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 malar

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 Chevette, 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, 1955; Kass, Mandel, Cohen, and Dressler, 1957; Kalinowski, Lloyd, and Moyes, 1961). 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 methyl dopa, 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 contraceptive 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.

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

Broad classification	Drugs groups	Principal general uses	Possible ocular side-effects
I ALIMENTARY SYSTEM	Antispasmodics (1)	Anticholinergic (parasympatholytic), <i>e.g.</i> Atropine	Mydriasis: risk of angle-closure glaucoma Cycloplegia: difficulty with near vision Diminished lacrimal secretion Diplopia Hallucinations
	Purgatives (2)	Parasympathomimetic, <i>e.g.</i> Carbachol	Miosis Lowering of intraocular pressure
II CARDIOVASCULAR SYSTEM (including Diuretics)	Cardiac glycosides (1)	<i>e.g.</i> Digitalis	Disturbances of colour vision "Snowy" vision Scotomata Cortical blindness Lowering of intraocular pressure Ocular palsies Conjunctivitis
	Antihypertensives (2)	Ganglion blocking agents, <i>e.g.</i> Hexamethonium (a) (b)	Mydriasis: risk of angle-closure glaucoma Cycloplegia: difficulty with near vision Diminished lacrimal secretion Intraocular pressure may be lowered in normal eyes and in cases of chronic simple glaucoma Loss of vision? toxic amblyopia or due to rapid fall in blood pressure Reserpine induces miosis and conjunctival irritation

(4) <i>Diuretics</i>	(a) Thiazidine diuretics, <i>e.g.</i> Chlorothiazide	Essential hypertension Oedematous conditions	Yellow vision (xanthopsia) Transient myopia Retinal oedema
	(b) Carbonic anhydrase inhibitors, <i>e.g.</i> 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			
(1) <i>Analgesics</i>	<i>e.g.</i> Morphine and Dipipanone <i>e.g.</i> Antipyrine	Powerful analgesia Mild analgesia and antipyresis	Miosis Urticaria of lids and kerato- conjunctivitis Toxic amblyopia Toxic amblyopia ? Cortical blindness Mydriasis Conjunctivitis (allergic) Nystagmus Ocular hyoptony Hallucinations
	<i>e.g.</i> Salicylates	Mild analgesia (also antipyretic and antirheumatic effects)	
	<i>e.g.</i> Barbiturates	Insomnia Anxiety states	Ptosis Extraocular palsies; diplopia Nystagmus Allergic conjunctivitis Blindness—usually temporary? of cortical or peripheral origin Miosis (mydriasis in overdosage) Diplopia Ptosis Allergic dermatitis and conjunctivitis Transient amaurosis
(2) <i>Hypnotics</i>	<i>e.g.</i> Chloral hydrate	Insomnia Anxiety states	
(3) <i>Sedatives and tranquillizers</i>	Phenothiazines, <i>e.g.</i> 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

Broad classification	Drug groups	Principal general uses	Possible ocular side-effects
	(4) <i>Anti-depressants</i>	<i>e.g.</i> Imipramine	Toxic amblyopia Mydriasis Cycloplegia Diplopia Glaucoma Mydriasis Cycloplegia Widening of palpebral aperture Disturbed colour vision Mydriasis Cycloplegia Nystagmus Extraocular muscle palsies Toxic amblyopia
		<i>e.g.</i> Amphetamines	
		<i>e.g.</i> Monoamine oxidase inhibitors	
	(5) <i>Anti-motion sickness</i>	<i>e.g.</i> Hyoscine hydrobromide	Parasympatholytic effects (see under Alimentary System: Antispasmodics)
		<i>e.g.</i> Antihistamine	Ditto
	(6) <i>Anti-convulsants</i>	<i>e.g.</i> Phenytoin sodium (Epanutin)	Allergic dermatitis and conjunctivitis Rarely: Diplopia, nystagmus, ptosis, hallucinations and blurred vision “Glare” phenomenon and photophobia Impaired colour vision Oedema of lids and orbit Visual hallucination See under Hypnotics: Barbiturates
		<i>e.g.</i> Troxidone (Tridione)	
		<i>e.g.</i> Primidone (Mysoline)	
		<i>e.g.</i> Phenobarbitone	
	(7) <i>Anti-parkinsonian</i>	<i>e.g.</i> Parasympatholytics (Belladonna alkaloids, etc.) <i>e.g.</i> Mephenesin	See under Alimentary system: Antispasmodics Ocular palsies: diplopia Nystagmus

