Doxycycline Treatment of Chronic Trachoma

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American Indian children with mild chronic trachoma were treated with doxycycline, 2.5 to 4 mg/kg of body weight, given as a single daily dose on five days each week, for a total of 28 doses given in 40 days. The study was carried out double-blind, with randomized placebo controls. Detailed ophthalmologic evaluation continued for five months after the treatment course. The trachoma in the doxycycline-treated children improved markedly, as compared to those receiving placebo ($P < .001$ at 20 weeks after treatment). Few untoward drug effects were observed. Serum levels of the drug were maintained through much of the treatment period, but drug levels in tears were low and irregular. This one-dose-a-day therapy deserves consideration for mass treatment of trachoma.

Trachoma is a chronic, infectious eye disease that afflicts millions of persons in Africa and Asia. It is also prevalent on the Indian reservations of the American Southwest and constitutes a major health problem for American Indians. In some boarding schools on Indian reservations, 10% to 20% of all students at present show signs of clinical trachoma.

The chlamydiae causing trachoma can be inhibited in laboratory models by several antimicrobial drugs. However, no optimal drug regimen for chronic trachoma has been established. Therefore, our group at the University of California and the Indian Health Service began controlled drug trials several years ago in Indian boarding schools. These trials have established thus far that topically administered tetracycline has only a marginal effect, whereas either trisulfapyrimidines or tetracycline hydrochloride in full daily doses given orally for more than three weeks can suppress clinical signs of trachomatous activity.[1-3] Unfortunately, these forms of treatment do not eradicate the infectious agent but only suppress it, permitting later relapses that require repeated courses of drug administration. Furthermore, trisulfapyrimidines or tetracycline are excreted rapidly and thus require several doses daily for the maintenance of drug levels. Since children with chronic trachoma do not feel ill, in-

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convenient drug regimens are exceedingly difficult to enforce. In order to enhance cooperation and secure compliance with treatment recommendations, the use of slowly excreted, long-acting drug dosage forms must be considered. Slowly excreted sulfonamides have a reputation for relatively frequent untoward effects in children[1] and are currently not favored by physicians of the Indian Health Service. We therefore explored the efficacy of a slowly excreted tetracycline, doxycycline, in the treatment of chronic trachoma in school children. We report here the effects of a single daily dose of doxycycline (given on five days each week for a total of 28 doses) on the clinical activity of trachoma, the prevalence of trachoma inclusion conjunctivitis (TRIC) agent in the conjunctiva, and the bacterial flora of the conjunctiva.

Methods

A preliminary treatment trial was carried out at the Intermountain Indian School, Brigham City, Utah, in Navajo Indian students aged 13 to 20 years. The definitive, controlled, treatment trial took place at Tuba City (Ariz) Indian Boarding School, in students aged 7 to 13 years, from Navajo Indian reservations. Students arrive at these boarding schools in September and are in residence there during each school week until May, at which time they return to their families and homes. Soon after arrival at the schools in the fall, all students had ophthalmologic examinations for presence of trachoma. Students suspected of having active trachoma were given detailed independent examinations with a biomicroscope by three ophthalmologists. Those determined to have signs of active disease by elaborate criteria published elsewhere[2] were included in the study. They were reexamined by the same ophthalmologists 10 and 20 weeks after the end of medication.

The administration of medication to individual students was supervised by a school nurse. Doxycycline capsules (50 mg) and a placebo of identical appearance and taste were used. Medications were coded as Drug A or Drug B, and the identity remained unknown to subjects, physicians, and nursing personnel until the results of all examinations had been recorded. Students with signs of active trachoma were randomly assigned placebo or drug. Students weighing less than 35 kg (77 lb) received 200 mg doxycycline or placebo the first day of each week, then 100 mg daily for the next four days. Those weighing more than 35 kg received 250 mg drug or placebo the first day of each week and 150 mg daily for the next four days. A total of 28 doses (on 28 days) was dispensed. All medication was administered between 8 and 11 AM daily between Nov 1 and Dec 10, 1971.

