ONE OR TWO DOSES OF 6-(PHENOXY-PROPRIONAMIDE)-PENICILLANIC ACID (BROXIL) IN ACUTE GONORRHOEA*

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Oral penicillin has a number of disadvantages in the treatment of gonorrhoea; absorption is uncertain and there is no guarantee that the patient will take the tablets in the prescribed amounts or at the proper times. If apparent cure results quickly there is also the danger that some of the tablets may be retained with a subsequent temptation towards self-medication with subcurative doses on a future occasion, and an encouragement of "black market" activity.

On the other hand, the advantages are obvious for those persons who really dislike injections, and the speed of administration is much quicker if the oral route is used. Also severe penicillin reactions in allergic patients tend to be less severe when the antibiotic is given orally rather than by injection.

Many of the objections to oral therapy are removed if the treatment can be administered in one single dose under supervision in the clinic. Failing this, if one dose is given in the clinic and the patient is then given a second to take after a few hours, this will probably be taken.

In a previous paper (Willcox, 1958), the use of phenoxymethyl penicillin (penicillin V) in gonorrhoea was described. This penicillin given by mouth was said to produce higher and more prolonged serum levels dose for dose than had previously been possible with the available penicillin preparations. Using 2-3 mega units (1.25-1.87 g.) of penicillin V in one or two doses, there were no failures in 33 white patients, but there were 28.6 per cent. of apparent failures in 49 followed out of 52 coloured patients.

Since this time there have been new developments (*Lancet*, 1959). Following the work in the U.S.A. of J. C. Sheehan, who first converted penicillin G to 6-aminopenicillanic acid (and who synthesised penicillin V), the English workers, Doyle and Robinson,

found an economic source of this compound in fermentation broths, and made possible the synthesis of innumerable penicillin compounds. One such compound is "Broxil", the potassium salt of 6-(phenoxy-propionamide)-penicillanic acid (otherwise known as "Syncillin" or BL P152). It is claimed that its antibiotic activity is slightly greater than that of penicillin V and that it gives blood levels substantially higher than with penicillin V. This new penicillin has been investigated in the treatment of acute gonorrhoea.

Case Material

A total of 148 male patients with uncomplicated gonorrhoea have been treated with 6-(phenoxy-propionamide)-penicillanic acid ("Broxil") as the potassium salt given orally. Of the 148 patients, 89 were Negroes (eighty from the West Indies, seven from West Africa, one from the Sudan, and one from Venezuela), 41 were from the United Kingdom, eleven from Eire, two from Hungary, and one each from France, Greece, India, Pakistan, and Poland. 118 men were single, 29 married, and one divorced. Their average age was 27.6 years (being 26.1 years for the Negroes and 29.9 years for the remainder).

53 had had no previous venereal incident but the remaining 95 had had no less than 200 previous attacks of gonorrhoea, forty of non-gonococcal urethritis, five of syphilis, five of venereophobia, two of scabies, and one each of condylomata acuminata, herpes genitalis, and unspecified penile sore (255 previous incidents). Among the 89 Negroes, 27 had had no previous incident, but the remaining 62 had had 142 previous attacks of gonorrhoea, 32 of non-gonococcal urethritis, two of syphilis, two of venereophobia, and one each of herpes genitalis, unspecified penile sore, and scabies (181 previous incidents). One West Indian patient accounted 23 previous attacks of gonorrhoea and five of non-gonococcal urethritis. The average number of previous attacks was thus two for the Negroes and 1.3 for the remainder.

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Clinical Findings

The duration of the discharge before treatment was 1 to 3 days in 119 patients, 4 to 7 in 24, 15 to 21 in two, and longer than 3 weeks in three. Dysuria was complained of by 105 patients and was not noted by 43. The disease had apparently been caught from a stranger in 96 instances, from a friend in 47, from the wife in four, and from a male in one. The apparent incubation period was 1 to 3 days in 83, 4 to 7 in 43, 8 to 14 in eleven, 15 to 21 in three, 21 to 28 in one, over 28 in four, and unknown in three.

Gonococci were found by urethral smear in all cases before treatment. The routine Wassermann reaction and VDRL (or Kahn) tests for syphilis from a stranger in 131; the Wassermann reaction was positive and the Kahn test negative in one West Indian; the Wassermann reaction was negative and the Kahn test positive in nine (six of whom were Negroes); and both tests were positive in seven (six of whom were West Indians). A number of the positive reactions in Negro patients were doubtless due to previous yaws infection. The gonococcal complement-fixation test was done in 63 cases. Negative reactions were obtained in 52, doubtful in five and positive in five. All but two of the non-negative reactions were in Negro patients. The serum in one case was haemolysed.

Treatment and Follow-up

25 patients were treated with single doses of 1 g. (four tablets each of 250 mg.). 57 received 1.5 g. given as 0.75 g. (three tablets) at once, followed by a further 0.75 g. (three tablets) after 6 hours. A third group of 66 patients were given two doses each of 1 g. (four tablets) also at an interval of 6 hours.

The patients were followed-up for varying periods of from 1 week to 3 months. No satisfactory criteria exist to distinguish relapse from re-infection apart from a history of further sexual exposure, which may or may not be admitted, and, even when risk is admitted, it is not always possible to secure the consort for examination. However, it is interesting to observe that in all but one of the cases which were judged to be treatment failures, gonococci were again noted in the urethral smear within 2 weeks from therapy, and that in all but one of the cases in which

re-infection was suspected the recurrence took place more than 2 weeks from therapy.

Results

The results of treatment are summarized in Table I.

