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Intermittent trachoma chemotherapy: a controlled trial of topical tetracycline or erythromycin*

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In communities with endemic blinding trachoma, mass (or "blanket") treatment with a topically applied tetracycline derivative is a standard control measure. The widely used "intermittent" treatment schedule consists of the twice daily application of antibiotic ointment for five consecutive days once a month for six months. In this study, the efficacy of "intermittent" treatment was evaluated for the treatment of severe and moderate intensity trachoma in children in southern Tunisia. Tetracycline or erythromycin ointments (specific antichlamydial drugs) were compared with 5% boric acid ointment (a simple antiseptic) given by the intermittent schedule during the winter and spring. There was a statistically significant degree of improvement at only one examination, four weeks after the full course of treatment had been completed. When re-examined five months later there were no differences in intensity in the three groups. The limited effect of topical chemotherapy might be attributable to several causes, among which could be inadequate drug levels, inadequate treatment periods, reinfection from non-treated children in the community, and auto-infection from extraocular sites (e.g., respiratory tract) in the same child. The possible value of short-term (two weeks) systemic antimicrobial therapy as an additional strategy to prevent blindness of children with potentially blinding active trachoma is discussed.

Despite the availability of specific chemotherapy and its use in control programmes for the last 30 years, trachoma continues to be the leading cause of preventable blindness in some developing countries of Africa and the Middle East. The application of antibiotics, particularly tetracyclines, to the eyes of children in trachoma endemic areas is based on the assumption that suppression of the inflammatory eye disease in childhood will prevent potentially disabling and blinding lesions (*16*). Since such control programmes have been most successful in regions where economic development has taken place, doubts have been expressed about the efficacy of chemotherapy alone as a control measure in the absence of improvements in living conditions and personal hygiene (*2*).

Previous studies of trachoma in southern Tunisia by our group have shown that 1% tetracycline, 1% erythromycin, and 1% rifampicin ointments administered for 60 days were all significantly more effective than 5% boric acid ointment in suppressing active trachoma in schoolchildren (*6*, *7*). The effect was short-lived, however, and trachoma activity was essentially identical in antibiotic and boric acid treated groups within 17–30 weeks after treatment. Antibiotic treatment was effective, however, in suppressing growth of the causative organism for up to 19 weeks. It is assumed that reinfection from untreated cases in the community is responsible for the recurrence of disease in treated individuals.

The most widely used treatment regimen in mass trachoma chemotherapy programmes is the so-called "intermittent" schedule originally suggested by Reinhards and Maxwell-Lyons and now recommended by the World Health Organization (*19*, *20*, *22*). This regimen consists of the application of antibiotic

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ointment (usually 1% chlortetracycline) to children twice daily for five consecutive days each month for six months each year. Although it was originally recommended that all children be treated in communities where trachoma is endemic, treatment is often given only to schoolchildren because they are easily accessible.

In order to test the relative efficacy of this regimen we compared tetracycline or erythromycin ointments with boric acid ointment in a southern Tunisian oasis where active trachoma and epidemics of purulent conjunctivitis are common in children and where there is a high prevalence of blindness due to trachoma in adults (*9*).

MATERIALS AND METHODS

Case selection

In the autumn of 1972, children entering the first and second grade of school in Douz, Tunisia, were examined and 173 with active, previously untreated trachoma were included in the study. Another 82 children who had been treated previously were followed during the course of the study.

Examination and recording of observations

Three ophthalmologists experienced in trachoma diagnosis examined each child independently with a slit lamp. The clinical signs recorded have been described previously (*8*). These signs included a direct estimate of the intensity of the trachoma (i.e., degree of conjuctival inflammation). The scores of each clinical sign were entered directly on a prepared form and were eventually transferred to punch cards for data processing.

