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# Trachoma therapy with topical tetracycline and oral erythromycin: a comparative trial*

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*Because topical antibiotic treatment has had a limited effect in previous controlled trials against trachoma, treatment with oral erythromycin was compared with topical tetracycline in 6 - 8-year-old children in southern Tunisia who had potentially blinding active trachoma. A total of 169 children were divided into two groups that were carefully matched for age, sex, locality, and intensity of disease. Oral erythromycin ethyl succinate in a paediatric dosage form was administered to one group and topical 1% tetracycline ointment to the other group, twice daily, six days a week for three weeks. The two treatments were equivalent in effectiveness and resulted in a substantial decrease in disease intensity and a marked reduction in chlamydial infection detected in conjunctival smears. To maintain blood levels of antibiotics known to be effective in the treatment of chlamydial infections with a dosage schedule possible in a trachoma control programme, one of the long-acting tetracyclines (doxycycline or minocycline) might be considered. Such systemic chemotherapy should be limited to selective treatment of individuals who can be adequately monitored.*

Blinding trachoma is still an important public health problem in the rural areas of some developing countries. Where the disease is endemic, control programmes consist of (*a*) mass (blanket) chemotherapy of children—the ones usually affected by the infectious phase of trachoma; and (*b*) the surgical correction of inturned eyelids in older children and adults. The main form of chemotherapy in developing countries is the topical application of an antibiotic (usually one of the tetracyclines) to the eye. The most widely used treatment schedule consists of twice-daily applications of ointment for five consecutive days each month for six months (*1*); an alternative schedule is twice-daily application for 60 consecutive days. The aims of chemotherapy are to reduce inflammation in individual cases so that there is less risk of blinding sequelae, and to decrease transmission of the causative agent, and other ocular bacterial pathogens.

Controlled therapy trials have shown that topical application of tetracycline, erythromycin, or rifampicin is significantly better than 5% boric acid (a simple antiseptic) in reducing trachoma intensity and eliminating the agent. The effects have been significant up to 17 weeks after the end of treatment but the benefits disappear after that (*2*, *3*). A controlled trial of intermittent therapy, however, showed that the effects were short-lived after six treatment cycles (*4*). Systemic treatment with sulfonamides, tetracycline,

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or doxycycline for three weeks (*5 – 7*) or intermittent doxycycline (*8*) have also had a significant effect on suppressing active trachoma. Although oral chemotherapy is usually given on a "selective" basis to cases of active trachoma detected by clinical screening, continuous topical treatment for 60 days is not practicable for mass therapy in most control programmes, and systemic chemotherapy has been considered too expensive and potentially hazardous.

New approaches to trachoma chemotherapy have been suggested by studies of newborns in the United States of America and Europe who acquire infection perinatally with the sexually transmitted chlamydiae. In adults, genital infection with *Chlamydia trachomatis* (serotypes D–K) causes a substantial amount of disease (e.g., salpingitis and nongonococcal urethritis). Infants exposed to the mother's infected birth canal during delivery may develop chlamydial ophthalmia neonatorum or a distinctive pneumonia syndrome, and the agent may be recovered from the eye and from the respiratory and gastrointestinal tracts (*9*). Current treatment for chlamydial infection of neonates consists of a course of oral erythromycin, because the infection is clearly a generalized one.

Recent studies in Egypt and Tunisia have shown that, in endemically affected communities, children with typical trachoma harbour the chlamydial agent in the nasopharynx and rectum as well as the eyes, suggesting that generalized chlamydial infection occurs regularly in endemic trachoma as it does in neonatal infection with sexually transmitted chlamydial agents (*10*).

Generalized chlamydial infection has several implications for the epidemiology of endemic trachoma. First, transfer of the chlamydial agent to the eye may occur not only by the direct transfer of ocular discharge but also by means of respiratory droplets or nasal or intestinal discharges. Secondly, in children treated with ocular antibiotic ointment, reinfection of the eye may occur from the other sites (e.g., the nasopharynx) of the treated individual. Finally, the disease spectrum of *C. trachomatis* infection in communities with endemic trachoma may include other syndromes, such as bronchopneumonia and otitis media, which have been encountered with infections due to sexually transmitted *C. trachomatis* strains (*11 – 13*). There is a rationale, then, for systemic therapy.

