

PENOTRANE IN BLEPHARITIS*† A DOUBLE-BLIND CONTROLLED TRIAL

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SINCE blepharitis is frequently a chronic condition, either resistant to treatment or liable to recurrence, ophthalmologists are receptive to claims for improved methods of treatment. Jackson (1965) reported good results from the use of "Penotrane" in chronic or recurrent, predominantly staphylococcal, lid lesions. Marmion and Silva (1967) mention a trial of the same agent in seborrhoeic blepharitis and report the result as "by no means dramatic".

According to Birkhaug (1933), phenylmercuric nitrate was first prepared by Robert Otto in 1870. Weed and Ecker (1931) and Levine (1933) found the substance a highly effective surface-acting antibacterial and antifungal agent. Goldberg, Shapiro, and Wilder (1950 a, b) claimed that the condensation of the phenylmercuric ion with a colloidal sulphonic anion as phenylmercuric dinaphthylmethane disulphonate gave enhanced antibacterial activity and resulted in good tissue penetration. This substance has subsequently been marketed as "Penotrane". Various reports have appeared on its usefulness as a surface-acting agent both for skin preparation (Reid, Black, and Dean, 1958) and for the treatment of skin lesions (Tiessen, 1957; Roberts, 1960; Hutfield, 1963), mycotic ear infections (Smyth, 1962), and vaginitis (Gourlay, 1955; Tiessen, 1957).

This paper reports the results of a further controlled double-blind trial of Penotrane in blepharitis.

Material and Methods

The agent under trial was Penotrane prepared as a 0.033 per cent. lotion in a "Lissapol" and glycerin base, and as a 0.033 per cent. hydroxymethylcellulose gel, as already described by Jackson (1965); these are known as "Octrane" lotion and gel. The control substances were the lotion base and the gel base without Penotrane. The "active" and "inert" preparations were identified by the letters "A" and "B" and their true identity remained unknown until the conclusion of the trial.

Thirteen patients entered the trial, all with either chronic or recurrent forms of blepharitis, and this formed the sole basis for selection. Six patients were thought on clinical and bacteriological grounds to have staphylococcal blepharitis, four were thought to have a predominantly squamous blepharitis, and three remained unclassified. They were initially assigned either to A or B on the basis of whether their birthday occurred on an odd or even date.

Patients were told to scrub or wipe their lid margins with a tissue soaked in the lotion and then to squeeze gel along the intermarginal strip and lower conjunctival fornix three times daily. In one patient the initial treatment was given for 5 weeks but, otherwise, unless circumstances prevented completion of the trial (see Table II), either A or B was used in each patient for 4 weeks and then treatment was switched to the alternative agent, B or A, for a further 4 weeks.

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Each patient was seen as far as possible at weekly intervals and an attempt was made to "score" the improvement or deterioration in the state of the lids on a specially designed card (Figure), wherein each sign or symptom was assessed as doubtful (+-) to very severe (4+). Scores were obtained for the objective (signs) and subjective (symptoms) state of the lids at Week 0, Week 4, and Week 8. Scores at Weeks 4 and 8 were then converted to percentage improvement or deterioration compared with either the untreated state (Week 0) or the state after 4 weeks' treatment with the initial agent. Conjunctival cultures were taken before beginning the trial and after the completion of treatment with both A and B.

FIGURE.—*Pro forma* used for charting results of treatment of blepharitis.