Selection of treatment groups

Previously untreated children were divided into three groups, with approximately equal numbers of severe, moderate, and mild intensity cases, on the basis of the diagnosis of a single observer. Since the ultimate intensity diagnosed for each child was determined by picking the mode diagnosis for three examiners, there was some inequality in the initial distribution of trachoma intensity in the three treatment groups.

Children in the non-treated group all received at least one course of antibiotic therapy that was completed one month before the intermittent therapy trial started. Because the effects of treatment could not be judged immediately after therapy, these non-treated children were clinically examined at intervals of one month during the course of the therapy trial. Like the children in the therapy trial, they received a course of topical tetracycline in the autumn of 1973.

Laboratory studies

Duplicate smears of the upper tarsal conjunctiva were taken after each examination. Fixation, Giemsa and immunofluorescent staining, and microscopical examination were carried out as described previously (*7*). Bacterial cultures were taken from the inferior conjunctival fornix of both eyes with a single broth-moistened swab and plated directly on a blood agar plate. To ensure the growth of *Haemophilus* spp., the culture plate was inoculated at three spots on the streak with a culture of *Staphylococcus epidermidis*. The plates were incubated at 36 °C and read 72 hours later as described previously (*25*).

Medications

The preparations employed in the study were 1% tetracycline ointment (Lederle), 0.5% erythromycin ointment (Lilly), and 5% boric acid ointment (Lilly). Medication was given twice daily with an interval of 2–4 hours, by a medical assistant experienced in the administration of eye ointment. Treatment was given for five consecutive days at a time. Following the last examination, all children, including those who were not treated during the actual trial, were treated with 1% tetracycline for 10 weeks (60 days) in the autumn of 1973.

Experimental design

Following the initial clinical examination and

Table 1. Schedule of the intermittent trachoma therapy trial

Procedure and dates	Weeks from first treatment
Initial clinical examination and laboratory tests	
October 1972	
Laboratory tests and treatment cycles	
November 1972	0
December 1972	4
January 1973	9
February 1973	14
March 1973	18
April 1973	22
Follow-up clinical examination and laboratory tests	Weeks after previous treatment
January 1973	3
March 1973	3
May 1973	4
November 1973	29
Retreatment with 1% tetracycline of all patients for 10 weeks	
November 1973–January 1974	

collection of specimens for laboratory examinations in October 1972, treatment was administered for six 5-day cycles at the times indicated in Table 1. Further clinical and laboratory examinations were made just before the subsequent treatment cycles (Table 1).

RESULTS

Clinical findings

Of the 175 children in the three treatment groups, 85% had severe or moderate intensity trachoma (Fig. 1), which carries some risk of eventual visual disability (*8*). When examined in March 1973 after four cycles of treatment, the severe or moderate cases had decreased equally in the three treatment groups, but still comprised 60–66% of each group. In May 1973, following the full course of therapy, the severe and moderate cases had decreased to 26% of the boric acid group, 22% of the tetracycline group, and 15% of the erythromycin group. Thus there was no significant difference in the overall prevalence of severe and moderate cases in the two antibiotic treated groups.

In November, five months after the last treatment and at the end of the usual seasonal epidemic of purulent conjunctivitis, the severe and moderate cases constituted 48% of the boric acid group, 50% of the tetracycline group, and 41% of the erythromycin group. In terms of overall effect, shifts to less severe degrees of clinical intensity appeared to be no better in the antibiotic groups than in the boric acid group.

In comparing the number of cases that improved by at least two degrees of clinical intensity (Table 2), the greatest effect of antibiotics was noted in May 1973, one month after the complete course of treatment. While the untreated and boric acid groups showed about the same incidence of improvement at this date, both the tetracycline and erythromycin treated groups had a significantly higher number of improved patients than the boric acid group. Thus intermittent antibiotic treatment produced a statistically significant decrease in trachoma intensity compared with boric acid one month after completion of the full course of therapy.