In order to evaluate the efficacy of systemic chemotherapy of endemic trachoma, we compared oral erythromycin and topical tetracycline treatments in southern Tunisia. Each medication was administered twice daily over a three-week period to a selected group of children 6–8 years old who had active trachoma. Erythromycin was chosen for oral administration because it is considered safer for systemic use in young children than one of the tetracyclines or sulfonamides. The effect of treatment was evaluated by observing the changes in clinical intensity of inflammation, and the prevalence of bacterial pathogens by culture and in smears.

## MATERIALS AND METHODS

### *Patients*

Children attending the first and second grades of the schools of four villages in the region of Douz, Tunisia, were screened for active trachoma. Those with severe or moderate intensity trachoma were selected for the treatment trial. In each school class, the selected children were divided into two groups that were equivalent in terms of number of cases with each category of intensity of disease, and of sex and age. One group in each class was assigned at random to one of the two treatments. At the initial examination, children affected by both vernal catarrh (a chronic allergic conjunctivitis) and active trachoma were included in the treatment groups, although the conjunctival inflammation of the former could not be expected to improve with antibiotic treatment. Thus a total of 169 children were treated but seven were omitted from the analysis of results because the individual had either vernal catarrh (four cases), or only mild intensity trachoma before treatment (two cases) or was not examined after treatment (one case).

### *Clinical examinations*

Three ophthalmologists examined all the children with a standard biomicroscope (slit lamp). At each examination the scoring of individual clinical signs was standardized among the three examiners by reviewing and discussing a set of clinical photographs and 5 – 10 cases. The remainder of the examinations were then done so that each child was examined independently by each of the three clinicians. The clinical signs recorded have been described elsewhere (*14, 15*). For each case, the examiner recorded the intensity of inflammation, which is based on a system of scoring for lymphoid follicles and infiltration on the upper tarsal surface. The final diagnosis assigned to each eye was the intensity most commonly diagnosed by the three examiners. For example, if one examiner diagnosed the intensity as severe and the other two diagnosed it as moderate, the disease in that eye was classified as being of moderate intensity. Each individual was then classified according to the more inflamed eye. Disagreement on the diagnosis of intensity occurred most often with cases of vernal catarrh (which were excluded from the final analysis of results) and with individuals who had severe conjunctival scarring.

*Bacterial cultures*

Specimens were taken with moistened swabs from both lower conjunctivas of each child. Each swab was streaked immediately onto a blood agar plate, which was subsequently placed in an incubator at 37 °C within six hours. Before incubation, each streak was inoculated at three sites with *Staphylococcus epidermidis* to enhance the growth of *Haemophilus* spp. Plates were read for bacterial pathogens within 48 – 72 h after transport to Tunis. Plates that developed substantial growth outside the lines streaked by swabs were regarded as contaminated and were not included in the tabulation of results.

*Conjunctival smears*

A smooth-edged (Kimura) platinum spatula was used to obtain a specimen from the conjunctiva of the upper lid. The slide was fixed the same day with absolute methanol. The smears were Giemsa stained and examined microscopically by one microscopist; doubtful inclusions were reviewed by two other observers.

*Antibiotic levels*

Capillary blood was obtained from all children by finger-prick. Serum was separated, frozen, and tested for erythromycin levels by a plate assay technique (*16*).

*Treatment*

Antibiotics were administered twice daily, six days each week, for three weeks. The treatments were:

1. *Topical tetracycline.* About 0.1 g of commercially available 1% tetracycline ophthalmic ointment was applied to each eye of one group of children by medical aides experienced in the administration of ointment.
2. *Oral erythromycin.* Erythromycin ethyl succinate was given as a paediatric chewable tablet (200 mg each), twice daily, six days a week, for three weeks. No loading dose was used. Children under 20 kg body weight received 300 mg twice daily, while those over 20 kg received 400 mg twice daily.

*Experimental design*

The therapeutic trial compared the outcome of treatment among children aged 6 – 8 years attending schools in four oasis villages in southern Tunisia. Only children with florid eye disease (i.e., severe or moderate intensity) that might lead to blindness were included in the trial.

Children for the treatment trial were selected on the basis of clinical examination. Those with trachomatous inflammation of severe or moderate intensity received either oral erythromycin or topical tetracycline six days a week, for three weeks. Treatment was carried out by personnel of the ministry of health (*Santé Publique*) who were experienced in trachoma control measures, including mass treatment with topical antibiotics. Careful records were kept of the drug dosage received by each child.

