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TREATMENT OF GONORRHOEA WITH ACTINOSPECTACIN*

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Since it first became available penicillin has been, and probably remains, the antibiotic of choice in the treatment of gonorrhoea. In recent years, however, the recognition of treatment failures due to less sensitive strains of *N. gonorrhoeae* (Medical Research Council Working Party Report, 1961) and the increasing risk of serious hypersensitivity reactions in patients given penicillin for a relatively benign infection, have encouraged venereologists to examine the value of other antibiotics in gonorrhoea. Streptomycin is no alternative because many strains of *N. gonorrhoeae* are now highly resistant and toxic reactions to this antibiotic, although not fatal, can be troublesome. Oral therapy finds no favour with the venereologist whose patients are ambulant and often cannot be relied upon to take pills as prescribed. An injectable tetracycline phosphate (Panmycin) was tried, but pain occurred at the injection site in a third of the patients and daily injection for 2 days was necessary to achieve a 90 per cent. rate of cure (Laird, 1960). The opportunity to assess the value of a new, injectable antibiotic in the treatment of gonorrhoea was therefore of interest and our results are reported below.

The Antibiotic

Actinospectacin (Trobicin†) is an antibiotic produced by *Streptomyces spectabilis* n.s., an actinomycete isolated from soil. Its spectrum of activity includes *Staphylococcus*, *Streptococcus*, *Proteus*, *Escherichia*, *Klebsiella*, and *Neisseria*. The value of Actinospectacin in the treatment of infections due to organisms other than *Neisseria* is still under investigation.

We were advised by the manufacturers that the peak serum level 1 hour after the recommended dose of 400 mg. actinospectacin sulphate would be of the order of 20 μg./ml.; that after this dose about 75 per cent. would be recoverable from the urine with levels reaching 500 μg./ml.; and that animal studies revealed no significant toxicity.‡ The drug was made available to us as a white powder in ampoules containing 2 g. actinospectacin sulphate (1·4 g. of the free base) which could be dissolved in 5 ml. sterile, distilled water. The dose recommended was 400 mg. every 6 hours; as this is impracticable for outpatients, it was decided to use a single dose only.

The Patients

The clinical trial was confined to 67 males with gonococcal urethritis attending the V.D. clinic of the Royal Infirmary, Manchester. Their ages varied from 18 to 41 years (average 24·8); their countries of origin are shown in Table I.

TABLE I

COUNTRY OF ORIGIN OF 67 MALE CASES OF ACUTE GONORRHOEA

Country of Origin	No. of Cases
United Kingdom	25
Eire	8
Pakistan	3
Other Non-negro	3
West Indies	24
West Africa	4
Total	67

Many of these patients had previously been treated for gonorrhoea or other venereal infections. In 65 cases, acute gonorrhoea, usually of short duration (Table II) was present, but in two patients urethritis had been present for 6 weeks and some months respectively and was of a sub-acute nature.

TABLE II

DURATION OF GONORRHOEA AT TIME OF TREATMENT

Duration	No. of Patients	Duration	No. of Patients
6 hrs	1	7 days	4
12 hrs	1	8 days	1
1 day	9	9 days	2
2 days	23	10 days	1
3 days	11	14 days	2
4 days	6	17 days	1
5 days	3	6 wks	1
6 days	—	Some mths	1

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† Trobicin is the Upjohn Company's trade name for Actinospectacin.

‡ Upjohn Company Scientific Brochure on Actinospectacin, 4th edition.

Methods

Diagnosis.—This was based on the finding of intracellular, Gram-negative diplococci in urethral smears; cultures were set up in all cases before treatment was started.

Dosage.—Actinospectacin was given as a single intramuscular injection into the gluteal muscles immediately the diagnosis was made. In fifty patients 2 g. actinospectacin sulphate (1·4 g. of free base) in 5 ml. sterile distilled water was used; in sixteen patients the dosage was 1 g. (0·7 g.) in 2·5 ml.; and one patient received 0·5 g. (0·35 g.) in 2 ml.

Patients were treated on either a Monday or a Wednesday. They were asked to return at the next clinic session (*i.e.* 2 or 5 days after treatment), then one week later, and thereafter fortnightly. They were advised to avoid alcohol for one week and coitus until told they were cured. They were also requested not to urinate for 3 hours before reporting for follow-up examinations at which the presence or absence of urethral discharge was noted and the urinary findings recorded. Unless the urethra was dry, smears and cultures were made. At the first follow-up visit, any subjective reaction to the injection, local or general, was noted.