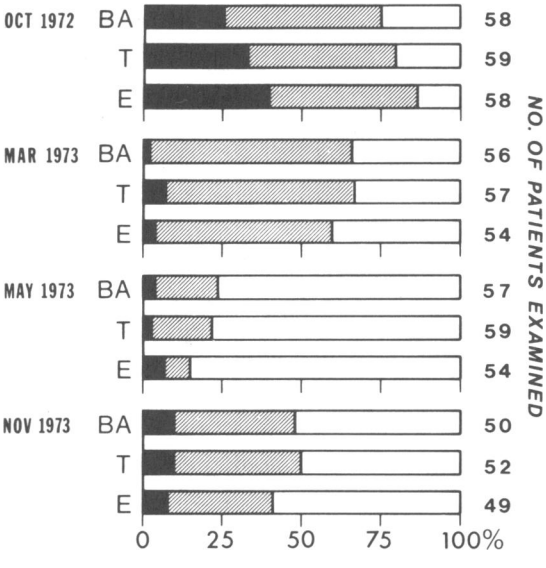

Fig. 1. Intensity of trachomatous inflammation in a trial in Tunisia in which intermittent treatment with boric acid (BA), tetracycline (T), and erythromycin (E) was compared. Black bar = severe; shaded bar = moderate intensity; white bar = mild or none.

Table 2. Proportion of trachoma cases with two or more degrees of clinical improvement in intensity during a trial of intermittent treatment[a]

Treatment group	March 1973	May 1973	November 1973
Previously treated (no intermittent treatment)	2% (1/55)	17% (9/54)	10% (5/51)
Boric acid	7% (4/56)	18% (10/57)	10% (5/50)
Tetracycline	9% (5/57)	36% (21/59)[b]	15% (8/52)
Erythromycin	13% (7/54)	46% (25/54)[b]	20% (10/49)

[a] Number improved/number examined in parentheses.

[b] Significant difference from boric acid group on the same date ($P < 0.05$ by Chi-square test).

Effects of treatment on chlamydial agent

The effect of treatment was also judged by the prevalence of trachoma inclusions in the Giemsa stained conjunctival smears taken at each examination (Fig. 2). In October 1972, before treatment, inclusions were present in 23% of the Giemsa-stained smears of the boric acid group, in 30% of those of each antibiotic group, and in only 9% of those of the previously treated (i.e., non-treatment) group. The mean number of inclusions per positive smear in the different groups varied from 2.3 to 5.2. Following treatment, the proportion of inclusion-positive smears in the boric acid group decreased to 2% in March, 7% in May, and 7% in November. In the tetracycline and erythromycin groups, the proportions dropped to 9% and 2% respectively in March, to zero in May, and to 5% in both groups in November. The differences among the

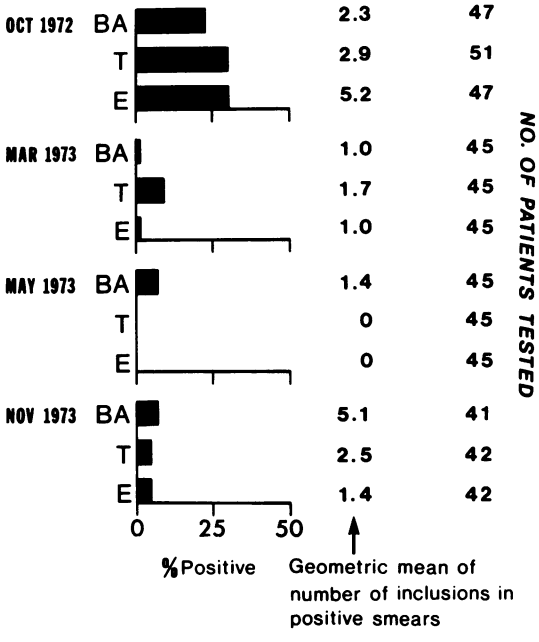

Fig. 2. Proportion of Giemsa-stained conjunctival smears positive for inclusions in a trial of intermittent topical chemotherapy. BA = boric acid; T = tetracycline; E = erythromycin.

treated groups in the proportions of smears with inclusions were not statistically significant at any time. The only significant difference noted was in October 1972 when the low number of inclusions in the "no treatment" group (not shown in Fig. 2) probably reflected the course of treatment they had received the previous summer.