The failure rate was highest (27.3 per cent.) when a single dose of 1 g. was given. When two doses each of 0.75-1 g. were given 6 hours apart, the failure rates were less (12.8-16.3 per cent.). However, there seemed to be no advantage in increasing the total dose from 1.5 g. to 2 g. when using the double-dose technique.

In all, there were twenty suspected failures and seventeen re-infections. There were also nine instances of non-gonococcal infection. One patient treated with 1.5 g. developed dark-field positive sero-negative primary syphilis 24 days after treatment which thus had no effect on the incubating syphilis in this case.

Only one patient (given two doses of 1 g.) complained of side-effects, and he had nausea and diarrhoea for 2 to 3 days following treatment.

There was no significant difference in the failure rates experienced in the white and negro groups (Table II, opposite).

Discussion

Few data are so far available in Britain concerning the effects of "Broxil" in gonorrhoea. Jefferiss and Rosedale (1961) treated 100 patients with a total dosage of 1 g. at an interval of 4 to 8 hours. There were twelve failures. In the current series, in which two doses were used, an interval of 6 hours was chosen so as to enable patients seen before 6 p.m. to complete their treatment before midnight.

Calculated on the basis of patients treated regardless of follow-up, the failure rates in this series would be 24.0 per cent. with a single dose of 1 g., 10.5 per cent. with two doses each of 0.75 g., and 12.1 per cent. with two doses each of 1 g.

Jefferiss and Rosedale (1961) treated a further

TABLE I
RESULTS OF TREATMENT

Schedule	No. Treated	No. Followed	Results				Per cent. Failure of those Followed
			Satisfactory	N.G.U.	Failure	Re-infection	
1 g. single dose	25	22	14	1	6	1	27.3
0.75 g. + 0.75 g. after 6 hrs	57	47	27	5	6	9	12.8
1 g. + 1 g. after 6 hrs	66	49	31	3	8	7	16.3
Total	148	118	72	9	20	17	16.9

TABLE II
RESULTS IN WHITE AND NEGRO PATIENTS

Race	No. Treated	No. Followed	Results				Per cent. Failure of those Followed
			Satisfactory	N.G.U.	Re-infection	Failure	
White	59	47	28	6	5	8	17.0
Negro	89	71	44	3	12	12	13.5
Total	148	118	72	9	17	20	16.9

small series of five patients with single doses of 1 g. (four tablets). Two (40 per cent.) failed to respond and two complained of acute indigestion after taking the tablets and this regime was abandoned.

In the present communication the results of treating 66 patients with two doses each of 1 g. and 25 with single doses of 1 g. are described, but gastrointestinal side-effects were reported in only one case.

Using one or two doses of 1 to 2 g. in the 148 patients here reported, an average success rate of 83.1 per cent. was obtained. This is not as good as may be achieved with single doses of penicillin by injection, but it does offer reasonable prospects of success for selected patients who are distressed by injections.

Summary and Conclusions

(1) The need is stressed for oral therapy in gonorrhoea which will be effective in a single dose, or at the most two doses.

(2) The results of treating 148 male cases of uncomplicated gonorrhoea with 6-(phenoxypropionamide)-penicillanic acid ("Broxil") in a dosage of 1-2 g. given as one or two doses are outlined. In 25 patients given a single dose of 1 g., the failure rate was 27.3 per cent. of those followed. In 57 patients given two doses of 0.75 g. each at an interval of 6 hours, the failure rate was 12.8 per cent. In 66 patients given two doses of 1 g. each at the same interval, the failure rate was 16.3 per cent. of those followed. There seemed to be no advantage, therefore, in increasing the total dose from 1.5 to 2 g. if two doses were used.

(3) In the entire series only one patient complained of side-effects (gastro-intestinal), although 66 patients received two doses each of 1 g. at an interval of 6 hours.

(4) The overall success rate of 83.1 per cent. obtained in this series is not as good as can be achieved with single doses of penicillin by injection.

"Broxil" by mouth cannot therefore be recommended for the mass treatment of gonorrhoea in the venereal disease clinic, although, by employing a double-dose method, reasonable prospects of cure can be offered to selected patients who have a marked distaste for injections. It would seem reasonable to investigate further multi-dose oral techniques for use in such cases.

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Une ou deux doses de "Broxil" en cas de blennorrhagie aiguë

RÉSUMÉ

(1) On souligne le besoin d'un médicament qui pourra guérir la blennorrhagie en une dose, deux au plus, par voie buccale.

(2) On a traité 148 cas de blennorrhagie masculins par une ou deux doses orales de "Broxil" (1 ou 2 g.). Chez 25 malades qui ont reçu une seule dose de 1 g., 27,3 % de ceux qui ont été suivis ont souffert une rechute. Chez 57 qui ont reçu deux doses de 0,75 g. à 6 heures d'intervalle, 12,8 % ont souffert une rechute. Chez 66 qui ont reçu deux doses de 1 g. au même intervalle, 16,3 % ont souffert une rechute. Il semble donc que si l'on donne deux doses il est inutile d'augmenter la dose totale de 1,5 à 2 g.

(3) Parmi tous ces malades, un seul se plaignit de réactions gastro-intestinales, bien que 66 reçurent deux doses de 1 g. chacune à 6 heures d'intervalle.

(4) Si l'on a réussi dans 83,1 % des cas, ce résultat ne vaut pas celui que peut donner une seule dose de pénicilline intramusculaire. On ne peut donc pas dire qu'il faut toujours employer le "Broxil" dans les cliniques vénériennes, mais s'il est donné en deux doses il offre un espoir raisonnable de guérison au malade qui craint les injections et à celui qui est hypersensible à la pénicilline.