Bacteriological Methods.—Specimens of urethral discharge were inoculated on "chocolate agar" and incubated at 37°C. for 48 hours in an atmosphere containing 10 per cent. CO_2. The cultures were then examined for the presence of *Neisseria*, using the oxydase test and microscopy. Pure cultures were established and their identity confirmed by fermentation reactions. The minimum inhibitory concentration (m.i.c.) was determined by a serial dilution method using 25 per cent. hydrocele fluid in infusion broth containing 1 per cent. glucose. The tubes were inoculated with 0·02 ml. of a 48 hours' growth of the gonococcus in hydrocele fluid broth and then incubated for 48 hours in an atmosphere containing 10 per cent. CO_2. The end point was taken as the most dilute solution of the antibiotic in which visible growth was not present. Strains of gonococcus isolated from cases in which treatment failed were similarly examined.

Results

Clinical.—Fifty cases received 2 g. actinospectacin sulphate in a single injection. Of these patients (Table III), ten (20 per cent.) did not return and their cure is presumed; thirteen (26 per cent.) re-attended once only within 7 days; and the remaining 27 (54 per cent.) each had several re-examinations up to 50 days after treatment (average 25 days).

32 patients (64 per cent.) were unequivocally cured. In a further five patients who achieved clinical cure, gonorrhoea reappeared after variable intervals and following further sexual exposures (definite reinfections). Combining observed cures, presumptive cures, and definite re-infections, 47 patients (94 per cent.) were considered to be cured by a single injection of 2 g.

Of the remaining three patients (possible re-infections), one had an infected wife and may have been re-infected before she was treated; and the remaining two were young single men known to be heavy drinkers and unreliable in their statements.

Sixteen patients received 1 g. actinospectacin sulphate in a single injection (Table III). Of these, two did not return and their cure is presumed; nine were unequivocally cured; and the remaining five (31 per cent.) were failures. Thus 1 g. actinospectacin sulphate was effective in only 69 per cent. and this dosage was discontinued.

One patient only was given 0·5 g. actinospectacin sulphate and no improvement was noted.

TABLE III

RESULTS OBTAINED WITH ACTINOSPECTACIN IN 67 MALE CASES OF GONORRHOEA

Dosage of Actinospectacin-sulphate		Definitive Treatment			Re-treatment with 2 g.	
		2 g.	1 g.	0·5 g.	After Failure with 1 g.	After Failure with 0·5 g.
Number of Cases Treated		50	16	1	5	1
Number of Observed Cures		32	9	—	2	1
Number which did not Re-attend—Presumptive Cures		10	2	—	—	—
Re-infection	Definite	5	—	—	—	—
	Possible	3	—	—	—	—
Total of Probable Cures	No.	47	11	—	2	1
	Per cent.	94	69	—	40	100
Total Failures	No.	0	5	1	3	—
	Per cent.		31	100	60	—

The six failures with reduced dosage were retreated with 2 g. actinospectacin sulphate, with a cure in three cases and failure in the other three.

Bacteriological — The gonococcus was cultured in 58 (79 per cent.) of the 73 specimens examined. In the remainder, the culture was negative (eight specimens) or overgrown either by *Proteus sp.* or *Bacillus sp.* (seven specimens). Some of the strains of gonococcus isolated died on subculture and the minimum inhibitory concentration (m.i.c.) of actinospectacin was estimated in 37 strains. It was found to vary from 1 to 4 μg./ml. (4 μg./ml. in fifteen strains, 2 μg./ml. in fifteen strains, and 1 μg./ml. in seven strains).

The m.i.cs. of eight strains of gonococcus isolated in a separate study were determined for actinospectacin and penicillin G. The m.i.cs. with penicillin G were 0·125 i.u./ml. (one strain), 0·25 i.u./ml. (four strains), and 0·5 i.u./ml. (three strains). The m.i.cs. with actinospectacin varied between 1 and 4 μg./ml. These results indicate that actinospectacin should have a similar clinical action on penicillin-resistant strains of gonococcus as it has on sensitive strains.

Re-isolation of the gonococcus after treatment with actinospectacin was successful in seven out of nine cases. Two strains died on subculture, but it was possible to determine the m.i.c. in five strains; it was either 2 or 4 μg./ml. in three strains, 16 μg./ml. in one, and 32 μg./ml. in the fifth. Thus, in two instances, there had been a clear rise in the m.i.c. after unsuccessful treatment with 1 g. actinospectacin sulphate.

