

Treatment of gonorrhoea with three different antibiotic regimes

Doxycycline 300 mg., Procaine penicillin plus benzyl penicillin 2.4 m.u., Benzyl penicillin 5 m.u. plus probenecid

R. C. F. GRAY, I. PHILLIPS, AND C. S. NICOL

St. Thomas's Hospital, London

Since the late 1950s an increasing proportion of strains of *Neisseria gonorrhoeae* have shown evidence of lowered sensitivity to penicillin which can be correlated with a high clinical relapse rate. To combat this, the dosage of penicillin has been raised, and the use of other antibiotics has been investigated.

Nicol, Ridley, and Symonds (1966), using one intramuscular injection of 600,000 u. procaine penicillin in the treatment of gonorrhoea in the male, found a failure rate of 14.3 per cent. and an overall incidence of less sensitive strains of 37 per cent.

In a further series of cases treated in 1968 (Lynn, Nicol, Ridley, Rimmer, Symonds, and Warren, 1970) better results were obtained with an intramuscular injection of 2.5 m.u. mixed penicillins (Triplopen): the relapse rate was only 6.2 per cent., but the incidence of less sensitive strains remained virtually unchanged at 35 per cent.

It has recently been reported from Greenland by Olsen and Lomholt (1969) that a 99 per cent. success rate can be achieved with 1 g. probenecid followed by an injection of 5 m.u. benzyl penicillin made up with lignocaine.

The present study has been undertaken to assess the clinical results of three one-dose antibiotic regimes:

- (1) Doxycycline (Vibramycin) 300 mg. in one oral dose.
- (2) Procaine penicillin plus benzyl penicillin (Distaquaine Fortified) 2.4 m.u. by intramuscular injection.
- (3) Probenecid 1 g. orally followed by benzyl penicillin 5 m.u. with lignocaine by intramuscular injection.

Only male patients with gonorrhoea were considered. A reassessment of the incidence of strains of *N. gonorrhoeae* with diminished penicillin sensitivity was undertaken during the probenecid-benzyl penicillin trial.

Received for publication January 12, 1970.
Requests for reprints should be addressed to I.P.

Material and methods

Diagnosis, treatment, and assessment of patients was carried out by the staff of the Venereal Disease Department of St. Thomas' Hospital, London. As in previous studies the diagnosis was based on the findings in Gram-stained urethral smears made by the clinic staff, and assessments of the results of treatment were made by the same staff. If, a week after treatment, a non-gonococcal urethritis was unmasked, this was initially treated with oxytetracycline 500 mg. three times a day for 5 to 10 days.

In distinguishing relapses from re-infections, the suggestion of Evans (1966) has been followed: if the gonococci reappear within 14 days of treatment and if further intercourse is denied by the patient, then the infection is considered to have relapsed, while the appearance of gonococci after 14 days, irrespective of the patient's history, is considered to be due to re-infection. Attempts were made to encourage patients to attend for follow-up for 3 months.

Antibiotics were given as follows:

VIBRAMYCIN

Three 100-mg. capsules were swallowed in the presence of a member of the clinic staff.

DISTAQUAINE FORTIFIED

This mixture of procaine penicillin (1.8 m.u.) and benzyl penicillin (0.6 m.u.) was given by deep intramuscular injection, half the dosage into each buttock.

PROBENECID AND BENZYL PENICILLIN

Two 500-mg. tablets of probenecid were given with a glass of water. This was followed after 15 minutes by a single injection into one buttock of 5 m.u. benzyl penicillin made up with 8 ml. 0.5 per cent. lignocaine. Serum penicillin levels were measured in eight patients after the administration of probenecid and penicillin.

During the investigation of penicillin plus probenecid treatment, an assessment was made of the penicillin sensitivity of the strains of *N. gonorrhoeae* isolated, using methods previously described (Lynn and others, 1970). W.H.O. reference strains III, V, and VII were included as controls.

Results

Clinical

Table I shows the distribution by age, race, and source of infection. Table II shows the follow-up achieved in the three groups of patients.