Clinical evaluation of children in the study groups was carried out before treatment and at intervals after treatment by the same three ophthalmologists (Table 1). Following the examination in June 1979, all children in the study received a standard course of topical tetracycline.

Conjunctival smears were taken from each child at the time of examination. These smears were examined for the causative agent of trachoma (*Chlamydia trachomatis*) and bacterial pathogens by light microscopy. Bacterial cultures of the eye were also obtained at each examination, to determine the prevalence of bacterial pathogens before and after treatment. These laboratory procedures constituted an independent measurement of the response of the infection to antibiotic treatment and of the rate at which reinfection occurred. Capillary bloods were taken once from each child on 28 February or 1 March, before the first daily dose, to determine serum antibiotic levels. The separated serum was refrigerated at 5 °C before transport on ice to San Francisco for bioassay.

Table 1. Schedule of operations

| Date | Action |
|---|---|
| 11 – 12 February 1979 | cases selected, smears and bacterial cultures obtained |
| 19 February – 10 March | treatment |
| 28 February | bacterial cultures and capillary blood specimens obtained |
| 24 March (2 weeks after treatment) | clinical examinations, smears and bacterial cultures obtained |
| 9 June (13 weeks after treatment) | clinical examinations, smears and bacterial cultures obtained |
| 18 – 19 November (36 weeks after treatment) | clinical examinations, smears and bacterial cultures obtained |

## RESULTS

*Number of antibiotic treatments administered*

The medication was given twice daily for three weeks. Of the 36 possible doses, 76 cases (47%) received at least 30 doses; another 77 (48%) received 20 – 29 doses, and only 9 (5%) received fewer than 20

doses. The school with the highest number of applications was also the most remote, and a single teacher at this school had taken the responsibility for administering the drugs.

*Serum erythromycin level*

No erythromycin or antimicrobial effect was detected in any of the serum specimens tested. This is not surprising in view of the rapid excretion rate of erythromycin ethyl succinate (*16*).

*Changes in clinical intensity of inflammation*

The distribution of clinical intensity is presented in Table 2. There was a marked improvement in both treatment groups when examined 2 weeks and 13 weeks after therapy had been completed. Although the erythromycin treated group had fewer severe-intensity cases at 2 and 13 weeks after treatment, the differences between the two groups are not statistically significant. In November, 36 weeks after treatment, the prevalence of severe-intensity cases had risen again but, in both groups, a substantial proportion (35 – 45%) remained mild or inactive. The statistical difference between the two treatments at this time is still not significant.

*Effect of treatment on the chlamydial agent*

The prevalence of Giemsa stained smears with chlamydial inclusions and the mean number of inclusions in each smear are compared for the two treatment groups in Table 3. Before treatment about 30% were inclusion positive. At 2 weeks after treatment, only one child had an inclusion-positive smear and that child had received all 36 applications of tetracycline ointment. At 13 weeks after treatment, four inclusion-positive smears (3%) were found, and by November the rate had increased to 15%. The post-treatment rates of chlamydial infection were all significantly lower than those before treatment, but the differences between the two treatment groups were not significant. At 2 and 13 weeks the effect of both treatments on the number of patients carrying the chlamydial agent appeared to be more profound than the clinical response. At 36 weeks, however, the prevalence of the agent was about what would be expected for the number of persisting severe and moderate cases.

The mean number of inclusions in positive smears was relatively low, in spite of examination under high magnification.

Table 2. Percentage distribution of trachoma intensity among patients, before and after treatment with erythromycin (E) or tetracycline (T)

| Month of examination | | Trachoma intensity | | | | No. examined |
|---|---|---|---|---|---|---|
| | | Severe | Medium | Mild | Inactive | |
| February (before treatment) | E | 36.7 | 63.3 | – | – | 79 |
| | T | 36.1 | 63.9 | – | – | 83 |
| March (2 weeks after treatment) | E | 3.2 | 33.3 | 60.3 | 3.2 | 63 |
| | T | 9.7 | 24.2 | 61.3 | 4.8 | 62 |
| June (13 weeks after treatment) | E | 13.0 | 33.3 | 52.2 | 1.4 | 69 |
| | T | 20.5 | 28.8 | 46.6 | 4.1 | 73 |
| November (36 weeks after treatment) | E | 30.4 | 34.2 | 34.2 | 1.3 | 79 |
| | T | 26.0 | 28.6 | 45.5 | – | 77 |

