

LETTERS TO THE EDITOR

Granulomatous uveitis and metipranolol

EDITOR,—Dr Jon Polansky of the University of California (San Francisco) recently asked me to look into the possibility that GlauLine formulations of metipranolol might cause granulomatous uveitis. In particular, I was asked to review the report by Akingbehin and Villada¹ which had indicated that prolonged use of these eyedrops in glaucoma patients caused the onset of granulomatous uveitis, among other side effects. Apparently, these observations had contributed to the withdrawal of GlauLine formulations of metipranolol eyedrops as anti-glaucoma medications in the United Kingdom. In the patients studied the uveitis subsided after the drug was stopped, but seven patients who were rechallenged with the same medication developed uveitis once again after a period of 2 to 14 days.

At the outset, it seemed strange that little or no uveitis had been noted among patients in other countries where metipranolol eyedrops had been used successfully for months or years. The parent drug is manufactured by Mann Pharma in Germany, but local distributors in each country control the packaging, sterilisation, and use of preservatives for the eye medications. GlauLine eyedrops, distributed by Smith and Nephew, in the United Kingdom, were packaged in plastic bottles that had been sterilised by γ irradiation. Benzalkonium chloride in relatively high concentration was used as the preservative, and this substance is known to be toxic to ocular cells. In addition, it has been shown that the pH of GlauLine formulations in irradiated plastic bottles decreases over time.

Based on these observations, and my understanding of mechanisms which could account for such a uveitis, I suggested to Dr Polansky that he examines the various available formulations of metipranolol eyedrops for differences between them and GlauLine. Studies in his laboratory showed a substantial oxidation reaction in GlauLine eyedrops, as measured by the conversion of Fe^{2+} to Fe^{3+} . The same was also true of the GlauLine vehicle which contained no metipranolol, provided it had been packaged in plastic bottles sterilised by γ irradiation. This increased oxidation reaction was not found in other commercial formulations of metipranolol, including Minims. It now seems highly likely that the method of sterilisation of the plastic bottles (irradiation) was the culprit.

Rao² has shown that oxygen-free radicals cause retinal damage in experimental autoimmune uveitis produced by the injection of small quantities of S antigen into Lewis rats. Although the circumstances are entirely different, the fact that oxygen-free radicals can cause necrotising damage to the internal structures of the eye may relate to the production of granulomatous uveitis. I have previously advanced the theory that every form of uveitis takes its origin from some form of injury to the internal ocular structures.³ The observations of Akingbehin and Villada may provide yet another example of toxic injury to the ocular tissues that results in uveitis. In this case, the offending agents are probably oxygen-free radicals.

Although the higher concentrations (0.6% and 0.3%) of metipranolol in certain formulations of the eyedrops produce some stinging or burning upon instillation, in common with some formulations of other β -adrenergic blockers, metipranolol appears to be highly useful and may have some advantages in the treatment of glaucoma. Metipranolol has also been shown to have good stability and compatibility when formulated with pilocarpine eyedrops. If multiple dose formulations of metipranolol eyedrops can be made for distribution in the United Kingdom without γ irradiation of the plastic bottles, this product might be considered for reinstatement as an agent for glaucoma treatment. The possible role of oxygen-free radicals in causing uveitis should also be looked at in other ophthalmic preparations that have been packaged in plastic bottles sterilised by γ irradiation.

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- 1 Akingbehin T, Villada JR. Metipranolol-associated granulomatous anterior uveitis. *Br J Ophthalmol* 1991; 75: 519–23.
- 2 Rao NA. Role of oxygen free radicals in retinal damage associated with experimental uveitis. *Trans Am Ophthalmol Soc* 1990; 88: 797–850.
- 3 O'Connor GR. Factors related to the initiation and recurrence of uveitis. *Am J Ophthalmol* 1983; 96: 577–99.

