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Therapeutic effect of oral doxycycline on syphilis

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SUMMARY Fifty-one patients with syphilis were treated with oral doxycycline. A course of the antibiotic treatment consisted of 200 mg of doxycycline daily in two divided doses for 28 days. The courses were repeated three to four times a year with an interval of several months. Quantitative Venereal Disease Research Laboratory (VDRL), Wassermann reaction (WR), and *Treponema pallidum* haemagglutination assay (TPHA) tests were performed monthly to evaluate the therapeutic effect of doxycycline treatment. The response rate was 100% for primary, 90% for early, 68% for late, and 90% for congenital syphilis in adults. No notable side effects were encountered except for epigastric fullness in one patient, which did not require the treatment to be discontinued. No abnormalities were detected in the results of laboratory tests.

Introduction

When given orally in the treatment of syphilis conventional antibiotics should be administered every six hours because of the short duration of their effective blood concentrations. Since anti-syphilitic treatments usually need to be carried out over long periods of time, patients may not strictly follow the treatment regimen.

Although the tetracycline group of antibiotics, including tetracycline itself and oxytetracycline, is known to have a treponemicidal action, these drugs should be given every six hours by mouth to maintain an effective blood concentration. The usual daily dose is 1 g in adults. The continuous use of tetracycline and oxytetracycline over long periods of time may cause a deposit of yellow pigment in the bone. Yellowish discoloration may develop in the teeth of children whose mothers have been given these tetracyclines during pregnancy. Other side effects such as a black tongue also occur in a few cases relatively early in the treatment and leads to discontinuing the administration. Accordingly, tetracycline and oxytetracycline are not satisfactory oral antibiotics in the treatment of syphilis.

The effective blood concentration of doxycycline (DOTC), a derivative of tetracycline, lasts for a period of 12 hours or longer after an oral dose of 100 mg. The daily dose of 200 mg (in two equal doses) of DOTC, therefore, is one-fifth of that of conventional tetracyclines and will rarely cause any side effects; furthermore, two doses daily are more convenient for patients than four doses daily.

This paper describes the results of DOTC therapy for syphilis over a period of eight years.

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Material and methods

PATIENTS

DOTC therapy was given to 51 patients with various stages of syphilis. Thirty-five patients with primary, early, or adult congenital syphilis had had no previous treatment, while seven of 16 patients with late latent syphilis had previously been given some antisyphilitic treatment.

DOSAGE AND ADMINISTRATION OF DOXYCYCLINE

A dose of 100 mg DOTC was given orally, immediately after the morning and evening meal. A course of DOTC treatment consisted of daily administration at this dosage over a period of four weeks (28 days) and was repeated every three to four months. Accordingly, patients received three to four courses of the treatment annually.

LABORATORY TESTS

Quantitative Wassermann reaction (WR), Venereal Disease Research Laboratory (VDRL), and *Treponema pallidum* haemagglutination (TPHA) tests were repeated once a month during the observation period in each case. Liver function was checked by

repeat determinations of serum aspartate transaminase (SGOT) and serum alanine aminotransferase (SGPT) levels at appropriate intervals.

OBSERVATION PERIOD

Observation periods ranged between two and nine months for five cases with primary syphilis; this period was short because the disease required only short periods of time for cure. Ten cases with early syphilis were followed over periods up to five years and seven months, 16 cases with late latent syphilis for up to four years and ten months, and 20 cases with adult congenital syphilis for up to seven years and nine months. Physical examination and laboratory tests were repeated every month in each case during the observation period.

CRITERIA FOR RESPONSE TO TREATMENT

The result of DOTC therapy was evaluated by comparing titres of the VDRL and WR tests before and after treatment. The response was considered excellent when titres of both tests decreased by more than two dilutions and when the titre of one test was decreased by one dilution or not at all but that of the other test was decreased by more than two dilutions. A good response was so defined when the titre of one test was decreased by two dilutions but the titre of the other test was decreased by one dilution or remained unchanged. The response was evaluated as poor when only a one dilution difference was observed in the titre of one test before and after DOTC therapy but none in the titre of the other test, or no difference was found in the titre of either test before and after treatment (Table 1).

Results

PRIMARY SYPHILIS

Laboratory data for a patient with primary syphilis whose antibody titres were decreasing to zero at short intervals after DOTC therapy are shown in Table 2.

