# Fucithalmic® in acute conjunctivitis

## Open, Randomized Comparison of Fusidic Acid, Chloramphenicol and Framycetin Eye Drops

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**Abstract.** Fucithalmic®, which is 1% fusidic acid in a sustained-release eye preparation, was shown to be superior to both chloramphenicol eye drops and framycetin (Soframycin®) eye drops in the treatment of bacterial conjunctivitis in Tanzania. The clinical success rate was 77/83 (93%) on fusidic acid compared with 22/46 (48% on chloramphenicol and 26/35 (74%) on framycetin ($P \leq 0.02$). The better effect of fusidic acid could be ascribed to a much lower rate of in vitro resistance (17%) compared to chloramphenicol (58%) and framycetin (41%). Because of the low resistance rate to fusidic acid among eye pathogens, especially in areas of the world with a high resistance towards other commonly used eye anti-infectives, Fucithalmic given twice daily would seem to be a valuable new eye anti-infective.

Key words: conjunctivitis – fusidic acid – chloramphenicol – framycetin – in vitro resistance.

Bacterial eye infections are usually effectively treated with available topical antibiotic preparations. However, treatment failures occur due to bacterial resistance towards specific antibiotics and to lack of patient complicance. Furthermore, allergic reactions may limit or contraindicate the use of available antibacterial ophthalmic agents. Fucithalmic is a newly developed topical eye preparation of fusidic acid. Besides a high activity against staphylococci (Gransden et al. 1984; Veraldo et al. 1984), fusidic acid is also clinically active against other eye pathogens, such as streptococci, pneumococci, Neisseria spp., Haemophilus aegyptius and Moraxella (Godtfredsen et al. 1962). Fusidic acid is not active against Enterobacteriaceae and Pseudomonas. However, these pathogens are rarely involved in external eye infections, and fusidic acid would therefore seem to cover most of the clinically relevant eye bacteria (Fedukowicz & Stenson 1985).

The rationale for conducting the present study has been to investigate the possible clinical benefit of fusidic acid in acute conjunctivitis in an area of the world where resistance to some of the commonly used eye anti-infectives is high. As active control drug, chloramphenicol has been chosen. In neonates and small children below the age of 6 months, however, our previous experience with chloramphenicol has been less promising and for that reason framycetin was chosen.

## Patients and Methods

The study includes in- and outpatients, admitted to Haydom Lutheran Hospital, Mbulu, Tanzania, with suspected bacterial conjunctivitis. Adults and children over the age of 6 months were randomly allocated to open treatment with either fusidic acid or chloramphenicol, referred to as group I. Children below 6 months of age were similarily allocated to either fusidic acid or framycetin, referred to as group II. In case of clinical failure of treatment on either chloramphenicol or framycetin, treatment was changed to fusidic acid. Test preparations were Fucithalmic® viscous eye drops which is a 1% microcrystalline suspension of fu-

sidic acid in a sustained-release carbomer preserved with benzalkonium chloride 0.001% and EDTA. Chloramphenicol was the commercially available Kloramfenikol® 0.5% eye drops (DAK) without preservative and framycetin the commercially available Soframycin® 0.5% eye drops preservated with phenylmercurinitrate (Roussel).

Fusidic acid was given 4 times daily on the first day and hereafter only morning and evening, whilst chloramphenicol and framycetin was given 8 times daily on the first day and then 4 times daily. All three preparations were given for a period of 7 to 14 days according to the severity of the infection and the clinical response to therapy.

At the first clinic visit the presence and severity of the following signs and symptoms were graded from 0 = absent to 3 = severe: conjunctival injection, photophobia, and conjunctival discharge. Conjunctival discharge was also assessed as purulent, mucopurulent or serous. This clinical evaluation was repeated days 1, 3 and 10 during the treatment period and in some cases more frequently. A bacteriological eye swab was obtained before and after treatment.

Eye specimens were obtained using a sterile cotton swab from the middle to the lateral conjunctiva. The swabs were plated on a blood agar and immediately incubated at 37°C for 20 to 26 h. From these pure cultures were isolated and a rough identification of bacteria was made by the oxydase test and Gram-stained microscopy.

Sensitivity testing was performed using an agar diffusion method on DST agar and Neo-Sensitabs® (Rosco). Bacteria have been classified as resistant according to breaking points as recommended by Rosco (Rosco 1984/85).

