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Double-blind clinical trial of topical steroids in anterior uveitis

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SUMMARY We present the results of a double-blind trial comparing the efficacy of betamethasone phosphate 0·1%, clobetasone butyrate 0·1%, and placebo in the treatment of acute unilateral nongranulomatous uveitis. The 2 steroids were equally comparable in improvement of the patients' symptoms, though betamethasone phosphate was significantly more effective than clobetasone butyrate in improving the ocular signs of uveitis. However, clobetasone butyrate had significantly less effect on raising intraocular pressure in known steroid responders and ocular hypertensives than did dexamethasone. The use of a bolometer as an objective measure in uveitis was significant only in the more severe cases of uveitis. In comparing the placebo group of patients with those on topical steroids, the former group, though improving, appeared to lag behind by approximately one week. Four cases on placebo, however, had to be withdrawn because of worsening of the condition. Mild cases of anterior uveitis would probably resolve without using topical steroids.

Although uveitis is essentially a self-limiting disease, it is none the less necessary to institute prompt treatment to reduce the inflammatory response, relieve pain, prevent posterior or peripheral anterior synechiae, and lower intraocular pressure in those eyes with secondary glaucoma.

Before the introduction of steroids mydriatrics were the mainstay of therapy, acting by abolishing the dilatation and constriction of the pupil and pull of the ciliary body during the movement of accommodation, thereby reducing iris and ciliary spasm and hence relieving pain and, in addition, breaking down the posterior synechiae. Steroids have been used locally as the standard form of therapy in acute and chronic uveitis since the early 1950s, their mechanism of action being to reduce the exudative inflammatory process. This is achieved to some extent by inhibiting capillary permeability, thereby decreasing the cellular and protein leakage from the circulating blood into the aqueous during inflammation. However, there have been no double-blind studies to evaluate therapy in this field.

Topical corticosteroid therapy can cause side effects and involves such hazards as potentiation of herpes simplex and other viral diseases (Patterson and Jones, 1967), increased susceptibility to fungal infections (Ley and Saunders, 1956), and possible increased spread of bacterial infection (Mitsui and Hanabusa, 1955). A specific ocular complication of local steroid therapy may be the increase in intraocular pressure that occurs in genetically predisposed individuals (Goldman, 1962; Becker and Mills, 1963; Becker, 1965) and in fact topical steroids are being used as a provocative test (Becker and Ballin, 1965).

It would seem reasonable to question the efficacy of steroids in uveitis, and this controlled double-blind clinical trial has therefore been devised to assess the response of anterior uveitis to topical steroids.

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Patients and methods

This was a double-blind trial between-patient study involving 3 treatment regimens: betamethasone phosphate (0·1%), clobetasone butyrate (0·1%), and placebo eyedrops. Patients selected for study were those presenting to the Casualty Department of St. Paul's Eye Hospital, Liverpool. Sixty patients were entered in the trial, all being cases of acute unilateral nongranulomatous anterior uveitis. Twelve did not complete for reasons stated below, and are omitted from Table 1.

On admission of the patient to the trial a clinical history was taken and a record form was completed. Details of the patient's subjective assessment of the discomfort of the eyes, a full detailed slit-lamp

Table 1 *Summary of patient details*

Treatment	*Clobetasone butyrate*	*Betamethasone phosphate*	*Placebo*
Number in group	16	18	14
Number of males	13	13	9
Number of females	3	5	5
Average age (years)	47	55	48
Range of age (years)	27–70	36–74	46–70
Affected eye: right	7	7	9
left	9	11	5
Recurrent iritis	11	13	8
Range of years since first episode of iritis	½–21	1–25	1/3–17
Number of days of symptoms before treatment:			
average	4	6	7
range	1–14	1–21	1–21

examination, visual acuity, and intraocular pressure were recorded on the patient record form. In addition corneal temperatures of both eyes were recorded with a bolometer (Mapstone, 1968a, b, c).

Patients were randomly allocated to clobetasone butyrate, or betamethasone phosphate, or placebo eyedrops. Comparative details for each group are given in Table 1. They were asked to instil the drops daily into the relevant eye using 2 drops 2-hourly each day for a period of 3 weeks. In addition, guttae atropinae 1% were instilled twice daily and, when necessary, acetazolamide for secondary glaucoma.