Reply

EDITOR,—I was interested to read O'Connor's review of the metipranolol induced granulomatous anterior uveitis literature and his opinion on the work of Dr Jon Polansky. It was not surprising that suspicion was not cast on metipranolol as a likely cause of uveitis or elevation in intraocular pressure as both conditions are clinical entities which can occur independently or together. Since these adverse drug reactions (ADRs) were first reported in the United Kingdom an increasing number of cases have been documented in Europe where the drug has been used for years. Metipranolol was introduced to the United States only in June 1991.

In our review of 26 eyes with metipranolol induced granulomatous anterior uveitis (GAU) the shortest interval between the commencement of metipranolol and the first episode of GAU was 2 months while the longest was 31 months with a mean interval of 12.46 months. In those patients who developed further attacks of uveitis the mean interval between the first and second episodes was 4.75 months (range 3–9 months). The mean interval between second and third episodes when it occurred was even shorter at 3.6 months (range 1–10 months). When some of these eyes were rechallenged with metipranolol the time taken to develop uveitis ranged from 5–14 days (mean 8.6 days). Prolonged use of the drug was therefore not essential in the production of GAU in already sensitised eyes. Novack and Leopold¹ reported on topical allergic reaction caused by β blockers occurring as early as the first week of therapy or as late as 1 year in patients who have suc-

cessfully taken the drug. The possibility of metipranolol induced GAU and elevation in IOP being part of a hypersensitivity reaction to metipranolol has not been excluded and remains the most likely pathogenetic hypothesis. Strong clinical evidence to support this view comes from our rechallenge study where all eyes treated with metipranolol developed an ADR. The ADRs varied showing lack of specificity in the type of response to metipranolol but these could have been different stages of a specific metipranolol hypersensitivity syndrome which, if the eyes had continued to be exposed to the drug for long enough, would have shown a similar final outcome. Unfortunately, the study was unable to address this question because we were bound by the ethics of the trial to terminate the rechallenge once there was objective evidence of adverse reaction.

The presence of free radical species in plastic bottles subjected to γ irradiation is a significant laboratory finding which has no relevance in the ocular toxicity of metipranolol at present. There is no single piece of evidence to suggest that the oxidation reaction which these free radicals might produce affects the drug metipranolol or the vehicle in any way as to alter either the bioavailability of the drug or its therapeutic response. Rao's work related to experimentally induced uveitis and is not relevant to this subject.

Table 1 shows the preservatives and pH values of the ophthalmic β blockers used in the United Kingdom for the treatment of glaucoma²; betaxolol, timolol, and metipranolol all have a relatively high concentration of benzalkonium chloride (0.01%) but betaxolol and timolol have not been shown to produce similar serious adverse reactions to those we documented for metipranolol.

There is no significant difference in the pH of metipranolol when compared with the pH of other β blockers. It would therefore appear that none of these three factors – γ irradiation, benzalkonium chloride, and pH in isolation – can be put forward as a contributing factor to the pathogenesis of the observed metipranolol induced ADRs, although O'Connor has suggested in his letter that the method of sterilisation of the plastic bottles by γ irradiation was the culprit. He provided no evidence to support a cause and effect relationship. On the contrary there is clinical evidence to prove that the γ irradiation of plastic bottles with the free radical oxidation reaction has no role to play in the pathogenesis of these serious adverse reactions of GAU and elevation of IOP caused by metipranolol. There is also some evidence to suggest that the metipranolol ADRs are due directly to the drug and are probably dose related.

Clinical evidence against γ irradiation as a causal factor in metipranolol induced GAU and elevation in IOP

1 The γ irradiation of multidose metipranolol plastic bottles was introduced in January 1989 into the United Kingdom. We documented cases of metipranolol induced GAU and elevation in IOP in patients who

Table 1 Preservatives and pH values of ophthalmic β blockers currently available for clinical use in the United Kingdom

β blocker	Preservative	pH
Betaxolol	Benzalkonium chloride (0.01%)	4.7
Carteolol	Benzalkonium chloride (0.005%)	6.7
Levobunolol	Benzalkonium chloride (0.004%); Disodium edetate	7.0
Metipranolol	Benzalkonium chloride (0.01%); Disodium edetate	5.5
Timolol	Benzalkonium chloride (0.01%)	about 7

received multidose metipranolol bottles sterilised by ethylene oxide pre-1989.

