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Treatment of Acne Vulgaris with Tetracycline Hydrochloride: a Double-blind Trial with 51 Patients

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Summary: Fifty-one patients with acne vulgaris were included in a double-blind trial to assess the therapeutic effect of 250 mg. tetracycline hydrochloride twice daily for three months. The results, assessed clinically and photographically, showed that tetracycline hydrochloride had a statistically significant beneficial effect. Hence, since it is cheap and rarely has side-effects in healthy young adults, its use is suggested, as well as local therapy, in the more severe forms of acne.

Introduction

Tetracyclines have been used in the treatment of acne vulgaris for over 15 years and yet their value is still uncertain. The results of double-blind trials are conflicting—for example, Stewart *et al.* (1963), Witkowski and Simons (1966), and Ashurst (1968) confirm their value, while Smith *et al.* (1962), Crounse (1965), and Fry and Ramsay (1966) are of the opinion that tetracyclines have no greater effect than a placebo (*Year Book of Dermatology, 1966–7*).

The *British Medical Journal* (1966) was critical of the long-term use of tetracyclines and emphasized the expense and the many possible side-effects. It was because of this continued controversy that we undertook yet a further trial with a tetracycline to see if it produced a significant effect in this condition.

The therapeutic results of more than one type of tetracycline, or of other broad-spectrum antibiotics, are not considered here. The questions of total duration of treatment and of possible relapse of acne after stopping tetracycline therapy are also beyond the scope of this paper.

Investigation

Sixty-one consecutive patients with acne vulgaris attending the skin department of the General Infirmary at Leeds were included initially in the trial. Five failed to attend after the first visit and five others attended twice only. The figures for this trial are based on the 51 patients who attended three times over a period of three months.

There were 25 females aged 12 to 29 years (mean 18 years) and 26 males aged 14 to 23 years (mean 18 years). None of the patients included in the trial had been treated with antibiotics within the previous two months. Forty-four of them had had local treatment in the past, and four had had superficial *x*-ray therapy over a year previously. The trial was conducted during the winter months (from December 1967 to April 1968), when sunshine was minimal.

At the first attendance a clinical assessment was made by completing a table which included descriptions of the lesions—

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that is, comedones, papules, pustules, and cysts—and these were then assessed on a scale as being absent, mild, moderate, or severe. The patient was then graded according to the Pillsbury classification 1 to 4 (see Appendix) (Pillsbury *et al.*, 1961) with the addition of half grades.

All patients were instructed not to use any local treatment and to rely entirely on the tablets prescribed. Great emphasis was placed on this, and the patients co-operated very well. They were asked to continue washing as before and to use cosmetics if they wished. Furthermore, they were requested to make no change in their diets. The pharmacist then issued tetracycline hydrochloride 250 mg. tablets, or a placebo identical in appearance, according to a prearranged system of random selection. The dose was one tablet twice a day. The tablets were taken for six weeks, when the patients were seen again by the same doctor. The clinical appearance was again assessed, but on a second form, so that the observer was not aware of the previous marking. The patients' impression of possible progress or deterioration was noted. More tablets were then issued, using the same code, for a further six weeks. After three months' therapy each patient's impressions of the treatment were recorded on a third form, the clinical assessment made, and a new Pillsbury grading given.

On the second and third visits the patients were asked by direct questioning about any side-effects occurring during treatment—for example, pruritus, diarrhoea, dyspepsia, or sore mouth. They were also asked whether they had used any additional treatment themselves.

Colour transparencies of the patients were taken on their first, second, and third visits. Forty-three patients had complete photographic records of each visit, four were photographed before treatment and after six weeks' treatment, and two were photographed before and after three months' treatment. Two patients were not photographed. Where there was no photograph the clinical assessment alone was taken.

Patients with acne on the face were photographed from the front and from each side at each visit, making a set of nine colour transparencies for each patient. The chest and/or back were photographed if indicated. Of the 49 patients photographed, 40 had transparencies of the face, six had transparencies of the face, chest, and/or back, and three had transparencies of the chest and/or back alone.

The photographic technique was standardized (Robinson, 1968) by using an Exa 2B camera with a 100-mm. lens, Kodachrome II film (ASA 25), an electronic flash, and a green backcloth. For photographing the face a 10-mm. extension tube at 3 ft. (0·9 m.) and a lens aperture of f.5·6 was used. For chest and/or back views no extension tube was necessary, the distance being 4 ft. (1·2 m.) and the lens aperture f.5·6.

