Metipranolol-associated granulomatous anterior uveitis

Tayo Akingbehin, Jose R Villada

Abstract

This paper presents for the first time documented evidence, clinical details, and photographic illustrations, of metipranolol-associated granulomatous anterior uveitis in 26 eyes of 15 patients being treated for glaucoma. There were 56 episodes of granulomatous anterior uveitis, all associated with large (mutton-fat) keratic precipitates, flare, cells, and 'white eyes' (except in seven episodes). In 30 (53.6%) of these episodes there was loss of control of intraocular pressure. Metipranolol 0.6% was implicated in 54 of the 56 episodes and metipranolol 0.3% in the remaining two. Fifty-one other cases of metipranolol-associated granulomatous anterior uveitis have so far been reported from other parts of the country to the Committee on Safety of Medicines. As a result multidose metipranolol in 0.1%, 0.3%, and 0.6% strengths has been withdrawn from clinical use in the United Kingdom. The pathogenesis of this adverse drug reaction is uncertain.

The use of β -blockers as topical ophthalmic preparations to reduce the intraocular pressure marked the start of a new era in the medical management of glaucoma, because of their efficacy, prolonged therapeutic action, and few serious systemic and ocular adverse effects.^{1,2} As a result they became the first choice for the medical treatment of glaucoma. However, in recent years the increasing number of systemic and ocular adverse effects have led to their more cautious use despite the development of newer drugs with supposedly fewer side effects.³

In the United Kingdom there are five β -blockers available as ophthalmic topical preparations approved for clinical use, namely, betaxolol, carteolol, levobunolol, metipranolol (now withdrawn), and timolol. Metipranolol (1,-(4 acetoxy-2,3,5-trimethylphenoxy)-3-isopropylacyno-propan-2-ol) was introduced in the UK in 1986 with the proprietary name of GlauLine and available in three strengths: 0.1%, 0.3%, and 0.6%. It is a non-selective β -blocker with no intrinsic sympathomimetic or membrane stabilising properties and only slight local anaesthetic activity.⁴

The efficacy of metipranolol in lowering intraocular pressure has been reported in several studies,⁵⁻⁹ and so have the adverse effects, which are similar to those of other ophthalmic topical β -blockers. The ocular adverse effects attributed to metipranolol have included: subjectively, burning or stinging on instillation, eye pain or uncomfortable dryness, foreign body sensation, itching, blurred vision; objectively, allergic blepharoconjunctivitis, conjunctival

hyperaemia, punctate keratopathy, corneal anaesthesia, and dry eye syndrome.¹⁰ It has been suggested that metipranolol is less tolerated than the other β -blockers because of the stinging and burning sensation on instillation.^{7,11}

This paper documents for the first time case histories of some patients receiving this drug for the treatment of glaucoma who developed granulomatous anterior uveitis. The clinical details are reviewed briefly, and photographic evidence submitted. The clinical presentation and behaviour of the affected eyes are analysed.

Methods and materials

At the beginning of 1990 a cluster of cases of severe metipranolol-associated blepharoconjunctivitis focused attention on this drug. The reaction was more severe than usually seen and two patients (three eyes) had coincidental granulomatous anterior uveitis. The bottles of metipranolol were collected from all the patients who suffered from both forms of adverse reactions and their batch numbers identified. There was no consistency in the batch numbers to suggest faulty preparation or contamination of the drug. During this inquiry six more patients were identified in the clinics and ophthalmic ward with granulomatous anterior uveitis while being treated with metipranolol for glaucoma. There were now eight patients, 15 eyes, with granulomatous anterior uveitis, all receiving metipranolol and no other common denominator.

In view of these findings we decided to review the case notes of all the patients in the department using metipranolol in any of its three strengths. The patients were identified through the Drug Register in the Pharmacy Department, the records from January 1989 to March 1990 being examined. All the patients on metipranolol 0.6% were then invited for an ocular examination.

