

SHORT COMMUNICATION**Therapeutic Agents in Acne Vulgaris****I. Tetracycline**

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A NUMBER of agents used in the treatment of acne vulgaris were subjected to controlled therapeutic trials and statistical evaluation by our group. The following report concerns a study of the effectiveness of tetracycline in the treatment of pustular and cystic acne.

Acne vulgaris is a disorder occurring chiefly during the adolescent and early adult years. It is so common that few North Americans escape without some signs of it by their twentieth year, and a small proportion go on to a chronic form of the disease that may last for years.

It is treated traditionally with sulfur and resorcin lotions, abrasive and de-fatting cleansing agents, hot medicated compresses, minor surgical procedures, dietary restrictions, and vitamin A administered orally. When they became available, antibiotics and chemotherapeutic agents were used to reinforce the aforementioned time-honoured techniques.¹⁻³ Many patients with severe forms of this disease still do not receive antibiotic therapy, however, because all physicians treating this potentially mutilating disorder do not agree as to the value of these medications.^{4, 5}

The word mutilating has been used, after due thought, to refer to the physical and psychological trauma that may occur during the acute inflammatory, painful early phases, and the deeper injuries manifested by the permanent scarring, sometimes of a startling degree, that may result from pustular and cystic varieties of this condition.

Acne vulgaris is associated with three distinct processes that may progress simultaneously. These are:

1. Comedone formation, with discoloured sebaceous plugs at follicular orifices, and retention of sebum: This occurs chiefly over the face, presternal area, and mid and upper back. Histologically, there may be follicular dilatation and adjacent minimal mononuclear cellular infiltrate.

2. Inflammatory papule formation from comedones: These lesions often become pustular and fluctuant with retained pus. Papules may leave no residual scars, but pustules, depending upon their size, often do. These lesions proceed through a natural course of development with rupture or absorption of retained material, and involution, taking from three to four days to two or three weeks to do so. Histologically, there is a marked

ABSTRACT

A total of 120 consecutive patients with pustular and cystic acne vulgaris were selected for study. Patients were assigned a placebo and a tetracycline medication in a random method. Of the 53 patients who were given tetracycline, 45 showed some response, which was fair in 19 and excellent in 26. Of the 55 patients who received placebo, 24 showed no response while 31 showed some improvement. No side effects were reported. The difference in response between the two groups is statistically significant. It is concluded that administration of 250 mg. tetracycline four times daily, even for periods as short as two weeks, enhances the likelihood of improvement of cystic or pustular acne vulgaris.

acute inflammatory reaction, which may be a foreign-body type of response, possibly provoked by the keratin component of the sebum.

3. Cyst formation: Here larger inflammatory cystic lesions form, with confluence of these lesions beneath the surface, resulting in distortion, tunneling and sinus tract formation of the cutaneous surface. Keloid-like scarring may be seen. Histologically, these lesions are deep, with marked acute, epithelioid, and granulomatous inflammatory infiltrates and much scar formation.³

One, two or all three of these processes may be present in a patient with acne vulgaris. Papules and cyst formation when present are usually associated with comedone formation. Comedones, however, may occur without either of the other two.

Cultures of pus-containing acne lesions reveal the presence of a mixed group of organisms. There may be little uniformity of bacteriological pattern, even when lesions from the same patient are cultured.⁴⁻⁶ Because of this, and imperfect knowledge in other areas concerning skin bacteria and their relationship to cutaneous disease, there are conflicting reports regarding the role of these organisms in the etiology of acne.^{3, 7} Attempts to treat acne vulgaris with antibiotics have resulted chiefly in improvement, but there have been some failures.^{3, 8, 9} Even successful antibiotic therapy shows little correla-

tion between the antibiotic sensitivity studies of bacteria cultured from the lesions and the choice of antibiotics used successfully in the treatment of acne.^{6, 10} Tetracyclines are felt by many observers to be the most effective antibiotics in this condition, varying dosage regimens being recommended, from 250 mg. to 1000 mg. a day.^{1, 2, 11} Some penicillin compounds are also satisfactory. Sulfonamides appear to be less so, but are still sufficiently effective to make them useful agents in the treatment of acne.^{6, 12}

This investigation was undertaken to evaluate the effectiveness of tetracycline in the treatment of acne vulgaris, under carefully controlled conditions. It was performed as a double-blind study, active medication or placebo being assigned in a randomized manner.

Patients were selected simply on the criterion of having active, moderate to severe pustular and cystic scarring acne vulgaris (two had pustular acne rosacea), with either facial involvement alone or facial involvement plus involvement of the chest and back. Non-pustular and comedone types of acne cases were excluded.

METHOD

A total of 120 consecutive patients with pustular and cystic acne were selected for study. Patients were assigned the coded medications (active tetracycline or inactive identical-appearing placebo) according to a randomization method. Irrespective of the medication assigned, each patient was given one capsule, four times a day for a period of two weeks. On completion of each course of medication the therapeutic results were assessed by the physician who made the initial diagnosis, in terms of "no response," "fair response" or "excellent response" to therapy. The occurrence and nature of side effects encountered during medication were also recorded. The double-blind technique was followed so that neither patient nor physician knew which medication was being given. Upon completion of the clinical study, the coded medications were identified as tetracycline (Panmycin hydrochloride 250 mg., Upjohn) and a placebo (lactose-talc) to permit a statistical analysis of results.

No other oral or parenteral medication was prescribed. If the patient was using a routine technique of washing with medicated soap, or used topical sulfur-resorcin lotion, these measures were continued. No such routines were started in association with this study.

RESULTS

A total of 108 patients were available for study, of whom 53 received tetracycline and 55 the placebo. The remaining 12 patients were eliminated from the study because they did not take the prescribed medication, or did not report for post-treatment observation, or developed intercurrent illness requiring other treatment. The study patients

comprised 58 men and 50 women. Their age range was from 13-39 years, with the exception of two patients aged 48 and 58 years respectively, who were diagnosed as having pustular acne rosacea. The dermatologic diagnoses of these 108 patients were acne vulgaris in 106 and acne rosacea in two.

The results of therapy as evaluated by clinical assessment were as follows:

TABLE I.—RESPONSE

	None	Fair	Excellent	Total
Tetracycline.....	8	19	26	53
Placebo.....	24	17	14	55
Total.....	32	36	40	108

It will be noted that (Table I) of the 53 patients who were given tetracycline, only eight showed no response to therapy while the remaining 45 showed some response, which was graded as fair in 19 and excellent in 26. Of the 55 control subjects, 24 showed no response while 31 showed some improvement—graded as fair in 17 and excellent in 14. No side effects were reported in any of the study patients.

CONCLUSIONS

Under the conditions of this clinical trial the samples indicated a significant difference in clinical improvement from the therapeutic agents used. The clinical improvement shown by the tetracycline-treated subjects, as compared with the control subjects, is significantly better than would have been expected from chance alone.

It would appear that a patient with acne vulgaris of the pustular or cystic variety has a better chance of improvement of his skin condition if tetracycline, in a dosage of 250 mg. four times daily, is prescribed than if it is not. This applies even with the short periods of therapy (two weeks) used in this study (chi square value=11.7, which is significant at level $P=0.01$ —i.e. the likelihood of obtaining a chi square value as great or greater than this, by chance alone, would occur only once in 100 trials).

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