Table 1 *Criteria for response to oral doxycycline therapy*

	*Decrease in antibody titre (dilutions)**	
Response	*VDRL*	*WR*
Excellent	2	2
	2	1
	2	0
Good	2	1
	2	0
	1	1
Poor	1	0
	0	0

*Difference in dilutions before and after treatment

The results of the serological tests for syphilis reverted to normal in each of five patients with primary syphilis at the end of DOTC therapy, which ranged in duration from two to nine months. Thus, the response was excellent in all of the five cases (Table 3).

SECONDARY SYPHILIS

The course of a case of early syphilis is shown in Table 4; an excellent response to DOTC therapy was seen during the observation period of one year and nine months.

Ten patients with secondary syphilis were treated with the same regimen. The shortest observation period was four months in four patients, while one patient was followed up for a period as long as five years and seven months (Table 5). The response to DOTC therapy was excellent in five patients, good in four, and poor in the remaining one. The patient with a poor response has been followed up for a period of only four months. Since excellent responses were achieved in two patients followed up for comparable periods of time, however, an evaluation of poor response was made in this patient.

LATE SYPHILIS

In one patient alopecia had developed due to a syphilitic infection which had occurred 10 years previously and was unnoticed and untreated (Table 6). Oral DOTC therapy consisting of 12 courses during a period of four years and four months produced an excellent response in this patient.

Of 16 cases of late syphilis nine had had no previous treatment while seven had previously received arsenicals or bismuth preparations. Of 16 cases with late syphilis, six (37·5%) responded excellently, five (31·3%) well, and five (31·3%) poorly to the treatment. Of nine cases previously untreated, five (55·6%) showed excellent responses, and four (44·4%) good responses (Table 7).

ADULT CONGENITAL SYPHILIS

A female patient who had positive results to serological tests at a premarital examination responded excellently to oral DOTC therapy. She received 21 courses during a period of seven years and nine months (Table 8).

Of 20 patients with adult congenital syphilis who had had no previous treatment, 12 (60·0%) showed excellent responses, six (30·0%) good responses, and two (10·0%) poor responses (Table 9).

SIDE EFFECTS

Epigastric fullness occurred in some patients, but it was only transient. No patient had to stop treatment because of gastrointestinal disturbances.

Table 2 *Laboratory data for a 36-year-old male patient with primary syphilis*

Date of examination	*Observation period (months)*	*Antibody titres*			*Course of DOTC therapy**
		VDRL	*WR*	*TPHA*	
October 1972	0	16	64	320	1st
November 1972	1	4	16	320	
February 1973	4	0	0	320	2nd
March 1973	5	0	0	320	
July 1973	9	0	0	320	

*Each course consisted of daily doses of 200 mg for 28 days

Table 3 *Laboratory data for five patients with primary syphilis*

Case no.	*Age (yrs)*	*Sex*	*Antibody titres*						*Observation period (months)*	*No. of courses of DOTC therapy*	*Response*
			Before treatment			*After treatment*					
			VDRL	*WR*	*TPHA*	*VDRL*	*WR*	*TPHA*			
1	36	M	16	64	320	0	0	320	9	2	Excellent
2	29	M	4	16	0	0	0	0	6	1	Excellent
3	32	M	2	40	1280	0	0	1280	4	1	Excellent
4	41	M	32	1024	5120	4	64	5120	3	1	Excellent
5	26	M	1	0	0	0	0	0	2	1	Excellent

Table 4 *Laboratory data for a 56-year-old male patient with early syphilis*

Date	*Observation period (months)*	*Antibody titres*			*Course of DOTC therapy**
		VDRL	*WR*	*TPHA*	
August 1975	0	32	128	5120	First
September 1975	1	32	256	5120	
October 1975	2	32	256	5120	Second
December 1975	4	32	128	1280	Third
January 1976	5	8	64	5120	
February 1976	6	8	32	5120	Fourth
April 1976	8	8	64	1280	
November 1976	15	4	16	5120	Fifth
January 1977	17	2	8	1280	
March 1977	21	2	16	1280	

*Each course consisted of 200 mg daily for 28 days

Table 5 *Laboratory data for 10 patients with early syphilis*

Case no.	*Age (yrs)*	*Sex*	*Antibody titres*						*Observation period (months)*	*No. of courses of DOTC therapy*	*Response*
			Before treatment			*After treatment*					
			VDRL	*WR*	*TPHA*	*VDRL*	*WR*	*TPHA*			
1	33	M	64	1024	5120	2	8	1280	4	1	Excellent
2	42	F	64	256	5120	32	128	1280	4	1	Good
3	28	F	32	256	>5120	4	32	1280	4	1	Excellent
4	25	F	2	32	5120	2	32	5120	4	1	Poor
5	25	M	128	1024	1280	4	64	5120	6	2	Excellent
6	23	M	32	128	1280	8	256	320	8	2	Good
7	45	M	32	128	5120	8	64	5120	13	2	Good
8	56	M	32	128	5120	2	16	1280	19	5	Excellent
9	24	M	64	256	5120	16	128	1280	45	7	Good
10	33	M	64	800	5120	1	0	320	67	1	Excellent