Results

Two hundred and forty-seven case notes of patients treated with metipranolol in all strengths were reviewed. There were 109 case notes of patients using metipranolol 0.6% and 76 patients from this group attended special metipranolol clinics for examination. Eleven patients had active granulomatous anterior uveitis when seen in either special or normal clinics, and four had had attacks, well documented in the case notes, but had quiet eyes when examined. In total there were 15 patients (13.8% of the patients on metipranolol 0.6%) with presumed metipranolol-associated granulomatous anterior uveitis, 11 of these with bilateral attacks and four with unilateral, making a total of 26 eyes. All

Department of
Ophthalmology, District
General Hospital,
Southport PR8 6NJ
T Akingbehin
J R Villada

Correspondence to:
Mr Tayo Akingbehin, FRCS.
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Table 1 Clinical details of patients with metipranolol-associated granulomatous anterior uveitis

Case	Sex	Age	Eyes involved	Dose of metipr.	No. of episodes	Other eyedrops	Ocular surgery
1	F	87	RE	0.6%	2	Dipivefrine	Cataract+IOL
			LE	0.6%	2	Dipivefrine	Cataract+IOL
2	F	76	RE	0.6%	1	—	—
			LE	0.6%	2	—	—
3	F	70	RE	0.6%	1	—	Cataract+IOL; trabeculectomy
4	F	79	RE	0.6%	1	Dipivefrine	—
5	M	70	RE	0.6%	3	—	—
			LE	0.6%	3	—	—
6	M	86	RE	0.6%	4	Adrenaline	—
			LE	0.6%	4	Adrenaline	—
7	F	85	RE	0.6%	1	—	—
			LE	0.6%	1	—	—
8	F	67	RE	0.6%	1	Levobunolol	—
			LE	0.6%	1	Levobunolol	—
9	M	76	RE	0.6%	2	Timolol 0.5%	—
			LE	0.6%	2	Timolol 0.5%	Cataract+IOL
10	F	84	RE	0.6%	1	Dipivefrine	—
			LE	0.6%	1	Dipivefrine	—
11	M	75	RE	0.6%	3	—	—
			LE	0.3%	2	—	—
12	F	74	RE	0.6%	3	—	—
			LE	0.6%	3	—	—
13	F	57	LE	0.6%	1	—	Trabeculectomy
14	F	58	LE	0.6%	2	Dipivefrine	Retinal detachment; cataract; trabeculectomy
15	F	82	RE	0.6%	4	Pilocarpine 2%	—
			LE	0.6%	5	Pilocarpine 2%	—
			26		56		

these eyes except one developed granulomatous anterior uveitis while being treated with metipranolol 0.6% to both eyes; one patient received metipranolol 0.3% in one eye as shown in Table 1. The table also shows the age/sex distribution of the patients.

Of the 15 patients with metipranolol-associated granulomatous anterior uveitis 11 were females with an age range 57–87 years (mean 74.4 years) and four males, age range 70–86 years (mean 76.7 years). The age range for all the patients was 57–87 years (mean 75 years).

The female to male ratio as 3:1, and the age range and mean age of the 15 patients were all consistent with those of the glaucoma population. Of the 26 eyes affected the right and left were equally involved (13 each), with a similar number of separate episodes of granulomatous anterior uveitis.

There were no systemic or ocular disorders common to these patients. Two of them had diabetes mellitus (one insulin-dependent and the other on oral hypoglycaemics).

Six eyes of five patients had intraocular surgery prior to treatment with metipranolol of any strength and the development of granulomatous anterior uveitis. A total of nine intraocular operations had been performed on the six eyes: cataract surgery (five eyes), trabeculectomy (two eyes), retinal detachment surgery with silicone oil (one eye). One eye (case 14, LE) had retinal detachment surgery, cataract extraction, and trabeculectomy at different times and developed the first episode of granulomatous anterior uveitis at least 15 months after the last operation.

Analysis of the drug history of the 15 patients with metipranolol-associated granulomatous anterior uveitis was unproductive. There was no common factor between the various systemic medications. Thirteen eyes of eight patients were on additional topical ophthalmic medications when they developed granulomatous anterior

Table 2 Period on drug before the first episode of granulomatous anterior uveitis and distribution of episodes versus metipranolol dose

Drug	No. eyes	No. episodes	Period on drug before 1st episode in months	
			Range	Mean
Metipranolol 0.3%	1	2		31
Metipranolol 0.6%	25	54	2–24	11.72
Total	26	56	2–31	12.46

uveitis: pilocarpine 2% eyedrops (three eyes), dipivefrine 0.1% eyedrops (four eyes), adrenaline 1% eyedrops (two eyes), levobunolol 0.5% eyedrops (two eyes), and timolol eyedrops 0.5% (two eyes) (Table 1).

Twenty-six eyes (13 right and 13 left) developed uveitis with at least 56 separate documented episodes (27 in the right eye and 29 in the left) over a period of 30 months, from October 1987 to March 1990. Fifty-four episodes occurred in 25 eyes treated with metipranolol 0.6% and two episodes in one eye treated with metipranolol 0.3%. The interval between the beginning of the treatment and the first episode of uveitis is shown in Table 2.