TREATMENT OF BLEPHARITIS—Wards 43-44, Royal Infirmary, Edinburgh—1966												DIAGNOSIS CULTURE		Right	Left	A. first			
NAME:				CASE NO:								Initial				B. first			
ADDRESS:				AGE:				SEX:				1 month							
Nature of Complaint & Duration:				CLINICAL DESCRIPTION (score: nil to 4+)								2 months							
WEEKS		0		1		2		3		4		5		6		7		8	
EYES		R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L
<u>Objective</u>																			
HYPERAEMIA—skin																			
—conjunctiva																			
THICKENING—diffuse																			
nodular																			
—cystic																			
EXUDATES																			
SCALING																			
CRUSTING																			
MEIBOMIANITIS																			
FOLLICULOSIS																			
LASHES—distortion																			
—thinning																			
ECTROPION																			
ENTROPION																			
PTOSIS																			
<u>Subjective</u>																			
PAIN																			
DISCOMFORT																			
ITCHING																			
PHOTOPHOBIA																			
BLURRING																			
OTHER																			
TOTALS:																			

Results

All six patients receiving Octrane as an initial treatment improved both objectively and subjectively, although it would be fair to say that this improvement was only slight in

some patients. Six of the seven patients receiving the control agents initially improved both objectively and subjectively; one of the seven showed a slight objective deterioration, and in another there was no change in subjective symptoms.

The progress after the cross-over in therapy was less uniform. Two of the seven patients given Octrane as the second treatment stopped using the medication after 2 and 3 weeks respectively, as they felt their lids increasingly uncomfortable after instilling the drugs, and another was taken off the trial after 1 week, as marginal corneal ulceration (thought to be due to uncontrolled staphylococcal infection) was noted. Altogether the results with Octrane after cross-over were poor; only one case improved objectively and five showed objective deterioration, whilst one appeared unchanged. Symptomatically three patients felt an improvement with Octrane, two no change, and two a deterioration. The results in patients given the inert control treatment after the cross-over appeared less bad. None had to be withdrawn from the trial, four showed objective improvement, and two showed objective deterioration. Two showed symptomatic improvement, three, already asymptomatic, did not develop any fresh symptoms, and only one showed symptomatic deterioration.

With regard to symptomatic changes, it is worth noting that three of the patients in the trial were children so that little reliance can be placed on their subjective scores (Table I).

TABLE I
MEAN PERCENTAGE CHANGES IN SYMPTOMS AND SIGNS AFTER
OCTRANE AND CONTROL TREATMENT

Period (wks)	Octrane		Control	
	Objective	Subjective	Objective	Subjective
0-4	< 35	< 76	< 28	< 41
4-8	> 8	< 10	< 27	< 31

< = better > = worse

Thus, after the first 4 weeks' treatment, twelve cases showed some objective improvement and the Octrane and control cases improved overall to about the same extent. The symptomatic improvement in cases treated with Octrane was better than in the control group, but this difference was not statistically significant at the 5 per cent. level ('t' test). During the second phase of treatment, after cross-over, the Octrane patients did worse objectively and symptomatically than the control group and actually showed an overall objective deterioration.

Conjunctival cultures were positive on eight occasions before starting Octrane treatment and cultures became negative on only one occasion after treatment. *Staphylococcus aureus* was cultured initially in four patients and the same organism was recovered after Octrane treatment in two of these patients. In one patient an initially negative culture became positive for *Staphylococcus aureus* after Octrane treatment. Patients on control treatment did rather worse. No staphylococcal infection was eliminated and on two occasions cultures which were negative before treatment became positive after treatment (see Table II, overleaf).