Bacterial pathogens

Bacterial cultures were made from specimens taken before treatment and three weeks after each treatment cycle from October 1972 to May 1973 and are discussed in detail elsewhere (*26*). Cyclical seasonal variations in ocular bacterial pathogens have been well documented previously in Egypt, North Africa, and the Middle East, so it was not surprising that the prevalence of *Haemophilus* spp. in the untreated and boric acid groups declined from January to April 1973, but increased with the warmer weather in May. Pneumococci showed an inverse relationship, increasing in prevalence in February and in May 1973.

In children treated with antibiotics, the prevalence of *Haemophilus* spp. decreased significantly only after the first treatment cycle in December 1972. Pneumococci were equally prevalent in the control and antibiotic treated groups also, except that there were significantly fewer in the erythromycin group in December 1972. Our previous studies showed a marked effect of antibiotics on bacterial pathogens during or immediately following antibiotic therapy (*7*) but, since in this trial cultures were taken three weeks after each cycle of treatment, it is probable that recolonization of the eye had taken place relatively rapidly.

DISCUSSION

This clinical trial was designed to test the most widely used form of trachoma chemotherapy, the intermittent application of antibiotic ointment. Systematic treatment is often given only to schoolchildren because of limited funds and numbers of health personnel that can be allocated to trachoma control. In this setting, then, the full course of intermittent antibiotic treatment applied over a six-month period was only marginally more effective in suppressing the intensity of clinical disease (Table 2) than boric acid. This slight clinical difference was no longer apparent in November 1973, six months after the last treatment, due in part to recurrent disease activity in the antibiotic groups.

The effect of antibiotic treatment on the prevalence and the amount of trachoma agent persisted longer than the clinical improvement (Fig. 2). This efficient suppression of the chlamydial agent implies that relatively small amounts of antibiotic treatment reduce transmission by reducing the amount of available agent. It has been supposed that those children who continued to have inclusion positive smears were reinfected by exposure to untreated siblings in the home. It is also possible that reinfection of the eye in treated cases occurs from organisms harboured or replicating at extraocular sites. Indeed, sexually transmitted *C. trachomatis* strains are known to cause pneumonia in newborns and otitis media in adults (*11*, *21*). In recent studies by our group in Egypt and Tunisia (unpublished results, 1980), chlamydial agents have been recovered from the nasopharynx and rectum of children with trachoma. Thus the greatest effect of topical antibiotic treatment may be suppression of the infectious load in the community with a reduction of eye-to-eye transmission rather than the elimination of the infection in treated individuals.

Bacterial cultures taken during the course of treatment revealed little difference in the boric acid and antibiotic treated groups (*26*). The predominant bacterial pathogen cultured in the autumn was *Haemophilus* spp., but by January pneumococcus was the single most common ocular pathogen. By May 1973, and again in November 1973, *Haemophilus* was again

dominant. Previous studies in Tunisia have shown an elimination of bacterial pathogens immediately after treatment (*6*, *7*). Since these two bacterial species are common inhabitants of the nose and throat, the eyes of treated children were probably recolonized rapidly from this nasopharyneal reservoir. The seasonal epidemics of purulent conjunctivitis associated with *Haemophilus* spp. during the hotter months (May–November) have been well described in North Africa, the Middle East, and North America (*3*, *15*, *16*).