Patients were seen at 3, 7, 14, and 21 days for reassessment and recording of findings. In those cases in which the uveitis became worse they were reviewed daily. The scoring of symptoms and signs were as in Table 2.

Results

Symptoms and signs were analysed separately. Initially, the Kruskal-Wallis one-way analysis of variance was used to determine if the 3 groups of patients were statistically different. If this test showed a difference, the Mann-Whitney U test was used to compare the individual pairs of treatment groups. In both tests the level of significance was taken as $P<0{\cdot}05$. When correlating the signs and symptoms with eye temperature, the Spearman rank correlation coefficient (r_s) was calculated.

SYMPTOMS

There was no difference in the 3 groups initially, and betamethasone phosphate and clobetasone butyrate drops were significantly better than placebo after 3 days' treatment. There was a difference at 7 days, though this just failed to reach a statistical significance, probably owing to the small numbers of the placebo group. The difference between steroid and placebo groups did not reach a statistical difference after 14 days and 21 days (Fig. 1).

SIGNS

The 3 treatment groups were not significantly different initially. Although there was a difference between steroid and placebo treatments at 3, 7, and 14 days, it failed to reach statistical significance. However, the groups were different after 21 days of treatment, and betamethasone phosphate

Table 2 *Scoring of symptoms and signs*

Symptoms				
Blurring	Scored as:	0=absent		
Redness		1=mild		
Watering		2=moderate		
Photophobia		3=severe		
Pain				
Signs				
Ciliary injection	0=nil	1=moderate	2=marked	
Corneal oedema	0=nil	1=moderate	2=marked	
Keratic precipitate	0=absent	1=present		
Flare	0=nil	1=+	2=++	3=+++
Cells in aqueous	0=nil	1=+	2=++	3=+++
Cells in vitreous	0=nil	2=+	3=++	4=+++
Exudate	0=absent	3=present		
Posterior synechiae	0=absent	1=present		
Ptosis	mm difference between 2 eyes 0=absent 3=present			
Hypopyon	0=absent	3=present		

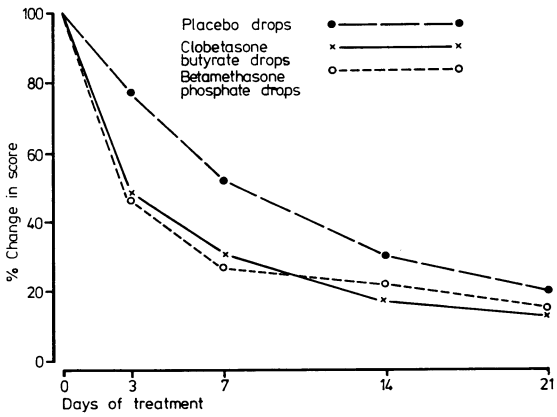

Fig. 1 *Percentage change in symptom scores*

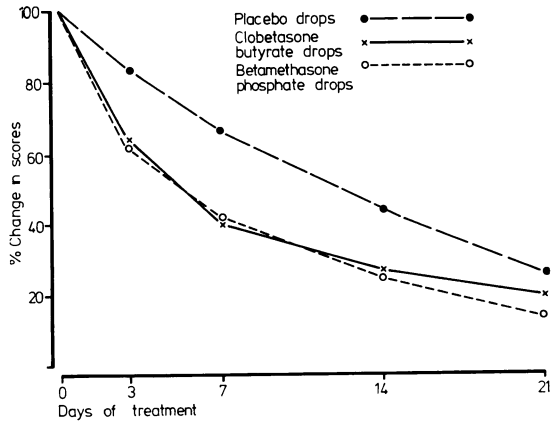

Fig. 2 *Percentage change in sign scores*

was significantly better than placebo; clobetasone butyrate was not significantly better than placebo (Fig. 2).

The correlation of initial eye temperature with initial symptom scores was $r_s=0{\cdot}33$; $t=2{\cdot}32$; $P<0{\cdot}05$.

The correlation of initial eye temperature with initial sign scores was $r_s=0{\cdot}24$; $t=0{\cdot}17$; $P>0{\cdot}05$.

Eye temperature was then correlated with selected signs: hypopyon, ptosis, exudate, cells in anterior vitreous, and ciliary injection; $r_s=0{\cdot}41$; $t=3{\cdot}46$; $P<0{\cdot}05$.

