One-session treatment of gonorrhoea in males with procaine penicillin plus probenecid*

R. J. C. COBBOLD
M.B.

*Consultant Venereologist,
South-west Wales Group of
Hospitals*

G. D. MORRISON
M.B.

*Senior Registrar,
United Bristol Group of Hospitals*

R. J. SPITZER
M.B.

*Consultant Venereologist,
Southend on Sea and Chelmsford
Group of Hospitals*

R. R. WILLCOX†
M.D.

*Consultant Venereologist,
St Mary's Hospital, London, and
King Edward VII Hospital, Windsor*

Summary

Six hundred and thirteen male patients with acute uncomplicated gonorrhoea have been treated alternately with single injections of 1.2 mega-units of aqueous procaine penicillin alone or with the same dose and preparation of penicillin with an additional 1.0 g of probenecid given orally immediately prior to injection.

Whether the failure rates were assessed on the basis of an absence of further sexual exposure or by classifying all recurrences within 1 or 2 weeks regardless of history as treatment failures the results were significantly better when probenecid was also given.

The use of a single dose of probenecid is thus capable of maintaining the success of single injection procedures for the treatment of gonorrhoea based on procaine penicillin and thus represents a bulwark for the future should the powers of penicillin against the gonococcus in London deteriorate further.

Introduction

That failure rates to the treatment of gonorrhoea with penicillin have risen through the years owing to the development of resistance of the gonococcus to penicillin, necessitating higher routine dosages, is not in dispute (Willcox, 1968). In parts of the Far East a failure rate of 28.6% has been reported following single injections of 2.4 mega-units of aqueous procaine penicillin (Holmes, Johnson & Floyd, 1967) while in some local areas of this region a failure rate of 30% has been experienced follow-

ing single injections of no less than 4.8 mega-units (World Health Organization, 1969). In these areas the limits of what can be achieved with a single injection of procaine penicillin unaided have been reached.

This situation, however, is less marked in countries with a developed clinic network, facilities for contact tracing, enforced legislation against the selling of antibiotics other than on a physician's prescription and the ready availability of other if more expensive antibiotics for the treatment of cases showing failure to penicillin—and indeed it may be reversible following a change in treatment practices (Letchner & Nicol, 1961; Morton, 1963; Odegaard & Gjessing, 1967). In fact the *in vitro* evidence of a recent increased resistance of the gonococcus to penicillin in London is currently conflicting (Nicol, Ridley & Symonds, 1968; Leigh, Le Franc & Turnbull, 1969).

A single session routine-treatment for gonorrhoea in males is generally preferred as it has considerable administrative, economic and epidemiological advantages. A fairly common standard treatment in recent years has been by means of single injections of 1.2 mega-units of aqueous procaine penicillin but failure rates of 11.7% have been obtained in London (Willcox, 1969) and some workers have increased the dose to 2.4 mega-units (Morrison *et al.*, 1968) with improved results and others (Nicol *et al.*, 1968) have indicated their intention to do so.

Enhancement of procaine penicillin serum levels with probenecid

An alternative to increasing the dose of penicillin is to retain the existing dose and give the renal

* This work was done at St Mary's Hospital, London, W.2.

† Dr Willcox is a member of the World Health Organization Panel on Venereal Infections and Treponematoses.

TABLE 1. Serum levels following 1.2 mega-units of procaine penicillin with and without probenecid (data relating to ten to eleven subjects from White *et al.*, 1956)

	Hours after injection			
	1	2	4	6
Maximum level ($\mu\text{g/ml}$)				
With probenecid	13.440	9.300	6.720	5.120
Without probenecid	8.000	9.600	4.800	3.520
Minimum level ($\mu\text{g/ml}$)				
With probenecid	0.960	2.176	2.272	1.536
Without probenecid	0.896	1.024	0.480	0.320
Mean level ($\mu\text{g/ml}$)				
With probenecid	6.472	6.480	4.749	3.192
Without probenecid	4.154	4.774	2.996	1.991
Ratio of maximum to minimum level				
With probenecid	14.0	4.3	3.0	3.3
Without probenecid	8.9	9.4	10.0	11.0

tubular blocking agent probenecid which delays the excretion of penicillin.

There is a dearth of information regarding serum levels obtained with the larger doses (1.2 mega-units and above) of procaine penicillin. The estimations by White *et al.* (1956) of the serum levels obtained during the 6 hr following the administration of 1.2 mega-units of procaine penicillin with and without 1.0 g of probenecid given orally 1 hr before and again 5 hr after injection are shown in Table 1.

