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Trimethoprim-Polymyxin Eye Drops versus Neomycin-Polymyxin-Gramicidin Eye Drops in the Treatment of Presumptive Bacterial Conjunctivitis – a Double-Blind Study

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Abstract. 48 patients with a diagnosis of presumptive bacterial conjunctivitis were assessed. They had been treated with either trimethoprim-polymyxin or neomycin-polymyxin-gramicidin eye drops in a randomised double-blind trial. There were 24 patients in each treatment group. There were no significant differences between the two preparations with regard to the eradication of organisms or clinical improvement, and both preparations proved to be very effective. Patient compliance was good and no adverse reactions were encountered with either preparation.

Introduction

A combination of trimethoprim and polymyxin would be expected to have significant activity against most bacterial causes of surface ocular infections with the notable exception of *Neisseria gonorrhoea* [*Bushby*, 1974; *Garrod* et al., 1973]. Such a combination has also been shown to have little potential for producing irritant or allergic reactions in the eye (unpublished data). It was therefore considered to be of clinical interest to test the effect of trimethoprim-polymyxin (TP) against an established eye preparation containing neomycin-polymyxin-gramicidin (NPG) in the treatment of surface ocular bacterial infections.

Subjects and Methods

TP and NPG ophthalmic solutions were supplied by Deutsche Wellcome.

Patients aged between 8 and 80 inclusive, attending the Augenklinik in Braunschweig, with a presumptive diagnosis of surface ocular bacterial infection, were entered into the trial with the following exclusions:

(i) Those who had received treatment with other eye preparations or systemic antibiotics within the 72 h prior to the commencement of the trial.

(ii) Those who had concomitant fungus, virus or tuberculous infections of the eye.

(iii) Those who required concurrent treatment with a systemic or local corticosteroid, antihistamine and/or antibiotic.

(iv) Those who had previously demonstrated allergic hypersensitivity to trimethoprim, polymyxin B, neomycin or gramicidin.

(v) Those who had contracted more than four infections of the external eye with the duration of one of these infections being longer than 2 weeks during the 12 months prior to being considered for admission into the trial.

Although the admission criteria could theoretically have allowed the entry of patients with a wider spectrum of disease processes, in fact all the patients entered had presumptive bacterial conjunctivitis. Informed consent was obtained in all cases and the patients were fully assessed clinically at the initial visit and at two follow-up appointments – one approximately 5–6 days after the start of therapy and the second follow-up approximately 12–15 days after the start of therapy.

Symptoms and signs were graded on a 0 – 3 scale (where 0 = not present; 1 = mild; 2 = moderate; 3 = severe). In addition, a colour photograph of the affected eye or eyes was taken to allow for independent assessment also using a 0 – 3 grading system (where 0 = normal, 1 = slight, diffuse or localised redness; 2 = generalised redness; 3 = generalised redness and redness and swelling of the eyelids).

Swabs for bacteriological assessment were taken from the lower conjunctival sac at each visit and these were directly plated onto blood agar and the plates incubated at 37 °C. In the latter part of the study, chocolate agar culture medium was used in addition to blood agar in order to enhance the possibility of culturing *Haemophilus* species. Smears of material from the lower conjunctival sac swabbing were also examined by direct microscopy.

The patients were allocated to one or other treatment in a randomised manner and the trial was conducted in a double-blind fashion. The dosage of either preparation was one drop into each affected eye six times daily for 10 days and the patients completed a record card to aid compliance.

Results

Of 66 patients enrolled into the trial, only 48 could be fully evaluated. These were equally divided between the two treatment groups.

The other 18 patients were excluded for the following reasons: failure to attend for follow-up visits (8 patients), proven viral infection (3 patients), poor compliance with the treatment regime (this is taken to mean the use of less than forty doses per treatment course – 6 patients) and inadequate information (1 patient).

