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EFFECTS OF LONG TERM TREATMENT WITH TETRACYCLINE

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Abstract. An investigation into some aspects of renal and hepatic function was performed n patients receiving long term, low-dosage tetracycline for dermatological conditions. No significant abnormalities were detected.

Tetracycline preparations have been used extensively in the treatment of acne, rosacea and related dermatoses in recent years (1). In the low doses used, there have been few side effects (6) even after prolonged administration. However, in larger doses, particularly in patients with significant renal disease, important metabolic, renal and hepatic changes may occur (7). There is experimental evidence in animals (4) that long-term tetracycline ingestion does not produce toxic effects.

The purpose of this present study is to determine whether patients receiving long-term low dosage treatment with tetracycline show changes in a number of simple laboratory tests which might indicate subclinical side effects.

METHOD

The 246 patients included in the survey were all healthy individuals attending an outpatient clinic with a condition for which long-term low-dosage tetracycline therapy is currently prescribed (Table I).

At each attendance, estimations of blood urea, bilirubin, SGPT, alkaline phosphatase, and plasma proteins were undertaken. A midstream specimen of urine was examined microscopically for cells, tested for albumin and glucose and submitted for bacteriological culture.

Included were 126 patients who had not received tetracycline derivatives or related antibiotics in the previous year, the results obtained on their initial attendance being recorded as controls. Of these patients, 76 did not proceed to tetracycline therapy (Group A). Fifty subsequently commenced therapy with oxytetracycline 250 mg twice daily (Group B), and were observed where possible approximately 1 month, 3 months, 6 months, 1 year and 2 years later. One hundred and twenty patients (Group C) were included who had already been receiving oxytetracycline at a dosage of 250 mg b.d. for varying periods of time (1 month to 5 years). Observations were obtained from them at similar intervals or annually when they had been taking the tablets for more than 2 years. A total of 348 sets of observations were made.

To determine the validity of the control values patients were questioned about duration of disease, family history of severe acne and, if female, ingestion of the contraceptive pill. No significant differences were found between groups A, B or C for any of these parameters (Table I).

RESULTS

There were no significant differences in levels of blood urea, bilirubin, SGPT, or alkaline phosphatase before and at varying times after treatment with oxytetracycline (Table II). Abnormalities in midstream specimens of urine (>4 WBCs/h.p.f. or growth of E. coli, B. proteus, or Str. faecalis) were found in 22% of patients, but they were found as frequently in patients who had not taken tetracycline as in those who had (Table III). These findings were in all cases transient; similar abnormal results were not obtained on subsequent retesting without specific treatment. The numbers for each individual abnormality were too small to have statistical significance. Protein electrophoresis showed slight variation within the normal range in all fractions in individual patients from estimation to estimation, though in the 50 patients for whom values were available before and during treatment, no significant pattern emerged.

DISCUSSION

Tetracycline and its derivatives are at present used for the treatment of acne, rosacea and related dermatoses. The dose usually administered, equivalent to oxytetracycline 250 mg b.d., is low, but treatment may be continued for many months or even years (5). Complications reported from this regime have been minor, such as gastrointestinal upsets and monilial vaginitis, possibly reflecting the general

Table I. *Comparison of control and treatment groups*

Group (see text)	A	B	C
Total no. of patients	76	50	120
Age			
Range	13–66 y.	16–57 y.	12–73 y.
Mean	26 y.	25 y.	28 y.
Sex			
Male	33%	26%	40%
Female	67%	74%	60%
Disease			
Acne	79%	74%	87%
Rosacea/Perioral D.	20%	24%	11%
Other	1%	2%	2%
Duration of disease			
Range	1/12–16 y.	2/12–16 y.	5/12–33 y.
Mean	4.5 y.	5.9 y.	6.1 y.
% of females on contraceptive pill	26%	30%	30%
Family history			
Positive	21%	40%	28%
Negative	53%	36%	37%
Unknown	26%	24%	35%

good health and relative youth of the patients (3). Where blood counts have been performed, little evidence of toxicity has been found (8).

There is no doubt that tetracycline, used in different clinical situations and at higher dosages, can cause many complications (10), the most important of which are renal, hepatic and metabolic. Our investigations suggest that the low-dose, long-term tetracycline regime is free from these effects.

