Fusidic acid in acute conjunctivitis
Single-blind, randomized comparison of fusidic acid and chloramphenicol viscous eye drops

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Multicenter study with 28 Danish eye specialists

Abstract. Fusidic acid 1% and chloramphenicol 0.5% eye drops were in a randomized, single-blind manner given as a one-week treatment to out-patients with acute, purulent conjunctivitis. A clinical success was recorded in 84% (102/121) of patients receiving fusidic acid and in 81% (104/129) of patients receiving chloramphenicol. More patients (14%) receiving chloramphenicol complained of trivial side effects such as stinging and local discomfort, compared with fusidic acid (5%). No serious side effects were recorded. It is concluded that fusidic acid dispensed in a carbomer eye vehicle represents an effective and well tolerated new topical eye preparation with the advantage of being administered twice daily.

Key words: conjunctivitis - clinical trial - chloramphenicol - fusidic acid - Fucithalmic.

Bacterial eye infections are usually effectively treated with available topical antibiotic preparations. However, treatment failures occur due to bacterial resistance towards specific antibiotics. Furthermore, allergic reactions may limit or contra-indicate the use of available antibacterial ophthalmic agents.

Recently a new topical eye anti-infective containing the potent antistaphylococcal antibiotic, fusidic acid, has been developed.

Besides a high activity against staphylococci, including MRSA (Multi Resistant Staphylococcus Aureus) strains, the antibacterial spectrum of fusidic acid covers many of the other common eye pathogens in acute conjunctivitis, such as streptococci, Neisseria, Haemophilus spp. and Moraxella spp. (Foldes et al. 1983; Godtfredsen et al. 1962; Guenthner & Wenzel 1984). In clinical studies conducted in Egypt (Bijsterveld et al., to be published) and Tanzania (Dirdal, to be published), fusidic acid has shown to be superior to both chloramphenicol and framycetin in the treatment of bacterial conjunctivitis. The better effect of fusidic acid could here be ascribed to a much lower incidence of in vitro resistance among eye pathogens in this area of the world.

In the present study we have investigated fusidic acid in acute conjunctivitis in a larger number of out-patients attending Danish eye specialists in order to see whether this new topical eye preparation could be an alternative to chloramphenicol in this part of the world. The evaluation is made on clinical parameters exclusively, and this is felt justified inasmuch as the study has been conducted investigator-blind. Furthermore, microbiological examinations are usually not made in acute conjunctivitis.

Patients and Methods

During a 6-month period (March–September 1984), 28 eye specialists from Jutland, Denmark, included 266 out-patients in the study. Each investigator contributed with median 8 cases (range 1–35). The patients were defined as children and adults presenting with clinical signs and symptoms of acute bacterial conjunctivitis with a history of
not more than 10 days. Patients were not allowed to have received other topical antibacterial treatment for their actual eye disease, and patients with a previous history of hypersensitivity to chloramphenicol or fusidic acid were excluded. Contact lenses were not permitted during the treatment period.

At the first visit, day 0, the presence and severity of the following clinical symptoms: conjunctival injection, discharge, and periorbital oedema were graded from 0 = absent to 3 = severe. At the second visit, day 7, the clinical examination was repeated and the overall effect classified as success, partial success, or no effect. The time needed from start of treatment until clinical cure was recorded.

In case of partial success it was up to the investigator to decide whether the test preparation should be stopped or continued for another week or whether a new treatment should be instituted. In case of no effect the test drug was discontinued and a new treatment instituted. Patients were asked in general terms, if the eye preparation gave rise to any discomfort.

The two test preparations were delivered randomized in identically looking packings with the patient instructions inside. Chloramphenicol was recommended to be given as 1–2 drops every hour on the first day and then 5–6 times daily. Fusidic acid was recommended to be given as one ‘drop’ every 4 h on the first day and then morning and evening. Chloramphenicol was the commercially available 0.5% viscous eye drops (DAK) (containing 0.5% oxypropyl methyl cellulose) and fusidic acid was dispensed as a 1% microcrystalline suspension in a carboxomer gel with benzalkonium and EDTA used as preservatives and pH adjusted to about 6.0 (Fucithalmic®).

