Bull. Org. mond. Santé
Bull. Wld Hlth Org. 1954, **10**, 619-626

TREATMENT OF EARLY INFECTIOUS SYPHILIS WITH *N,N'*-DIBENZYLETHYLENEDIAMINE DIPENICILLIN G*

A Second Report

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Manuscript received in January 1954

SYNOPSIS

A new penicillin salt—*N,N'*-dibenzylethylenediamine dipenicillin G (Bicillin)[a]—was given, in single injections of 2,500,000 units, to 196 patients with early infectious syphilis. The seronegativity rates after three months were 65% for primary syphilis cases and 25% for secondary syphilis patients; after six months, the rates were 80% and 60%, respectively. At the end of the 21-month observation period, satisfactory results were recorded in 96.6%-100.0% of the primary syphilis patients, and in 92%-95% of those treated for secondary syphilis. The respective cumulative re-treatment rates were 3.4% and 4.1%.

The results of the secondary syphilis treatment were then compared with those obtained with single-injection schedules of 2,400,000 and 4,800,000 units of procaine penicillin G in oil with 2% aluminium monostearate (PAM). The cumulative re-treatment rates 21 months after treatment were : Bicillin, 4.1%; PAM (2.4 million units), 14.2%; and PAM (4.8 million units), 5.1%. It would thus appear that a single injection of 2,500,000 units of Bicillin is as effective as one of 4,800,000 units of PAM.

The history of research in penicillin therapy reveals four main routes of inquiry : (1) applicability of the antibiotic in various diseases, (2) characteristics of various penicillins and the impurities associated with them, (3) time-dosage relationships and total dosage requirements, and (4) the intensive search for a preparation of penicillin maintaining extended

* This article will also be published, in Spanish, in the *Boletín de la Oficina Sanitaria Panamericana.*

[a] Trade names are used for identification only and do not represent an endorsement by the Public Health Service. This antibiotic is also known as benzathine penicillin G.

effective blood-levels so that the treatment of disease could be achieved with a few injections, or even one.

The study of penicillin therapy in syphilis has shared in all of these paths of research. But subsequent to the establishment of penicillin as an effective therapeutic agent in syphilis, the determination of proper schedules of treatment, and the elimination of less effective penicillin fractions, the main path of study and investigation has been in the direction of testing preparations which promised a reduction in the number of injections. Penicillin in oil and beeswax was a major improvement over aqueous penicillin in that it reduced the daily dosage from twelve injections to one. Subsequently, many other preparations were tested without marked success.

More recently, procaine penicillin G in oil gelled with 2% weight-by-volume aluminium monostearate (PAM) became the most widely used of the delayed-absorption preparations, since it maintained effective blood concentrations in most patients for 4 or more days. PAM is commonly used in multiple injections repeated every 4 to 7 days, but has been used effectively at a single treatment session. This single-session therapy offered the distinct possibility of ambulatory, outpatient treatment with less necessity for case-holding procedures.

In 1951, the Wyeth Laboratories offered the US Public Health Service a new penicillin salt, *N,N'*-dibenzylethylenediamine dipenicillin G (Bicillin), for evaluation. This drug not only avoided the use of oil and aluminium compounds, but maintained impressive blood-levels over a much longer period. Following the injection in a single site of 2,500,000 units of this drug, mean blood-levels (unit per ml, cup-plate method employing *Sarcina lutea*) of 0.134 for the first week, 0.058 for the second week, and 0.097 for the two-week period of observation were obtained.[1] It seemed probable that these long-sustained blood concentrations would render 2,500,000 units of *N,N'*-dibenzylethylenediamine dipenicillin G equally as effective as 4,800,000 units of procaine penicillin and aluminium monostearate—the dosage generally recommended in the USA for the treatment of early infectious syphilis.

Cases for the evaluation have been generously contributed by treatment facilities at Chicago, Illinois, New Orleans, Louisiana, and Durham, North Carolina. All patients were treated with a single injection of 2,500,000 units of *N,N'*-dibenzylenediamine dipenicillin G.

A previous report [2] based on 127 patients presented results 12-15 months following treatment. This report includes 196 patients with darkfield-positive primary or secondary syphilis with a maximum observation period of 21 months.

