety states | Ptsis Extraocular palsies: diplopia Nystagmus Allergic conjunctivitis Blindness—usually temporary? of cortical or peripheral origin Miosis (mydriasis in overdosage) Diplopia Ptsis Allergic dermatitis and conjunctivitis Transient amaurosis |
| e.g. Chloral hydrate | Insomnia Anxiety states |

### (3) Sedatives and tranquillizers

<p>| Phenothiazines, e.g. Chlorpromazine | Schizophrenia and other psychiatric disorders Confusional states in the elderly Pruritic skin disorders Anti-emesis | Oculogyric crises in a Parkinsonian-type extrapyramidal syndrome Ocular melanosis involving lids, conjunctiva, cornea, lens (cataract forming), and retina with defective vision Miosis Temporary cycloplegia Temporary toxic amblyopia Possibly glaucoma |</p>
<table>
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<tbody>
<tr>
<td>(4) Anti-depressants</td>
<td>e.g. Imipramine</td>
<td>Endogenous depression, Tension and anxiety states, Insomnia and anorexia, Schizophrenia</td>
<td>Toxic amblyopia, Mydriasis, Cycloplegia, Diplopia, Glaucoma, Mydriasis, Cycloplegia, Widening of palpebral aperture, Disturbed colour vision, Mydriasis, Cycloplegia, Nystagmus, Extraocular muscle palsies, Toxic amblyopia</td>
</tr>
<tr>
<td></td>
<td>e.g. Amphetamines</td>
<td>Narcolepsy, Stimulation of respiration, Obesity, Depression, Angina pectoris, Essential hypertension</td>
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<tr>
<td></td>
<td>e.g. Monoamine oxidase inhibitors</td>
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<td>(5) Anti-motion sickness</td>
<td>e.g. Hyoscine hydrobromide</td>
<td>Prophylaxis against motion sickness</td>
<td>Parasympatholytic effects (see under Alimentary System: Antispasmodics)</td>
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<td></td>
<td>e.g. Antihistamine</td>
<td>Ditto, Anti-emesis, Sedation, Allergic diseases</td>
<td>Ditto</td>
</tr>
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<td>(6) Anti-convulsants</td>
<td>e.g. Phenytoin sodium (Epanutin)</td>
<td>Grand mal epilepsy</td>
<td>Allergic dermatitis and conjunctivitis, Rarely: Diplopia, nystagmus, ptosis, hallucinations and blurred vision, &quot;Glare&quot; phenomenon and photophobia, Impaired colour vision, Oedema of lids and orbit, Visual hallucination, See under Hypnotics: Barbiturates</td>
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<td>e.g. Troxidone (Tridione)</td>
<td>Petit mal, Psychomotor epilepsy</td>
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<td></td>
<td>e.g. Primidone (Mysoline)</td>
<td>Grand mal, Petit mal, Epilepsy, Parkinsonism</td>
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<td>e.g. Phenobarbitone</td>
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<td>(7) Anti-parkinsonian</td>
<td>e.g. Parasympatholytics (Belladonna alkaloids, etc.)</td>
<td>Parkinsonism</td>
<td>See under Alimentary system: Antispasmodics, Ocular palsies: diplopia, Nystagmus</td>
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<tr>
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<td>e.g. Mephenesin</td>
<td>Parkinsonism</td>
<td></td>
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<tr>
<td>(8) Cholinergic</td>
<td>(parasympathomimetic)</td>
<td>Myasthenia gravis</td>
<td>Miosis</td>
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</table>
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<tr>
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<th>Side-effects</th>
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<tr>
<td>10 Local anaesthetics</td>
<td>e.g. Cocaine&lt;br&gt;Local anaesthesia&lt;br&gt;Formerly in Gram-positive infections, malaria, and influenza</td>
</tr>
<tr>
<td>1 Sulphonamides, etc.</td>
<td>(a) Sulphonamides&lt;br&gt;Urinary and gastrointestinal infections, especially with <em>E. coli</em>, dysentery bacilli, <em>B. haemolytic streptococci</em>, pneumococci, meningococci, and TRIC virus&lt;br&gt;Exudative or pemphigoid conjunctivitis in a Stevens-Johnson type syndrome&lt;br&gt;Ocular palsies&lt;br&gt;Iritis&lt;br&gt;Retinal oedema and haemorrhages&lt;br&gt;Toxic amblyopia</td>
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<td>(b) Ethambutol&lt;br&gt;TB resistant strains&lt;br&gt;Toxic amblyopia</td>
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<td></td>
<td>(c) Ethylhydrocupreine hydrochloride (Optochin)&lt;br&gt;Formerly in pneumococcal infections&lt;br&gt;Toxic amblyopia</td>
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<td></td>
<td>(d) Furaladone (withdrawn)&lt;br&gt;Various systemic infections and trypanosomiasis&lt;br&gt;Ocular palsies&lt;br&gt;Diplopia&lt;br&gt;Nystagmus&lt;br&gt;Blurring of vision</td>
</tr>
<tr>
<td></td>
<td>(e) Isonicotinic acid hydrazide (INAH)&lt;br&gt;Tuberculosis&lt;br&gt;Toxic amblyopia</td>
</tr>
<tr>
<td></td>
<td>(f) Thiacetzone&lt;br&gt;Paraminosalicylic acid&lt;br&gt;Tuberculosis&lt;br&gt;Ocular palsies&lt;br&gt;Diplopia&lt;br&gt;Nystagmus&lt;br&gt;Blurring of vision&lt;br&gt;Keratoconjunctivitis secondary to arsenical dermatitis&lt;br&gt;Toxic amblyopia&lt;br&gt;Transient myopia&lt;br&gt;Retinal and vitreous haemorrhages</td>
</tr>
<tr>
<td>2 Heavy metals</td>
<td>(a) Arsenicals&lt;br&gt;Syphilis&lt;br&gt;Yaws&lt;br&gt;Relapsing fever&lt;br&gt;Trypanosomiasis&lt;br&gt;Keratoconjunctivitis secondary to arsenical dermatitis&lt;br&gt;Toxic amblyopia&lt;br&gt;Transient myopia&lt;br&gt;Retinal and vitreous haemorrhages</td>
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</tbody>
</table>
| (b) Antimony compounds | Leishmaniasis  
Schistosomiasis  
Filariaasis | Toxic amblyopia  
Yellowing of skin and sclerae |
| (c) Mercurials | Syphilis  
Formerly in teething powders | Mercury deposits in conjunctiva and cornea  
Photophobia (e.g. in “pink disease”) |
| (d) Gold salts | Rheumatoid arthritis | Chrysosisis of conjunctiva, cornea, and lens  
Keratoconjunctivitis  
Involvement of lids by exfoliative dermatitis  
Ocular palsy and nystagmus secondary to encephalitis |
| (e) Thallium | Formerly as depilatory in ringworm | Cataract  
Ptoasis  
Extraocular muscle palsy  
Mydriasis  
Toxic amblyopia |
| (f) Lead compounds | Formerly as astringents by ingestion, now only for external applications | Toxic amblyopia  
Ocular palsy  
Papilloedema  
Mydriasis  
Cycloplegia |
| (g) Antiprotozoan | e.g. Quinine  
Malaria  
Myotonic conditions  
Illegally as abortifacient | Toxic amblyopia  
Peripheral contraction of visual fields and central scotomata  
Diplopia  
Ocular anaesthesia  
Iris atrophy  
Keratopathy  
Pigmentary retinopathy and macular degeneration  
Ocular palsy  
Ptoasis  
Whitening of eyelashes  
Decreased corneal sensitivity  
Corneal oedema (Menopause)  
Gingivalis |
| V ANTI-BIOTICS | (1) Chloramphenicol | Typhoid fever
*Haemophilus influenzae*
meningitis | Toxic amblyopia |
| (2) Streptomycin | Tuberculosis
Urinary tract infections | Toxic amblyopia |