EVALUATION OF INTRAOCULAR PRESSURE CHANGES

The intraocular pressure changes in 5 cases (2 steroid responders and 3 ocular hypertensives) known to sustain raised intraocular pressures with topical steroids are shown for dexamethasone 0·1% t.i.d. for 6 weeks (Table 3) and in the same cases for clobetasone butyrate 0·1% t.i.d. for 6 weeks (Table 4). In case 1 clobetasone butyrate was stopped after 2 weeks as there was a significant pressure rise.

A summary of the results showing mean percentage of change in symptoms and sign scores with treatment is shown in Table 5. A formal analysis

Table 3 *After dexamethasone 0·1% 3 times daily for 6 weeks*

Case no.		*Baseline IOP mmHg*	*'C' tonography values µl/min/mmHg*	*Final IOP mmHg*	*'C' tonography values µl/min/mmHg*
1	Steroid responder	16	0·27	34	0·09
2	Steroid responder	17	0·23	32	0·16
3	Ocular hypertensive	20	0·15	29	0·14
4	Ocular hypertensive	28	0·09	37	0·05
5	Ocular hypertensive	24	0·06	36	0·07

Table 4 *After clobetasone butyrate 0·1% 3 times daily for 6 weeks. Treatment of case 1 was stopped after 2 weeks as there was a significant pressure rise*

Case no.	*Baseline IOP mmHg*	*'C' tonography values µl/min/mmHg*	*Final IOP mmHg*	*'C' tonography values µl/min/mmHg*
1	14	0·13	20	0·15
2	16	0·24	20	0·25
3	22	0·22	18	0·19
4	23	0·14	22	0·11
5	20	0·11	21	0·14

Table 5 *Summary of results*

	Days of treatment	*Clobetasone butyrate*	*Betamethasone phosphate*	*Placebo*
Mean % change in symptom scores on days of treatment	3	51·7	53·2	22·7
	7	69·0	73·4	47·4
	14	82·8	76·6	70·1
	21	86·2	84·7	79·4
Mean % change in sign scores on days of treatment	3	36·8	38·7	18·3
	7	59·4	58·6	33·9
	14	73·7	75·2	59·6
	21	80·5	86·2	74·3
Mean % change in sign and symptoms scores on days of treatment	3	42·7	45·5	20·4
	7	63·2	65·4	40·3
	14	77·3	75·8	63·6
	21	82·7	85·6	76·7
Number of patients where scores (signs and symptoms) rose greater than pretreatment level after treatment	—	1	1	6
Number of patients where scores (signs and symptoms) rose during treatment but not greater than pretreatment level		3	1	2

based on the clinical signs divided the 3 groups into mild and severe cases (Table 6). Those cases with flare, cells, and keratic precipitates only were classed as mild uveitis, while the severe cases on initial examination had, in addition, one or more of either ptosis, exudate, or hypopyon.

Figs. 3 and 4 show the duration of uveitis in mild and severe cases in each of the 3 treatment groups.

Twelve patients did not complete the trial. Four patients were withdrawn because of worsening of the condition and they were later found to have been on placebo eyedrops. One patient was given another medication in error after starting the trial, 1 patient was withdrawn after 7 days due to development of bilateral anterior uveitis, and 6 patients defaulted.

Table 6 *Formal analysis*

	Number of cases		
	Mild	*Severe*	*Total*
Clobetasone butyrate	9	7	16
Betamethasone phosphate	10	8	18
Placebo	9	9 (4 withdrawn)	18

Discussion

Steroids are used locally as the standard form of therapy in acute and chronic uveitis. Their efficacy is accepted (Duke-Elder, 1951; Duke-Elder *et al.*, 1951; Woods, 1951; Fitzgerald, 1951; Woods, 1952a, b; Ashworth, 1954), though there have been no controlled double-blind studies to evaluate therapy in this field.