			raising intraocular pressure
(10)	Local anaesthetics	<i>e.g.</i> Cocaine	Allergic conjunctivitis Mydriasis Cycloplegia Ptosis Transitory amblyopia Toxic amblyopia Ptosis
		<i>e.g.</i> Isopentylhydrocupreine dihydrochloride (Eucupin)	Local anaesthesia, especially in anorectal surgery and anal pruritis Formerly in Gram-positive infections, malaria, and influenza
IV CHEMOTHERAPEUTIC DRUGS			
(1)	Sulphonamides	(a)	Urinary and gastrointestinal infections, especially with <i>E. coli</i> , dysentery bacilli, <i>B. haemolytic streptococci</i> , pneumococci, meningococci, and TRIC virus
		(b)	Exudative or pemphigoid conjunctivitis in a Stevens-Johnson type syndrome Transient myopia Ocular palsies Iritis Retinal oedema and haemorrhages Toxic amblyopia
		(c)	TB resistant strains Toxic amblyopia
		(d)	Formerly in pneumococcal infections Toxic amblyopia
		(e)	Various systemic infections and trypanosomiasis Ocular palsies Diplopia Nystagmus Blurring of vision
		(f)	Tuberculosis Toxic amblyopia
(2)	Heavy metals	(a)	Ocular itching and burning Rare reports of toxic amblyopia
		(a)	Keratoconjunctivitis secondary to arsenical dermatitis Toxic amblyopia Transient myopia Retinal and vitreous haemorrhages

<i>Broad classification</i>	<i>Drug groups</i>	<i>Principal general uses</i>	<i>Possible ocular side-effects</i>
	(b) Antimony compounds	Leishmaniasis Schistosomiasis Filariasis	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	Chrysoesis of conjunctiva, cornea, and lens Keratococonjunctivitis Involvement of lids by exfoliative dermatitis Ocular palsies and nystagmus secondary to encephalitis
	(e) Thallium	Formerly as depilatory in ringworm	Cataract Ptosis Extraocular muscle palsies Mydriasis Toxic amblyopia
	(f) Lead compounds	Formerly as astringents by in- gestion, now only for external applications	Toxic amblyopia Ocular palsies Papilloedema Mydriasis Cycloplegia

(3) 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 palsies Ptosis Whitening of eyelashes
	e.g. Chloroquine	Malaria Amoebic hepatitis Rheumatoid conditions Discoid and systemic lupus erythematosus	

Toxic amblyopia with mydriasis
Occasionally permanent blindness
with optic atrophy

Tapeworm infestation

e.g. Aspidium (*Filix mas.*)

V ANTIBIOTICS	(1) Chloramphenicol	Typhoid fever <i>Haemophilus influenzae</i> meningitis	Toxic amblyopia
	(2) Streptomycin	Tuberculosis Urinary tract infections	Toxic amblyopia
VI DRUGS AFFECTING METABOLISM	(1) Antithyroid <i>e.g.</i> Carbimazole, <i>e.g.</i> Radioactive iodine <i>e.g.</i> Iodides	Hyperthyroidism	Risk of precipitating malignant exophthalmos and ophthalmoplegia Conjunctivitis Keratitis Iritis Intraocular haemorrhage
	(2) Hypoglycaemic <i>e.g.</i> Chlorpropamide	Diabetes mellitus Schizophrenia (insulin)	Mydriasis Diplopia Exudative conjunctivitis Toxic amblyopia Visual hallucinations Change in refractive error
VII HORMONES	ACTH and steroids (1)	Replacement therapy Suppression of inflammatory, allergic, and antibody-forming reactions Some malignant diseases, <i>e.g.</i> 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

<i>Broad classification</i>	<i>Drug groups</i>	<i>Principal general uses</i>	<i>Possible ocular side-effects</i>
VIII VITAMINS	(2) 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)
	(1) Vitamin A	Hypovitaminosis Empirically in some skin disorders	Loss of brows and eyelashes Ocular palsies Nystagmus Exophthalmos Papilloedema Retinal haemorrhage
IX MISCELLANEOUS	(2) Vitamin D (often plus calcium)	Rickets Osteomalacia Hypocalcaemic tetany	Band-shaped corneal degeneration with calcium deposits in conjunctiva and cornea
	(1) Butazolidin	Gout Rheumatoid arthritis	Conjunctivitis Retinal haemorrhages Toxic amblyopia
	(2) Indomethacin	Rheumatoid arthritis	Mydriasis Diplopia Toxic amblyopia
	(3) Chrysarobin and Resorcinol	Various skin disorders	Conjunctivitis Keratitis
	(4) Oxygen	Neonatal asphyxia and prematurity	Retrolental fibroplasia in premature infants