Table 3. Prevalence of chlamydial inclusions in conjunctival smears

| Month of sampling | Tetracycline | | Erythromycin | |
|---|---|---|---|---|
| | Prevalence[a] | Mean no. of inclusions[b] | Prevalence[a] | Mean no. of inclusions[b] |
| February (before treatment) | 27/82 (33%) | 2.7 | 24/79 (30%) | 2 |
| March (2 weeks after treatment) | 1/63 (1.6%) | 12 | 0/60 | – |
| June (13 weeks after treatment) | 3/73 (4%) | 7.6 | 1/69 (1.4%) | 12 |
| November (36 weeks after treatment) | 11/76 (14%) | 3.1 | 12/78 (15%) | 7.4 |

[a] Number of smears with chlamydial inclusions/number taken (% positive).

[b] Geometric mean number of inclusions per positive smear.

*Bacterial pathogens*

*Cultures.* The changes in the bacterial species found in cultures from the conjunctiva were fairly rapid (Table 4). Before treatment about 25% of children in the study had bacterial pathogens on the conjunctiva, for the most part *Haemophilus* spp. and pneumococci. On the tenth day of treatment, the pneumococci had disappeared, the recovery of *Haemophilus* had increased somewhat, and *Staphylococcus aureus* and Gram-negative rods were found more frequently. Within two weeks after the completion of treatment, *Haemophilus* spp. and pneumococci were again the dominant pathogens recovered, and the staphylococci and Gram-negative rods were un-

Table 4. Conjunctival bacterial pathogens cultured during a trial of trachoma treatment with erythromycin (E) or tetracycline (T)

| Month of sampling | | *Haemophilus* | *Streptococcus pneumoniae* | *Staphylococcus aureus* | Gram-negative rods | No. positive/ no. tested (%) |
|---|---|---|---|---|---|---|
| February (before treatment) | E | 3 | 7 | – | 2 | 12/41 (29%) |
| | T | 7 | 2 | 1 | 1 | 11/43 (23%) |
| March (during treatment) | E | 9 | – | 6 | 10 | 25/80 (31%) |
| | T | 5 | – | 2 | 9 | 16/74 (22%) |
| March (2 weeks after treatment) | E | 4 | 7 | – | – | 11/58 (19%) |
| | T | 5 | 4 | 1 | – | 10/59 (17%) |
| June (13 weeks after treatment) | E | 17 | 3 | 1 | – | 20/67 (29%) |
| | T | 11 | 5 | – | 1 | 17/68 (25%) |
| November (36 weeks after treatment) | E | | | | | 16/77 (21%) |
| | T | | | | | 23/74 (31%) |

common. By June, 13 weeks after treatment, the prevalence of *Haemophilus* spp. had increased markedly, following the seasonal pattern of the ocular bacterial flora in Tunisian subjects described previously (*18*, *19*). The differences between the bacterial flora of the two treatment groups were not significant at any time.

*Smears.* The occurrence of certain bacterial species that have a distinctive appearance on Giemsa-stained smears correlates well with the clinical presence of purulent conjunctivitis (*18*) and with trachoma intensity and inflammation of the cornea (*21*). Those bacterial species that can be identified with some certainty include the small diplococci of pneumococcus, the slender, slightly curved rods of the Koch-Weeks bacillus (previously designated *H. aegyptius* but now regarded as a variant of *Haemophilus influenzae*) (*22*) and the large diplobacilli of *Moraxella* spp. (*21*). Prior to treatment, about one-third of smears had one of these pathogenic forms (Table 5). Immediately after treatment, only 13% of smears had bacterial pathogens, but by June, 13 weeks after treatment, the prevalence was 37%. In November the overall prevalence was 22%. The changes in individual bacterial species reflect both the effect of treatment and seasonal variations in the prevalence of ocular bacterial pathogens and purulent conjunctivitis observed in this and other trachoma endemic communities (*19*).