A double-blind trial was devised with the following aims: (1) to determine the place of steroids in the treatment of acute anterior uveitis by comparing steroid and placebo treated groups of patients; (2) to determine the clinical efficacy of the steroid clobetasone butyrate compared with betamethasone phosphate; (3) to confirm that the measurement of corneal temperature is a useful objective parameter for the assessment of inflammation due to anterior uveitis and to establish the correlation between this and the subjective assessment by means of a scoring system for signs and symptoms (Ashford and

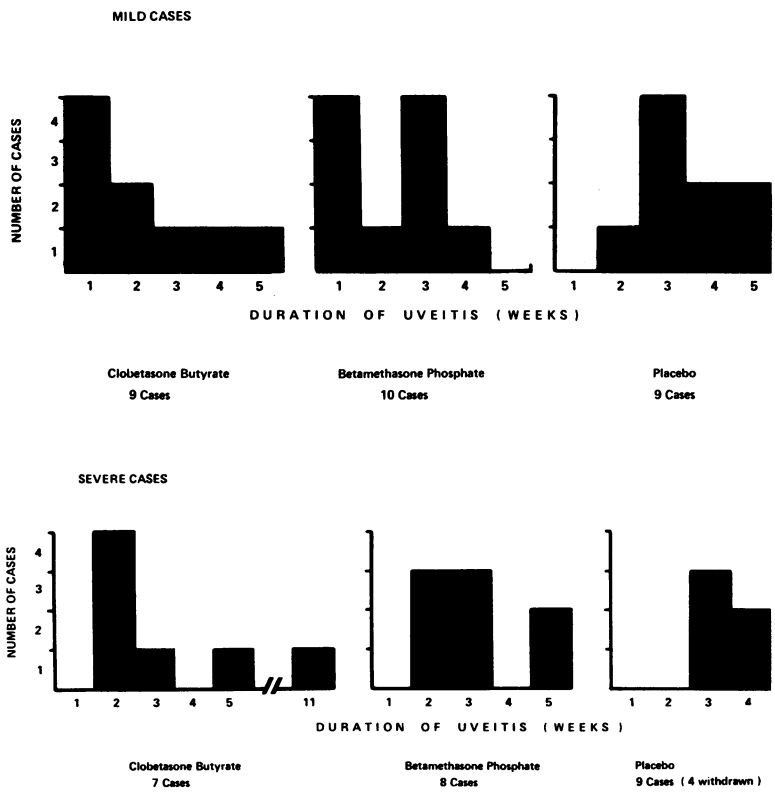

Fig. 3 *Histograms showing duration of uveitis in weeks in mild uveitis cases in each of the 3 treatment groups: clobetasone butyrate, betamethasone phosphate, and placebo*

Fig. 4 *Histograms showing duration of uveitis in severe uveitis cases in each of the 3 treatment groups: clobetasone butyrate, betamethasone phosphate, and placebo*

Lamble, 1974); and (4) to evaluate intraocular pressure changes on clobetasone butyrate.

The results have shown, as regards symptoms, that although the steroid-treated group of patients were significantly better than the placebo-treated group within the first 10 days, there was no significant difference in the 2 groups between 14 and 21 days. There is therefore more improvement symptomatically in the initial stage of treatment in those patients on steroids than those on placebo. Of the improvement in signs, however, the patients on betamethasone phosphate were significantly better than the placebo group after 21 days. Clobetasone butyrate did not appear to be significantly better than placebo.

Figs. 1 and 2 show that the improvement of those patients on placebo lagged behind that of those on topical steroids by approximately 1 week. Therefore it could be argued that topical steroids are merely speeding up the resolution of an otherwise self-limiting disease by a period of 7 to 10 days.

One of the difficulties in evaluating steroids in the treatment of uveitis is that one is dependent on the subjective assessment of the signs and symptoms resulting from the inflammatory response. However, Mapstone (1968a, b, c) and Ashford and Lamble (1974) have shown that the assessment of corneal temperature by means of bolometry provides an objective parameter which is directly influenced by the degree of inflammation of the iris.

In the present trial series, however, the measurement of corneal temperatures became significant only in the severe cases with selected signs, such as hypopyon, ptosis, exudate, or cells in the anterior vitreous. The milder cases of uveitis did not show significantly different corneal temperatures when compared with the fellow normal eye.