Methods of Assessment of Therapeutic Response

Two separate methods of assessment were used—namely, clinical and photographic—and the following comparisons were made: (1) the skin lesions before treatment and after six weeks' treatment, and (2) the skin lesions before treatment and after three months' treatment. The key to the therapy was retained by the pharmacist until all patients had been assessed.

Clinical Assessment

On completion of the trial marks were allocated according to the patient's progression or regression along our modification of the Pillsbury scale (see Appendix), one mark being equivalent to half a grade—for example, if a patient was grade 2½ at the first attendance and grade 2 at the second, he had improved a ½ grade and his marking would be +1. The results ranged from −4 to +4 (see below), equal weighting being given to deterioration as to improvement. Each observer marked his own patients independently, and the results were later discussed by both observers working together. The tables listing the lesions were of considerable help in placing the patients on the Pillsbury scale, and thus awarding marks.

Much worse	−4	Worse
Worse	−3	
Moderately worse	−2	
Slightly worse	−1	
No change	0	No change
Slightly better	+1	Improvement
Moderately better	+2	
Better	+3	
Much better	+4	

Photographic Assessment

The colour transparencies were assessed as follows. The sets of slides for each patient were mounted in a Roger's plastic slide holder, and viewed by hanging them in front of an *x*-ray viewing box (Kodak Coldlight Illuminator) set at a constant level of illumination in a dark room. A hand lens was used throughout. Thus the sequential changes in a patient's condition at six weeks and at three months could be seen at one viewing. Marks were allocated for each view of the patient by using the same method as that used for the clinical assessment.

Each observer, working independently, marked all the transparencies. The total marks of each patient were added together and the average was taken. For example, if patient X was given +2 (face), +1 (right profile), +2 (left profile) by observer A and +2 (face), +2 (right profile), +2 (left profile) by observer B, the total marks given were 11, the number of observations six and the average, taken to the nearest whole number, was +2. In this way the photographic assessment was thus brought on to the same scale as the clinical assessment. It was thought that by combining the clinical and photographic assessments a more accurate index would be obtained than by taking either assessment alone.

A third independent observer was asked to assess the colour transparencies "blind," using the same method of assessment. His marking was not incorporated into our own final results.

Results

Method 1

The sum of the clinical and photographic assessments (see Tables I and II) helps to minimize any discordant observations —for example, if a patient was thought to have slight clinical improvement (+1 on the marking scale) but slight deterioration on photography (−1), the final interpretation was less likely to be reliable than in the case where both clinical and photographic assessments were the same. In this case the patient would register the sum of +1 and −1=no change. Whereas, if a patient was given +1 clinically and +2 photo-

TABLE I.—*Results of* 51 *Patients After Six Weeks' Therapy. Method* 1 (*See Text*)

Results	Tetracycline Hydrochloride		Placebo	
	No. of Patients	%	No. of Patients	%
Improved ..	20	84	11	41
No change ..	2	8	9	33
Worse ..	2	8	7	26
Total ..	24	100	27	100

graphically he would score +3 and count as "improved." Similarly, if he rated −1 clinically and −1 photographically he would score −2 and count as "worse." But it must be admitted that if he scored +1 clinically and 0 photographically he would register as "improvement," and if he were 0 clinically and −1 photographically he would register as "worse."

TABLE II.—*Results of 51 Patients After Three Months' Therapy. Method 1 (See Text)*

Results	Tetracycline Hydrochloride		Placebo	
	No. of Patients	%	No. of Patients	%
Improved ..	23	96	15	55
No change ..	0	0	4	15
Worse ..	1	4	8	30
Total ..	24	100	27	100

It will be seen from Table I that when using this method of obtaining an index of assessment 20 (84%) patients out of 24 on tetracycline therapy showed improvement after six weeks whereas 11 (41%) out of 27 patients on the placebo showed improvement. These results showed a marked statistical significance in favour of tetracycline therapy ($P<0.01$, $\chi^2=7.9$).

Similar results were obtained after three months' treatment (see Table II), when 23 (96%) out of 24 patients showed improvement on tetracycline and 15 (55%) out of 27 showed improvement on placebo. These results are also statistically significant ($P<0.01$, $\chi^2=8.8$).