Samples of venous blood were obtained from all participants once or twice on days 10 and 11 of medication. Serum was separated, stored at −20 C, and levels of doxycycline in serum were estimated by a microbiologic assay in liquid medium.[3] Antimicrobial activity was expressed in terms of a standard of doxycycline hyclate.

At the time of serum collection, tears were also obtained from one third of the students, as described elsewhere.[5] The cellulose sponges containing tears were stored at −20 C. They were thawed just prior to testing, 0.1 ml phosphate-buffered saline was added, and the saturated sponge was placed on one-eighth segment of a 140-mm Petri plate containing Mueller-Hinton agar, the surface of which had been inoculated with 10^7 *Bacillus cereus*, var. *mycoides* (ATCC 9634). The plates were incubated at 20 C for 48 hours, and then the zone of inhibition around each sponge was compared to the zones around similar sponges saturated with doxycycline solutions of known concentration.

At each examination, scrapings were collected from the upper tarsal conjunctival epithelium of each eye. These scrapings were examined later by immunofluorescence, as described previously.[6] A single fluorescein-labeled rabbit anti-TRIC serum was used for all examinations in this, as in previous trials.[2] All slides were read by the same two observers. Results were recorded as positive or negative, with no attempt at quantitation.

During clinical examination, moistened swabs were used to obtain sam-

Table 1.—Treatment Effect on Clinical Activity of Trachoma

	Clinical Activity Present					
	October 1971		February 1972		April 1972	
	No.	%	No.	%	No.	%
Treatment A (placebo)	54	100.0	44	81.5	40	74.1
Treatment B (doxycycline)	49	100.0	28	57.1	19	38.8

Table 2.—Treatment Effect on Presence of TRIC Antigen Inclusions in Conjunctival Scrapings

	TRIC Antigen Present by Immunofluorescence					
	October 1971		February 1972		April 1972	
	No./Total	%	No./Total	%	No./Total	%
Treatment A (placebo)	26/52	50.0	29/54	53.7	21/54	38.9
Treatment B (doxycycline)	28/49	57.1	24/49	49.0	17/48	35.4

Table 3.—Treatment Effect on the Prevalence of "Potential Bacterial Pathogens"*

	No. Positive Cultures of No. Total Specimens			
	October 1971	November 1971	February 1972	April 1972
Treatment A (placebo)	6 of 19	15 of 51	17 of 51	12 of 51
Treatment B (doxycycline)	3 of 21	4 of 49	5 of 49	8 of 49
Significance of difference, *P*	.36	.01	.01	.52

*More than ten colonies of any one or more of *Staphylococcus aureus, Hemophilus influenzae, Moraxella* species, pneumococcus, enteric gram-negative rods cultured from a conjunctival swab.

ples for bacterial cultures of the conjunctivae of a majority of students participating in the drug trial. The swabs were immediately streaked on sheep blood agar plates and on cooked blood agar plates with isovitalex and incubated at 37 C for 48 hours or more. Colonies of *Staphylococcus aureus*, pneumococci, *Hemophilus influenzae*, moraxellae, and enteric gram-negative rods were identified, and the approximate numbers of each type of colony recorded. These species were considered to be "potential bacterial pathogens" in the eye.

Results

A preliminary trial of doxycycline was undertaken at Intermountain School in 1970-1971 in students aged 13 to 20 years, having chronic active trachoma. The results suggested that a single daily dose of doxycycline for 28 consecutive days might suppress signs of active trachoma. However, many adolescent and adult students missed doses of medication or were absent without leave from the school for prolonged periods, and had to be removed from the study. At ten weeks after the end of medication, 18 of 36 students (50.0%) in the doxycycline group had clinically active trachoma, whereas 22 of 30 students (73.3%) in the placebo-treated group had clinically active trachoma. This difference was suggestive but not statistically significant. At 20 weeks after the end of medication, the difference between placebo- and drug-treated groups was even smaller. Therefore, we decided to repeat the trial on a larger group of younger children in another boarding school where attendance could be better controlled.