### *Outcome in individual cases*

The interaction of treatment and ocular chlamydial and bacterial infection with clinical disease is illustrated by the following cases:

*Case 0-000-00-15.* This 6½-year-old boy had moderate intensity trachomatous inflammation in both eyes before treatment, when 14 inclusions were found in smears but no bacterial pathogens were noted in the smear or culture. He received 32 of a possible 36 doses of tetracycline ointment. No bacterial pathogens were found on

Table 5. Number of conjunctival smears containing bacterial pathogens

| Bacterial forms | February (before treatment) | March (2 weeks after) | June (13 weeks after) | November (36 weeks after) |
|---|---|---|---|---|
| pneumococcus-like | 21 (13%) | 6 (5%) | 26 (18%) | 9 (6%) |
| Koch-Weeks-like | 18 (11%) | 2 (2%) | 12 (8%) | 23 (15%) |
| diplobacilli | 31 (19%) | 11 (9%) | 42 (30%) | 19 (12%) |
| any pathogen | 52 (32%) | 16 (13%) | 52 (37%) | 34 (22%) |
| total tested | 161 | 123 | 142 | 154 |

culture during treatment. At 2 and 13 weeks he had mild intensity disease and at 36 weeks had mild disease in one eye and inactive disease in the other eye. No inclusions or bacterial pathogens were found at any of the post-treatment examinations.

*Comment.* This case is an example of the desired goal of treatment, with the suppression of clinical activity and elimination of microbial pathogens.

*Case 0-000-00-19.* This 6½-year-old girl from the same school class as the previous case had moderate intensity trachoma before treatment, when the smears had no inclusions but did have pneumococcus-like and *Moraxella*-like forms, although the bacterial culture had no pathogens. She received 30 of a possible 36 doses of erythromycin tablets and bacterial cultures did not have pathogens during treatment. At 2 weeks after treatment, she had mild-intensity trachoma, and the conjunctival smear had no inclusions but did have *Moraxella*-like forms; bacterial cultures were negative. At 13 weeks after completion of treatment, she had moderate-intensity disease; 24 inclusions but no bacterial pathogens were found in the smears and *Haemophilus* spp. was recovered on culture. At 36 weeks she had severe disease in one eye and moderate in the other. In the smear, a single inclusion was present and there were no bacterial pathogens.

*Comment.* This case, whose initial disease intensity was moderate, had bacterial pathogens but no inclusions before treatment and initially responded well to treatment with mild-intensity disease two weeks after treatment. The recurrence of moderate-intensity disease at 13 weeks with inclusion-positive smears and *Haemophilus* spp. in cultures suggests that ocular reinfection had taken place, with the development of even more florid disease at 36 weeks.

*Case 4-194-01-03.* This 6-year-old boy had moderate-intensity disease before treatment, but no chlamydial inclusions or bacterial pathogens were found. He received 24 doses of tetracycline ointment and *Haemophilus* spp. were found by culture during treatment. At the 2 and 13 weeks' examinations, he had only mild-intensity trachoma and neither chlamydial inclusions nor bacterial pathogens were seen in smears, nor were pathogens found in cultures. At 36 weeks, he had moderate-intensity trachoma in the right eye and severe in the left eye, with 194 inclusions on the right and 129 on the left, but no bacterial pathogens.

*Comment.* This child initially responded well to treatment but his eyes apparently became reinfected by the autumn. Smears very rarely have so many inclusions and this may represent heavy growth of the chlamydial agent during the first few days of a new infection.

*Case 0-000-00-24.* This 6-year-old girl had moderate-intensity trachoma before treatment, with 7 inclusions but no bacterial pathogens in the smears; *Haemophilus* was recovered in the culture. During treatment she received 30 of a possible 36 doses of erythromycin and the bacterial cultures yielded Gram-negative rods. At the 2 and 13 weeks' examinations, she was clinically inactive and there were no inclusions, although pneumococcus-like forms were observed in June. By November there was mild-intensity trachoma, but inclusions and bacterial pathogens were not found in the smear.

*Comment.* This again is a desirable outcome with suppression of disease despite bacterial infection with Gram-negative rods during treatment and with pneumococcus at 13 weeks.

## DISCUSSION

Antimicrobial treatment of trachoma is intended to suppress inflammatory disease in childhood so that there is less scarring of the conjunctiva and cornea, thus preventing blindness in later life. The main rationale for chemotherapeutic treatment, then, is prevention of blindness, but this is such a temporally remote event that the effect of treatment must be judged on the more readily observable changes in the clinical intensity of inflammation and the microbial flora of the eye.

In most trachoma control programmes mass or blanket treatment is given to all children in a community (*1*, *15*). In the present treatment trial, however, the treatment was selective because only cases with severe or moderate trachoma were included in the study. This trial of systemic chemotherapy, then, should be considered in the context of selective treatment of high-risk cases, and cannot be considered as a model for mass distribution of the medication.

