Acta Dermatovener (Stockholm) 53: 153–156, 1973

BACTERIOLOGICAL EXAMINATION OF RECTAL SPECIMEN DURING LONG-TERM OXYTETRACYCLINE TREATMENT FOR ACNE VULGARIS

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Abstract. Treatment with oxytetracycline in doses of 500 mg daily exerts a strong influence on bowel flora after 1 week. The influence on *E. coli* is most pronounced, resistant forms of the strains emerging very frequently. Following continued administration of 250 mg daily, a further reduction in the number of strains of *E. coli* sensitive to tetracycline occurs in the intestinal tract. Simultaneously with this change to tetracycline-resistant strains of *E. coli*, resistant strains of *Str. faecalis* and micrococci emerge, and *Proteus* were also found with increasing frequency. As to streptomycin, an increase in coli strains resistant to this drug is seen throughout the experimental period, whereas changes in the sensitivity of *E. coli* to sulphonamides occur within 1 week of treatment, after which the pattern appears to remain constant. Furthermore, as regards ampicillin, a certain change seems to occur, so that more resistant strains of coli emerge.

About 20 years ago, Barnard & Orens (1) published a report concerning the favourable effects of streptomyces derivatives ("mycins") on acne vulgaris. The authors used terramycin in doses which were considerable lower than those normally used for therapeutic purposes, the average daily dose being between 50 and 100 mg. All the 34 patients treated improved considerably but, after withdrawal of terramycin, acne recurred in 7 out of 19 patients who were kept under observation for 6 months.

Knothe (3) examined the bowel flora during antibiotic treatment, in particular with tetracycline, after administration of both therapeutic doses (1–2 g daily) and sub-therapeutic doses (0.5–1 g daily). Furthermore, the pattern of the bowel flora was examined after intravenous administration of 250 mg of pyrrolidino-methyltetracycline. Following the intake of therapeutic doses, the strains of coli bacteria changed; the sensitive strains were suppressed and replaced by strains resistant to tetracycline which, in the majority of patients, had been present in smaller numbers prior to institution of treatment. No later than 48 hours after commencement of treatment, only resistant strains of *E. coli* were present. After withdrawal of treatment, sensitive strains of *E. coli* appeared within a few days. When tetracycline was given parenterally, no changes were observed in the bowel flora.

During recent years, drugs of the tetracycline group have been increasingly used in the treatment of acne vulgaris, acne rosacea and perioral dermatitis and, in most reports, clinical effects have been reported in about 80% of the treated patients (4).

Treatment with antibiotics has the advantage that external therapy, which is often cosmetically unacceptable and, as regards certain preparations, produces dryness and cracking of the skin, can be completely avoided.

Several reports have been published on studies of skin and throat flora during tetracycline treatment in patients with acne. Consequently, we wanted to examine the influence exerted on the ecological conditions in the intestinal tract by therapeutically low doses of tetracycline.

The sole purpose of the present study was to examine intestinal changes rather than to study the etiology or bacteriology of acne vulgaris.

MATERIAL AND METHODS

Forty-four patients with acne vulgaris (26 males and 18 females) were treated with oxytetracycline over the period March to August 1971. During the first week the dose was 250 mg twice daily; during the following weeks it

Table I. *Bacteriological findings from the anal canal in 44 patients treated for acne vulgaris with tetracyclines*

S = sensitivity, R = resistance

	Before treatment		After 1 week's treatment		After 10 weeks' treatment	
	S	R	S	R	S	R
E. coli	36	9	5	32	2	47
Proteus	0	1	0	6	0	8
Klebsiella pneumoniae	0	0	1	0	0	0
Citrobacter freundii	0	0	0	0	0	1
Providencia B	1	0	0	0	0	0
Streptococcus faecalis	1	0	2	17	0	7
Staphylococcus aureus	1	0	0	0	0	0
Other micrococci	4	1	0	10	0	6
Haemolytic streptococci	1	1	1	0	0	1
Corynebacterium	4	0	0	0	0	0

was reduced to 250 mg daily. The patients were kept under observation for a period of 13 weeks; all were seen as outpatients. Before commencing treatment, culture from the anal canal was made. Samples were collected by means of a carbon-imbibed cottonwool swab which, immediately after incubation, was sent in Stuart medium to the Regional Department of the State Serum Institute. Here, culture was made on the usual substrate, and examination for fungi was carried out. Culture was also started on the same day for primary sensitivity testing on the medium of Frølund Thomsen and with tablets manufactured by "Rosco". Strains with zones of 22 mm or less were recorded as resistant to tetracycline, corresponding to a minimal inhibitory concentration of 6 ng/ml or more (2). The corresponding MIC for streptomycin, sulphonamides, erythromycin, ampicillin and chloramphenicol were 20, 18, 6, 5 and 20 ng/ml, respectively.

The patients were given 250 mg Oxitetracyclin tablets ICI®. They appeared for check-up cultures, for the first time after 1 week's treatment, afterwards at intervals of 3 weeks, and at these visits new swabs from the anal canal were collected.

RESULTS

The bacteriological findings in cultures from the anal canal in patients before treatment, after 1 week's treatment, and after 10 weeks' treatment are given in Table I. The bacterial findings are listed according to sensitivity or resistance to tetracycline. It appears from the table that the bowel flora contained the normal intestinal bacteria, dominated by *E. coli*. Before treatment was begun, 45 coli strains were isolated from the 44 patients comprising the series, and 36 of these strains (80%) were sensitive to tetracycline. After 1 week's treatment with 250 mg twice daily, 37 coli strains were isolated, five of which (14%) were sensitive to tetracycline, the remainder being resistant to tetracycline. Ten weeks after commencement of treatment, the last 9 weeks on a 250 mg dose daily, 49 coli strains were isolated, two of which (4%) were sensitive to tetracycline, the remainder being resistant.