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[1] O'Brien, J. F. & Smith, C. A. (1952) *Amer. J. Syph.* **36**, 519

[2] Smith, C. A., O'Brien, J. F., Simpson, W. G., Harb, F. W. & Shafer, J. K. (1954) *Amer. J. Syph.* **38**, 136

Reactions to Treatment

In the original series of patients treated with *N,N'*-dibenzylethylenediamine dipenicillin G, it was found that the incidence of reactions of significance was less than 0.3%.[3] Since that time, additional experience has shown an incidence of dermatitis medicamentosa with erythema, oedema, and urticaria of less than 1%. There is no correlation between the occurrence of reactions and the height of the assayable penicillin blood-levels, nor does the maintenance of these blood-levels prevent early subsidence of the reaction. Two anaphylactoid reactions have been reported in detail by Grekin & O'Brien.[4] Again, these reactions subsided in a matter of hours without sequelae, although the penicillin blood-levels remained high. No fatalities have occurred.

Results of Treatment

As reported previously, the initial results following *N,N'*-dibenzylethylenediamine dipenicillin G are the same as results following adequate treatment with procaine penicillin. Darkfield examinations became negative within a 15-hour period, the majority within 8 hours following treatment, and there was a similar regression of the rash of secondary syphilis.

Although the number of cases is small, results indicate that *N,N'*-dibenzylethylenediamine dipenicillin G is effective in the treatment of syphilis in pregnancy. Ten women treated before or during pregnancy have now delivered. One pregnancy resulted in a non-syphilitic stillbirth at 7½ months. The other nine pregnancies resulted in normal deliveries and the babies were serologically negative for syphilis from six weeks to seven months after birth. One of the women was re-treated for serorelapse four months after delivery, but the baby remained negative through six months of observation.

Five patients with positive spinal-fluid examinations prior to treatment were negative when examined six months later. The results of the spinal-fluid examinations scheduled for a year following treatment are available for 49 patients, or 55% of those observed for one year. With one exception, all were completely negative. The one patient was re-treated for serorelapse and, at that time, examination of the spinal fluid showed 13 cells as the only spinal fluid abnormality.

Of the 196 cases included in the evaluation, 21 had received antisyphilitic treatment for a previous infection. These cases have been omitted in table I, which shows results of treatment by stage of syphilis. The 175 previously untreated cases include 33 patients with seronegative primary, 38 seropositive primary, and 104 patients with secondary syphilis.

[3] O'Brien, J. F. & Smith, C. A. (1952) *Amer. J. Syph.* **36**, 519

[4] Grekin, R. & O'Brien, J. F. (1954) *Amer. J. Syph.* **38**, 143

TABLE I. TREATMENT OF DARKFIELD-POSITIVE SYPHILIS WITH A SINGLE INJECTION OF 2,500,000 UNITS OF BICILLIN *

Observation period (months)	Cases re-treated on basis of						Total re-treated			Cases not re-treated				Total cases
	serology			probable reinfection						seropositive		seronegative		
	number	%	cumulative percentage	number	%	cumulative percentage	number	%	cumulative percentage	number	%	number	%	
Seronegative Primary														
–1	—	—	—	—	—	—	—	—	—	2	6.1	31	93.9	33
1–2	—	—	—	—	—	—	—	—	—	—	—	32	100.0	32
2–3	—	—	—	—	—	—	—	—	—	—	—	31	100.0	31
3–4	—	—	—	—	—	—	—	—	—	—	—	30	100.0	30
4–5	—	—	—	—	—	—	—	—	—	—	—	27	100.0	27
5–6	—	—	—	—	—	—	—	—	—	—	—	22	100.0	22
6–7	—	—	—	—	—	—	—	—	—	—	—	20	100.0	20
7–8	—	—	—	—	—	—	—	—	—	—	—	20	100.0	20
8–9	—	—	—	—	—	—	—	—	—	—	—	17	100.0	17
9–10	—	—	—	—	—	—	—	—	—	—	—	16	100.0	16
10–11	—	—	—	—	—	—	—	—	—	—	—	15	100.0	15
11–12	—	—	—	—	—	—	—	—	—	—	—	14	100.0	14
12–15	—	—	—	—	—	—	—	—	—	—	—	9	100.0	9
15–18	—	—	—	—	—	—	—	—	—	—	—	4	100.0	4
18–21	—	—	—	—	—	—	—	—	—	—	—	1	100.0	1
Seropositive Primary														
–1	—	—	—	—	—	—	—	—	—	32	84.2	6	15.8	38
1–2	—	—	—	—	—	—	—	—	—	22	57.9	16	42.1	38
2–3	—	—	—	—	—	—	—	—	—	12	35.3	22	64.7	34
3–4	—	—	—	—	—	—	—	—	—	8	23.5	26	76.5	34
4–5	—	—	—	—	—	—	—	—	—	6	17.6	28	82.4	34
5–6	—	—	—	—	—	—	—	—	—	6	20.0	24	80.0	30
6–7	—	—	—	1	3.4	3.4	1	3.4	3.4	4	13.8	24	82.8	29
7–8	—	—	—	—	—	3.4	—	—	3.4	2	6.9	26	89.7	29
8–9	—	—	—	—	—	3.4	—	—	3.4	2	8.8	20	87.8	23
9–10	—	—	—	—	—	3.4	—	—	3.4	1	5.1	18	91.5	20
10–11	—	—	—	—	—	3.4	—	—	3.4	1	5.7	16	90.9	18
11–12	—	—	—	—	—	3.4	—	—	3.4	1	5.7	16	90.9	18
12–15	—	—	—	—	—	3.4	—	—	3.4	1	7.4	12	89.1	13
15–18	—	—	—	—	—	3.4	—	—	3.4	—	—	9	96.6	9
18–21	—	—	—	—	—	3.4	—	—	3.4	—	—	3	96.6	3