In 1971-1972 at Tuba City Indian Boarding School, 120 students with clinically active trachoma were randomly assigned to drug or placebo medication. Most of these students completed the intake of medication satisfactorily and were available for follow-up examinations. When the code was broken 21 weeks after the end of medication, it became apparent that 54 students who had received placebo and 49 students who had received doxycycline were available for analysis. The others had to be eliminated because of definite gaps in intake of medication, because serum levels of drug could not be documented, or because they were unavailable for one or more follow-up examinations.

The results of the treatment trial are shown in Table 1. Starting with 100% active trachoma, it is evident that the rate of clinical activity could only decline between October 1971 and April 1972. However, the decline in activity was far greater in the group receiving doxycycline than in the group receiving placebo. The difference in clinical activity between the two groups is significant both at ten weeks (February 1972) ($\chi^2 = 6.11$, $P < .02$) and at 20 weeks (April 1972) after the end of treatment ($\chi^2 = 11.70$, $P < .001$). However, the suppression of clinical activity was not accompanied by the elimination of TRIC agent. As shown in Table 2, the prevalence of TRIC-positive immunofluorescent inclusions was similar in the conjunctival scrapings from drug and placebo groups at all examinations.

Serum levels of doxycycline were estimated in the middle of the second treatment week. At four to six hours after drug intake, the range was 2μg to 4μg/ml, with an average of 2.9μg/ml in 24 children. At 20 to 24 hours after drug intake, the range was 0.25μg to 2.0μg/ml in 29 children, with an average of 0.6μg/ml. In six children, blood was obtained 24 to 28 hours after drug intake. The range of doxycycline levels was from less than 0.25μg to 1.0μg/ml, with an average of 0.5μg/ml.

Tears were collected from 18 children receiving doxycycline treatment four to six hours after the last dose. In eight of these no drug activity could be detected in tears, although serum levels were measurable. In the remaining ten children, the range of doxycycline concentration in tears was from 0.02μg to 0.1μg/ml, with an average of 0.03μg/ml. All of these children had doxycycline serum levels of 2.0μg/ml or more at the time the tear specimens were obtained.

Bacterial cultures were obtained only from 40 students prior to treatment. Nine yielded more than ten colonies of one or more "potential bacterial pathogens" in conjunctival specimens (Table 3). The difference in prevalence of positive cultures between drug and placebo groups was significant ($P = .01$) during the time medication was administered (November 1971) and at the first post-treatment examination (February 1972). This suggests that most "potential bacterial pathogens" were suppressed for several weeks following treatment, but reappeared soon thereafter. At the final assessment in April 1972, the great improvement in the drug-treated group could not have been due to any suppression of "potential bacterial pathogens."

At the time of each day's medication, each student was questioned in Navajo language about symptoms referable to the gastrointestinal tract, skin, mouth and throat, general malaise, and anorexia. They were also examined for skin rashes and mouth lesions. Surprisingly few such symptoms or signs were elicited. The children appeared to consume their daily medication with eagerness, swallowing up to five capsules in a single gulp! Anorexia, nausea, vomiting, or diarrhea occurred in three children between the 15th and 25th days of medication. Two of these children were receiving doxycycline, one placebo, and the disturbances lasted only a single day in each child, in spite of continuing medication.

Between day 21 and 28 of medication, transient macular rashes and one-day illnesses with low-grade fever and anorexia occurred in four children. Two of them had received drug, and two placebo. It is likely that an intercurrent, unrelated illness was responsible. Gross enamel dysplasia or tooth discoloration was not observed on examination 20 weeks after the end of medication.

