DEMETHYLCHLORTETRACYCLINE IN THE TREATMENT OF GONORRHOEA*

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With the rising incidence of gonorrhoea throughout the world, with greater numbers of circulating strains of gonococci less sensitive to penicillin and completely resistant to streptomycin than formerly, and with an appreciable number of persons now allergic to penicillin, it is more than ever necessary that alternative methods of therapy should be kept under review.

There are numerous antibiotics other than penicillin able to cure gonorrhoea, the majority but not all (*e.g.* streptomycin, ceporin, kanamycin, spectinomycin) of which are given by mouth. Oral therapy for this condition is not widely favoured, as patients, particularly those with venereal disease, are often unreliable in taking their treatment in the doses and at the times required. A number will discontinue therapy when the condition improves and some of the antibiotic may be retained and be used for self-treatment later should the occasion arise: in addition a "black market" may be fostered whereby unused tablets are sold to others.

These objections can be overcome if the treatment is given as a single dose under supervision in the clinic. Most patients can perhaps be relied to take one additional dose on the same day and therefore schedules consisting of one or two oral doses are to be preferred to those requiring multiple doses for some days. The present paper concerns the results of treating 119 male patients with uncomplicated gonorrhoea with one or two oral doses of demethylchlortetracycline ("Ledermycin").

Material

119 male patients with acute uncomplicated gonorrhoea have been treated with oral demethylchlortetracycline. 52 were Negroes (5 from West Africa and 47 from the West Indies) and the remainder 49 were born in the United Kingdom, five in Eire, four in Pakistan, two in Spain, and one each in Australia, Czechoslovakia, Iceland, Italy, Germany, Holland, and Poland. 27 of the

patients were married, one was separated and 91 were single. Their average age was 28.2 years.

Only 45 patients (nine Negroes) had had no previous venereal incident. The remainder had had between them no less than 206 previous attacks of gonorrhoea (one of which was rectal), 63 of non-gonococcal urethritis, five of syphilis, five of unspecified sore, two of warts, two of scabies, one of lymphogranuloma venereum, and four of anxiety concerning venereal disease—a total of 288 incidents. No less than 210 of these, including 153 of gonorrhoea and 44 of non-gonococcal urethritis, had been incurred by the 52 Negroes, who thus had an average of four previous attacks compared with 1.2 for the remainder.

The duration of the discharge before treatment was 1–3 days in 78 cases, 4–7 days in 27, and 8–14 days in fourteen; 97 patients complained of some dysuria and 22 did not. The apparent incubation period was 1–3 days in 46 cases, 4–7 days in 46, 8–14 days in nineteen, 15–21 days in two, 22–28 days in two, and (allegedly) over 28 days in three. In one case sexual risk was denied. The disease was apparently caught from a stranger in sixty cases, from a friend in 45, from the wife in three, and from a man in ten; in one case the source was unknown.

Routine Wassermann reaction and VDRL tests were both negative before treatment in 113 cases, and both positive in five patients four of whom were Negroes, in whom the reaction was possibly due to past yaws in some instances. In one case the tests were not performed.

Management

Three treatment schedules were used.

(1) 33 patients received a single oral dose of 0.9 g. demethylchlortetracycline given under supervision in the clinic.

(2) 52 patients were given a single oral dose of 1.2 g.

(3) 34 were treated with two doses of 1.2 g. each at an interval of 4 to 6 hours; the first dose was given in the clinic and the patient was supplied with four tablets to take himself at home.

Gonococci were seen in Gram-stained urethral smears in all cases before treatment when blood for routine serum tests for syphilis was also taken. The diagnosis was confirmed by culture in the majority of those who received more than 0.9 g.

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After treatment it was planned that the patients should be seen after 2 to 3 days and again after approximately 7, 14, 28, 56, and 90 days. At each visit the patient was examined for urethral discharge; a smear was taken if discharge was present, a culture was made when relapse was suspected, and the urine was inspected for haze and threads. The routine was also to make at least one examination of the prostatic fluid during surveillance and to perform final serum tests for syphilis after 3 months.

Results of Therapy

By no means all patients attended at the times requested and the results are presented according to the follow-up achieved.

Single Doses of 0.9 g. (Table I)

Of 33 patients treated, thirty were followed; there were six recurrences in the first 2 weeks (20 per cent.) and one re-infection after 3 months.