Method 2

As many of the patients in the trial showed only minor changes during the period of observation, it became apparent that those showing indefinite change should not be listed under such a positive label as "improved" or "worse." It seemed preferable to include these borderline cases in the category of "no change." These particularly include those patients who registered ±1 on either the clinical or photographic rating, but 0 on the other method of assessment. With this in mind, an index of assessment was calculated by taking the *mean* of the combined clinical and photographic marks of each patient, and all those patients with an index of ±0·5 were counted as "no change." Thus if the clinical assessment of a patient was +1 and the photographic assessment was +1, then the mean was also +1, and counted as "improvement." But if the clinical assessment was +1 and the photographic assessment was 0, or vice versa, then the mean was +0·5 and counted as "no change."

When this index is used a different pattern is seen in the placebo response (Tables III and IV). At six weeks 13 (54%) out of 24 patients on tetracycline improved whereas only 2 (7%) showed improvement on the placebo ($P<0.01$, $\chi^2=8.0$). After three months' treatment with tetracycline 18 (75%) showed improvement as compared with 9 (33%) on the placebo: ($P<0.01$, $\chi^2=7.3$). It was thus seen that more of the indeterminate and minimal changes occurred in the placebo group. By this means it would appear that indeterminate changes were not distorting the results in Tables I and II.

TABLE III.—*Results of 51 Patients After Six Weeks' Therapy. Method 2 (See Text)*

Results	Tetracycline Hydrochloride		Placebo	
	No. of Patients	%	No. of Patients	%
Improved ..	13	54	2	7
No change ..	11	46	20	74
Worse ..	0	0	5	19
Total ..	24	100	27	100

TABLE IV.—*Results of 51 Patients After Three Months' Therapy (See Text)*

Results	Tetracycline Hydrochloride		Placebo	
	No. of Patients	%	No. of Patients	%
Improved ..	18	75	9	33
No change ..	5	21	14	52
Worse ..	1	4	4	15
Total ..	24	100	27	100

Quantitative Assessment

It was considered desirable to assess the average quantitative improvement shown in each group to demonstrate how much actual improvement had taken place. This was again done by averaging the clinical and photographic assessments, but this time the average represented a whole group on one particular treatment. By doing this it was found that the tetracycline group showed a mean improvement of 1.0 ± 0.3 at six weeks, while that shown by the placebo group was 0.0 ± 0.3—the difference between the groups is significant ($P<0.001$, $t=3.9$). At three months the mean improvement of the tetracycline group had increased to 1.8 ± 0.3 and that of the placebo group to 0.3 ± 0.3—the difference between the groups was again highly significant ($P<0.001$, $t=4.0$).

Discussion

It is a common clinical observation that there is a natural variation in the severity of acne, and a double-blind trial is essential. As the results of most previous trials were assessed at the end of two to eight weeks' treatment, it was thought advisable to extend the trial for a minimum of three months and an intermediate assessment was also done at six weeks.

We were advised that it was unnecessary to incorporate a cross-over method into the trial in order to obtain a significant result. By not using this method, any possible residual therapeutic effect in the tetracycline group was also avoided.

It was soon seen that the majority of the patients were rated around the Pillsbury grade 2 level, and that changes in the lesions would be small, thus making clinical observation and grading difficult. For this reason, as already described, two separate methods of assessment—namely, clinical and photographic—were used.

Assessment of Colour Transparencies by a Third Observer.—When the third observer's marks of the photographic transparencies were used instead of our own in the calculation of both methods of assessment the results were almost identical with our own.

Local Treatment.—Unlike some observers in the past we did not give patients any local treatment whatsoever, as this would have led to further difficulties in the interpretation of results. For this reason we asked patients on the second and third visits whether they had used any additional treatment. One patient admitted to using his own ultraviolet lamp during the period of observation and was excluded from the trial after his second visit.

Patients' Own Assessment.—The patients' opinion of their progress or deterioration was found to be very close to our own observations and calculations when using the method shown in Tables I and II.

Placebo Response.—Many observers have found the placebo response in acne to be around 40 to 50% of patients treated. Our findings in Tables I and II are in accord with this. When a less sensitive but more realistic index of assessment is used, however, the placebo response is very much less marked, being 7% at six weeks and 33% at three months (see Tables III and IV). By chance, the placebo group could have included most of the patients with severe acne—that is, grades 3 and 4—which might have biased the results in favour of the tetracycline group. But a retrospective study of the gradings showed

that there were nine patients with grades 3 and 4 in the tetracycline group as compared with four in the placebo group (see Table V). It is also noteworthy that more patients on placebo (4 out of 27 patients) than on tetracycline (1 out of 24) became worse during the period of observation.