A total of 179 patients were admitted to the study, 100 to group I (50 fusidic acid, 50 chloramphenicol), and 79 to group II (40 fusidic acid adn 39 framycetin). Fifteen patients were excluded, 13 because they defaulted follow-up (6 fusidic acid, 4 chloramphenicol and 3 framycetin), one because the treatment diagnosis was an advanced panophthalmia (fusidic acid), and one premature child died (framycetin). Thus clinical evaluation was possible in group I: 45 fusidic acid, 46 chloramphenicol, and group II: 38 fusidic acid, 35 framycetin. There were no significant differences in the patient characteristics between the treatment groups as shown in Table 1.

*Table 1.*
Patients included in the study.

| | Group I Patients >6 months of age | | Group II Patients <6 months of age | |
|---|---|---|---|---|
| | Fusidic acid | Chloramphenicol | Fusidic acid | Framycetin |
| No. of patients | 45 | 46 | 38 | 35 |
| Sex M : F | 27 : 18 | 22 : 24 | 15 : 23 | 16 : 19 |
| Adults : Children | 13 : 32 | 9 : 37 | – | – |
| Age in months (mean) | – | – | 1.3 | 1.2 |
| In-patients : Out-patients | 19 : 26 | 16 : 30 | 27 : 11 | 27 : 8 |
| Treatment diagnosis | | | | |
| Conjunctivitis | 38 | 35 | 33 | 25 |
| Conjunctivitis – blepharitis | 5 | 7 | 5 | 10 |
| Conjunctivitis – keratitis | 2 | 4 | – | – |
| Disease history | | | | |
| </= 3 days | 21 | 22 | 21 | 20 |
| 4–7 days | 16 | 16 | 9 | 10 |
| > 7 days | 8 | 8 | 8 | 5 |
| Conjunctival discharge pre-treatment | | | | |
| Purulent | 8 | 8 | 10 | 6 |
| Mucopurulent | 28 | 32 | 27 | 27 |
| Serous | 9 | 6 | 1 | 2 |

*Table 2.*
Clinical and bacteriological effect of fusidic acid, chloramphenicol and framycetin eye drops in bacterial eye infections.

| | Group I Patients >6 months of age | | Group II Patients </= 6 months of age | |
|---|---|---|---|---|
| | Fusidic acid | Chloramphenicol | Fusidic acid | Framycetin |
| Clinical | | | | |
| Success | 41 | 22 | 36 | 26 |
| Failure | 4 | 24 | 2 | 9 |
| $\chi^2$ | $P < 0.001$ | | $P < 0.02$ | |
| Bacteriological | | | | |
| Success | 39 | 25 | 35 | 23 |
| Failure | 3 | 15 | 2 | 9 |
| Not evaluable* | 3 | 6 | 1 | 3 |
| $\chi^2$ | $P = 0.002$ | | $P = 0.03$ | |

## Results

The clinical success rate with fusidic acid was 77/83 (93%). Corresponding success rates were 22/46 (48%) in the chloramphenicol group and 26/35 (74%) in the framycetin group (cf Table 2). In nearly all cases of clinical failure this corresponded to a bacteriological failure. Thus, the bacterilogical success rates were 74/79 (94%) with fusidic acid compared with 25/40 (63%) on chloramphenicol and 23/32 (72%) on framycetin (a few patients could not be evaluated bacteriologically due to negative culture pre-treatment). The better clinical and bacteriological effect seen with fusidic acid is statistically significant, both compared to chloramphenicol in group I ($P \leq 0.002$) and compared to framycetin in group II ($P \leq 0.03$) (cf Table 2).

Table 3 shows the various eye pathogens isolated in cases of bacteriological success and failure, respectively. Success was defined as the eradication of the offending eye pathogen. Failure was defined as the persistence of the initial eye pathogen or the emergence of a new eye pathogen.

*Table 3.*
Antibacterial effect against eye pathogens.

| Eye pathogens | Fusidic acid | Chloramphenicol | Framycetin |
|---|---|---|---|
| Success | | | |
| Staphylococci | 36 (1) | 6 ( 4) | 12 (3) |
| Other Gram-positive | 18 (1) | 7 ( 1) | 4 (2) |
| Gram-negative cocci | 3 (1) | 3 ( 1) | 2 (1) |
| Gram-negative rods | 17 (3) | 9 ( 1) | 5 (3) |
| Failure | | | |
| Staphylococci | 3 (2) | 11 (11) | 1 |
| Other Gram-positive | – | 1 ( 1) | 4 (3) |
| Gram-negative cocci | 1 (1) | 1 | 1 (ND) |
| Gram-negative rods | 1 (1) | 2 ( 1) | 3 (3) |

Figures in brackets indicate number of strains resistant in vitro to the respective test drug.