TABLE I *Classification of patients by age, race, and source of infection*

Classification	Therapy		
	Vibramycin	Distaquaine Fortified	Probenecid and benzyl penicillin
Total treated	100	217	200
Age (yrs)			
Under 24	36	87	63
24 and over	64	130	137
Race			
White	49	109	108
Negro	39	90	69
Other	12	18	23
Source of infection			
Heterosexual	88	195	188
Homosexual	12	22	12

TABLE II *Follow-up*

Type of follow-up	Therapy		
	Vibramycin	Distaquaine Fortified	Probenecid and benzyl penicillin
1. None	6	21	17
2. Returned at least once but defaulted before 3 weeks	52	136	124
3. Followed up for at least 3 weeks	42	60	59
4. Total for assessment	94	196	183
Total cases	100	217	200

VIBRAMYCIN

107 male patients with gonococcal urethritis were seen. Seven patients were given alternative treatment because of a suspected syphilitic lesion, and 100 were treated with Vibramycin, of whom 94 attended for follow-up examination. Those in whom the infection was not cured were retreated with 2.5 m.u. penicillin (Triptopen) or 2 g. kanamycin (Kantrex).

The gonococcus reappeared in 21 cases; twelve were classified as relapses and nine as re-infections. Seventeen were considered to have a non-gonococcal infection after treatment (Table III). Patients treated for a non-gonococcal infection, irrespective of further sexual intercourse, within 28 days of their treatment for gonorrhoea have been included. The relapse rate was therefore 12 per cent. of those treated (12.7 per cent. of the 94 cases followed up) (Table IV).

TABLE III *Incidence of post-gonococcal urethritis (per cent.)*

Vibramycin	Distaquaine fortified	Probenecid and benzyl penicillin
17	30.9	25.5

TABLE IV *Post-treatment gonorrhoea*

Therapy	Vibramycin	Distaquaine fortified	Probenecid and benzyl penicillin
No. treated	100	217	200
No. assessed	94	196	183
Relapses			
No.	12	6	1
Per cent.	12.7	3.1	0.5
Re-infections	9	20	6

DISTAQUAINE FORTIFIED

Between April and July, 1969, 236 male patients with gonorrhoea were seen: 226 had urethritis and ten proctitis. Nineteen patients were given alternative treatment because of penicillin hypersensitivity, a suspected syphilitic lesion or because the patient knew he would be unable to attend the clinic for follow-up. The relapse rate was 2.8 per cent. of those treated (3.1 per cent. of the 196 followed up) (Table IV). 67 were treated for a post-gonococcal urethritis (Table III).

Cases of relapse were treated with an injection of 2 g. kanamycin and cases of re-infection with penicillin or kanamycin.

PROBENECID AND BENZYL PENICILLIN

Between July and September, 1969, 222 male patients with gonorrhoea were seen (216 with urethritis and 6 with proctitis). Alternative treatment was given to 22 and 200 were treated with probenecid and benzylpenicillin, of whom 183 returned for follow-up.

There were six cases of re-infection and one relapse, a failure rate of 0.5 per cent.

The one patient whose infection was considered to have relapsed was originally infected with a highly sensitive strain of *N. gonorrhoeae* (minimum inhibitory concentration 0.007 µg./ml.) and gonococci were not detected in the routine urethral smear taken on the day after treatment. However, on the sixth day after treatment he complained of a return of the discharge on the previous day; but denied further exposure to risk. At this stage, gonococci were seen in the smear and he was treated with kanamycin. He attended only once more, 14 days after the injection of kanamycin, when the smear was negative. His contact could not be traced.

The six cases of re-infection were successfully re-treated with probenecid and benzyl penicillin. 51 patients were treated for post-gonococcal urethritis (Table III).

Bacteriological

Probenecid and benzyl penicillin group

The incidence of strains relatively resistant to penicillin (minimum inhibitory concentration $\geq 0.06 \mu\text{g./ml.}$) was 35 per cent.—about the same as in 1966 and 1968.

Penicillin levels were measured serially in one patient who was admitted to the wards for treatment; 2 hours after the injection the serum level was $45 \mu\text{g./ml.}$, falling to $9.6 \mu\text{g./ml.}$ after 4 hours, $1.7 \mu\text{g./ml.}$ after 6 hours, and $0.8 \mu\text{g./ml.}$ after 8 hours. After 8 hours there was no detectable penicillin.

In a second case the serum penicillin level 8 hours after treatment was $3.4 \mu\text{g./ml.}$ and in six more cases there was no detectable penicillin 14 to 16 hours after treatment.

Discussion

Treatment of gonorrhoea by any oral antibiotic necessarily suffers from the disadvantage of variable absorption. This may have played a part in the high failure rate with Vibramycin. In one case of relapse, the patient had vomited 10 minutes after taking the capsules, and two patients who were successfully treated vomited 30 minutes and 3 hours after taking the capsules. A number of other patients complained of nausea and abdominal discomfort. The low incidence of post-gonococcal urethritis after Vibramycin would be predictable with one of the tetracycline group of drugs.