2 In Europe, where bottles of metipranolol are not sterilised by irradiation, there were several spontaneous reports of metipranolol associated anterior uveitis before the publication of our first paper in early 1991.

Clinical evidence in support of metipranolol as a causal agent and the ADRs as dose related

1 Of the 26 eyes with metipranolol induced GAU, 25 eyes received metipranolol 0.6% and only one eye received metipranolol 0.3%. There were no cases of GAU observed with metipranolol 0.1%. In total there were 56 separate concluded episodes of GAU, 54 of which were associated with metipranolol 0.6% and only two episodes with metipranolol 0.3% (see Table 2).

2 There were 45 episodes of metipranolol induced ADRs accompanied by a secondary elevation in IOP and in a further 27 eyes of 14 patients we documented a significant elevation in IOP (>5 mm Hg) before the development of any recognisable signs of ADRs. The distribution of these episodes and the eyes with metipranolol related elevation in IOP was confined to metipranolol 0.6% exclusively, apart from three episodes which were related to metipranolol 0.3% as shown in Table 3.

The IOP in these eyes with or without metipranolol ADR returned to within normal limits with the withdrawal of the metipranolol therapy.

3 There is a disproportionately high number of metipranolol induced serious ADRs reported in the United Kingdom compared with the figures from other European countries where more units of the drug have been sold and for a longer period. In Europe there is a prescribing practice of using weaker strength drugs, metipranolol 0.6% is therefore not sold in most European countries and, where available, it is not often used by ophthalmologists. In the United States, metipranolol is available only in 0.1% and 0.3% strengths. There is a similar prescribing practice for Timoptol where the 0.5% strength is mainly for the United Kingdom market and the lowest strength 0.1% is available only in Europe; to date it has not been considered for introduction into the United Kingdom. Several workers have shown that higher strength preparations of ophthalmic topical β blockers do not have significantly better therapeutic efficacy and there is an increasing trend to prescribing weaker strengths of β blockers for the medical treatment of glaucoma.

Accepting therefore that most of the metipranolol used in other European countries and the United States is the 0.1% strength, it is consistent with our findings that very few metipranolol induced ADRs would have been reported.

In summary, metipranolol was a welcomed addition to the range of ophthalmic topical β blockers when introduced as GlauLine into the United Kingdom in 1986 but the seriousness of these adverse reactions should not be overlooked particularly the secondary elevation of IOP which was often interpreted as progression of the glaucoma for which the drug was prescribed. Polansky's laboratory findings of free radicals producing an oxidation reaction has yet to be given any relevance and O'Connor's review does not provide any scientific/clinical evidence to support a cause and effect relationship between these free radicals and metipranolol induced GAU and secondary elevation of IOP. His plea to consider the reinstatement of metipranolol as an

Table 2 Distribution of granulomatous anterior uveitis and different strengths of metipranolol³

	Total	Met 0.1%	Met 0.3%	Met 0.6%
No of patients reviewed	247	35	103	109
No of eyes with GAU	26	0	1	25
No of episodes of GAU	56	0	2	54

Table 3 Distribution of episodes of ADRs associated with loss of IOP control and different strengths of metipranolol³

ADR	Metipranolol 0.1%	Metipranolol 0.3%	Metipranolol 0.6%
GAU	0	0	27
BC	0	1	10
BC and GAU	0	0	5
MK	0	2	0
PD	0	0	0
Total	0	3	42

GAU=granulomatous anterior uveitis; BC=blepharoconjunctivitis; MK=marginal keratitis; PD=periobital dermatitis

agent for glaucoma treatment is premature and should await the results of further research including cytotoxic cellular studies, animal studies comparing various multidose formulations of metipranolol drops of different strengths, and also further analysis of human clinical data. We as clinicians have a responsibility to protect our patients from known serious adverse drug reactions particularly when there are other therapeutically effective preparations with fewer adverse effects. As long as the safety profile of metipranolol is in doubt, particularly the higher strength formulations, the re-introduction of the drug for clinical use must be challenged.

