Single-dose treatment of gonorrhoea with cotrimoxazole

A report on 1,223 cases

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A large number of workers throughout the world are occupied in trials to assess an easy and efficient oral treatment for gonorrhoea, using either a one-day course or a single dose. This has considerable advantages in V.D. clinics as it facilitates handling of patients, requires rather less care and attention, and is particularly convenient in small clinics—although it would not be preferred by all patients, especially immigrants. Parenteral penicillin remains the drug of choice in the treatment of gonorrhoea, but oral penicillins have yet to prove their effectiveness when given a single dose (Gundersen, Ødegaard, and Gjessing, 1969; Alergant, 1973; Willcox, Woodcock, Latto, John, Redmond, Parker, Rees, Cobbold, 1973).

Since the work of Csonka and Knight (1967), cotrimoxazole has been tried in various regimens by many workers, *e.g.* Csonka (1969), Arya, Pearson, Rao, and Blowers (1970), Jørgensen and Kvorning (1971), Siboulter (1971), and Lawrence, Phillips, and Nicol (1973).

Following the encouraging results obtained with cotrimoxazole ('Septrin': Burroughs Wellcome) in a dose of two tablets three times daily for 3 days, the author decided to assess a single-dose schedule in both males and females suffering from gonorrhoea. The manufacturers do not warn against any particular toxic dose and it was decided to use a single dose of eight tablets, giving the alternative dose of two tablets three times daily for 3 days to those who failed to respond to the single dose.

Material and methods

Patients

Between May, 1971, and March, 1973, 1,223 patients with uncomplicated gonococcal infection were treated at the Special Clinics of the Royal Hospital, Wolverhampton, and the Manor Hospital, Walsall. There were 986 men and 327 women. Eight of the men were homosexuals and one acquired the infection by orogenital contact. The

age distribution, nationality, and marital status are presented in Tables I, II, and III. The number of cases of gonorrhoea treated in each town is also shown in the Tables.

TABLE I Age distribution of patients, by sex

Hospital	Sex	Age group (yrs)				
		<16	16-17	18-19	20-25	>25
Wolverhampton	Male	3	35	85	191	255
	Female	6	36	51	72	69
Walsall	Male	1	15	39	107	165
	Female	2	14	18	24	35

TABLE II Nationality of patients, by sex

Hospital	Sex	Nationality			
		British	West Indian	Indian	Other
Wolverhampton	Male	198	309	49	13
	Female	174	51	7	2
Walsall	Male	203	95	18	11
	Female	90	1	1	1

TABLE III Marital status of patients, by sex

Sex	Single	Married	Separated	Divorced	Widowed
Male	586	271	29	9	1
Female	183	103	28	7	6

The only exclusion from the study were pregnant women and patients with pre-existing complications. The treatment was given only to patients whose direct smears and/or cultures were positive for *N. gonorrhoeae*.

Treatment

Every patient was given eight tablets of cotrimoxazole (each containing 80 mg. trimethoprim and 400 mg. sulphamethoxazole) under supervision in the clinic with a drink of milk. The patients were instructed to have a snack after they left the clinic. They were advised to refrain from intercourse and to avoid taking alcohol for the next 2 weeks.

Laboratory tests

In males urethral smears and in females Gram-stained urethral and cervical smears were examined. Cultures of material from these sites were made on modified Thayer-Martin medium, and incubated in an atmosphere of 3 per cent. CO₂ for 48 hrs. Antibiotic sensitivity testing was performed in a proportion of the cases using the disc diffusion technique. The antibiotic discs were penicillin 1 unit (Evans Medical Ltd.) and cotrimoxazole 25 µg. (23.75 µg. sulphamethoxazole and 1.25 µg. trimethoprim) (Oxoid).

A wet smear in a drop of saline was prepared from the urethra in men and from the vaginal wall in women to test for the presence of trichomonads.

Two-glass urine tests were performed at each attendance and the time to complete clearance of the first glass was recorded. A prostatic massage with a smear and culture of the fluid was performed on the third or fourth attendance only if the meatus was dry and the first glass of the two-glass urine test clear.

Blood for STS was taken at the first attendance and every 4 weeks for 3 months.

Follow-up

Every patient was asked to attend after the initial attendance at 3-7 days, 10-15 days, 17-21 days, and 4-5 weeks. Patients who failed to attend were reminded by letter and in some cases visited by contact tracers. Defaulters who failed to attend after the initial treatment were excluded from the final assessment of the results.