Comment

This study establishes for the first time that a single daily dose of doxycycline given 28 times in 40 days can effectively suppress the signs of active trachoma for at least 20 weeks. This provides a regimen that is practical for mass treatment of American Indian school children and may be applicable elsewhere as a public health measure. Since repeated courses of treatment may well be necessary for permanent suppression or eradication of trachoma, it is encouraging that the doxycycline regimen was tolerated remarkably well.

The apparent benefit of placebo medication has been observed in each

of our previous studies.[1-3] It is attributable to the students' residence in an environment of good hygiene, ample washing facilities, and a stringent attitude toward cleanliness in the boarding school. This "beneficial effect of placebo" emphasizes the need for rigidly controlled double-blind studies in the evaluation of treatment for chronic trachoma.

In terms of the suppression of signs of clinical activity, the results of the present study are more favorable than any observed previously with systemically administered tetracyclines or sulfonamides.[2,3] This may be attributed in part to host factors and in part to features of the treatment. The children in this study were younger (average age, 9.9 years), and their trachoma was in an earlier stage of progression than in our previous studies in American Indians. In the present study, most cases were classified as trachoma stage I (MacCallan classification[7]), whereas in previously treated groups, either trachoma stage II or IIA was predominant. It is probable that early disease manifestations and tissue changes are suppressed more readily than more advanced ones. In the present trial, fewer students possessed antibodies to chlamydiae (unpublished observations) than in previous trials, again suggesting that their exposure to chlamydial antigens has been less intense and less prolonged.

In the present trial, the dose of doxycycline was relatively high and the treatment was prolonged. The usual doxycycline dose in systemic infections is 2.2 to 4.4 mg/kg of body weight per day. In this study, children weighing less than 35 kg received 100 mg (2.8 to 4.1 mg/kg) daily, and those weighing more than 35 kg received 150 mg (2.6 to 4.2 mg/kg) daily. Each child received an additional loading dose of 100 mg on the first day of each five-day school week. The total duration of drug administration was prolonged in that each student received medication on 28 days in a period of 40 days. It is probable that antichlamydial effective drug concentrations were present at least part of each weekend while medication was not administered. Thus, most of the 40-day period constituted active antimicrobial treatment—a longer time than we have previously employed in systemic therapy of trachoma.[1-3]

During much of each treatment day, serum levels of doxycycline ranged from 1μg to 4μg/ml, and this level may be assumed to have been present in the vascular conjunctiva. By contrast, measurable doxycycline levels were found in only half of the tear specimens, and these levels were very low. This is in keeping with observations on other secretions, such as saliva.[8] However, levels of doxycycline in conjunctival tissue probably were sufficient to inhibit trachoma chlamydiae. These agents are usually inhibited in vitro by 0.5μg to 4.0μg/ml tetracycline.[9]

While a single course of doxycycline produced striking clinical improvement by suppressing trachoma chlamydiae, it manifestly failed to eradicate the infectious agent from tissue. Chlamydial antigens (and presumably infectious chlamydiae) persisted in chronic infection in spite of suppressive treatment and made possible recurrent clinical activity.[6] It remains to be seen whether repeated courses of treatment and prolonged suppression of clinical activity will favor the loss of chlamydiae from both the individuals and the population. A gradual disappearance of trachoma regularly accompanies marked gains in socioeconomic standing and hygiene in any population.[10] Perhaps, effective drug treatment can greatly accelerate that process. Results of the present study are encouraging in this regard.

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Emery Johnson, MD, and John Porvaznick, MD, gave permission to perform the trial; Virginia Williams, RN, and Angelina Greeley, LVN, arranged and supervised medication; Odeon Briones and Hermine Keshishyan performed the examination of smears by immunofluorescence; and Jack Gow, MD, Ronald Smith, MD, and Thomas Stevens, MD, helped with ophthalmologic examinations and securing specimens for laboratory study.

Nonproprietary and Trade Names of Drugs

Doxycycline—*Vibramycin.*

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