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- 1 Novack GD, Leopold IH. The toxicity of topical ophthalmic beta-blockers. *J Toxicol* 1987; 6: 283-97.
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Response

EDITOR,—I appreciate Mr Akingbehin's thoughtful responses to my letter. The clinical condition described in his papers is certainly of considerable interest as to its cause, and continued dialogue on this subject, along with research into possible mechanisms, appears warranted.

Allergic reactions of the type described by Novack and Leopold are generally restricted to blepharoconjunctivitis, and are not likely to cause granulomatous uveitis, the apparent anamnestic response of the rechallenged patients notwithstanding. Granulomatous reactions, in which macrophages are the principal participants, are much more likely to be caused by necrotising reactions in the tissue. Such reactions are seen in infectious processes, sarcoidosis, or diseases in which vessel occlusion may produce tissue necrosis, but rarely if ever in purely allergic reactions. Cases of allergic reactions have occasionally occurred outside the United Kingdom with the use of metipranolol or other β blockers, but these have not been associated with a notable incidence of the peculiar uveitis syndrome described by Mr Akingbehin.

My statement that multidose units of metipranolol in containers sterilised by methods other than γ irradiation might be considered for reinstatement in the United Kingdom should hardly be considered a 'plea'. However, the wholesale condemnation of a useful drug should also be avoided, especially when the high incidence of complications appears primarily to occur with the 0.6% solution and is isolated to one country, where other factors may be producing the effect.

In the response to my letter, Mr Akingbehin presents data which clearly demonstrate that the highest concentration of metipranolol, distributed as GlauLine, appears to be the main culprit, the vast majority of granulomatous uveitis cases occurring among those patients who had received the 0.6% solution. This may contribute to the 'clustering effect'—that is, the production of an unusually high number of complications in the United Kingdom. However, a high concentration of metipranolol alone may not be the cause of the problem. When Dr Novack was contacted regarding his review of the toxicity of β adrenoceptor antagonists, he commented that there is a notable lack of uveitis reactions with 0.6% metipranolol in Germany and in other countries in Europe where the 0.6% formulation remains available and accounts for nearly 12% of all metipranolol eyedrops distributed (approximately 4.5 million units/year). Although the suggestion that lower dose metipranolol formulations (0.3% and 0.1%) could be used in preference to the 0.6% formulation appears reasonable in view of the apparent effectiveness of these concentrations in lowering IOP, I am still interested in understanding the possible pathogenic mechanisms for the granulomatous uveitis observed.

My proposal that oxygen radicals alone, or some alteration of metipranolol associated with increased reactive oxygen species, might be to blame has not yet been proved. Of course, other mechanisms involving differences in the formulations, the patient populations affected, and concomitant medications should also be examined. However, the fact that soluble oxidation products were detected in the GlauLine solutions but not in other formulations of metipranolol tested is a potentially interesting clue which might provide experimental direction to investigate the high incidence of granulomatous uveitis in the United Kingdom. At present, a role for metipranolol in combination with an oxidation product cannot be excluded, and a high metipranolol concentration might favour such an interaction. It would be useful

to review the cases of uveitis occurring with GlauLine distributed in ethylene oxide sterilised bottles, as mentioned by Mr Akingbehin. If the same peculiar pattern of uveitis were to be observed, one might look for similar mechanisms. Minims, a unit dose product that is still approved for sale in the United Kingdom as 0.3% and 0.1% solutions of metipranolol, is distributed in plastic containers that are not sterilised by γ irradiation. These formulations, as well as the multidose metipranolol formulations available in the United States made using aseptically produced sterile bottles, show no free oxygen reactions in assays of their eyedrop solutions in contrast to the GlauLine data.