In the other intestinal bacteria isolated, resistance to tetracycline appears to develop, as far as micrococci and *Str. faecalis* are concerned, whereas *Proteus* were more frequent after treatment than before. The remaining bacteria isolated were present in such limited numbers that no conclusion can be drawn as to the influence of tetracycline on the bowel flora.

Candida albicans were not demonstrated at any of the examinations, and no dominance of *Staph. aureus* was observed.

Table II shows the sensitivity pattern of the *E. coli* strains isolated, as far as the other antibiotics examined are concerned, i.e. penicillin, streptomycin, erythromycin, ampicillin, sulphonamides and chloramphenicol. All the *E. coli* strains isolated were found to be resistant to penicillin, and only one strain was sensitive to erythromycin.

Table II. *The sensitivity pattern of E. coli isolated from the anal canal at various intervals following treatment with tetracycline*

		Before treatment	After 1 week's treatment	After 10 weeks' treatment
Penicillin	S	0	0	0
	R	45	37	49
Tetracycline	S	36	5	2
	R	9	32	47
Streptomycin	S	34	21	26
	R	11	16	23
Erythromycin	S	1	1	1
	R	44	36	48
Ampicillin	S	42	28	39
	R	3	9	10
Sulfonamide	S	33	18	24
	R	12	19	25
Chloramphenicol	S	44	36	45
	R	1	1	4

Before treatment was begun, 34 out of 45 (75%) were sensitive to streptomycin; after 1 week of treatment 21 out of 37 (57%) were sensitive; and after 10 weeks, 26 out of 49 (53%).

Initially, 42 out of 45 strains of *E. coli* (94%) were sensitive to ampicillin; after 1 week of treatment, 28 out of 37 (78%) were sensitive; and after 10 weeks, 39 out of 49 (80%).

Prior to tetracycline therapy, 33 out of 45 of the isolated strains of *E. coli* (73%) were sensitive to sulphonamides; after 1 week of treatment, 18 out of 37 (49%); and after 10 weeks, 24 out of 49 (49%) were sensitive.

No definite change in sensitivity to chloramphenicol seems to occur during the experimental period.

Hence, the most pronounced changes in sensitivity are seen in respect to tetracycline, streptomycin and sulphonamides.

Table III *a, b, c* shows, by means of "2 × 2" tables, the resistance pattern of *E. coli* to sulphonamides and streptomycin, respectively, as regards tetracycline-sensitive and tetracycline-resistant strains of *E. coli*. At the beginning of the experiment, 9 strains of *E. coli* (Table III *a*) were resistant to tetracycline. Five of them were resistant to both streptomycin and sulphonamides, whereas three strains were sensitive to sulphonamides and streptomycin, respectively.

Out of 36 strains of *E. coli*, sensitive to tetracycline (Table III *b*) and isolated at referral, 28 were sensitive to both sulphonamides and streptomycin. Three and two, respectively, were resistant to these drugs. Thirty strains were found to be sensitive to sulphonamides and 31 to streptomycin.

At the termination of the experiment after a period of 10 weeks (Table III *c*), 18 out of 47 strains of *E. coli* were sensitive to both sulphonamides and streptomycin, whereas 16 were resistant to both drugs. Twenty-three strains were sensitive to sulphonamides and 26 to streptomycin.

There are significantly ($P < 1\%$) more streptomycin- and sulphonamide-resistant strains among the tetracycline-resistant *E. coli* strains than among the tetracycline-sensitive.

Table III *a*. *The sensitivity pattern against sulfonamide and streptomycin of 9 E. coli strains, tetracycline-resistant on arrival*

Sulfonamide	Streptomycin S	Streptomycin R	Total
S	2	1	3
R	1	5	6
Total	3	6	

Table III *b*. *The sensitivity pattern against sulfonamide and streptomycin of 36 tetracycline-sensitive E. coli strains before treatment with tetracycline*

Sulfonamide	Streptomycin S	Streptomycin R	Total
S	28	2	30
R	3	3	6
Total	31	5	

Table III *c*. *The sensitivity pattern against sulfonamide and streptomycin of 47 tetracycline-resistant E. coli strains after 10 weeks' treatment with tetracycline*

Sulfonamide	Streptomycin S	Streptomycin R	Total
S	18	5	23
R	8	16	24
Total	26	21	

DISCUSSION

Oxytetracycline administrated in sub-therapeutic doses appeared capable of changing the sensitivity of *E. coli* strains, not only to tetracycline, but also to sulphonamides and streptomycin.

The incidence of tetracycline-resistant *E. coli* strains presenting concurrent resistance to sulphonamides and streptomycin, is higher than might have been expected, had the occurrence of strains of *E. coli* resistant to sulphonamides and streptomycin been mutually independent.

This should be borne in mind when complicating bacterial infection, e.g. perforated appendix or urinary tract infections, develop in patients during long-term treatment with antibiotics providing a wide spectrum. In such cases both bacteriological studies and sensitivity tests should be carried out to prevent infections, produced by microorganisms which iatrogenically are made resistant, from being overlooked or wrongly treated.

In concluding our observations we do not want to argue in favour of the abandonment of low-dose treatment with broad-spectrum antibiotics for disorders in which such antibiotics have been known for many years to produce a salutary effect. Most of these patients are young adults with a low morbidity, and consequently, the risk is supposedly predictable and acceptable. However, if complicating bacterial infections should develop in some of the tetracycline-treated patients, bacteriological examinations and sensitivity tests must be carried out without delay, in order that infections caused by microorganisms which iatrogenically are rendered resistant, are not neglected.

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Received May 1, 1972

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