TABLE II
RESULTS IN 13 PATIENTS

Patient No.	Age (yrs)	Type of Blepharitis	Treatment I	Per cent. Change in Condition	Treatment II	Per cent. Change in Condition	Culture (wks)	Side-effects
1	65	Staphylococcal	Control 4 wks	Obj. <20 Subj. <17	Octrane 4 wks	Obj. <25 Subj. No change	0 +ve 4 -ve 8 +ve S	Smarting with both I and II
2	75	Non-specific	Octrane 4 wks	Obj. <28 Subj. <50	Control 4 wks	Obj. <47 Subj. <100	0 +ve 4 -ve 8 +ve	Some discomfort with II
3	48	Staphylococcal	Control 4 wks	Obj. <15 Subj. <20	Octrane 3 wks	Obj. >8 Subj. No change	0 +ve S 4 +ve S 7 +ve S	? Allergy in 7th week
4	9	Staphylococcal	Octrane 4 wks	Obj. <48 Subj. <100	Control 4 wks	Obj. <9 Subj. No change	0 +ve S 4 +ve S 8 +ve S	Nil
5	50	Staphylococcal	Control 4 wks	Obj. >10 Subj. <50	Octrane 1 wk	Obj. >5 Subj. >57	0 +ve S 4 +ve S 5 -	Irritation with both I and II
6	46	Squamous	Octrane 4 wks	Obj. <15 Subj. <83	Control 4 wks	Obj. >18 Subj. >75	0 +ve 4 +ve 8 +ve	Nil
7	68	Squamous	Control 4 wks	Obj. <28 Subj. <59	Octrane 2 wks	Obj. >11 Subj. <20	0 -ve 4 +ve 8 +ve	? Allergy in 6th week
8	67	Staphylococcal	Octrane 4 wks	Obj. <10 Subj. <25	Control 4 wks	Obj. >10 Subj. <67	0 +ve S 4 +ve S 8 +ve S	Nil
9	13	Squamous	Control 4 wks	Obj. <10 Subj. No change	Octrane 4 wks	Obj. No change Subj. <100	0 +ve 4 -ve 8 -ve	Smarting with II
10	21	Squamous	Octrane 4 wks	Obj. <31 Subj. <100	Control 4 wks	Obj. <67 Subj. No change	0 +ve 4 +ve 8 -ve	Nil
11	34	Staphylococcal	Control 5 wks	Obj. <70 Subj. <58	Octrane 4 wks	Obj. >50 Subj. >40	0 +ve S 5 +ve S 9 +ve S	Nil
12	9	Non-specific	Octrane 4 wks	Obj. <80 Subj. <100	Control 4 wks	Obj. <67 Subj. No change	0 -ve 4 -ve 8 -ve	Smarting with both I and II
13	25	Non-specific	Control 4 wks	Obj. <61 Subj. <86	Octrane 4 wks	Obj. >10 Subj. <50	0 -ve 4 -ve 8 -ve	Much smarting with both I and II

< = better

> = worse

S = *Staphylococcus aureus*

Discussion

Although the number of patients treated in this trial is small, the results in the author's opinion are sufficiently clear-cut to demonstrate that Penotrane is an ineffective agent in the treatment of blepharitis. It is worth noting that the initial objective improvement could have given the impression of reasonable effectiveness, had not the control agent shown that the improvement had nothing to do with Penotrane. Also, the impression that Octrane initially relieved symptoms more effectively than the control may be due to chance only, and certainly tends to be modified by the poor subjective performance of Octrane in the second half of the trial. The failure of Octrane to control rather florid staphylococcal blepharitis is especially damning. Three of these cases of staphylococcal blepharitis subsequently showed a very clear-cut and rapid remission of symptoms after treatment with established local antibiotic agents.

Side-effects.—A certain amount of nipping and smarting was noted with both control and active lotions and gels and was probably unconnected with Penotrane. On the other hand, two patients using Octrane stopped their treatment on account of various rather severe discomforts which followed instillation of the medication. The lid appearances in these cases did not, however, at all convince the author that a definite drug allergy was present. It did not appear that the incidence of side-effects in itself precludes the use of Penotrane in lid disease.

The frequent mechanical cleansing of the lid margins and the protective or detergent action of the ointment and lotion bases might account for the overall improvement shown in the majority of patients. No doubt psychological factors played their part, especially in the symptomatic improvement, which consistently exceeded the objective improvement. As there is evidence that phenylmercuric dinaphthylmethanedisulphonate is an effective agent *in vitro* and *in vivo* at other sites, the results here are certainly disappointing.

Summary

A double-blind controlled trial of Octrane gel and lotion containing Penotrane was carried out in thirteen patients with blepharitis. There was some overall improvement using both Octrane and the inert control substances, but the difference in response was considered insignificant. It is concluded that Penotrane is not an effective agent in the treatment of blepharitis.

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