The prevention of blindness or visual disability is the primary rationale for most antibiotic treatment of children in trachoma endemic areas. Antibiotic treatment suppresses conjunctival inflammation (i.e., clinical intensity) by reducing or eliminating the infectious load of both chlamydial and bacterial ocular pathogens and by suppressing transmission and thus reinfection of children in the community. By reducing the intensity of inflammatory disease, there is less likelihood that the trachomatous child will develop conjunctival scarring sufficiently severe to distort the lids causing the eyelashes to abrade the cornea (trichiasis/ entropion). The constant abrasion of inturned eyelids inexorably leads to disabling corneal scarring. Thus the effect of antibiotic treatment suppressing inflammation in childhood reduces the risk of blindness in adult life.

Previous studies have suggested that children with severe and moderate intensity trachoma have a substantial risk of developing blinding complications in adult life (*8*). In individual children, the trachoma intensity tends to remain the same for prolonged periods, probably as a result of factors in the child's immediate environment, such as a scarcity of household water supplies, eye-seeking flies, and close contact with infected siblings. Even with prolonged topical treatment that significantly suppresses trachoma intensity and chlamydial infection, the disease intensity returns to its previous levels in many children after treatment.

Since even carefully monitored treatment with topical antibiotics appears to have a limited effect, other routes of administration should be considered. Prior to 1960 most blanket treatment for endemic trachoma was carried out with orally administered sulfonamides (*16*) and this form of treatment was found to be highly effective (*1*, *2*, *4*). The toxicity of oral sulfonamide, however, was so great that other drugs and treatment regimens were introduced: continuous (60-day) treatment with topical tetracyclines is indeed effective, but unsuitable in the context of most public health programmes; intermittent topical treatment with tetracyclines is more practicable to carry out but much less effective. It is necessary, then, to consider the use of oral macrolides (e.g., erythromycin) or tetracyclines for therapy of severe and moderate intensity cases in addition to blanket treatment with topical tetracyclines in affected communities.

Previous studies of systemic chemotherapy for trachoma amongst American Indians show that, for sulfonamides, it was necessary to achieve therapeutic drug levels and that suboptimal doses were clinically less effective (*4*). Full therapeutic doses of oral tetracycline or doxycycline for three weeks have also been shown to be effective (*5*, *14*, *17*). Recent treatment trials of chlamydial urethritis have shown a good clinical response and elimination of infection after two weeks' treatment with either macrolides or tetracyclines, although some cases and some chlamydial isolates are resistant to macrolides (*23*). For use in trachoma control programmes, then, a single two-week course of orally administered chemotherapy once yearly should be considered.

Before systemically administered chemotherapy is recommended for selective treatment in endemic blinding trachoma, there must be a clear demonstration that oral chemotherapy with or without topical treatment is clearly more effective than topical therapy alone. Thus there is a need for small carefully controlled clinical trials to evaluate the role of oral chemotherapy. These trials should involve only children with severe and moderate intensity trachoma in communities where the disease is endemic. In addition to following the effect of the antibiotic on the disease intensity, children in such trials should be carefully monitored for untoward effects.

Of the drugs available, one of the macrolides (excluding the estolate or ethyl succinate derivative of erythromycin) would appear to be the most useful since these drugs are not contraindicated in the paediatric age group. All the derivatives available, however, must be administered four times daily, a distinct disadvantage in the communities where trachoma is most serious. Moreover, the erythromycin derivatives produce abdominal discomfort in a large proportion of patients. The tetracyclines are generally considered to be contraindicated in children under seven years of age, mainly because of staining of the permanent front teeth and photodermatitis with some derivatives (*12*, *18*, *24*). Other derivatives, particularly oxytetracycline and doxycycline, have substantially less propensity to stain the teeth; one study of doxycycline given by mouth for 6–17 days to 25 infants under 2 months of age resulted in barely detectable tooth staining in only one child (*10*, *13*). It is likely that these two tetracyclines are relatively safe for use in young children when given in short courses (2–3 weeks) once a year to children with severe and moderate intensity trachoma. A single short course of systemic antibiotics would appear to carry some risk but this would be outweighed by the possibility of

preventing blinding complications.

