PAPERS AND ORIGINALS

Untoward Effects Associated with Practolol Administration: Oculomucocutaneous Syndrome

PETER WRIGHT

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Summary

Keratoconjunctivitis sicca, conjunctival scarring, fibrosis, metaplasia, and shrinkage developed in 27 patients as an adverse reaction to practolol. Rashes, nasal and mucosal ulceration, fibrous or plastic peritonitis, pleurisy, cochlear damage, and secretory otitis media also occurred in some cases. Three patients suffered profound visual loss though most retained good vision. Symptoms and signs improved on withdrawal of the drug, but reduction of tear secretion persisted in most patients.

Introduction

Scarring of the conjunctiva with a reduction in tear flow occurs in many disorders, though patients are all too often regarded as untreatable or offered only symptomatic relief with artificial tear drops because they are thought to have Sjögren's syndrome or ocular pemphigoid, signs such as transient skin eruptions during long-term treatment having been ignored. Nevertheless, there are often specific changes in the conjunctiva which may enable an accurate diagnosis to be made and the long-term prognosis decided (Jones, 1961).

Patients

Twenty-seven patients (11 men 16 women) with unusual eye signs and a distinctive pattern of involvement of skin and other organs were seen over 18 months. All were taking practolol for ischaemic heart disease, arrhythmia, or hypertension (see table), and 19 were also taking diuretics, cardiac glycosides, or anticoagulants. The patient's unusual ocular conditions, which resulted from gross reduction in tear flow, had been managed conventionally with artificial tear drops, mucolytics, and control of infection, and routine investigations had shown no systemic cause for the reduced tear flow. The symptoms had proved recalcitrant, and three patients had developed corneal lesions quite unlike those seen in keratoconjunctivitis sicca which caused corneal opacity, perforation, and profound impairment of vision.

EYES

The patients all complained of hot, gritty, foreign-body sensations and photophobia typical of dry eyes (Wright, 1971) but got little relief from frequent use of artificial tears. Most were also troubled by stringy tenacious mucus. Vision was good in some patients and profoundly reduced in others; the extent of impairment depended on the degree of corneal involvement. The ocular signs were graded as follows: grade 1, gross reduction of tear flow with conjunctival scarring and shrinkage and corneal stromal involvement resulting in opacification, stromal melting, or corneal perforation; grade 2, lesser impairment of tear flow and conjunctival scarring and shrinkage but with corneal changes limited to the epithelium; grade 3, some reduction of tear flow and minimal conjunctival signs without corneal involvement.

The first conjunctival signs were hyperaemia and increased prominence of the papillary tufts. A less ordered pattern of blood vessels later developed, with some areas of relative avascularity and other areas where vessels actively proliferated, with fresh vascular loops growing from the vessels in the normal papillae. The changes were most obvious in the depths of the upper and lower fornix and in the conjunctiva of the tarsal plate. As those abnormal vessels developed they were followed by fibroblasts and a subconjunctival sheet of fibrovascular tissue was produced, which later contracted to produce the typical scarring, conjunctival shrinkage, and fornix obliteration (figs. 1 and 2). In the most severe cases the proliferative reaction extended on to the bulbar conjunctiva and produced an exuberant

FIG. 1—Lower conjunctival fornix showing abnormal vessels, fibrosis, and shallowing.