There was not a substantial difference in the clinical results in the two treatment groups, although there was a suggestion that oral erythromycin was more effective in suppressing severe intensity disease at 2 and 13 weeks after treatment. In both treatment groups there was marked suppression of chlamydial infection. Although there were no significant differences in chlamydial infection in the two groups, early reappearance of the agent was seen in a few cases.

Earlier treatment trials in this region have compared antibiotic ointments given daily for 60 days, or by an intermittent schedule, with boric acid ointment, a simple antiseptic (*2–4*). The degree of suppression of clinical disease (about 60% of cases becoming mild or inactive) in those previous trials is about the same as that observed with the shorter duration of treatment in the present study. The 3-week period was selected because studies on sexually acquired *C. trachomatis* infections have shown this to be an adequate period for the eradication of chlamydial eye infection by antimicrobial drugs given orally (*11*, *23*). Thus 18–21 days appears to be an appropriate duration for systemic chemotherapy of chlamydial eye infections. It is of interest that topical medication given for this period also substantially reduced the intensity of inflammation.

The actual number of treatments received was substantially less than ideal in over one-half of the cases, even among schoolchildren who constitute the most available group for treatment in this community. This

disappointing proportion of treatment doses administered is probably typical of developing countries and may represent the degree of compliance that can be expected, even with selective treatments such as this. For single treatment schedules, partial compliance should be anticipated and the duration of treatment extended.

The failure to detect serum levels of erythromycin is also illustrative of the problems encountered in administering treatment in the school setting. The drug used, erythromycin ethyl succinate, is the most rapidly absorbed and rapidly excreted of the erythromycin derivatives (*17*). Because children were treated in school only during the mornings and afternoons, it was not possible to give the drug in four equally spaced doses as recommended, and it was to be expected that the drug would not be detected in blood taken the following morning, 18 hours after the previous dose. For this purpose, enteric-coated capsules of erythromycin base might be more suitable, although this dosage form would be difficult to administer to young children (*17*).

In this and other hyperendemic trachoma communities, the highest rates of prevalence occur by age 2 years and there is a steady decline in active disease between 5 and 14 years of age (*24*). Thus the schoolchildren in this study would be expected to show a high rate of spontaneous remission during the nine-month period of observation. Our previous studies, however, have shown that treatment does significantly increase cure rates in children of this age (*2–4*).

Recurrent disease may be due to persistence of the chlamydial agent in the conjunctiva, but it is probable that most cases are reinfected either by transfer of the agent from other cases in the community or from extraocular sites in topically-treated individuals. Because recurrent infection and disease were the same in systemically and topically-treated cases in this study, it seems likely that exogenous reinfection is more common. Indeed, one of the major reasons for mass treatment is to reduce the total level of chlamydial infection in a community and thus lower the risk of reinfection. Thus the rates of ocular chlamydial infection are an important indicator of the long-term effect of chemotherapy for endemic trachoma, both for the individual and for the community as a whole.

While bacterial pathogens contribute to the intensity of trachoma intensity and to the corneal inflammation (*21*), bacterial conjunctivitis alone does not lead to blinding as does trachoma. Ocular bacterial pathogens commonly infect the nasopharynx and thus can recolonize the eye very rapidly. Moreover they are less affected by systemic treatment.

In this study, then, oral erythromycin ethyl succinate administered twice daily appeared to offer little advantage over topical tetracycline ointment applied locally to the eye. It is apparent that this particular form of erythromycin and this dosage schedule were not ideal (*17*). Previous studies of systemic treatment of trachoma in American Indians showed that a beneficial effect was achieved only when full therapeutic levels of chemotherapeutic substances were maintained in the blood (*5, 6*). It would be desirable to employ a drug that achieved such blood levels when given once daily or even on five days out of seven each week.

Among the available chemotherapeutic agents effective against *C. trachomatis* are sulfonamides, macrolides, tetracyclines, and rifampicin. Systemic treatment with sulfonamides, including very long-acting derivatives, has been widely used and was indeed effective (*25*). However, the high rate of untoward reactions with systemic sulfonamides led to their being replaced in the 1950s and 1960s by tetracycline derivatives applied topically. Most of the macrolides, like the drug tested in this study, must be given four times daily, which is rarely possible in community-based treatment programmes. Rifampicin and its derivatives are effective against *Chlamydia* in concentrations 10 – 100-fold less than tetracyclines or macrolides (*26, 27*) but are the only drugs to which resistance has emerged rapidly in laboratory models (*28*). Thus the tetracyclines and macrolides are most likely to be used in trachoma control for reasons of efficacy, cost, and safety.