| VI DRUGS AFFECTING
METABOLISM | (1) Antithyroid | e.g. Carbimazole
e.g. Radioactive iodine
e.g. Iodides | Hyperthyroidism | Risk of precipitating malignant
exophthalmos end
ophthalmoplegia
Conjunctivitis
Keratitis
Iritis
Intraocular haemorrhage |
| (2) Hypoglycaemic | e.g. Chlorpropamide | Diabetes mellitus
Schizophrenia (insulin) | Mydriasis
Diplopia
Exudative conjunctivitis
Toxic amblyopia
Visual hallucinations
Change in refractive error |

| VII HORMONES | (1) ACTH and steroids | Replacement therapy
Suppression of inflammatory,
allergic, and antibody-forming
reactions
Some malignant diseases,
e.g. lymphatic leukaemia | Transient myopia (ACTH)
Posterior subcapsular cataract
Glaucoma
Potentiation of viral, bacterial,
and fungal ocular infections
? Papilloedema from raised
intracranial pressure during
therapy or on withdrawal |
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</thead>
</table>
| (a) Female sex hormones | Menstrual and ovulatory disorders  
| | Suppression of lactation  
| | Carcinoma of prostate and breast  
| | Oral contraception | Papilloedema  
| | Ocular palsies with diplopia  
| | Nystagmus  
| | Optic neuritis  
| | Occlusion of central retinal artery and vein  
| | Retinal perivasculitis  
| | Cyclitis  
| | Cycloplegia and mydriasis  
| | Homonymous hemianopia  
| | Hallucinations  
| | Phosphenes  
| | Migraine  
| | Scotomata  
| | (All reported, particularly in patients taking oral contraceptives, but evidence for drug responsibility indefinite) |
| (b) Vitamin D (often plus calcium) | Vitamin A  
| | Hypovitaminosis  
| | Empirically in some skin disorders | Loss of brows and eyelashes  
| | Ocular palsies  
| | Nystagmus  
| | Exophthalmos  
| | Papilloedema  
| | Retinal haemorrhage  
| | Rickets  
| | Osteomalacia  
| | Hypocalcaemic tetany | Band-shaped corneal degeneration with calcium deposits in conjunctiva and cornea |
| (c) Miscellaneous | Butazolidin  
| | Gout  
| | Rheumatoid arthritis | Conjunctivitis  
| | Retinal haemorrhages  
| | Toxic ambyopia  
| | Indomethacin | Rheumatoid arthritis  
| | Various skin disorders | Conjunctivitis  
| | Keratitis |
| (3) Chrysarobin and Resorcinol | Various skin disorders |
| (4) Oxygen | Neonatal asphyxia and prematurity  
| | Hypoxic states | Retrolental fibroplasia in premature infants  
| | Blurring of vision |
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