*Table 4.*
Correlation between in vitro sensitivity of eye pathogens and antibacterial effect of treatment.

| | In vitro sensitivity* | | | | | |
|---|---|---|---|---|---|---|
| | Fusidic acid | | Chloramphenicol | | Framycetin | |
| | S </= 2 µg/ml | R > 2 µg/ml | S </= 8 µg/ml | R > 8 µg/ml | S </= 8 µg/ml | R > 8 µg/ml |
| Success | 68 | 6 | 18 | 7 | 14 | 9 |
| Failure | 1 | 4 | 2 | 13 | 2 | 6 |

* Disc diffusion method (Rosco) translated into MICs according to regression lines.

Emergence of new pathogens was recorded in two cases in the chloramphenicol group and in two cases in the framycetin group.

There was a good correlation between in vitro susceptibility of eye pathogens to fusidic acid and the antibacterial effect inasmuch as 68/69 strains classified as sensitive responded to treatment. Chloramphenicol and framycetin also showed a good correlation (18/20 and 14/16, respectively) (cf Table 4).

In those patients showing a clinical success the period until complete clinical cure was noted. With fusidic acid this was achieved after a mean of 5.9 and 6.6 days of treatment in group I and group II, respectively. With chloramphenicol and framycetin a mean of 8.1 and 7.2 days, respectively, was needed. These differences are not statistically significant.

Fifteen patients in group I and 5 in group II who were clinical and bacteriological treatment failures on either chloramphenicol or framycetin, had treatment changed to fusidic acid. These treatment failures were in all 20 cases caused by eye pathogens fully susceptible to fusidic acid. A clinical and bacteriological success was achieved in 19 of the patients. In the last case fusidic acid-resistant pneumococci emerged. The mean period until complete clinical cure was 5.8 days in this group.

Eye pathogens including both pre- and post-treatment isolates (n = 160) were susceptibility tested towards a range of antibacterials. Fusidic acid showed the lowest rate of in vitro resistance (17%) followed by gentamycin and neomycin (37% and 41%, respectively). Chloramphenicol, tetracyline and polymyxin showed higher rates of resistance (58%, 49% and 77%, respectively).

### Side effects

No side effects were recorded with any of the three test preparations.

## Discussion

Although it is generally assumed that bacterial conjunctivitis should be treated with drugs covering a broad antibacterial spectrum, the results from this study show that fusidic acid, which is characterized by its potent antistaphylococcal activity, can be the treatment of choice. Staphylococci were the most commonly isolated eye pathogens, constituting approximately 50%. Other Gram-positive and Gram-negative cocci, which are also within the spectrum of fusidic acid, constituted another 20%. That fusidic acid was also shown to be active against the vast majority of the remaining 30% Gram-negative rods, may be ascribed to its good activity against Haemophilus aegyptius and Moraxella spp. Another possibility is that the breaking point of more than 2 µg fusidic acid/ml, which in this study has been used to classify eye pathogens as in vitro resistant, applies for systemic use of the drug. By local use a much higher concentration in the eye is achieved. Consequently bacteria classified as resistant in vitro may be sensitive to local treatment. Due to less sophisticated laboratory facilities, it was not possible to make a more detailed identification of eye pathogens.

In this study Fucithalmic viscous eye drops were shown to be statistically significantly better than both chlorempheniсol and framycetin eye drops. It is therefore unjustified to perform further

studies in areas with similar high primary resistance rate among eye pathogens to these antibiotics.

Our results are also in close agreement with another study conducted by Bijsterveld (van Bijsterveld et al. 1986), who compared the effect of Fucithalmic with that of chloramphenicol eye drops in 248 Egyptian children suffering from acute conjunctivitis. He found clinical success rates of 84% with Fucithalmic and 48% with chloramphenicol. The better effect could also here be ascribed to a much lower resistance rate to fusidic acid (16%) than to chloramphenicol (55%).

The special sustained formulation used in fucithalmic viscous eye drops results in a long eye contact time. Antibiotic concentrations in lacrimal fluid of 5 μg/ml, which exceed MICs of fusidic acid-susceptible organisms, have been detected for up to 12 h after dropping (personal communication; van Bijsterveld & Andriesse, to be published). On this basis we decided to use a twice daily dosage. Especially in less developed areas of the world a simple b.d. regimen is essential. Our good clinical results with fusidic acid seem to justify the continued use of this simpler regimen.

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