The bacteriological results are shown in table I. Bacteria were isolated from the pre-treatment swabs of 14 of the patients treated with NPG and 8 treated with TP. Bacteria were eradicated in all except 2 of the patients receiving NPG. In 1 case, *Staphylococcus epidermidis* was still isolated following treatment and in another, *Streptococcus viridans,* isolated on entry to the trial, was replaced by *Klebsiella oceanae* following treatment. However, in both these patients, signs and symptoms completely disappeared following treatment. In the 8 patients receiving TP from whom bacteria were cultured initially, bacteria were eradicated in all the cases following treatment. However, the initial swab from 1 patient in the TP group failed to grow an organism whereas the post-therapy culture grew *Streptococcus viridans,* although the patient's signs and symptoms had improved following treatment.

Swabs from the remaining 25 patients failed to grow any organisms. In nearly all the cases, however (42 out of the 48), leucocytes were found in the pre-treatment smears.

It will be seen from table I that many of the organisms grown are traditionally regarded as being non-pathogenic but it would appear that they may be pathogenic in the eye and elsewhere under certain circumstances [*Jarudi* et al., 1975; *Munro,* 1981].

Table I. Bacteriological results by treatment group

Patient No.	Pathogen before therapy	Pathogen after therapy
Trimethoprim-Polymyxin		
7	*S. aureus*	nil
22	*S. viridans*	nil
24	*S. epidermidis*	nil
31	nil	*S. viridans*
38	*S. viridans*	nil
42	*S. aureus*	nil
43	*S. epidermidis*	nil
45	*Haemophilus parainfluenzæ*	nil
49	*S. epidermidis*	nil
	S. viridans	
Neomycin-Polymyxin-Gramicidin		
6	*S. aureus*	nil
19	*S. viridans*	nil
21	*Proteus spp.*	nil
23	*S. aureus*	nil
33	*S. epidermidis*	nil
34	*S. aureus*	nil
41	*S. aureus*	nil
44	*S. viridans*	*K. oceanæ*
50	*S. epidermidis*	*nil*
51	*S. aureus*	*nil*
55	*S. viridans*	*nil*
	S. epidermidis	
56	*S. viridans*	*nil*
	S. epidermidis	
H	*S. viridans*	*nil*
	S. epidermidis	
I	*S. epidermidis*	*S. epidermidis*

Table II. Signs and symptoms assessed

Single items for analysis	Grouped items for analysis	
Angular hyperaemia	Sensation of foreign body Sensation of grittiness	
Burning		
Diffuse hyperaemia	Watery discharge	discharge
	Purulent discharge	discharge
Itching	Eyelids stuck together in the morning	discharge
Meibomitis		
Photophobia	Eyelid oedema Eyelid erythema Eyelid tenderness	eyelid effects
	Scaling of eyelid margins	eyelid margin effects
	Erythema of eyelid margins	eyelid margin effects
	Ulceration of eyelid margins	eyelid margin effects

The signs and symptoms which were assessed are indicated in table II. For the purpose of statistical analysis, signs and symptoms recorded on the patient record form were in some instances grouped together (see table II) and the means of such groups analysed. Scores for each of the single or grouped symptoms and signs obtained from the three assessment periods were considered as data from a split plot design and subjected to analysis of variance: subject, occasion and treatment effects were thus examined simultaneously. Further investigation was carried out by Duncan multiple range test if and when significant differences were demonstrated.

In all cases, significant ($p < 0.05$) occasion differences were revealed. There was no significant difference between the treatment groups either before treatment or at either follow-up visit. Mean scores for single or grouped signs and symptoms are shown in table III.