Single Doses of 1.2 g. (Table II)

Of 52 patients treated, 46 were followed and within the first 2 weeks there were three apparent re-infections with gonorrhoea—all in Negroes—and six recurrences (13 per cent.) were adjudged to be failures.

Two Doses Each of 1.2 g. (Table III, opposite)

Of 34 patients treated, 27 were followed and there were four apparent failures (14.8 per cent.), all noted during the first 2 weeks. There was also one re-infection during this time and two later.

Comparison of Results

Methods of Assessment Almost insuperable difficulties exist in distinguishing relapse from re-infection and with to-day's increased prevalence of gonorrhoea the chances of early re-infection are higher than formerly. No satisfactory criteria exist apart from a history of further sexual exposure. This is the criterion usually used but it has considerable limitations in so far as the opportunity is seldom offered to demonstrate that the new contact is infected and, even should this be proved, relapse cannot definitely be excluded.

Studies of the patterns of the sensitivity of gonococci to penicillin before the first treatment and in recurrences has shown a marked trend towards a higher proportion of less sensitive strains being noted in recurrences in the first week than after this time. In later recurrences the pattern more closely resembles that of untreated cases (Curtis and

TABLE I
RESULTS OF TREATING 33 PATIENTS WITH SINGLE DOSES OF 0.9 g.

Length of Follow-up	No. Followed	Results			
		Satisfactory	Non-gonococcal Infection	Re-infection	Failure
1-7 days	30	8	2	—	4
8-14 days	16	1	—	—	2
15-21 days	13	1	2	—	—
22-28 days	10	—	—	—	—
1-2 mths	10	1	—	—	—
2-3 mths	9	1	—	—	—
Over three mths	8	3	4	1	—
Total	30	15	8	1	6 (20 per cent.)

TABLE II
RESULTS OF TREATING 52 PATIENTS WITH SINGLE DOSES OF 1.2 g.

Length of Follow-up	No. Followed	Results			
		Satisfactory	Non-gonococcal Infection	Re-infection	Failure
1-7 days	46	10	—	—	5
8-14 days	31	1	—	3	1
15-21 days	26	—	3	1	—
22-28 days	22	—	—	—	—
1-2 mths	22	2	2	1	—
2-3 mths	17	1	—	1	—
More than 3 mths	15	3	7	5	—
Total	46	17	12	11	6 (13 per cent.)

TABLE III
RESULTS OF TREATING 34 PATIENTS WITH TWO DOSES EACH OF 1.2 g.

Length of Follow-up	No. Followed	Results			
		Satisfactory	Non-gonococcal Infection	Re-infection	Failure
1-7 days	27	6	3	1	2
8-14 days	15	3	1	—	2
15-21 days	9	1	—	1	—
22-28 days	7	—	1	—	—
1-2 mths	6	1	—	—	—
2-3 mths	5	—	—	1	—
Over 3 mths	4	2	2	—	—
Total	27	13	7	3	4 (14.8 per cent.)

Wilkinson, unpublished data). It has therefore been suggested that a fair degree of accuracy may be obtained if all recurrences noted in the first week are classified as relapses and those seen after this time as recurrences. As the normally accepted incubation period of gonorrhoea is 1 to 14 days, the author prefers to use 2 weeks as a more realistic dividing line, and this period has been adopted in this paper. Both methods of calculating failure rates have been used, and calculations have been made on the basis of the total numbers of patients treated as well as on that of the numbers of those actually followed, as it is likely that the majority of those who default immediately do so because they are apparently cured.

Overall Results By all three methods of assessment (Table IV), it would appear that only slight improvement was obtained by increasing the dose and that little additional advantage was gained by giving a second dose of 1.2 g. after an interval of 4 to 6 hours.

This was not, however, quite the case, as becomes clear when the results in Negro and non-Negro patients are considered (Table V).