Among the derivatives of tetracycline, dimethylchlortetracycline, doxycycline, and minocycline achieve effective blood levels when given once daily. Indeed doxycycline was effective and widely used to treat trachoma in American Indians (*6, 7*). Tetracyclines are not generally recommended for treatment in children under 6 years of age because they cause staining of permanent teeth (particularly incisors) and are deposited in the epiphyseal plates of long bones, with a slowing of growth (*29, 30*). These complications occurred most prominently in children with cystic fibrosis who were on long-term tetracycline or chlortetracycline treatment in North America and Europe. Moreover some derivates, notably doxycycline, have a lower degree of calcium-binding and thus are less likely to stain teeth, even when given to very young children (*29, 30*). The other problem with tetracyclines is that of photosensitization, a tendency to sunburn more easily, which is quite marked with dimethylchlortetracycline, much less with doxycycline, and not found with minocycline (*20*). Thus a short course of 2 – 3 weeks with oral doxycycline or minocycline may be acceptable for systemic treatment even of children under 6 years of age in communities with endemic trachoma. Indeed, intermittent therapy with large doses of doxycycline once a month has been shown to reduce chlamydial carrier rates in the eyes of

Iranian children in communities where trachoma is endemic (*8*).

Erythromycin and its derivatives are preferred for treatment of chlamydial infections in pregnant women and newborns. For trachoma treatment, macrolides have the disadvantage that they must be administered four times daily. Moreover, the estolate and ethyl succinate derivatives may produce a toxic hepatitis (*32*). Nevertheless, the more slowly excreted erythromycin base might be considered for systemic administration in the treatment of severe and moderate cases of trachoma.

Recent evidence has shown that nasopharyngeal and rectal shedding of *C. trachomatis* are common in children in communities with hyperendemic trachoma (*10*). If such generalized infection is shown to be associated with pneumonia or other systemic disease, as it is with perinatal chlamydial infections, there would be strong justification for the use of systemic treatment of endemic trachoma. At present, however, systemic treatment must be judged by its effect on the eye disease when compared with the topical antibiotics now widely used.

## RÉSUMÉ


### THÉRAPEUTIQUE DU TRACHOME À L'AIDE DE TÉTRACYCLINE LOCALE ET D'ÉRYTHROMYCINE PAR VOIE BUCCALE : ESSAI COMPARATIF

Les programmes de lutte contre le trachome endémique entraînant la cécité comportent une chimiothérapie de la phase infectieuse évolutive chez les enfants et la correction chirurgicale de l'entropion chez les enfants plus âgés et les adultes. La forme de chimiothérapie la plus usitée est l'application d'antibiotique (en général une des tétracyclines) sur la conjonctive de tous les enfants dans les collectivités atteintes. Comme le traitement local n'avait eu qu'un effet limité dans les essais contrôlés précédents, on a comparé le traitement au moyen d'érythromycine par voie buccale avec le traitement local par la tétracycline, dans le sud de la Tunisie, chez des enfants de 6 à 8 ans souffrant d'un trachome évolutif susceptible d'entraîner la cécité.

Un total de 169 enfants ont été répartis en deux groupes soigneusement appariés en ce qui concerne l'âge, le sexe, la localité et l'intensité de la maladie. L'éthylsuccinate d'érythromycine, sous une forme pharmaceutique destinée aux enfants, a été administré à un groupe et une pommade à 1% de tétracycline en traitement local à l'autre groupe deux fois par jour, six jours par semaine pendant trois semaines. Les deux traitements se sont montrés équivalents et ont entraîné un abaissement considérable de l'intensité de la maladie et une diminution marquée des *Chlamydia* décelés dans les frottis conjonctivaux. En vue de maintenir des concentrations sanguines d'antibiotiques qu'on sait efficaces pour le traitement des infections chlamydiennes avec une posologie applicable dans des programmes de lutte contre le trachome, une des tétracyclines retard (doxycycline ou minocycline) pourrait être envisagée. Une telle chimiothérapie par voie générale doit être réservée au traitement sélectif de cas individuels susceptibles d'être correctement surveillés.


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