Until the mechanisms responsible for the adverse reactions of GlauLine eyedrops are more clearly defined, caution should, of course, be exercised. Experimental studies in tissue culture using corneal endothelial cells and other cell types may help to sort out the independent effects of γ irradiation from other sterilisation procedures. These and additional investigations may reveal whether or not the metipranolol molecule could participate under certain conditions in an immunological reaction capable of evoking a granulomatous process. Such studies could help to clear up a mystery that has not yet been solved regarding the unusual, reversible uveitis syndrome that has been reported primarily with high dose metipranolol distributed under the GlauLine trademark in the United Kingdom.

G RICHARD O'CONNOR

Deep lamellar keratoplasty in the treatment of bullous keratopathy

EDITOR,—We read with interest the article by Chau *et al.*¹ We agree with the authors that even though, nowadays, penetrating keratoplasty has a high success rate and a better visual outcome, deep lamellar keratoplasty might still be indicated in certain conditions. They mention, that the procedure is indicated only in eyes with a normal, functioning endothelium. We feel that the indication can be extended even to corneas in which the disease is caused by a decompensated endothelium such as bullous keratopathy after cataract surgery. In these cases, however, a full thickness graft must be used as donor material. In our experience, if a supernumerary anterior chamber is formed between the retained host's Descemet's membrane and the graft, the transplanted endothelium may function properly, assuring graft clarity.^{2,3} McCulloch *et al* have reported that if the endothelium is left on the donor tissue in lamellar keratoplasty it does not survive.⁴ This is probably true only when the anterior face of the retained Descemet's membrane and the graft's endothelium are in close contact. However, when a double anterior chamber exists, the aqueous that separates these two layers prevents the damage to the endothelium. Concerning the surgical technique, in oedematous corneas of bullous keratopathy, dissection of the stroma from the underlying Descemet's membrane is not difficult since a cleavage plane exists owing to the marked oedema. We feel that air injection is not necessary in these cases.

Deep lamellar keratoplasty is a safe procedure, with an acceptable visual outcome. It might be indicated in severely damaged and high risk eyes with bullous keratopathy, in which opening the anterior chamber might necessitate difficult and major reconstruction of the anterior ocular segment, intraocular lens

exchange, and vitrectomy. Performing an 'extraocular' procedure might avoid severe complications in these selected cases and achieve acceptable results.

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- 1 Chau GK, Dilly SA, Sheard CE, Rostron CK. Deep lamellar keratoplasty on air with lyophilised tissue. *Br J Ophthalmol* 1992; 76: 646-50.
- 2 Loewenstein A, Geyer O, Lazar M. Intentional retention of Descemet's membrane in keratoplasty for the surgical treatment of bullous keratopathy. *Acta Ophthalmol* 1993; 71: 280-2.
- 3 Lazar M, Loewenstein A, Geyer O. Intentional retention of Descemet's membrane during keratoplasty. *Acta Ophthalmol* 1991; 69: 111-2.
- 4 McCulloch C, Thompson GA, Basu PK. Lamellar keratoplasty using full thickness donor material. *Trans Am Ophthalmol Soc* 1963; 61: 154-80.

Reply

EDITOR,—Loewenstein *et al* are to be congratulated on their innovative variation of deep lamellar keratoplasty in which fresh tissue with intact endothelium is used in the treatment of corneal endothelial failure. In their series,¹ five of six grafts remained clear with functioning endothelium, and there was only one graft failure where the supernumerary anterior chamber was lost and the host Descemet's membrane came into apposition with the donor endothelium.

The risk of rejection with Loewenstein's technique is probably no different from that in conventional full thickness penetrating keratoplasty, and the advantages of an 'extraocular' technique are balanced against the risk of endothelial failure owing to contact between the donor endothelium and the host Descemet's membrane.