Details of Patients with Oculomucocutaneous Syndrome

Case No.	Sex	Age (Years)	Reason for Practolol	Dose of Practolol (mg)	Skin Condition	Duration of Treatment before Symptoms (Months)		Deafness and Tinnitus	Other Clinical Features	Grade Severity
						Skin	Eye			
1	F.	66	I.H.D.	400			6	+		2
2	F.	75	A.	300	H.P.	18	18	+	Dry cough	2
3	M.	65	I.H.D.	600	Ps., H.P.	14	14	+	Oral ulcer + +	1
4	M.	54	I.H.D.	300	Ps.	36	42	±	Dupuytren contracture	2
5	M.	40	I.H.D.	600	Ps.	24	25	+	Recurring abdominal pain	2
6	M.	63	I.H.D.	300			30	—		2
7	M.	42	I.H.D.	1200	Ps.	14	26	+		2
8	F.	60	H.	300	Ps.	11	11	—		2
9	F.	90	I.H.D.	300			28	—		2
10	M.	52	I.H.D.	600			36	—	Transurethral resection for urethral stricture	2
11	M.	51	I.H.D.	200			14	—		2
12	F.	58	I.H.D.	500	Ps., H.P.	18	24	—		2
13	F.	57	I.H.D.	400	Ps.	31	24	+ +		2
14	M.	59	I.H.D., A.	300			20	—		2
15	F.	63	I.H.D.	500			15	+	Nasal ulceration	2
16	M.	49	I.H.D.	200	H.P.	6	18	—		2
17	F.	61	I.H.D.	300	H.P.	12	24	—		2
18	F.	52	A.	400	Ps., H.P.	29	28	—		2
19	M.	57	I.H.D.	300	Ps.	24	12	+ +	Pleurisy and fibrosing peritonitis	2
20	F.	47	A.	300	Ps., H.P.	24	24	—	Oral ulcer	2
21	F.	53	I.H.D.	600	H.P.	26	24	—		2
22	F.	62	I.H.D.	400	Ps.	43	21	—	Nasal and oral ulcer	2
23	F.	62	A.	1200			36	+		2
24	F.	49	A.	200	Ps.	8	10	+ +	Nasal and oral ulceration	1
25	F.	62	A.	200	Ps.	18	18	+		2
26	F.	62	I.H.D.	400	Ps., H.P.	5	7	+ +		2
27	M.	61	I.H.D.	400	Ps., H.P.	48	48	—	Fibrosing peritonitis	1

I.H.D. = Ischaemic heart disease. A. = Arrhythmia. H. = Hypertension. H.P. = Hyperkeratosis palmaris or plantaris. Ps. = Psoriasiform condition.

FIG. 2—Conjunctiva of lower fornix showing regression of abnormal vessels with persistent subconjunctival fibrosis.

FIG. 3—Case 24. Proliferative fibrovascular reaction in severely affected patient extending to bulbar conjunctiva.

roll of subconjunctival tissue adjacent to the limbus and even overhanging the limbus superiorly (fig. 3).

A reduction in tear flow seemed to have preceded the conjunctival changes in most patients, which together with the absence of secretory IgA and reduction of lysozyme content confirmed the selective effect on the lacrimal glands. The reduction of tear flow produced signs in the precorneal film and marginal tear strip similar to those seen in patients with Sjögren's syndrome. The pattern of staining with Bengal rose, however, was atypical. In many patients staining extended into the lower and upper fornix, where there were areas of thickened conjunctiva with surface changes suggestive of metaplasia or keratinization, which were later confirmed histologically (figs. 4-6).

The corneal changes in the most severely affected patients were unusual. Dense yellow or white opacities appeared suddenly in the central zone of the cornea involving the full thickness of the stroma though without disturbing the epithelium initially (fig. 7). Alternatively sudden stromal melting and loss of corneal substance lead to rapid perforation. No bacterial or other cause was apparent for the infiltrates or corneal ulceration, and the changes seemed rather to be related to some alteration of the corneal substance itself.

Five eyes perforated, and four needed emergency keratoplasty. One patient was managed medically with collagenase inhibitors but later developed extensive corneal vascularization, though neither pannus nor deep vascularization occurred in the less severe cases. In all

FIG. 4—Lower fornix showing keratinization.

patients the eye signs were remarkably symmetrical. The most severe cases showed great thickening of the eyelids, which were hyperaemic and sometimes had a "café au lait" pigmentation of the periorbital skin.

FIG. 5—Upper tarsal conjunctiva showing plaque of keratinization.

FIG. 6—Histological specimen of superficial layers of conjunctiva showing increased thickness, disorganization, and keratinization of superficial cells.

FIG. 7—Case 24. Corneal lesion in severely affected patient.