Of the 26 eyes identified with uveitis 16 had further episodes while they remained on the metipranolol drops. The mean interval between the first and second episodes in these 16 eyes was 4.75 months (range 3–9 months). Nine of the 16 eyes had a third episode after a mean interval of 3.6 months (range 1–10 months). Four out of 26 eyes had four episodes each; the intervals between the third and fourth episodes ranged from one to 6 months, mean 2.5 months. Only one of these eyes developed a fifth episode of uveitis after a period of six months (Tables 3 and 4).

The 56 episodes of granulomatous anterior uveitis were managed in various ways, as summarised in Table 5.

Brief reports on some of the 15 patients follow.

CASE 2

This was a 76-year-old Caucasian female with no relevant past medical history or drug history. Her bilateral open angle glaucoma was diagnosed in July 1986 and she was started on timolol 0.25%. Owing to poor intraocular pressure

Table 3 Distribution of episodes of granulomatous anterior uveitis

No. of episodes of anterior uveitis	No. of eyes	% of total eyes	Cumulative total of no. of episodes
1	26	100	26
2	16	61.5	42
3	9	34.5	51
4	4	15.5	55
5	1	3.5	56

Table 4 Time interval between episodes in eyes which developed several attacks of granulomatous anterior uveitis

Episodes of anterior uveitis	Interval in months	No. of eyes	Range in months	Mean in months
1st–2nd	3,3,3,3,3,9,9,4,4,3,5,7,7,4,3,6	16	3–9	4.75
2nd–3rd	1,1,1,1,4,10,10,2,3	9	1–10	3.60
3rd–4th	1,1,6,2	4	1–6	2.50
4th–5th	6	1		

Table 5 Management of episodes of granulomatous anterior uveitis

Topical steroid used	No. episodes	Mydriatics	Other glaucoma treatments	Average time of resolution (weeks)
Prednisolone 1%	24	Atropine 1%×2 Cyclopent 1%×2 Tropicamide 1%×2	Acetazolamide×8	3.8
Dexamethasone 0.1%	12	Cyclopent 1%×4	Acetazolamide×6	2.6
Fluoromethalone 0.1%	5	Cyclopent 1%×4	Acetazolamide×4	4.4
Betamethasone 0.1%	4	Cyclopent 1%×4	Acetazolamide×2	3.5
Prednisolone 0.5%	1	—	—	1.0
No steroids	6	—	—	6.0

In four of the episodes the time of resolution was not clear from the case notes and they are not included in this table.

×2=in two episodes, and likewise for ×4.

(IOP) control her medications were varied until January 1988, when timolol was stopped and she was started on metipranolol 0.6% twice daily to both eyes as the only antiglaucoma treatment. Two years later (January 1990) she developed bilateral anterior uveitis with keratic precipitates and loss of IOP control. This episode was treated with topical steroids (fluorometholone eye-drops), mydriatics, and acetazolamide, and recovered completely in three weeks with return of the IOP to normal. She was recalled to the Special Metipranolol Review Clinic in April 1990 and found to have bilateral blepharoconjunctivitis, left anterior uveitis with keratic precipitates, and loss of IOP control in both eyes. The left eye was photographed (Fig 1). This second episode was not treated with topical steroids, the metipranolol 0.6% was stopped, and she was started on carteolol 2% twice daily to both eyes. Two weeks later both eyes were white and quiet, the keratic precipitates old, and IOPs within normal limits.

CASE 6

This was an 86-year-old Caucasian man who suffered from gastrointestinal haemorrhage and secondary anaemia treated with ferrous sulphate tablets. Glaucoma was diagnosed in about 1983. The first record of treatment with metipranolol 0.6% was in September 1987; in addition he received adrenaline 1% twice daily to both eyes. He developed bilateral anterior uveitis with keratic precipitates and posterior synechiae in April 1989. He was treated as a case of bilateral Fuchs's cyclitis at another hospital and registered fully blind. Later he was transferred to a rest home in Southport and an ophthalmic opinion was requested. At this time he had

Figure 1 Case 2. Left eye: keratic precipitates.

bilateral anterior uveitis with mutton-fat keratic precipitates, posterior synechiae (Fig 2), and uncontrolled IOPs. The possibility of metipranolol-associated uveitis was being investigated, hence the metipranolol was discontinued, and he was started on timolol 0.5% and treated with eyedrops of prednisolone acetate, and atropine 1%. The condition resolved in two months. The visual acuity improved from hand movements in both eyes when was registered blind to 6/12 RE and 6/36 LE. The IOPs were controlled with timolol 0.25%.