Ten of the Negro patients (19.2 per cent.) did not return after the first visit. By all three methods of assessment, the results obtained with the schedule in which two doses each of 1.2 g. were used, were apparently worse than those employing single doses

TABLE IV
OVERALL COMPARISON OF RESULTS IN ALL PATIENTS

Dosage Schedule (g.)	No. Treated	No. Followed	Suspected Failures within 3 mths	Recurrences within 2 wks	Percentage Failure of No. Followed	Percentage recurrence in 2 wks	
						of Followed	of Treated
0.9	33	30	6	6	20.0	20.0	18.2
1.2	52	46	6	9	13.0	19.6	17.3
1.2 + 1.2	34	27	4	5	14.8	18.5	14.7
Total	119	103	16	20	15.5	19.4	16.8

TABLE V
RESULTS IN NEGRO AND NON-NEGRO PATIENTS

Patients	Dosage Schedule (g.)	No. Treated	No. Followed	Suspected Failures within 3 mths	Recurrences within 2 wks	Percentage Failure of No. Followed	Percentage recurrence in 2 wks	
							of Followed	of Treated
Negro	0.9	12	10	2	2	20.0	20.0	16.7
	1.2	27	23	2	5	8.7	21.7	18.5
	1.2 + 1.2	13	9	3	4	33.3	44.4	30.8
	Total	52	42	7	11	16.7	26.2	21.1
Non-Negro	0.9	21	20	4	4	20.0	20.0	19.0
	1.2	25	23	4	4	17.4	17.4	16.0
	1.2 + 1.2	21	18	1	1	5.6	5.6	4.8
	Total	67	61	9	9	14.8	14.8	13.4

of 0.9 or 1.2 g. This paradoxical result is likely to be due to the fact that a number of the supposed recurrences were in fact re-infections. The much greater promiscuity in this group, as evidenced by the larger percentage of previous venereal incidents than in other patients has already been noted.

The results for the non-Negro patients (Table V) show that six (9 per cent.) did not return after the first visit. In this group for all three schedules of treatment there are identical failure rates whether the failures are assessed by history of further sexual exposure or by classification as a failure of any within the first 2 weeks, whether suspected to be a re-infection or not.

Substantially better results (only 4.8-5.6 per cent. of failures) were obtained in non-Negro patients to whom double doses of 1.2 g. were given than in those treated with single doses.

Summary

- (1) 119 male patients with acute uncomplicated gonorrhoea were treated with single oral doses of 0.9 or 1.2 g. demethylchlortetracycline or with two doses of 1.2 g. each at an interval of 4 to 6 hours.
- (2) The failure rates were assessed either according to a history of further sexual exposure or regardless of such a history, all recurrences within 2 weeks of treatment being classified as failures and those after this time as re-infections. When the latter method was used the rates were also calculated on the basis both of those followed and of those treated.
- (3) The overall results showed that some improvement was gained by increasing the dose from 0.9 g., but this not apparent in the Negro patients in whom there was a high rate of previous infection and therefore a greater liability to re-infection.

- (4) In non-Negro patients substantially better results (failure rates of only 4.8 to 5.6 per cent. by the three methods of assessment) were obtained with the schedule involving two doses of 1.2 g. each at an interval of 4 to 6 hours. It is therefore recommended that the investigation of this schedule should be extended for non-Negro patients.

La déméthylchlortétracycline dans le traitement de la blennorragie

RÉSUMÉ

- (1) 119 hommes atteints de blennorragie aiguë sans complications ont été traités par une seule dose de 0,9 ou 1,2 grammes de déméthylchlortétracycline administrée par voie buccale ou par deux doses de 1,2 g. chacune à un intervalle de 4 à 6 heures.
- (2) Le taux d'insuccès avait été évalué d'après un historique d'autres possibilités de contagion sexuelle ou sans cet historique, toutes les rechutes ayant lieu pendant les deux semaines de traitement étant classifiées comme des cas d'insuccès et les rechutes après ces deux semaines étant comptées comme des réinfections. Quand la dernière méthode avait été employée les taux avaient été calculés sur la base de cas suivis et de cas traités.
- (3) Les résultats totaux ont démontré qu'une certaine amélioration avait été obtenue en augmentant la dose de 0,9 g., mais cette amélioration n'avait pas été apparente chez les patients nègres chez qui il y avait un fort taux d'infections antérieures et de ce fait un plus grand risque de réinfection.
- (4) Chez les non-nègres des résultats sensiblement meilleurs (les taux d'insuccès étant seulement de 4,8 à 5,6 pour cent par les trois méthodes d'évaluation) avaient été obtenus par la posologie employant deux doses de 1,2 g. chacune à un intervalle de 4 à 6 heures. Il est ainsi recommandé que les recherches au sujet de cette posologie devraient être étendues aux patients non-nègres.