Table 6 *Laboratory data for a 33-year-old male patient with late latent syphilis who had had alopecia due to a previous infection*

Date of examination	*Observation period*	*Antibody titres*			*Course of DOTC therapy**
		VDRL	*WR*	*TPHA*	
February 1973	0	128	256	5120	First
March 1973	2	64	256	5120	Second
September 1973	7	8	8	5120	Third
December 1973	10	8	32	5120	Fourth
May 1974	15	4	32	1280	Fifth
December 1974	22	2	16	5120	Sixth
April 1975	26	8	32	1280	Seventh
August 1975	30	8	32	1280	Eighth
January 1976	35	2	8	1280	Ninth
July 1976	41	2	16	1280	Tenth
November 1976	45	2	8	1280	Eleventh
April 1977	50	1	8	320	Twelfth
June 1977	52	1	8	1280	

*Each course consisted of 200 mg doses daily for 28 days

Table 7 *Laboratory data for 16 patients with late syphilis*

*Case no.**	*Age (yrs)*	*Sex*	*Antibody titres*						*Observation period*	*No. of courses of DOTC therapy*	*Response*
			Before treatment			*After treatment*					
			VDRL	*WR*	*TPHA*	*VDRL*	*WR*	*TPHA*			
(1)	37	F	1	0	80	0	0	80	4	1	Excellent
(2)	65	M	4	16	1280	2	8	1280	4	1	Good
(3)	55	M	2	4	320	2	32	320	13	3	Poor
4	63	M	2	32	1280	2	8	1280	15	3	Good
5	33	F	1	16	320	1	4	320	16	4	Good
6	29	M	4	8	320	2	4	320	16	4	Good
7	52	M	1	8	320	2	8	320	16	2	Poor
8	55	M	2	8	320	1	0	80	23	4	Excellent
9	38	M	16	160	320	4	8	320	26	7	Excellent
(10)	65	F	128	1024	5120	64	512	5120	26	7	Good
(11)	52	M	32	256	5120	32	128	5120	26	4	Poor
(12)	45	F	8	16	320	4	16	5120	40	7	Poor
13	51	F	8	32	320	2	8	1280	48	10	Excellent
14	33	M	128	256	5120	1	8	1280	52	12	Excellent
15	49	M	2	16	1280	2	0	320	58	7	Excellent
16	31	M	8	32	1280	2	16	5120	58	12	Good

*Case nos. in parenthesis indicate those having had previous treatment

Table 8 *Laboratory data for a 23-year-old female patient with adult congenital syphilis*

Date	*Observation period*	*Antibody titres*			*Course of DOTC therapy*
		VDRL	*WR*	*TPHA*	
February 1970	0	16	128	81920	First
November 1970	9	32	128	20480	Third
May 1971	15	8	128	5120	Fourth
November 1971	21	16	32	5120	Fifth
May 1972	27	8	64	5120	Sixth
October 1972	32	16	64	5120	Seventh
March 1973	37	16	128	5120	Eighth
July 1973	41	8	32	5120	Ninth
February 1974	48	8	32	5120	Eleventh
November 1974	57	16	64	5120	Thirteenth
March 1975	61	8	64	5120	Fourteenth
November 1975	69	8	32	5120	Sixteenth
March 1976	73	8	64	5120	Seventeenth
November 1976	81	8	32	5120	Nineteenth
March 1977	85	8	64	5120	Twentieth
July 1977	89	8	128	5120	Twenty-first
September 1977	91	4	16	5120	—
November 1977	93	4	32	5120	—