CASE 9

This was a 76-year-old Caucasian male with no relevant medical history. He was diagnosed as suffering from bilateral cataracts and open angle glaucoma in December 1987, and was started on treatment with metipranolol 0.3% twice daily to both eyes. He underwent left cataract extraction with IOL in January 1988, and the IOPs remained stable without treatment for six months. The pressures then rose in both eyes and led to gradually increasing treatment, eventually to metipranolol 0.6% and timolol 0.5% twice daily to both eyes in March 1989. The first episode of bilateral anterior uveitis with keratic precipitates was in November 1989; it was treated with topical steroids (prednisolone acetate), and recovered in three weeks. The second episode with fresh keratic precipitates and loss of IOP control occurred in March 1990 (both eyes photographed, Figs 3 and 4) and led to the metipranolol drops being changed to timolol 0.5% twice daily to both eyes. This episode was not treated with steroids. He had a slower recovery but with complete resolution in eight weeks.

CASE 10

This was an 84-year-old diabetic woman on oral hypoglycaemic treatment and also being treated for systemic hypertension and arthritis. She had bilateral open angle glaucoma which needed increasing treatment, and her first contact with metipranolol 0.6% was in April 1989. She was listed for filtration surgery in December 1989, and at that time her treatment was metipranolol 0.6% twice daily and dipivefrine 0.1% twice daily to both eyes. When admitted for surgery, in February 1990, she was found to have bilateral anterior uveitis with mutton-fat keratic precipi-

Figure 2 Case 6. Posterior synechiae after repeated episodes of anterior uveitis.

Figure 3 Case 9. Right eye: keratic precipitates.

Figure 4 Case 9. Left eye: keratic precipitates.

tates and very elevated IOPs (62 mm Hg in the right eye and 66 mm Hg in the left). There were no positive radiological or biochemical findings and she was treated with topical steroids (prednisolone acetate). The metipranolol was changed to timolol 0.5% twice daily, and acetazolamide. She continued with the dipivefrin 0.1%. The uveitis recovered in three weeks with normal intraocular pressures on the above treatment until bilateral trabeculectomy.

CASE 11

This was a 75-year-old Caucasian man suffering from angina and pernicious anaemia. He was diagnosed as having open angle glaucoma first in the right eye and two years later in the left. In February 1989 his treatment was increased to metipranolol 0.6% to the right eye and metipranolol 0.3% to the left eye. He developed right anterior uveitis with keratic precipitates and loss of pressure control seven months later (September 1989). This eye was treated with dexamethasone-hypromellose eyedrops, with full recovery from the uveitis and return to normal of the IOP. Three months later (December 1989) he developed bilateral anterior uveitis with keratic precipitates; both eyes were treated with prednisone eyedrops, with full recovery. He had a third episode of bilateral blepharoconjunctivitis, bilateral anterior uveitis with keratic precipitates, loss of pressure control, and right ectropion secondary to the skin changes. The metipranolol drops were stopped, he was started on timolol 0.25% twice daily to both eyes, and both eyes were treated with prednisolone eyedrops. The ectropion and the ocular inflammation resolved in six weeks.

Discussion

Almost all the ocular adverse effects of the ophthalmic topical β -blockers reported to date have affected adnexal or external ocular structures and are thought to be related to their property of membrane stabilisation or to reflect the different vehicles, the pH, and concentrations of the drugs.¹⁰ Metipranolol is known to produce external ocular inflammatory reactions which include periorbital dermatitis, urticaria, blepharitis, blepharoconjunctivitis, keratitis and 'eye pain' (Committee on Safety of Medicines, personal communication). There has also been a

case report of metipranolol-associated conjunctivitis with epithelial keratinisation, similar to the conjunctival reaction seen after oral use of practolol.¹² We have documented a case of bilateral marginal keratitis associated with metipranolol 0.3%.

This paper presents the first documented reports of ophthalmic topical β -blocker-associated intraocular inflammation. In 1980 Van Buskirk¹³ reviewed 547 reports of adverse reactions to timolol maleate received by the American National Registry for Drug induced ocular side effects and found six cases of uveitis associated with the use of timolol in an 11-month period. No details were available. Three years later Zimmermann *et al*¹⁴ updated the review of the American National Registry of Drug induced ocular side effects of timolol, and the number of associated cases of uveitis had increased to 14, but no details were given. To put this in perspective, they also found 98 cases of ocular irritation, 64 cases of blepharoconjunctivitis, 38 cases of keratitis, and 29 cases of 'corneal lesions' due to timolol from 1472 case reports. No cause-and-effect relationship was implied or demonstrated for any of these reported reactions.