Failures

Any patient showing gonococci on direct smear and/or culture during the follow-up period without a history of further sexual exposure was regarded as a treatment failure. Any patient with a recurrence who admitted further sexual relations since treatment was regarded as a re-infection.

Cure

In men the criteria of cure were absence of discharge, clear urine, and negative urethral and prostatic smears and cultures taken during the follow-up attendances. In women the criterion of cure was three negative smears and cultures taken 1, 2, and 4 weeks after treatment, but this could not always be achieved because of a high default rate after the second follow-up attendance.

TABLE IV *Number of patients seen initially and at each follow-up examination, by sex*

Sex	Initial attenders	Defaulters	Duration of follow-up			
			Days		Weeks	
			3-7	10-15	17-21	4-5
Male	896 No. Per cent.	102 11.4 ^a	794 100 ^b	606 76.3 ^b	454 57.2 ^b	334 42.1 ^b
Female	327 No. Per cent.	52 15.9 ^a	275 100 ^b	225 81.8 ^b	150 54.6 ^b	31 11.3 ^b
Total	No. Per cent.	154 12.6	1,069 100	831 77.8	604 56.5	365 34.1

^arefers to percentage of numbers seen initially

^brefers to percentage of numbers seen at first follow-up

Post-gonococcal urethritis

Non-specific post-gonococcal urethritis was diagnosed only if the patient had presented with a discharge which contained an average of 12 cells or more in 10 oil-immersion fields and/or hazy urine in the first glass of the two-glass urine test with a fair number of pus threads, but no evidence of gonococci in smear or culture. The diagnosis was not made before the second follow-up attendance.

Results

Of the 1,223 patients 1,069 were followed, of whom 794 were males and 275 females. The defaulters comprised 102 males and 52 females. Table IV shows the numbers who attended each follow-up session. Of the 1,069 patients who were followed, 46 (29 males and 17 females), or 4 per cent., failed to respond to the eight tablet regimen and were considered as treatment failures (Table V).

TABLE V *Results of treatment, by sex*

Sex	Male	Female	Total	
			No.	Per cent.
No. of patients treated	896	327	1,223	100
No. of patients followed	794	275	1,069	87
No. of failures	29	17	46	4

There were 135 cases of re-infection (124 males and 11 females). Eighteen males and one female were found to be re-infected within a fortnight of treatment. The rest of the re-infections were encountered at varying periods later on.

Table VI shows various other findings encountered during the trial. One case of epididymo-orchitis

TABLE VI *Other findings*

Early syphilis	2
Epididymo-orchitis	2
Salpingitis	1
Post-gonococcal urethritis	46
<i>Trichomonas vaginalis</i>	Males 8
	Females 73
Total	132

occurred on the fourth day after treatment, and the other case of epididymo-orchitis and the case of salpingitis were encountered during the second follow-up attendance. Tests for the gonococcus were negative at the time these complications occurred. There were 46 cases of non-specific urethritis encountered during the follow-up period among the 794 male patients, an incidence of approximately 6 per cent.

Sensitivity testing

It was possible to study the sensitivity pattern of the gonococci by the disc-diffusion method in only 134 cases. These included essentially the organisms isolated from those patients who attended with repeated episodes of infection or who failed to respond to cotrimoxazole. The majority of the strains showed almost identical zones of inhibition (20 mm. diameter) to cotrimoxazole and penicillin. In the cases of 28 strains with a zone of inhibition to cotrimoxazole of less than 20 mm. diameter, 21 of the patients concerned responded satisfactorily to therapy. The remaining seven cases were among the treatment failures. Nearly all of the patients with gonococci sensitive to the combination *in vitro* responded.

Urine clearance

Excluding those who failed to attend after the first follow-up and those who failed to respond to treatment, 548 men were followed up with regard to their urine clearance tests. 44 per cent. showed clear urine by the end of the first post-treatment week and another 32 per cent. showed clear urine by the end of the second post-treatment week. The remainder took longer (Table VII).

TABLE VII Length of time taken for clearance of urine

No. of days after treatment	3-7	10-15	17-21	24+
Cases	242	173	82	51
No. Per cent.	44	31.6	15	9.4

Side-effects

Very few side-effects were observed. Two of the treatment failures complained of vomiting and gastric discomfort. One patient reported a skin rash lasting only 2 hours a few hours after receiving the eight tablets; the significance of this was uncertain.