It is noted that the maximum, minimum and mean levels were heightened during this period by the use of probenecid and the differences between the maximum and minimum levels tended to be reduced after the 1st hour.

Clinical experience of probenecid in areas of high resistance

In areas of high resistance, inadequate schedules involving crystalline benzylpenicillin G have been made more adequate by the simultaneous use of probenecid (Jensen, Kvorning & Norredam, 1963). Complete success has been achieved in Greenland with single injections of 5 mega-units of crystalline penicillin G, dissolved in 8 ml of 0.5% lidocaine to obviate pain, combined with one oral dose of 1.0 g of probenecid given $\frac{1}{2}$ hr before injection (Lomholt & Berg, 1966; Olsen & Lomholt, 1969). In the Far East the failure rate of 28.6% following single injections of 2.4 mega-units of aqueous procaine penicillin was reduced to only 2% if 1.0 g of probenecid was given 1 hr before injection followed by three doses each of 0.5 g at 6-hr intervals (Holmes *et al.*, 1967) while in promiscuous women in Australia, Wren (1967) achieved complete success by combining 8-hourly injections of 2.0 mega-units of crystalline penicillin G combined with 2.0 g of

probenecid daily for 2 days.

In this country only limited trials have in the past been undertaken with probenecid, but in combination with small doses of repository penicillins (Hilton, 1959). There is little or no information concerning the use of probenecid in one dose given simultaneously with an injection of aqueous procaine penicillin. It was thought worthwhile, therefore, to investigate this method under the conditions currently pertaining in London.

Case material and management

The study concerns 613 male patients with acute uncomplicated gonorrhoea treated at St Mary's Hospital. Alternate patients were given single injections of 1.2 mega-units of aqueous procaine penicillin or the same dose of procaine penicillin plus two 0.5 g tablets of probenecid, administered orally under supervision in the clinic.

Of the 306 patients receiving procaine penicillin alone 115 were born in the United Kingdom and 191 were immigrants, of whom 114 were Negroes. Of the 307 receiving probenecid in addition, 112 were born in the United Kingdom and 195 were immigrants of whom 111 were Negroes.

Although cultures were used in some cases diagnosis was based on Gram-stained urethral smears. Following treatment the patients were instructed to attend after 2-3 days. It was intended they should be subsequently seen at approximately 1, 2, 4, 8 and 12 weeks from treatment, but, as is common experience, by no means all patients attended at the times instructed.

Results obtained with procaine penicillin alone

The results obtained with 1.2 mega-units of procaine penicillin alone are shown in Table 2.

TABLE 2. Results obtained with 1.2 mega-units of procaine penicillin alone

Length of follow-up	Followed	Satisfactory	Non-gonococcal urethritis	Reinfection	Failure
0	306	—	—	—	—
1-3 days	261	29	9	—	14
4-7 days	209	15	9	2	11
8-14 days	172	10	17	—	7
15-21 days	138	4	8	3	2
22-28 days	121	14	4	5	1
1-2 months	97	12	7	7	1
2-3 months	70	3	1	9	—
More than 3 months	57	27	16	14	—
Total	261	114	71	40	36 (13.8%)

TABLE 3. Results obtained with 1.2 mega-units of procaine penicillin plus 1.0 g of probenecid

Length of follow-up	Followed	Satisfactory	Non-gonococcal urethritis	Reinfection	Failure
0	307	—	—	—	—
1-3 days	264	22	7	1	2
4-7 days	232	30	10	1	7
8-14 days	184	27	20	1	7
15-21 days	129	7	7	3	1
22-28 days	111	11	4	3	1
1-2 months	92	13	3	7	0
2-3 months	69	6	1	6	—
More than 3 months	56	21	6	29	—
Total	264	137	58	51	18 (6.8%)

TABLE 4. Comparison of results

Schedule	Treated	Followed	Failure based on history		Recurrences within 1 week		Recurrences within 2 weeks	
			No.	%	No.	%	No.	%
Without probenecid	306	261	36	13.8	27	10.3	34	13.0
With probenecid	307	264	18	6.8	11	4.2	19	7.2

Thus of 306 patients treated 261 were followed and based on a history of no further sexual exposure there were adjudged to be thirty-six treatment failures of 13.8% of those followed.

No satisfactory criteria exist to distinguish relapse from reinfection apart from a history or absence of same of further sexual exposure. It has been shown by Curtis & Wilkinson (1958), however, on the basis of penicillin-sensitivity findings of the gonococci in question, that recurrences in the 1st week are likely to be failures and those after this time to be reinfections. Calculated in this way there were twenty-seven recurrences in the 1st week or 10.3% of those followed. Others have considered the dividing line of 2 weeks will provide a fairer assess-

ment and the thirty-four recurrences noted in this time would give a failure rate of 13.0%.