If systemic chemotherapy were shown to be more effective than topical therapy in clinical testing, its use in trachoma control programmes should be restricted to severe and moderate intensity cases in communities where mass treatment with topical antibiotics was being done at the same time.

Doxycycline offers the advantage of once daily doses, an important factor in community-based treatment programmes, but is now more expensive than other tetracyclines. Savings in personnel, however, offset the drug costs in trachoma control programmes among American Indians (*14*). Alternative drugs for oral administration are erythromycin (either the base or the stearate) and oxytetracycline, both of which require four divided daily doses. With any drug, systemic chemotherapy even on a selective basis would require more personnel for case-finding and for dispensing and monitoring treatment.

There would also be disadvantages to the communities in which selective systemic chemotherapy was carried out. Inevitably there would be a selection of drug-resistant strains of intestinal bacterial pathogens such as *Shigella* spp. and *Salmonella* spp. that are major causes of morbidity and mortality in trachomatous communities. Restricting systemic treatment to once yearly would limit this problem somewhat but would not eliminate it entirely. From this point of view, erythromycin derivatives are less widely used than the tetracyclines and are not useful for the common bacterial diarrhoeas, so would seem to be preferable. Tetracyclines, however, are widely used in most countries, so their application to trachoma would usually not constitute the distribution of a drug that was otherwise unavailable. Unlike ophthalmic ointments, oral antimicrobials should probably not be distributed to families for self administration so that inappropriate use of the drug could be avoided.

Antibiotic treatment is just one component of public health programmes designed to prevent blindness in trachoma endemic regions. Comprehensive trachoma control programmes should also carry out corrective lid surgery, improve water supplies and disposal of human and animal wastes, and undertake health education. These activities imply surveillance to determine the priority cases for antibiotic treatment and to select cases for corrective lid surgery (which can be carried out in villages by specially equipped teams). While economic development is fundamental to the elimination of active infectious trachoma, the scarred, inturned eyelids in older children and adults will necessitate the continuation of surgical programmes long after the active infectious disease has disappeared from a community.

RÉSUMÉ

CHIMIOTHÉRAPIE INTERMITTENTE DU TRACHOME: UN ESSAI CONTRÔLÉ DE PRÉPARATIONS TOPIQUES DE TÉTRACYCLINE OU D'ÉRYTHROMYCINE

Dans les collectivités où règne à l'état endémique une forme de trachome responsable de cécité, un traitement de masse (ou de «couverture») à l'aide d'un dérivé de la tétracycline en applications topiques est une mesure de lutte classique. Le schéma thérapeutique «intermittent» couramment utilisé consiste en l'application biquotidienne d'une pommade antibiotique pendant cinq jours consécutifs par mois pendant six mois. Dans la présente étude, l'efficacité du traitement «intermittent» a été évaluée pour le traitement du trachome infantile d'intensité grave ou modérée dans le Sud tunisien. Des pommades à la tétracycline ou à l'érythromycine (substances spécifiquement antichlamydiennes) ont été comparées à la pommade à l'acide borique à 5% (simplement antiseptique) administrée selon le schéma intermittent au cours de l'hiver et du printemps. On n'a constaté une amélioration statistiquement significative qu'à un seul examen, quatre semaines après la fin du traitement complet. Un nouvel examen pratiqué cinq mois plus tard n'a révélé aucune différence d'intensité des lésions dans les trois groupes. L'effet limité de la chimiothérapie topique peut être attribué à diverses causes, entre autres l'insuffisance de concentration du médicament, celle des périodes de traitement, la réinfection par des enfants non traités faisant partie de la communauté et l'auto-infection à partir de localisations extra-oculaires chez le même enfant (par exemple, appareil respiratoire). L'intérêt possible d'une thérapeutique antimicrobienne générale de brève durée (deux semaines) à titre complémentaire pour prévenir la cécité chez les enfants souffrant d'un trachome évolutif susceptible d'aboutir à la perte de la vision est ici discuté.

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