Secondary														
−1	—	—	—	—	—	—	—	—	—	103	99.0	1	1.0	104
1–2	—	—	—	—	—	—	—	—	—	94	91.3	9	8.7	103
2–3	—	—	—	—	—	—	—	—	—	75	75.0	25	25.0	100
3–4	—	—	—	—	—	—	—	—	—	55	58.5	39	41.5	94
4–5	—	—	—	1	1.1	1.1	1	1.1	1.1	45	50.0	44	48.9	90
5–6	—	—	—	—	—	1.1	—	—	1.1	33	38.9	51	60.0	85
6–7	—	—	—	—	—	1.1	—	—	1.1	25	32.5	51	66.4	77
7–8	—	—	—	—	—	1.1	—	—	1.1	20	26.7	54	72.2	75
8–9	—	—	—	1	1.5	2.6	1	1.5	2.6	15	21.8	52	75.6	69
9–10	1	1.5	1.5	—	—	2.6	1	1.5	4.1	13	19.8	50	76.1	66
10–11	—	—	1.5	—	—	2.6	—	—	4.1	8	14.2	46	81.7	56
11–12	—	—	1.5	—	—	2.6	—	—	4.1	7	13.2	44	82.8	53
12–15	—	—	1.5	—	—	2.6	—	—	4.1	6	12.5	40	83.4	48
15–18	—	—	1.5	—	—	2.6	—	—	4.1	1	3.1	30	92.8	32
18–21	—	—	1.5	—	—	2.6	—	—	4.1	1	4.6	20	91.4	22
Total Cases														
−1	—	—	—	—	—	—	—	—	—	137	78.3	38	21.7	175
1–2	—	—	—	—	—	—	—	—	—	116	67.1	57	32.9	173
2–3	—	—	—	—	—	—	—	—	—	87	52.7	78	47.3	165
3–4	—	—	—	—	—	—	—	—	—	63	39.9	95	60.1	158
4–5	—	—	—	1	0.7	0.7	1	0.7	0.7	51	33.8	99	65.6	151
5–6	—	—	—	—	—	0.7	—	—	0.7	39	28.5	97	70.8	137
6–7	—	—	—	1	0.8	1.5	1	0.8	1.5	29	23.0	95	75.5	126
7–8	—	—	—	—	—	1.5	—	—	1.5	22	17.8	100	80.8	124
8–9	—	—	—	1	0.9	2.4	1	0.9	2.4	17	15.7	89	82.0	109
9–10	1	1.0	1.0	—	—	2.4	1	1.0	3.4	14	13.8	84	82.8	101
10–11	—	—	1.0	—	—	2.4	—	—	3.4	9	10.1	77	86.5	89
11–12	—	—	1.0	—	—	2.4	—	—	3.4	8	9.4	74	87.2	85
12–15	—	—	1.0	—	—	2.4	—	—	3.4	7	9.9	61	86.7	70
15–18	—	—	1.0	—	—	2.4	—	—	3.4	1	2.2	43	94.4	46
18–21	—	—	1.0	—	—	2.4	—	—	3.4	1	3.9	24	92.8	26

*** Patients with no previous treatment**

It will be observed that, of the 175 cases, only 26 were examined 18-21 months following treatment. This tremendous decrease is due principally to the accretion of new patients rather than to the loss of patients from observation. Based on the number of patients who could have been observed for various periods, the overall post-treatment observation rate is 77%, with 85% observed for one year and 68% observed for 18-21 months.

