CLINICAL TRIAL OF CLOMOCYCLINE (MEGACLOR) IN GONOCOCCAL AND NON-GONOCOCCAL URETHRITIS*

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Clomocycline is the approved name of a methylol derivative of chlortetracycline and is sold commercially in the United Kingdom under the name of Megaclor. It is presented as an oil-based suspension in the form of red, oblong, soft gelatine capsules each containing 170 mg. clomocycline. This drug has been reported to be noticeably free of side-effects such as nausea, vomiting, and diarrhoea (Chappell, 1965; Wells, 1966). It has been used successfully in urinary tract infections (Kelly, 1966), but has not been tried in gonorrhoea and non-gonococcal urethritis (NGU).

Present Study

Preliminary Tests

Sensitivity disks, ranging in potency from 0.125 to 2.0 $\mu\text{g.}$, were prepared from a sample of working standard of clomocycline containing 1,000 $\mu\text{g.}$, using water as a diluent (clomocycline, unlike other tetracyclines is highly water soluble). Ten random strains of gonococci were tested against the disks; two strains were sensitive to 0.125 $\mu\text{g.}$, five to 0.25 $\mu\text{g.}$, two to 0.5 $\mu\text{g.}$, and one to 1.0 $\mu\text{g.}$ It was therefore decided to use disks of 1.0 $\mu\text{g.}$ potency in the trial.

FIG. 1.—Racial distribution of 110 men treated with clomocycline.

(Minimum inhibitory concentrations of clomocycline ranged from 0.02 to 0.34 $\mu\text{g./ml.}$ in six strains and were 3.125 $\mu\text{g./ml.}$ in five, 6.25 $\mu\text{g./ml.}$ in two, and 25.0 $\mu\text{g./ml.}$ in one of the fourteen strains of gonococci tested by Martin and Kliger (1967) by tube dilution method.)

Clinical Material

Between October, 1966, and May, 1967, in the Venereal Diseases Clinic in Bradford, 110 male patients, sixty suffering from gonorrhoea and fifty from NGU, were treated with clomocycline. Of these 49 were born in the United Kingdom, forty were from Asia (mostly from Pakistan), sixteen from the West Indies, and five from the European continent. The racial distribution was different in the two groups of patients. In the gonorrhoea group Europeans accounted for 30 per cent. of cases and coloured patients (28 from Asia and 14 from the West Indies) for 70 per cent., whereas in the NGU group 72 per cent. were Europeans and only 20 per cent. were coloured (Fig. 1).

The two groups of patients differed also with regard to the alleged sources of infection (Fig. 2). Of the sixty with gonorrhoea, thirty claimed to have been infected by prostitutes, 21 by casual contacts, and only four by wives or regular consorts; four would not reveal or pretended not to know the source of their infection and one was homosexual. Of the fifty patients with NGU,

FIG. 2.—Sources of infection in 104 men treated with clomocycline. Five in whom the source was unknown and one homosexual are excluded from the total series of 110.

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25 were infected by wives or regular consorts, nineteen by casual contacts, and five by prostitutes, while one denied sexual exposure to risk of infection.

The ages of the patients with gonorrhoea ranged from 16 to 50 years and of those with NGU from 17 to 51 years; the age distribution was almost the same.

Management and Follow-up

A preliminary diagnosis was made on the results of Gram-stained smears of urethral discharge and in all cases specimens were submitted in transport medium for later inoculation of growth media suitable for *N. gonorrhoeae* and *T. vaginalis*. Disk sensitivity tests, using penicillin at four concentrations between 0.06 and 0.5 unit, streptomycin 10 µg., tetracycline 10 µg., clomocycline 1 µg., were carried out on sub-cultures of organisms identified as *N. gonorrhoeae*.

Of the sixty patients with gonorrhoea, ten were treated with approximately 17 mg./kg. (1 capsule per 10 kg.) of clomocycline, six in a single dose and four in two doses taken at an interval of 6 to 8 hours; fifty were treated with 34 mg./kg. (2 capsules per 10 kg.), thirty taking this amount of the drug divided into two doses, 20 into three doses at intervals of 6 hours.

Of the fifty patients suffering from NGU, twenty received six 170 mg. capsules of clomocycline on each of 3 consecutive days, and thirty received six capsules on each of 4 days. The scheme of treatment was to give alternate patients three capsules twice a day or two capsules three times a day.

Patients were, as far as possible, followed up for 13 weeks. Most patients with gonorrhoea had no urethral discharge by the fourth day after treatment had started and, in those that had some discharge, gonococci were absent and pus-cells few. At the third visit, usually at the end of the second week, a prostatic bead was obtained and tested by smear and culture. The presence of gonococci in the urethral discharge before these tests were performed was regarded as failure of treatment. Patients who ceased to attend before the tests were counted as defaulters.

Patients in the NGU series were seen 1, 2, and 4 weeks after the beginning of treatment and the majority twice more at monthly intervals. The prostatic bead was usually obtained after the fourth week. Persistence of the urethral discharge for more than a week was regarded as a failure of treatment; its reappearance before the 28th day was regarded as an early relapse and after 28 days as a late relapse, irrespective of

whether further sexual exposure had occurred. The remainder were looked upon as successfully treated.

Results

Gonorrhoea (Table I)

In the cases of nine of the ten patients who were treated with 17 mg./kg. clomocycline, gonococci were found in the urethral discharge at the first visit within 5 days; the success of this dose in the remaining case was confirmed at eight follow-up examinations.