Results obtained with procaine penicillin plus probenecid

The results obtained with 1.2 mega-units of procaine penicillin with 1.0 g of probenecid given orally immediately prior to injection are shown in Table 3.

Thus of 307 patients treated 264 were followed and based on no history of further sexual exposure there were eighteen failures (6.8% of those followed). If all eleven recurrences in the 1st week were taken as failures the failure rate was 4.2%, and if the

nineteen recurrences within 2 weeks were chosen the figure was 7.2%.

Comparison of results

The results obtained with the two schedules are compared in Table 4.

Thus by all three methods of assessment the results obtained were significantly better when additional probenecid was given.

Acknowledgment

Grateful thanks are expressed to Dr Geoffrey Rose, St Mary's Hospital, London, W.2 for statistical advice.

References

- CURTIS, F.R. & WILKINSON, A.E. (1958) Comparison of the in vitro sensitivity of gonococci to penicillin with the results of treatment. *British Journal of Venereal Diseases*, **34**, 70.
- HILTON, A.L. (1959) Treatment of gonorrhoea with P.A.M. and probenecid. *British Journal of Venereal Diseases*, **34**, 249.
- HOLMES, K.K., JOHNSON, D.W. & FLOYD, T.M. (1967) Studies of venereal disease. I. Probenecid-procaine penicillin G combination and tetracycline hydrochloride in the treatment of 'penicillin resistant' gonorrhoea in men. *Journal of the American Medical Association*, **202**, 461.
- JENSEN, P.E., KVORNING, S.A. & NORREDAM, K. (1963) Probenecid as an adjuvant in the treatment of gonorrhoea with penicillin. *British Journal of Venereal Diseases*, **39**, 238.
- LEIGH, D.A., LE FRANC, J. & TURNBULL, A.R. (1969) Sensitivity to penicillin of *Neisseria gonorrhoeae*: relationship of results to treatment. *British Journal of Venereal Diseases*, **45**, 151.
- LETCHNER, E.H. & NICOL, C.S. (1961) A comparison of sensitivity to penicillin of *N. gonorrhoeae*, 1960 and 1958. *British Journal of Venereal Diseases*, **37**, 158.
- LOMHOLT, G. & BERG, O. (1966) Gonorrhoea situation in South Greenland in the summer of 1964. *British Journal of Venereal Diseases*, **43**, 1.
- MORRISON, G.D., COBBOLD, R.J.C., BOR, S., SPITZER, R.J., FOSTER, D.N. & WILLCOX, R.R. (1968) Treatment of gonococcal urethritis with single injections of 2.4 mega units of aqueous procaine penicillin. *British Journal of Venereal Diseases*, **44**, 319.
- MORTON, R.S. (1963) Epidemiology of gonorrhoea. *British Journal of Venereal Diseases*, **39**, 105.
- NICOL, C.S., RIDLEY, M. & SYMONDS, M.A.E. (1968) The problem of penicillin-resistant gonococci. *British Journal of Venereal Diseases*, **45**, 315.
- ODEGAARD, K. & GJESSING, H.C. (1967) Is gonococcal sensitivity to antibiotics increasing in Norway? *British Journal of Venereal Diseases*, **43**, 284.
- OLSEN, G.A. & LOMHOLT, G. (1969) Gonorrhoea treated by a combination of probenecid and Sodium Penicillin G. *British Journal of Venereal Diseases*, **45**, 144.
- WHITE, A.C., COUCH, R.A., FOSTER, F., GALLOWAY, J., HUNTER, W. & KNIGHT, V. (1956) Absorption and antimicrobial activity of Penicillin V (phenoxymethyl penicillin). *Antibiotics Annual*, 490.
- WORLD HEALTH ORGANIZATION (1969) Report of Second WHO Regional V.D. Seminar, Manila, Philippines. WHO, Manila.
- WILLCOX, R.R. (1968) Treatment of gonorrhoea in the male. *Current Problems in Dermatology: Antibiotic treatment of Venereal Diseases* (Ed. by A. Luger), pp. 101-140. Karger, Basel.
- WILLCOX, R.R. (1969) Some recent developments in the treatment of gonorrhoea. Paper presented at XXVIIth General Assembly of the International Union against Venereal Diseases, Budapest.
- WREN, B.G. (1967) Gonorrhoea amongst prostitutes. *Medical Journal of Australia*, **1**, 847.