As mentioned previously, however, 4 cases removed from the trial because of worsening of the condition were found to be on placebo. Three of the 4 cases had presented initially with severe uveitis—that is, ptosis or exudate, on the first visit—and the fourth case had presented with moderate uveitis initially with flare and cells, but developed ptosis and exudate at 14 days. As shown in Figs. 3 and 4, of the other 5 severe cases on placebo 3 had resolved by 21 days and the other 2 by 35 days. Two of these cases had exudate on the first visit only, 3 had ptosis and exudate initially, but one or other of these signs was abating after 7 days on the trial. Of the mild cases on placebo, 7 out of 9 were fully resolved by 28 days; the remaining 2 cases were fully resolved by 35 days.

The ability of topically applied corticosteroids to cause ocular hypertension in susceptible individuals is one of the factors limiting their usefulness. Clobetasone butyrate was evaluated to see if it had a reduced propensity to cause a rise of intraocular pressure when compared with dexamethasone. The results have shown that there was no increase in intraocular pressure in 4 out of 5 cases on clobetasone butyrate, the remaining case being withdrawn after 2 weeks because of a pressure rise. Whereas all 5 cases on dexamethasone responded with a pressure rise, it appears that clobetasone butyrate shows a dissociation of anti-inflammatory from ocular hypertensive effects.

From this trial series it would appear that milder cases of uveitis, without inflammatory ptosis or exudate, resolve without topical steroids and that only those cases in which these signs exist need have topical steroid therapy. Certainly the more severe cases of anterior uveitis have inflammatory ptosis, exudate, and even hypopyon, which was why these signs were given high loading scores in the scoring system. Do all cases of anterior uveitis necessarily require topical steroids? Further trials are probably needed on a larger series of patients before this question can be satisfactorily answered.

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References

Ashford, J. J., and Lamble, J. W. (1974). A detailed assessment procedure of anti-inflammatory effects of drugs on experimental immunogenic uveitis in rabbits. *Investigative Immunology*, **13**, 414–421.

Ashworth, A. N. (1954). M.D. thesis. The use of cortisone in ophthalmology, Manchester Royal Eye Hospital, 106–169.

Becker, B. (1965). Intra-ocular pressure response to topical corticosteroids. *Investigative Ophthalmology*, **4**, 198–205.

Becker, B., and Ballin, N. (1965). Glaucoma and corticosteroid provocative testing. *Archives of Ophthalmology*, **74**, 621–624.

Becker, B., and Mills, D. W. (1963). Corticosteroids and intra-ocular pressure. *Archives of Ophthalmology*, **70**, 500–507.

Duke-Elder, S. (1951). The clinical value of cortisone and A.C.T.H. in ocular disease; preliminary assessment for M.R.C. *British Journal of Ophthalmology*, **35**, 637–671.

Duke-Elder, S., Duthie, O. M., Law, F. W., and Lister, A. (1951). A series of cases treated locally by cortisone. *British Journal of Ophthalmology*, **35**, 672–694.

Fitzgerald, J. R. (1951). Early results of A.C.T.H. and cortisone treatment of ocular disease. *Archives of Ophthalmology*, **45**, 320–333.

Goldmann, H. (1962). Cortisone glaucoma. *Archives of Ophthalmology*, **68**, 621–626.

Ley, A. P., and Saunders, T. E. (1956). Fungus keratitis. *Archives of Ophthalmology*, **56**, 257–264.

Mapstone, R. (1968a). Determinants of corneal temperature. *British Journal of Ophthalmology*, **52**, 729–741.

Mapstone, R. (1968b). Measurement of corneal temperature. *Experimental Eye Research*, **7**, 237–243.

Mapstone, R. (1968c). Thermometry and the eye. *Transactions of the Ophthalmological Societies of the United Kingdom*, **88**, 693–699.

Mitsui, Y., and Hanabusa, J. (1955). Corneal infections after cortisone therapy. *British Journal of Ophthalmology*, **39**, 244–250.

Patterson, A., and Jones, B. R. (1967). The management of ocular herpes. *Transactions of the Ophthalmological Societies of the United Kingdom*, **87**, 59–84.

Woods, A. C. (1951). The present status of A.C.T.H. and cortisone in ophthalmology. *American Journal of Ophthalmology*, **34**, 945–960.

Woods, A. C. (1952a). Uses and limitations of A.C.T.H. and cortisone in ophthalmology. *British Journal of Ophthalmology*, **36**, 401–431.

Woods, A. C. (1952b). The value of A.C.T.H. and cortisone in ocular diseases. *Transactions of the Ophthalmological Societies of the United Kingdom*, **72**, 171–189.