In the technique of Chau *et al.*,² deep lamellar keratoplasty with lyophilised tissue has the advantage of lack of graft rejection and lack of sensitisation of the host to donor antigens, and this is balanced against potential problems with re-epithelialisation of the graft and of interface opacification.

No doubt both of these techniques are valuable new options for treatment of selected cases of corneal disease.

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- 1 Loewenstein A, Geyer O, Lazar M. Intentional retention of Descemet's membrane in keratoplasty for the surgical treatment of bullous keratopathy. *Acta Ophthalmol* 1993; 71: 280-2.
- 2 Chau GK, Dilly SA, Sheard CE, Rostron CK. Deep lamellar keratoplasty on air with lyophilised tissue. *Br J Ophthalmol* 1992; 76: 646-50.

BOOK REVIEWS

Colour Guide Ophthalmology. By J J Kanski. Pp 92. £7.95. Edinburgh: Churchill Livingstone, 1992.

Mr Kanski has yet again produced a concise pocket sized and beautifully illustrated colour guide of basic ophthalmology. I am sure that most students and trainee doctors will find this

book of great benefit. Within its pages, including an adequate index, the book manages to cover a wide variety of ophthalmic disorders. It is logical and sequential in its description of disease and is easy to read, with well reproduced pictures and succinct text. It manages to cover both common ophthalmic problems which would be of interest to non-ophthalmologists and also the more specific ophthalmic disorders particularly retinal disease; it would act as good aide memoire for the trainee ophthalmologist. Medical students I am sure will find this book of use during their short clinical attachments in ophthalmology.

ANDREW DICK

Ultrasound of the Eye and Orbit. By Sandra Frazier Byrne, Ronald L Green. Pp 506. £81. London: Mosby Year Book Europe, 1992.

Ophthalmic ultrasonography (echography) has experienced great advances and widening application in the past two decades. This technique is now the method of choice in the investigation of many ocular lesions and is an excellent alternative and support to computed tomography and magnetic resonance imaging in the investigation of orbital diseases. The low cost, safety, and ability to perform echography in the office, bedside, or operating theatre will ensure its prominent role for many years to come. Such views are echoed in the Foreword of this book by two eminent ophthalmologists; Edward Norton at the Bascom Palmer Eye Institute and Stephen Ryan at the Doheny Eye Institute, who experienced at first hand the valuable services of the two authors in their respective institutions.

This book is, to date, the most comprehensive work on this subject. Comprising 506 pages, it describes in detailed but easy to read text the technique and application of ultrasonic diagnosis in ophthalmology. A superb set of echograms among the 415 illustrations is clearly labelled and consistently displayed to be read from left to right; a pleasing feature that avoids confusion. Many echograms are also supported by line drawings and, particularly in the orbital section, by computed tomograms and magnetic resonance images.

A relevant and to the point description of ultrasound physics is contained in the first chapter. Thereafter, the chapters are logically arranged into two major sections; the Eye and Orbit. Each section is further divided into indications, methods of examination, followed by a number of specialised sections. In the eye these are vitreoretinal, trauma, intraocular tumours, and axial eye length measurements, and in the orbit they comprise orbital tumours, vascular lesions, extraocular muscles, optic nerve, and trauma and periorbital diseases. A useful feature is a concluding glossary of technical terms. The book is well referenced with each chapter containing its own bibliography.

Throughout the book, the wide experience of the two authors is tangible, especially their description of the method and applications of standardised A-scan. This technique, developed by K Ossoinig and yet to be popularised in the United Kingdom, is a valuable diagnostic tool, particularly in the tissue differentiation of ocular and orbital tumours, and in the detection of extraocular muscles and optic nerve diseases. The chapter on orbital vascular lesions is an excellent example of the merit of combining standardised A-scan, B-scan, and Doppler ultrasound in the investigation of such lesions.

The best chapter overall, however, must be