Discussion

This trial of actinospectacin was confined to male patients with gonococcal urethritis because in such cases the duration of infection could be established, the clinical response to therapy was easily observed, and examples of failure or relapse were almost certain to return to the clinic.

Many patients were examined 48 hours after the single injection of actinospectacin and the rapidity of resolution of inflammation was impressive in successful cases; such resolution seemed even faster than with effective penicillin treatment and, in particular, the clarity of the urine specimen and the early disappearance of "threads" were noteworthy.

The 2 g. actinospectacin sulphate required 5 ml. distilled water for solution. Although this volume was given as one injection, local discomfort was experienced by only two patients. The same two patients had also complained of mild local discomfort after initial treatment with 1 g. dissolved in 2·5 ml. Only three (4·5 per cent.) of 67 patients mentioned local discomfort and in no case was pain produced. No other reaction was noted in any patient. One patient who had been seen to have a severe anaphylactic reaction after penicillin given for a previous gonococcal infection, was treated for two further attacks of gonorrhoea with 2 g. actinospectacin sulphate on each occasion, without any unfavourable effects.

The m.i.c., in all the 37 strains for which it could be determined, showed that these gonococci were highly sensitive to actinospectacin and the high rate of cure using 2 g. actinospectacin sulphate confirmed the findings *in vitro*. Thus 47 out of fifty patients were cured. Of the other three, classified as "possible re-infections" (Table III), the m.i.cs. of the strains were 4 μg./ml. in the two patients in which they could be determined. In fact, there was evidence that cure was probable in these patients, which would raise the cure-rate with 2 g. actinospectacin to 100 per cent.

The clinical results after a single injection of 1 or 0·5 g. actinospectacin sulphate showed that these smaller doses were inadequate. The m.i.cs., determined in two of the five failures with 1 g., were 2 and 4 μg./ml. In one case treated with 0·5 g. without success, the m.i.c. was 4 μg./ml.

In two instances after unsuccessful treatment with 1 g., the m.i.c. of the re-isolated strain increased to 16 and 32 μg./ml. respectively. The patient with a m.i.c. of 16 was cured with 2 g., but this dose failed to cure the patient in whom the m.i.c. had increased to 32 μg./ml. These clinical and laboratory observations indicate that dosage of 1 g. or less may lead to failure and the development of drug resistance.

The excellent results in fifty patients with a single injection of 2 g. and the freedom from side-effects encourage the conclusion that actinospectacin is an effective alternative to penicillin for the out-patient treatment of gonorrhoea, particularly for strains of gonococcus with increased resistance to penicillin and streptomycin or for patients known to be hypersensitive to these antibiotics.

Summary and Conclusions

Actinospectacin (Trobicin), produced by an actinomycete (*Streptomyces spectabilis* n.s.) isolated from soil, was given to 67 men suffering from gonococcal urethritis.

A single injection of 2 g. actinospectacin sulphate cured at least 94 per cent. of fifty cases. A single injection of 1 g. or less gave unsatisfactory clinical results, and there was laboratory evidence of the development of strains of gonococcus resistant to actinospectacin. It produced no general reactions and mild local discomfort was noted in only 4·5 per cent. of patients.

No cross-resistance between actinospectacin and penicillin was demonstrated and it is therefore suggested that this new antibiotic would be especially valuable in cases of gonorrhoea in which penicillin has proved ineffective, or in patients known to be hypersensitive to penicillin.

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La blennorragie traitée per l'Actinospectacine (Trobicin)

RÉSUMÉ

67 hommes atteints d'urétrite gonococcique ont reçu de l'actinospectacine (Trobicin), produit d'un actinomycète isolé de la terre (*Streptomyces spectabilis* n.s.).

Une seule injection de 2 g. de sulfate d'actinospectacine a guéri au moins 94% d'une série de 50 malades. Une seule injection de 1 g. ou moins donna des résultats cliniques peu satisfaisants, et d'ailleurs il sembla que quelques souches devenaient résistantes au médicament.

Elle n'évoqua pas de réactions générales et seulement 4,5% des malades notèrent une douleur locale moyenne.

On ne remarqua aucune résistance réciprocale entre la pénicilline et l'actinospectacine. Il semble donc que ce nouvel antibiotique sera utile pour les malades chez qui la pénicilline ne prévient pas et chez les sujets hypersensibles à la pénicilline.