TABLE V.—*Showing Average Response of Different Grades of Acne to Treatment at Six Weeks and Three Months*

Grade	Tetracycline (24 Patients)			Grade	Placebo (27 Patients)		
	No. of Patients	Average Response			No. of Patients	Average Response	
		6/52	3/12			6/52	3/12
1	0	—	—	1	2	−0·25	−0·25
2	15	+0·7	+1·5	2	21	+0·1	+0·5
3	8	+1·7	+2·3	3	4	−0·4	−0·25
4	1	+0·5	+1·5	4	0	—	—

Absorption of Tetracycline.—It was suggested by Crounse (1965) that a possible cause of the conflicting results of previous double-blind trials may have been variation in the absorption of tetracycline. Crounse (1965) took particular care to instruct his patients to take the tablets before meals so as to give maximum opportunity for absorption. In the present series tablets were prescribed morning and evening with no special instructions relating to mealtimes. We did not specifically check whether the patients had really taken their tablets—failure to do so being a common cause of "malabsorption" of a drug—but from the results it would appear that sufficient absorption had occurred to give a significant effect. We would not, therefore, attach undue importance to the precise timing of the administration of the tablets.

The *British Medical Journal* (1966) posed three main questions. Firstly, do tetracyclines help in the treatment of acne? Secondly, if so, is this treatment too expensive to be practical? Thirdly, are the side-effects serious enough to contraindicate their use?

Do Tetracyclines Help in Treatment of Acne Vulgaris?—Our results show that tetracyclines are of benefit to about 75% of patients with acne. The figures after both six weeks' and three months' treatment are significantly in favour of the actively treated group. The group improvement on tetracycline after six weeks' treatment was +1 with a standard error of ±0·3—that is, "slightly better"—which may help to explain the variable reports from trials which have been conducted in the past. The group improvement after three months' treatment, however, was 1·8 with a standard error ±0·3—that is, "moderately better"—a change easier to interpret both clinically and photographically. Although the numbers of the tetracycline group are not large enough to show a statistically significant improvement at three months' treatment as compared with six weeks' treatment, the general trend to further improvement at three months should be noted. The response of each of the Pillsbury grades of acne to tetracycline hydrochloride therapy is shown in Table V. These figures are shown for interest, as the numbers are not large enough to show statistical significance.

Expense.—The cost of treating a patient with acne from a hospital dispensary is about four shillings a week when using tetracycline hydrochloride in a dosage of two tablets a day.

Toxic Effects.—The toxic effects of the tetracyclines are well summarized by Clendenning (1965). None of our patients had such well-recognized complications as nausea, pruritus ani, etc., but we did have one patient complain that she had great discomfort with her contact lenses after being on the tablets for 10 weeks. Previously she had had no trouble with the lenses, which she had worn for two years. This discomfort was relieved as soon as she stopped taking the tablets, but returned within one week of restarting them. So far as we know this side-effect has not been mentioned before. We would suggest that the young, fit age group with acne is less liable to side-effects than the middle-aged and elderly group with rosacea.

We agree that tetracyclines should not be given during pregnancy, and patients should be warned to stop the tablets should they miss a period. In our opinion the side-effects of tetracycline, as used in acne in healthy young adults, are grossly overexaggerated.

Suggestion

We agree with Pillsbury that patients with acne vulgaris of grades 3 and 4 should be treated with tetracyclines. We also agree that tetracyclines are not indicated in grade 1 acne, as the effect of the drug on comedones remains uncertain. Likewise we do not advocate the initial use of tetracyclines in the lower grade 2 patients, as the response to local treatment is often good.

Each case, of course, must be treated on its own merits. In clinical practice, therefore, we would expect to use tetracyclines as well as local therapy in the more severe grade 2 acnes and in grades 3 and 4.

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Appendix

Grade 1.—Sparse to profuse comedones with little or no inflammatory reaction.

Grade 2.—Acne consisting of comedones and *superficial* small pustular and inflammatory lesions at the follicular orifice. This process is ordinarily confined to the face.

Grade 3.—Acne characterized by comedones, small pustules, and a tendency to *deeper* inflamed lesions. These inflammatory nodules are not definitely related to the follicular pore and apparently result from rupture of the sebaceous duct . . . usually sterile. The inflammatory lesions tend to be confined to the face, neck, tops of the shoulders, and presternal region.

Grade 4.—This is an extensive secondarily infected cystic acne (acne conglobata). The face and neck may be severely involved, with extensive lesions of the upper trunk . . . boggy canalized sinuses . . . scarring . . . cord-like bands and hypertrophic ridges . . . considerable resultant disability.

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