With the exception of two patients who became positive following treatment and then reverted to seronegativity, all patients treated for seronegative primary syphilis maintained a seronegative status throughout their period of observation.

Of the patients treated for seropositive primary syphilis, 65% had achieved seronegativity by the third month following treatment, and 80% by the sixth month. One patient had definite epidemiological and clinical evidence of reinfection, resulting in a cumulative re-treatment rate of 3.4%. The one patient who remained positive for more than one year had a pre-treatment titre of 1,024 Kahn units and, when last observed, a VDRL test reported as positive in 1:1 dilution. If this is considered a satisfactory result, *N,N'*-dibenzylethylenediamine dipenicillin G was effective in 96.6%-100.0% of the patients treated for seropositive primary syphilis.

In patients treated for secondary syphilis, the seronegativity rate was 25% at the third month, 60% at the sixth, and 83% at the twelfth. Three patients required additional treatment (two for reinfection and one for serorelapse) giving a cumulative re-treatment rate of 4.1%. Six patients remained positive for more than one year. Two of these later reversed to negative, and two showed a satisfactory course; but the other two, with 16 and 32 Kahn units, respectively, at last observation represent possible treatment failures. If considered as such, the rate of satisfactory results following a single injection of 2.5 million units of *N,N'*-dibenzylethylenediamine dipenicillin G in secondary syphilis ranges from 92% to 95%. The " range " allows for an interpretation of reinfection as a satisfactory or unsatisfactory result of treatment.

Comparison of Bicillin and PAM in the Treatment of Secondary Syphilis

The three facilities contributing cases to this therapy evaluation study have also furnished cases for an evaluation of procaine penicillin and aluminium monostearate. The two schedules available for comparison are single-session schedules of 2,400,000 and 4,800,000 units. To eliminate variations between centres, these two schedules have been weighted by the facility-distribution of the cases treated with *N,N'*-dibenzylethylenediamine dipenicillin G.

Results in terms of rate of reversal to seronegativity in previously untreated secondary syphilis for the three schedules of treatment are shown

FIG. 1. COMPARISON OF RESULTS OF BICILLIN AND OF PAM IN PREVIOUSLY UNTREATED SECONDARY SYPHILIS: RATE OF REVERSAL TO SERONEGATIVITY

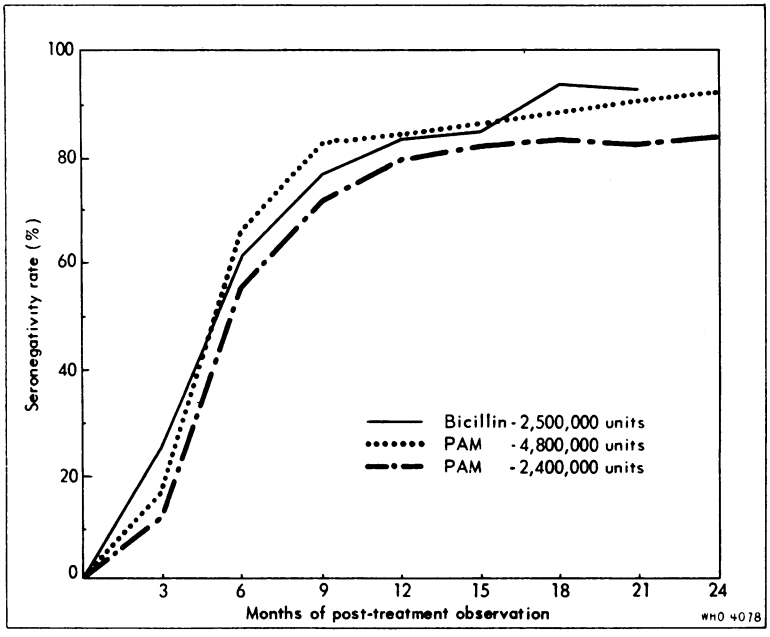
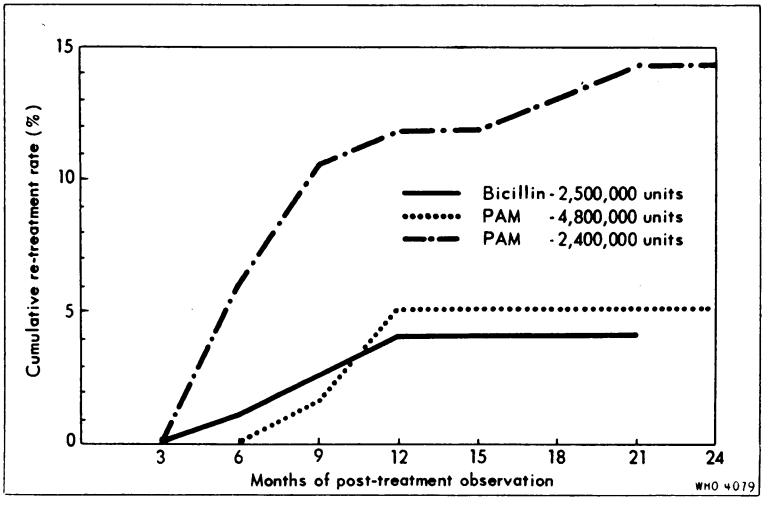