Of the fifty patients treated with a total dose of 34 mg./kg., six failed to respond (12 per cent.), four in the group of thirty in which the dose was divided into two portions and two in the group of twenty in which it was divided into three portions. The failures could not be related to the results of *in vitro* sensitivity tests as measured by 1 µg. clomocycline disks. All strains of gonococci on this series were sensitive *in vitro* to 10 µg. tetracycline.

NGU developed in five patients between 8 and 20 days after successful treatment of gonorrhoea; *T. vaginalis* was cultured from the urethral discharge of one of these patients. In another patient with no evidence of a urethral discharge and clear urine, *T. vaginalis* was found in the fluid expressed by prostatic massage 3 weeks after treatment.

NGU (Table II, overleaf)

In this series there were six immediate failures and three relapses within 4 weeks and two within 8 weeks of completing treatment. Five of the failures and two early relapses occurred in the group of twenty patients treated with clomocycline for 3 days, while only one failure, one early relapse, and two late relapses occurred in the group of those thirty patients who had been taking the drug for 4 days. The failures were equally distributed between patients who took 3 capsules twice daily and those who took two thrice daily.

Side-effects

All patients were carefully interrogated about possible side-effects after completing treatment.

TABLE I
RESULTS OF TREATING GONORRHOEA WITH DOSES OF 17 AND 34 mg./kg. CLOMOCYCLINE

Dose (mg./kg./day)	No. Treated	Result			Failure Rate (per cent.)
		Cured	Failed	Defaulted	
17 one dose two doses	6	0	6	0	90
	4	1	3	0	
34 two doses three doses	30	21	4	5	12
	20	15	2	3	
Total	60	37	15	8	

TABLE II
RESULTS OF TREATING NGU WITH CLOMOCYCLINE

Dose (mg.)			No. Treated	Result				
				Cured	Failed	Relapsed after 4 weeks after 8 weeks		Defaulted
340	three times a day	3 days	11	7	3	0	0	1
510	twice daily	3 days	9	4	2	2	0	1
340	three times a day	4 days	14	8	0	1	1	4
510	twice daily	4 days	16	10	1	0	1	4
Total			50	29	6	3	2	10

The unusually large doses of clomocycline used in this trial for the treatment of gonorrhoea were very well tolerated. 57 patients had no trouble whatever. Out of four patients weighing over 80 kg. who had received two doses of 8 capsules each, one vomited and one complained of nausea and epigastric pain lasting for an hour after the second dose. One patient who took three doses each of 5 capsules had shortlived nausea after each dose.

Antibiotics of the tetracycline group, taken for the treatment of NGU in generally accepted doses, rarely give rise to serious side-effects; but loose stools and sometimes pruritus ani are not uncommon complaints by fourth day of treatment. In our series of patients with NGU, only one reported loose motions on the fourth day.

Summary and Conclusion

Clomocycline in varying doses was used for the treatment of 110 cases of urethritis in men, sixty of acute gonococcal urethritis, and fifty of non-gonococcal urethritis.

In the gonorrhoea group ten patients were treated with a total of 17 mg./kg. (1 capsule per 10 kg.) in a single dose or two doses taken at an interval of 6-8 hours, and fifty were given 34 mg./kg. divided into two or three doses taken at 6-hourly intervals. Nine of ten cases failed to respond to 17 mg./kg. and six of fifty failed to respond to 34 mg./kg.

In the NGU group all patients received 6 capsules daily, twenty for 3 days and thirty for 4 days. Urethral discharge persisted after completion of treatment in six patients and relapses within 8 weeks occurred in five, irrespective of whether the daily dosage was divided into two or three portions. Five of the immediate failures and two of the relapses occurred in those twenty patients who were treated for 3 days.

The results suggest that in gonorrhoea clomocycline, at a total dose of 34 mg./kg. taken on one day, is no more effective than other derivatives of chlortetracycline given in comparable dosage schedules. In cases of NGU treatment with six capsules a day each of 17 mg. clomocycline taken for 4 days compares favourably with other treatment methods.

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Un essai clinique de la Clomocycline (Megaclor) dans l'urétrite gonococcique et non-gonococcique

RÉSUMÉ ET CONCLUSION

La clomocycline à doses variées a été employée dans le traitement de 110 cas d'urétrite chez les hommes, 60 étant atteints d'urétrite gonococcique aigue et 50 d'urétrite non-gonococcique.

Chez le groupe gonococcique 10 malades ont été traités avec un total de 17 mg./kg. (1 capsule par 10 kg.) à une dose unique ou à deux doses prises à un intervalle de 6 à 8 heures, et 50 avaient reçu 34 mg./kg. divisés en deux ou trois doses prises à intervalles de 6 heures. Neuf des dix cas n'avaient pas répondu à 17 mg./kg. et six des cinquante n'avaient pas répondu à 34 mg./kg.

Chez les groupes d'urétrite non-gonococcique tous les malades avaient reçu six capsules par jour, vingt pendant 3 jours et trente pendant 4 jours. L'écoulement urétral avait persisté après la fin du traitement chez six malades et des rechutes avaient eu lieu chez cinq malades au cours des huit semaines qui avaient suivi le traitement, sans tenir compte si la dose quotidienne avait été divisée en deux ou trois. Cinq des échecs immédiats et deux des rechutes avaient eu lieu chez ceux des vingt malades qui avaient été traités pendant trois jours.

Les résultats suggèrent que, dans la gonococcie, la clomocycline à un dosage total de 34 mg./kg. pris en un jour est plus efficace que d'autres dérivés de la chlortétracycline donnée en dosages comparables. Dans les cas d'urétrite non-gonococcique le traitement avec 6 capsules de 17 mg. de clomocycline chacune par jour prises pendant 4 jours se compare favorablement aux autres traitements.