Distaquaine fortified penicillin gave better results than were obtained in 1968 with Triplopen 2.5 m.u.; the failure rates were 3.1 and 6.2 per cent. respectively.

Olsen and Lomholt treated 832 cases of uncomplicated gonorrhoea in males and females using 1 g. probenecid with 5 m.u. benzyl penicillin and achieved a success rate of 99 per cent. This trial was carried out in Greenland between 1964 and 1968, during which time it was noted that the incidence of less sensitive strains of gonococci in that area was reduced from 54 to 19 per cent. The cure rate of 99.5 per cent. with probenecid and benzyl penicillin in our series is very satisfactory. It is to be hoped that, should this treatment be adopted nationally, we may also see a fall in the incidence of less sensitive strains. The few estimations of serum levels suggest that the efficiency of this large dose of penicillin enhanced by probenecid is associated with a high initial serum level of penicillin which falls within 8 to 10 hours to undetectable levels.

The one case of relapse after 5 m.u. penicillin was shown to have had a fully sensitive strain of gonococcus initially. This would indicate that his second attack of urethritis was more likely to have been a re-infection in spite of his denial of further sexual intercourse; gonococci were not isolated between the

two attacks and it is perhaps significant that his contact could not be traced.

It is worthy of note that patients experienced less pain with the large injection of benzyl penicillin and lignocaine than might have been expected. No toxic side-effects were noted with the two penicillin regimes. This contrasts with the not infrequent nausea and gastrointestinal symptoms which patients experienced with Vibramycin.

Summary

During 1968 and 1969 three one-dose antibiotic regimes were used to treat 517 males with gonorrhoea. Doxycycline (Vibramycin) 300 mg. gave a failure rate of 12.7 per cent., and an injection of 2.4 m.u. procaine penicillin and benzyl penicillin (Distaquaine Fortified) gave a failure rate of 3.1 per cent. 1 g. probenecid followed by 5 m.u. benzyl penicillin with lignocaine yielded a failure rate of only 0.5 per cent.

The percentage of strains of gonococci partially resistant to penicillin was 35 per cent., which differs little from that found in the same hospital in 1966 and 1968.

If the use of probenecid and benzyl penicillin with lignocaine could be adopted on a national level, the incidence of less sensitive strains of *Neisseria gonorrhoeae* might well be substantially reduced, as has been the case in Greenland.

Our thanks are due to Messrs. Glaxo Laboratories Ltd. for a supply of benzyl penicillin (Crystapen) and to Messrs. Pfizer Ltd. for a supply of doxycycline (Vibramycin).

References

- EVANS, A. J. (1966) *Brit. J. vener. Dis.*, **42**, 251.
 LYNN, R., NICOL, C. S., RIDLEY, M., RIMMER, M. D., SYMONDS, M. A. E., and WARREN, C. (1970) *Ibid.*, **46**, 404.
 NICOL, C. S., RIDLEY, M., and SYMONDS, M. A. E. (1968) *Ibid.*, **44**, 315.
 OLSEN, G. A., and LOMHOLT, G. (1969) *Ibid.*, **45**, 144.

Traitement de la gonococcie selon trois différents schémas de traitement antibiotique: doxycycline 300 mg. procaïne pénicilline + benzyl-pénicilline 2,4 méga unités; benzyl pénicilline 5 méga unités + probénécid

SOMMAIRE

Pendant 1968 et 1969, 517 cas de gonococcie masculine furent traités selon trois schémas d'antibiothérapie, à dose unique. La doxycycline (*Vibramycine*) 300 mg. échoua dans 12,7 % des cas; une injection de 2,4 m.u. de pénicilline-procaïne + benzyl-pénicilline (*Distaquaine Fortified*) échoua dans 3,1 % des cas. Un g. de probenecid suivi de 5 m.u. de benzyl-pénicilline, avec lignocaïne, ramena le pourcentage des échecs à seulement 0,5 %.

Le pourcentage des souches de gonocoques partiellement résistantes à la pénicilline fut de 35 %, ce qui diffère peu de ce qui avait été trouvé dans le même hôpital en 1966 et 1968.

Si l'utilisation de probenecid et de benzyl-pénicilline + lignocaïne pouvait être adopté à un niveau national, l'incidence des souches moins sensibles de *Neisseria gonorrhoeae* pourrait être bien diminuée, comme ceci l'a été au Grönland.