This paper presents evidence for metipranolol-induced granulomatous anterior uveitis in 15 patients, with 26 eyes affected. We are also aware of 51 patients, at the time of submitting this paper, from other parts of the country with suspected metipranolol-induced anterior uveitis (Committee on Safety of Medicines, personal communication). In this study 25 affected eyes were receiving metipranolol 0.6%, and one eye metipranolol 0.3%. By comparing the number of cases reported with sales figures for metipranolol 0.6% and metipranolol 0.3% in the UK we believe the incidence of metipranolol-associated anterior uveitis is about 3.8 per thousand for metipranolol 0.6%, 1.13 per thousand for metipranolol 0.3%, and 0.5 per thousand for metipranolol 0.1% (Smith and Nephew Pharmaceuticals Ltd, personal communication). These figures appear to be increasing with greater awareness of this adverse drug reaction.

Granulomatous anterior uveitis is characterised by a tendency to form iris nodules (Koeppe or Busacca type) and mutton-fat keratic precipitates. Non-granulomatous anterior uveitis has little or no tendency to form either nodules or mutton-fat keratic precipitates.¹⁵ All 26 eyes affected had keratic precipitates on the first and

subsequent attacks of anterior uveitis. The attacks of granulomatous anterior uveitis recorded in the case notes before the establishment of the Special Metipranolol Clinics recorded mutton-fat keratic precipitates in about 50% of the episodes and diagrammatically showed large keratic precipitates in the other 50%. All the cases of active uveitis found by chance at the beginning of this investigation and during the recall examinations had mutton-fat keratic precipitates. The keratic precipitates seen by the investigators were white initially, with no particular pattern to their distribution on the corneal endothelium. No episode of anterior uveitis was associated with Koeppe or Busacca type nodules.

All 56 episodes of anterior uveitis in the 26 eyes were therefore characterised by keratic precipitates, flare, and cells in the anterior chamber. Most of the eyes were described as 'white' when the diagnosis of anterior uveitis was made, but seven episodes had coexisting significant blepharoconjunctivitis. Three eyes developed posterior synechiae. In 30 out of the 56 attacks of granulomatous anterior uveitis (53.8%) the IOP was raised, and additional therapy was required to control the pressure in most of them. Acetazolamide was used on every occasion (Table 5). The IOP of eyes with metipranolol associated side effects is the subject of a separate investigation.

All but six episodes of anterior uveitis were treated with topical steroids (Table 5). The average resolution period of the anterior uveitis when treated ranged from 2.6 to 4.4 weeks, but in the six eyes which received no topical steroids and were treated only by discontinuation of the metipranolol drops the average time for recovery was longer at six weeks. This difference was statistically significant ($p < 0.0125$). A mydriatic was used in combination with topical steroids in treating 18 episodes of granulomatous anterior uveitis. The eyes recovered fully without any sequelae except for the three eyes which developed posterior synechiae. The IOP in the eyes which required additional glaucoma therapy returned to preuveitic levels on recovery and did not need the continuation of the additional therapy. When metipranolol was discontinued, the IOP was controlled easily with an alternative therapy.

All the 26 eyes have now been followed up for a minimum period of 10 months following the discontinuation of metipranolol. None of the eyes has shown any evidence of further intra-ocular inflammation with the substituted antiglaucoma therapy, which includes other commonly used ophthalmic topical β -blockers.

In conclusion, this paper presents clinical and photographic evidence for the first time of a hitherto unreported adverse association between metipranolol therapy and granulomatous

anterior uveitis. As a result of reporting these cases to the Committee on Safety of Medicines and to Smith and Nephew Pharmaceuticals Ltd a letter was written by Smith and Nephew to all ophthalmologists in the UK on 2 April 1990 to advise them on the possible association of metipranolol 0.6% with granulomatous anterior uveitis. A subsequent communication to all ophthalmologists, general practitioners, and pharmacists on 3 August 1990 from Smith and Nephew announced the withdrawal of metipranolol 0.6% from the UK market as from 1 October. The 0.1% and 0.3% strengths of metipranolol continued to be available for prescription for another six months. After further reports of metipranolol-associated granulomatous anterior uveitis (the latest figures being: 48 patients on metipranolol 0.6%, 17 on 0.3%, and 1 on 0.1% - Committee on Safety of Medicines, personal communication) Smith and Nephew wrote again, on 4 January 1991, to all ophthalmologists announcing the withdrawal from the market of the remaining two strengths of metipranolol 0.1% and 0.3%. This drug is still available for prescription in the single disposable form. The pathogenesis of these adverse reactions remains uncertain but is being investigated.

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