FIG. 2. COMPARISON OF RESULTS OF BICILLIN AND OF PAM IN PREVIOUSLY UNTREATED SECONDARY SYPHILIS: RE-TREATMENT RATE



in fig. 1. It will be observed that the curves for the *N,N'*-dibenzylethylenediamine dipenicillin G and 4,800,000-unit PAM schedules crossed twice during a 21-month observation period. The average difference in seronegativity rates for the 21 months was only slightly more than one-tenth of one percentage point. The curve for *N,N'*-dibenzylethylenediamine dipenicillin G, however, was an average of six percentage points higher for the 21 months than the curve for the 2,400,000-unit PAM schedule. This difference, although not large, is about the difference expected between 2,400,000 and 4,800,000 units of penicillin.

When judged by re-treatment rates, as shown in fig. 2, there is still no difference observed between a single injection of 2,500,000 units of *N,N'*-dibenzylethylenediamine dipenicillin G and 4,800,000 units of PAM. From the 12th through the 21st month the rates were 4.1% for *N,N'*-dibenzylethylenediamine dipenicillin G and 5.1% for PAM. These rates were both lower than the re-treatment rate following 2,400,000 units of PAM, which was 14.2% at the 21st month.

From the comparisons of *N,N'*-dibenzylethylenediamine dipenicillin G and PAM presented here it would appear that the prediction that 2,500,000 units of *N,N'*-dibenzylethylenediamine dipenicillin G in one dose would prove equally as effective as 4,800,000 units of PAM was well founded.

RÉSUMÉ

Une nouvelle préparation de pénicilline, la dipénicilline G *N,N'*- dibenzyléthylènediamine (Bicillin) a été soumise à des essais d'efficacité depuis 1951. Cette préparation, comparée à celles qui ont été utilisées précédemment, a l'avantage de ne contenir ni huile ni aluminium et d'assurer, en outre, une pénicillinémie de plus longue durée (0,134 unité par ml de sérum durant la première semaine, 0,058 durant la seconde, la moyenne pour les deux semaines étant de 0,097).

Les auteurs résument dans cette étude les résultats obtenus dans le traitement de 196 malades, atteints de syphilis primaire ou secondaire confirmée par l'examen microscopique, dont quelques-uns furent suivis pendant 21 mois.

Le pourcentage de virage des cas séropositifs à la négativité a été, pour la syphilis primaire, 65 après trois mois, et 80 après six mois; pour la syphilis secondaire, 25 après trois mois, 60 après six mois et 83 après une année.

Les résultats du traitement de la syphilis secondaire par la « Bicillin » ont été comparés à ceux du traitement par le PAM. Après 21 mois, la proportion des cas pour lesquels un second traitement était nécessaire a été de 4,1% pour la « Bicillin » (administrée en une injection de 2,5 millions d'unités), de 14,2% pour le PAM (2,4 millions d'unités) et de 5,1 % pour le PAM (4,8 millions d'unités). Il semble donc que 2,5 millions d'unités de « Bicillin » ont la même action que 4,8 millions d'unités de PAM. La proportion des effets secondaires nocifs du médicament, de quelque importance, a été inférieure à 0,3 %.