SKIN

A skin eruption of some sort occurred in 19 of the patients. The rash varied in morphology, extent, and severity, and in eight patients it preceded the onset of eye symptoms by an average of six and a half

months (range 1-12 months). In five patients the eye symptoms preceded any skin signs by an average of seven months (range 1-12 months). Some patients mentioned the rash only on specific questioning because of spontaneous improvement while continuing the drug. Three patients, however, consulted dermatologists, who most commonly found non-irritant raised patches unlike the lesions usually associated with scarring of the conjunctiva. These reddened and scaling patches occurred everywhere except the face. Most patients complained also of thickening and cracking of the palmar skin and hyperkeratosis over the palms, heels, elbows, knuckles, and finger tips, with fissuring of the skin of finger tips. The nails were thickened in one patient and showed psoriasiform changes in another, but the remainder had no nail signs.

OTHER ORGANS

Ear.—Some months after skin and eye lesions appeared 15 patients complained of deafness and tinnitus, and two became profoundly deaf. Simple tests suggested a mixture of conduction defect and cochlear damage and five patients needed surgical treatment for secretory otitis media.

Gut.—One patient was thought to have recurring subacute appendicitis, which had first been noted after two years' treatment with practolol, and two others developed acute intestinal obstruction requiring laparotomy, also after two years' treatment. At operation the whole of the gut was found to be matted together and the appearances were identical to those seen after the fibrous or plastic form of tuberculous peritonitis. A biopsy of the gut of one patient showed nothing specific, and a second episode of intestinal obstruction was managed conservatively.

Mouth and Nose.—Five patients had recurrent ulceration of the oral or nasal mucosa though the classical xerostomia of Sjögren's syndrome was not present.

Investigations

Examination of the tears obtained on cellulose sponges from several patients showed reduction of lysozyme and absence of secretory IgA. Extensive investigation of all the patients failed to show any systemic disorder other than the organ involvement shown in the table. Antinuclear antibodies, often present in high titre, were found in all 27 patients, and a circulating antibody binding to epithelial tissue was found in 25 patients (Amos *et al.*, 1975). No other evidence of drug-induced systemic lupus erythematosus (S.L.E.) was found, and, in particular, there was no arthralgia, fever, or raised erythrocyte sedimentation rate or blood urea, and lupus erythematosus cells were not seen in peripheral blood.

Lymphocyte transformation studies were performed on two severely affected patients with high titres of antinuclear and intercellular epithelial antibodies but no significant abnormality was found. The DNA-binding capacity of the serum (Hughes, 1971) was investigated in 13 patients and preliminary results suggested an increase within the normal range. Both these investigations will be repeated on this group of patients and reported in more detail.

Treatment and Progress of Lesions

Local management of the dry-eyed state followed the general principles (Wright, 1971) of frequent rehydration with artificial tears (BJ6 or hypromellose eye drops) and local mucolytic drops (acetylcysteine 5% or 10%) to deal with stringy tenacious mucus and control of secondary infection of lid margins and conjunctival sac. Prednisolone 20-40 mg/day was given to two patients, which resulted in rapid improvement of previously persistent skin lesions but had no effect on ocular symptoms or signs.

Because of the recent discovery of the antibody binding to epithelial cells (Amos *et al.*, 1975) and confirmation of its presence in the conjunctiva of three patients severely affected eyes were also treated with intensive local steroid drops (dexamethasone 0.1%/h), which resulted in a more rapid regression of the signs. In particular, the abnormal proliferating vessels in the subconjunctival tissues seemed less active, and the development of fibrosis, scarring, and conjunctival shrinkage was correspondingly reduced. Local steroids were not used in those cases with

progressive corneal stromal melting because steroids can enhance the effect of the locally liberated collagenases which are probably responsible for this type of tissue loss. The intraocular pressure was regularly measured in all patients to detect any steroid-induced rise.

All patients were followed for at least four months two for over a year after stopping practolol, during which time all but one showed uniform improvement in symptoms and signs. The remaining patient (case 3) developed a progressive disorder suggestive of an atypical drug-induced S.L.E. syndrome and was treated with systemic steroids and azathioprine.