**Results**

Sixteen patients (10 on fusidic acid and 6 on chloramphenicol) have been excluded from the efficacy evaluation for the following reasons: defaulter (6), diagnosis revised (3), incomplete follow-up (2), wrong dosage (3), suspected previous hypersensitivity (1), and intolerance and premature discontinuation (1); this latter patient has been included in the tolerance evaluation.

Of the remaining 250 patients, 121 were allocated to fusidic acid and 129 to chloramphenicol. The two groups were comparable with regard to age/sex distribution, disease history, and single or double infection of the eye (cf Table 1).

Clinical effect of treatment evaluated after one week’s medication showed a success in 99 patients (77%) receiving chloramphenicol and in 89 patients (74%) receiving fusidic acid. Corresponding figures for partial success were 23 and 26, respectively, and finally 7 patients on chloramphenicol and 6 on fusidic acid showed no effect. Five out of

<table>
<thead>
<tr>
<th>Table 1.</th>
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<tr>
<td>Demographic data of 250 patients with acute conjunctivitis.</td>
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<thead>
<tr>
<th></th>
<th>Fusidic acid 121 patients</th>
<th>Chloramphenicol 129 patients</th>
</tr>
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<tbody>
<tr>
<td>Sex</td>
<td>F:M</td>
<td>78:43</td>
</tr>
<tr>
<td>Children:adults</td>
<td>14:107</td>
<td>15:114</td>
</tr>
<tr>
<td>Age</td>
<td>Children median (range)</td>
<td>9 (1-14)</td>
</tr>
<tr>
<td></td>
<td>Adults median (range)</td>
<td>41 (16-89)</td>
</tr>
<tr>
<td>Disease history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 days</td>
<td>72</td>
<td>78</td>
</tr>
<tr>
<td>4–10 days</td>
<td>49</td>
<td>51</td>
</tr>
<tr>
<td>One eye infected*</td>
<td>55</td>
<td>57</td>
</tr>
<tr>
<td>Two eyes infected*</td>
<td>54</td>
<td>65</td>
</tr>
</tbody>
</table>

* Information missing for some patients.

<table>
<thead>
<tr>
<th>Table 2.</th>
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<tr>
<td>Overall clinical effect of Fucithalmic 1% viscous eye drops and chloramphenicol 0.5% viscous eye drops in 250 out-patients with acute purulent conjunctivitis.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical evaluation</th>
<th>Chloramphenicol 1 drop × 6 daily*</th>
<th>Chloramphenicol 1 drop × 2 daily*</th>
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<tr>
<td></td>
<td>Day 7</td>
<td>Day 14</td>
</tr>
<tr>
<td>Success</td>
<td>99</td>
<td>104</td>
</tr>
<tr>
<td>Partial success</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>Failure</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

* First day one drop every hour.
** First day one drop every 4 h.
11 patients on chloramphenicol and 13 out of 17 patients on fusidic acid, who showed partial success after one week, were cured when treatment was continued for another week (cf Table 2). This gives an overall success rate of 84% (102/121) on fusidic acid and 81% (104/129) on chloramphenicol. The differences in clinical effect are not statistically significant.

Incidence and severity of conjunctival injection, discharge, and periorbital oedema were the same in the two treatment groups before treatment. The two test drugs were equally effective in reducing these symptoms (cf Fig. 1) and the period of treatment until clinical success was the same with the two test drugs (cf Fig. 2).

The mean number of days until clinical cure was 3.3 on fusidic acid and 3.6 on chloramphenicol.

Out of 15 patients, who showed a clinical failure on the test drugs, 10 responded successfully after change to another eye anti-infective. In 2 patients who initially received fusidic acid, change to chloramphenicol and neomycin/bacitracin, respectively, was without effect, and in the last 3 cases the clinical response to treatment was not stated.