Renal complications of tetracycline therapy are

Table II. *Comparison of blood investigations before and during treatment and number of patients observed*

Observed values	Duration of treatment						
	Untreated	1 month	3 months	6 months	1 year	2 years	Over 2 years
UREA (mg/100 ml)							
10–19	13	5	6	6	0	0	1
20–29	68	23	34	21	19	9	8
30–39	39	6	15	18	13	9	11
40+	6	2	7	5	2	1	1
Bilirubin (mg/100 ml)							
0.1–0.4	24	4	18	7	7	6	2
0.5–0.8	82	25	37	29	22	10	17
0.9–1.2	16	4	3	11	5	3	1
1.2+	4	3	4	3	0	0	1
SGPT (IU/l)							
0–9	61	19	22	22	13	8	10
10–19	40	6	25	15	10	3	6
20–29	22	8	13	7	9	7	4
30+	3	3	2	6	2	1	1
Alk. phos. (K.A. units/100 ml)							
0–4	13	2	3	8	4	1	3
5–9	60	21	29	30	26	14	10
10–14	42	9	22	11	4	4	8
15+	11	4	8	1	0	0	0
Total observations	126	36	62	50	34	19	21

Table III. *Urine examination*

	Pre-treatment	During treatment
Total observations	126	222
Abnormalities	29 (23%)	47 (21%)

well documented (12). Patients with chronic renal failure may be precipitated into terminal renal failure, apparently due to a true deterioration in renal function. However, drugs of the tetracycline group in doses of 1–2 g per day can produce a rise in blood urea in people with normal kidneys (11), an effect which is probably due to an antianabolic action on amino acid incorporation into protein. The fact that in our patients, there is no significant change in urea or albumin levels, seems to indicate that neither of these actions occurs at the low dose used.

The transient abnormal urinary findings were not significant, since they were found equally frequently in the control patients.

Hepatic damage in association with tetracycline has often been described, but this is usually related to high-dose parenteral therapy in pregnant or ill patients (2, 9). Although normal levels of serum bilirubin, SGPT, alkaline phosphatase, and plasma proteins do not exclude minor or early liver disease, they indicate that there are no gross changes in the patients investigated.

CONCLUSIONS

In the present study we have been unable to demonstrate any significant harmful effects of long-term, low-dose tetracycline therapy as currently used for acne, rosacea and related dermatoses. Even in those patients who have been on treatment for 3–5 years no obvious abnormalities were found. It seems reasonable, therefore, to continue with this effective form of treatment although more refined tests of renal and hepatic function would be helpful in confirming these results.

REFERENCES

1. Baker, H.: Systemic therapy. *In* Textbook of Dermatology (ed. A. Rook, D. S. Wilkinson and F. J. G. Ebling), p. 2041. Blackwell Scientific Publications, Oxford, 1972.
2. Breitenbucher, R. B. & Crowley, L. V.: Hepato-renal toxicity of tetracycline. Minn Med *53:* 949, 1970.
3. Committee on Drugs: The treatment of acne with antibiotics. Paediatrics *48:* 663, 1971.
4. Deichmann, W. B., Bernal, E., Anderson, W. A. D., Keplinger, M., Landeen, K., MacDonald, W., McMahon, R. & Stebbins, R.: The chronic oral toxicity of oxytetracycline hydrochloride and tetracycline hydrochloride in the rat, dog and pig. Industr Med Surg *33:* 787, 1964.
5. Ebling, F. J. G. & Rook, A.: Treatment of acne. *In* Textbook of Dermatology (ed. A. Rook, D. S. Wilkinson, and F. J. G. Ebling), p. 1551. Blackwell Scientific Publications, Oxford, 1972.
6. Gilgar, R. S.: Complications of tetracycline therapy for acne. North Carolina Med J *33:* 331, 1972.
7. Olson, C. A. & Riley, H. D.: Complications of tetracycline therapy. J Paediatr *68:* 783, 1966.
8. Osment, L. S. & Hammack, W. J.: The long term use of tetracycline in acne vulgaris. South Med J *63:* 1156, 1970.
9. Peters, R. L., Edmondson, H. A., Mikkelsen, W. P. & Tatter, D.: Tetracycline-induced fatty liver in non pregnant patients. Am J Surg *113:* 622, 1967.
10. Pflug, G. R.: Toxicities associated with tetracycline therapy. Am J Pharm *135:* 438, 1963.
11. Shils, M. E.: Renal disease and the metabolic effects of tetracycline. Ann Intern Med *58:* 389, 1963.
12. Tetracycline and Blood Urea. (Leading article.) Br Med J *III:* 370, 1972.

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