Photographic data from the two groups were examined by analysis of variance. Differences between the treatment groups did not achieve significance either prior to or

Table III. Mean scores for symptoms and signs by treatment group

	NPG			TP		
	pre-treatment	1st follow-up	2nd follow-up	pre-treatment	1st follow-up	2nd follow-up
Symptoms						
Itching	1.83	0.96	0.33	2.29	1.25	0.54
Burning	2.21	1.13	0.33	2.29	1.00	0.42
Foreign body/grittiness sensation	2.27	0.92	0.23	2.15	0.96	0.40
Photophobia	2.13	1.04	0.25	1.71	0.71	0.21
Discharge	2.19	0.92	0.28	2.35	1.04	0.32
Signs						
Effects on eyelid	1.53	0.74	0.32	1.56	0.71	0.32
Effects on eyelid margins	0.72	0.32	0.11	0.94	0.50	0.14
Meibomitis	1.13	0.63	0.38	1.50	1.13	0.54
Angular hyperaemia	1.54	0.92	0.25	1.46	0.71	0.25
Diffuse hyperaemia	2.58	1.25	0.46	2.50	1.38	0.46

Table IV. Mean scores assigned to photographs taken before and after treatment with NPG or TP eye drops

	Pre-treatment	Post-treatment
NPG	2.50	1.07
TP	2.27	1.27

following treatment. However, a significant difference ($p < 0.05$) was detected between mean scores of photographs taken before and after treatment with NPG and before and after treatment with TP (table IV).

No patient reported adverse reactions from either antibacterial preparation.

Discussion

This double-blind trial comparing ophthalmic drops containing TP and NPG, showed the two preparations to be equally effective both clinically and bacteriologically. Improvement of signs and symptoms and eradication of pathogens was found to be good with both combinations. No side effects were observed with either preparation and good compliance was found in this study, especially considering that the drops were used six times a day for 10 days.

The rate of isolation of pathogenic organisms was found to be low. In only 22 of the 48 patients (46%) was an organism isolated from the swab taken prior to therapy and this includes isolation of *S. epidermidis* and *S. viridans*. It must be borne in mind, however, that some authorities regard these organisms as pathogenic in the eye in certain circumstances. It would appear that many cases diagnosed as presumptive bacterial conjunctivitis either have some other cause for their conjunctivitis or there is a failure of the clinician's ability to isolate the bacterial organisms responsible. Statements by various au-

thors would appear to give support to this view [*Jarudi* et al., 1975; *Miller*, 1978].

In conclusion, it would appear that ophthalmic drops containing TP are a safe and effective therapy for presumptive bacterial conjunctivitis and that such a preparation will be especially useful in patients where contact allergic hypersensitivity to chloramphenicol, neomycin or sulphonamide has been previously demonstrated. They may also be considered in preference to chloramphenicol eye preparations when long-term use of such products is being considered, as an occasional case of fatal aplastic anaemia following the long-term use of chloramphenicol eye preparations has been reported [*Abramowicz*, 1980]. However, further studies, especially those with more complete bacteriological assessment, will be needed to establish the full potential of this novel combination.

Résumé

48 malades présentant vraisemblablement une conjonctivite bactérienne ont été évalués. Ils ont reçu un traitement, soit avec triméthoprim-polymyxine, soit avec néomycine-polymyxine-gramicidine, sous forme de gouttes pour application ophtalmique, pendant un essai randomisé en double aveugle. Chaque groupe sous traitement se composait de 24 malades. Aucune différence significative n'a été trouvée entre les deux préparations en ce qui concerne l'élimination des organismes ou bien les progrès cliniques, et toutes les deux préparations se sont avérées très efficaces. Les malades se sont bien conformés au traitement. Ni l'une ni l'autre préparation n'a provoqué de réactions adverses.

Zusammenfassung

Die Behandlungsergebnisse von 48 Patienten mit einer bakteriellen Konjunktivitis wurden ausgewertet. Die Patienten (je Gruppe 24) erhielten im Rahmen dieser randomisierten Doppelblindstudie entweder Trimethoprim/Polymyxin- oder Neomycin/Polymyxin/Gramicidin-Augentropfen. Die Untersuchung ergab keine signifikanten Unterschiede der beiden Kombinationen hinsichtlich der Keimeliminierung oder einer klinischen Besserung; die Wirkung beider Präparate wie auch die Verträglichkeit waren gut.

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