**Side effects**

Six out of 122 patients (5%) receiving fusidic acid and 18 out of 129 (14%) receiving chloramphenicol complained of side effects (cf Table 3). The lower frequency of side effects on Fucithalmic is statistically significant ($P = 0.03, \chi^2$, two-tailed). In most cases side effects were mild to moderate local discomfort, itching, and stinging. In one patient receiving fusidic acid moderate stinging when dripping lead to discontinuation on day 4 of treatment. There were two cases of suspected

**Incidence and severity of conjunctival injection, discharge and oedema in patients with acute conjunctivitis assessed before and after treatment with chloramphenicol (129 patients) or fusidic acid (121 patients) viscous eye drops.**

![Incidence and severity of conjunctival injection, discharge and oedema in patients with acute conjunctivitis assessed before and after treatment with chloramphenicol (129 patients) or fusidic acid (121 patients) viscous eye drops.](image)
Number of days until complete clinical cure in patients with bacterial conjunctivitis receiving chloramphenicol (129 patients) or fusidic acid (121 patients) viscous eye drops.

treatment. There were two cases of suspected hypersensitivity, which was seen after one and two weeks treatment, respectively, with chloramphenicol.

Discussion

Patients attending with acute conjunctivitis are in most cases treated without any bacteriological guidance. Although the bacterial aetiology is uncertain, it is generally accepted that Gram-positive cocci, especially Staphylococcus aureus and Staphylococcus epidermidis, are among the most frequently isolated pathogens (Fedukowicz & Stenson 1985). Fusidic acid is one of the most active antistaphylococcal agents available, and it is chemically unrelated to any other antibacterials in clinical use. There is no cross-resistance nor cross-sensitivity between fusidic acid and other antibacterials. Many years of experience with fusidic acid cream as a topical antibiotic in skin infections has shown that the drug rarely gives rise to hypersensitivity reactions (Baldwin & Cranfield 1981; Cassels-Brown 1981; Pakrooh 1977/78).

In order to achieve a long eye contact time fusidic acid has been dispensed in a carbomer vehicle. In a pharmacokinetic study in rabbits it has been shown that this formulation gives rise to long-lasting antibiotic concentrations, and in human volunteers the elimination half-life of fusidic acid from tears has been determined to be 1.9 h (Bijsterveld & Andriesse, to be published). This means that useful antibiotic concentrations are maintained for up to 12 h after application, enabling a twice daily dosage regimen.

In a clinical study conducted in Tanzania (Dir-

<p>| Table 3. Tolerance of fusidic acid 1% and chloramphenicol 0.5% viscous eye drops to patients with acute purulent conjunctivitis. |
|---------------------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Fusidic acid</th>
<th>Chloramphenicol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without side effects</td>
<td>116</td>
<td>111</td>
</tr>
<tr>
<td>With side effects</td>
<td>6</td>
<td>18*</td>
</tr>
<tr>
<td>Severity of side effects</td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Itching</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Stinging</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Local discomfort</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td></td>
<td></td>
</tr>
</tbody>
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* P = 0.03 (χ², two-tailed).
A twice daily application of fusidic acid in bacterial conjunctivitis was shown to be superior to both chloramphenicol and framycetin eye drops given four times daily. The success rate with fusidic acid was 93% (77/83) compared to 54% (22/41) on chloramphenicol and 74% (26/35) on framycetin. Another study (Bijsterveld et al., to be published) compared fusidic acid and chloramphenicol eye drops both given 4–6 times daily in 248 Egyptian children with conjunctivitis. The clinical success rate was 84% with fusidic acid and 48% with chloramphenicol. In both studies there was a good correlation between in vitro resistance and clinical outcome, so the better effect of fusidic acid could be ascribed to a much lower incidence of in vitro resistance among eye pathogens to this antibiotic.

In the present study fusidic acid and chloramphenicol showed to be equally effective. This is probably because the incidence of resistance to chloramphenicol is low in Denmark. Fusidic acid would, however, seem to be a valuable new eye anti-infective also in areas with low resistance, because it has the advantage of an easy twice daily application, it shows a good tolerance, and the drug is devoid of known severe toxic effects.

Acknowledgment

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References


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