Discussion

The sensitivity of the gonococcus to the various antibiotics seems to vary both geographically and chronologically, so that it may not be valid to compare the therapeutic results obtained in one country

with those of another, nor even those from two clinics in the same country, or, indeed, the same clinic at different times.

The synergistic effect of trimethoprim and sulphonamides has proved very effective against many organisms, including the gonococcus (Csonka and Knight, 1967; Darrell, Garrod, and Waterworth, 1968). Since the work of Csonka (1969), cotrimoxazole has been used in various dosages with a recorded failure rate varying between 1 and 18 per cent. depending upon the dosage. It is too early to predict the long-term value of this drug combination with regard to the gonococcus, bearing in mind the resistance which the organism developed to sulphonamides when these products were used in the treatment of gonorrhoea between 1938 and 1946.

Siboulet (1971) treated 266 males and 32 females with a single dose of eight tablets with failure in fifteen males and five females. In South Africa, Kloosman (1972) obtained a cure rate of 100 per cent. with the same dose of cotrimoxazole in a comparative study with ampicillin and tetracycline, with which the cure rates were 94 per cent. (1 g. ampicillin), 92 per cent. (3 g. ampicillin), and 80 per cent. (1 g. tetracycline). No cultures were performed in his study. On the other hand, Keys (1972) reported a 33 per cent. failure rate in 32 patients treated with a single dose of eight tablets, but does not state clearly how cure or failure was determined. Further, he found *N. gonorrhoeae* in expressed prostatic secretion in an unstated number of the patients at 21 days and claims that cotrimoxazole '... rapidly cures the urethritis, but is less successful in eradicating the organisms from the prostate and seminal vesicles. ...' However, he did not appear to consider the possibility of re-infection during the period of review.

With very strict criteria, Lawrence and others (1973) obtained a cure rate of 90 per cent. in 190 men and of 100 per cent. in 41 women given a single dose of eight tablets; an overall cure rate of 92 per cent. at 2 weeks after therapy.

Our results, with criteria very similar to those of Lawrence and others, show an overall success rate in men and women of 96 per cent. after a single dose of eight tablets of cotrimoxazole taken under supervision in the clinic. These include cases of re-infection treated by the same regimen. As yet, there is no indication that resistance to the drug has developed or that it induces a carrier state.

To the 46 patients who failed to respond to the single-dose treatment of eight tablets, cotrimoxazole was again given in doses of two tablets three times daily for 3 days; 34 patients responded satisfactorily and only eleven failed to respond.

From our own results (unpublished) and those of others (Jørgensen and Kvorning, 1971; Wigfield, Selkon, and Rich, 1973), it would appear that a single dose of six tablets is much less effective than eight

tablets in eradicating the gonococcus, and we would suggest the latter schedule to be the minimum number of tablets which should be given as a single dose.

Although it was not possible to perform any assays for levels of trimethoprim or sulphamethoxazole in the blood of our treatment failures, the results of the MIC determinations on the gonococci cultured showed that some of these strains were unusually resistant to cotrimoxazole. The failure to respond to cotrimoxazole could be due, therefore, to the resistance of the infecting strains or the absence of the usual synergism between the two components. It was unlikely to be due to failure of the patients to take their tablets during the 3-day treatment as each patient was questioned on this point, and failure to absorb the drugs seems only a remote possibility. Two cases of primary sore were encountered 2 and 5 weeks after treatment with cotrimoxazole. These confirm the already known fact (Lawrence and others, 1973) that treatment with cotrimoxazole does not mask concomitant syphilis, an important point in its favour.

Summary

1,223 ambulant patients with gonorrhoea were each treated with a single dose of eight tablets of cotrimoxazole.

1,069 patients were followed up (794 males and 275 females). Of these, only 46 (4 per cent.) failed to respond.

Cotrimoxazole in the dosage used was well tolerated by all the patients, with very few side-effects. There

was clear evidence that cotrimoxazole did not mask concomitant syphilitic infections; neither did it produce a gonococcal carrier state.

The incidence of post-gonococcal non-specific urethritis was 6 per cent. At present cotrimoxazole seems to be the most useful alternative to penicillin in the treatment of gonorrhoea.

I am indebted to Dr. L. S. Bernstein, of the Wellcome Foundation Ltd., for his help and suggestions, and to Dr. R. S. Khatri for his participation in the management of cases.

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