Table 9 *Laboratory data for 20 patients with adult congenital syphilis*

Case no.	Age (yrs)	Sex	Antibody titres: Before treatment VDRL	WR	TPHA	After treatment VDRL	WR	TPHA	Observation period	No. of courses of DOTC therapy	Response
1	57	M	1	8	320	0	0	5120	6	2	Excellent
2	63	M	16	128	1280	8	64	5120	12	4	Good
3	42	F	16	64	5120	8	32	5120	14	4	Good
4	45	F	2	8	320	1	0	80	18	8	Excellent
5	36	F	4	64	320	1	16	80	21	2	Excellent
6	28	M	8	128	5120	2	8	1280	24	3	Excellent
7	30	M	2	4	1280	1	16	1280	34	8	Poor
8	55	F	4	16	320	2	8	320	37	10	Good
9	32	M	32	256	5120	8	16	5120	38	9	Excellent
10	30	M	16	128	5120	8	32	5120	39	9	Good
11	63	F	16	128	320	8	16	80	42	10	Excellent
12	34	M	32	128	5120	1	8	5120	49	10	Excellent
13	48	M	4	16	320	4	16	320	55	12	Poor
14	34	M	32	256	5120	8	64	5120	59	15	Excellent
15	26	F	16	128	320	8	8	320	60	13	Excellent
16	24	M	2	16	5120	2	0	1280	61	9	Excellent
17	29	M	32	256	20480	16	64	5120	63	15	Good
18	27	F	32	256	5120	4	16	1280	85	11	Excellent
19	30	F	2	32	320	1	16	320	89	5	Good
20	23	F	16	128	81920	4	32	5120	93	20	Excellent

SGOT and SGPT levels remained within normal range during the entire period of observation in each case. Herxheimer's phenomenon was not observed even in those patients with primary and secondary syphilis.

Discussion and conclusion

Oral penicillins, cephalexins, macrolides, and tetracyclines are effective in the treatment of syphilis. Oral administration of these antibiotics is inconvenient since they should be taken every six hours to maintain an effective blood concentration. Unless the regimen is strictly followed, satisfactory results will not be obtained even with the most potent drugs. Oral antibiotics characterised by long-lasting effective blood concentrations are required for the treatment of syphilis where effective blood concentrations should be maintained without interruption over prolonged periods of time.

DOTC was found to satisfy these criteria for the treatment of syphilis. Two daily doses were sufficient to maintain effective blood concentrations, and such a regimen was convenient for patients. Few side effects developed because daily doses were low. Generally, patients followed the regimen precisely, and changes in antibody titres due to the therapy could be serially observed.

Alexander and Schoch (1966), Steppert (1968), and Wodniansky *et al.* (1969) have reported their short-term observations of patients after treatment with DOTC, and they all noticed excellent results. I have also treated a patient with primary syphilis using DOTC 100 mg daily for 14 consecutive days with excellent results. Tsutogawa *et al.* (1971), Minami *et al.* (1972) and Maruta and Shirouzu (1973) reported good results using the same dose of DOTC for patients with syphilis.

The overall effective rates in this study were 100% for patients with primary syphilis, 90% for those with early syphilis, 68·7% for those with late syphilis (90% for those without previous treatment), and 90% for those with adult congenital syphilis (Table 10).

Table 10 *Summary of the effects of oral doxycycline treatment for syphilis*

Stage of syphilis	Response and number of patients treated: Excellent No.	%	Good No.	%	Poor No.	%	Total no. of cases
Primary	5	100·0	0	0	0	0	5
Early	5	50·0	4	40·0	1	10·0	10
Late	6	37·5	6	37·5	4	25·0	16
Adult congenital	12	60·0	6	30·0	2	10·0	20

Onoda *et al.* (1977) treated 61 cases of syphilis with amoxycillin for two years in a previous clinical trial. This oral treatment was effective in 100% of cases of primary and early syphilis, in 66·7% of cases of late syphilis, and in 60% of cases of adult congenital syphilis.

Treatment with both amoxycillin and DOTC proved effective in 100% of cases of primary syphilis. For early syphilis, the effective rate with DOTC therapy was lower than that with amoxycillin therapy, although the difference did not seem to be significant. Also, there was no significant difference between the therapeutic effect of amoxycillin and DOTC on late syphilis. Treatment with DOTC was more effective than with amoxycillin for adult congenital syphilis, probably because of the longer observation periods used for the former therapy than for the latter.

The antisyphilitic effect of oral DOTC was proved to be comparable or somewhat superior to that of oral penicillins, probably because less frequent doses were required with DOTC than with penicillins. The more frequent the daily doses the more easily patients would forget to take the drug. In addition, few side effects were caused by DOTC treatment. Thus, oral DOTC therapy is suitable for the treatment of late syphilis and congenital syphilis in adults, which require treatment over long periods of time.

As a result of the introduction of penicillins the number of patients with syphilis has been notably reduced. The disease has by no means been eradicated, however, but its incidence has tended to increase in recent years. Injections of penicillins may be contraindicated in occasional cases and, generally, patients prefer oral administration to injection. The development of satisfactory oral antibiotic treatment regimens for syphilis, such as discussed in this paper, are needed.

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