The conjunctival signs regressed with disappearance of the abnormal keratinization and reduction of the hyperaemia and vascular abnormalities leaving only a persistent subconjunctival fibrosis. Lacrimal gland function recovered enough for artificial tear drops to be used less often, though most patients still had reduced tear secretion.

Three to four months after stopping the drug the most striking feature was the normal appearance of the conjunctiva. It had become a mobile epithelium moving freely over a deeper subconjunctival fibrous sheet which made the fornices shallower but which was quite unlike the abnormal conjunctiva firmly bound to a dense fibrous mass which produces dense symblepharon in such conditions as mucous membrane pemphigoid. Though they remain at risk from secondary infection, reduced tear flow, and secondary changes in the lids, eyes that have shown adverse reactions to practolol can recover nearly normal function unless severely damaged at the time of the initial drug reaction.

Discussion

Two distinct adverse reactions to practolol have been described. Raftery and Denman (1973) described a S.L.E. syndrome, but nobody has noted any ocular abnormality in drug-induced S.L.E. syndromes. Felix *et al.* (1974) described a group of patients with various practolol-induced rashes, but in retrospect only three patients were found to have ocular symptoms or signs, and only five patients (24%) had antinuclear antibody in the serum. The patients described here showed remarkably constant ocular

signs and high titres of antinuclear antibodies and antibody binding to epithelial tissue. They showed no other signs of drug-induced S.L.E., however, and their syndrome seems to represent another clearly defined reaction to practolol.

The mechanism by which the tissue damage occurs remains unknown though two separate processes are probably responsible for the damage to the lacrimal gland and the conjunctiva. There is some evidence that the drug accumulates locally in lacrimal tissue and may have a local toxic effect on secretory cells. The conjunctiva, however, seems to be damaged by the antibody, which binds to intercellular components of the epithelium, and the vascular and fibrotic changes follow as a secondary effect. The relevance of these latter findings to other disorders in which conjunctival fibrosis and shrinkage occur has still to be shown, but this adverse drug reaction may provide valuable information about the processes which cause such damage in many types of ocular inflammation. The suggestions that practolol stimulates cyclic adenosine phosphate activity and impairs the functions of the T-lymphocyte population have not been confirmed or refuted, but further studies are in progress. It should be possible to show whether there is a genetically determined group involved and confirm the best method for assessing the early signs of the adverse reaction. Meanwhile, any patient receiving treatment with practolol who develops ocular irritation or discomfort should be examined for evidence of conjunctival abnormality and reduced tear flow.

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Untoward Effects Associated with Practolol: Demonstration of Antibody Binding to Epithelial Tissue

H. E. AMOS, W. D. BRIGDEN, R. A. MCKERRON

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Summary

An antibody which sticks to the intercellular region of xenogenic epidermal tissue has been shown by indirect immunofluorescence to be present in the serum of patients with practolol-induced eye damage. These antibodies and those found in patients with pemphigus were compared for their ability to bind to isolated epidermal cells. Binding was achieved only with the pemphigus antibody, which suggests that it may have a different specificity from the antibody associated with practolol-induced eye damage.

Department of Immunology, Institute of Dermatology, London E.9
H. E. AMOS, M.B., PH.D., Head of Department
W. D. BRIGDEN, M.B., M.R.C.P., M.R.C. Clinical Research Fellow
R. A. MCKERRON, A.I.S.T., Senior Technician

Introduction

Practolol may be associated with an ill-defined rash (Wiseman, 1971; Felix *et al.*, 1974), and lupus erythematosus cells and antinuclear antibodies are present in some patients taking practolol (Raftery and Denman, 1973). In most patients reported so far only vague reference has been made to possible eye damage, but Wright (1974, 1975) has described conjunctival signs which were associated with practolol consumption and sufficiently unique to constitute a new clinical entity.

We describe here an immunological investigation of sera from patients with adverse effects probably induced by practolol. Most patients had conjunctival damage, but some had rashes and signs of drug-induced lupus erythematosus.

Patients and Methods

Sera were obtained from three groups of patients. Group 1 consisted of patients who had taken practolol and were assessed as having specific conjunctival eye signs (Wright, 1975). These patients were