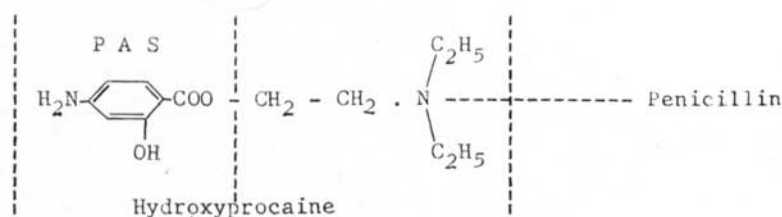


A NEW REMEDY FOR LEPROSY, HYDROXYPROCAINE-PENICILLIN

RUDOLF TRAPPMANN, M.D.

*Leprosy Research Institute
Djakarta, Indonesia¹*

Hydroxyprocaine-penicillin (HPP) represents a compound formed by penicillin G and the salt hydroxyprocaine, originating from para-aminosalicylic acid (PAS). Its structural formula is as follows:



This compound has been used up to now in 116 patients altogether, by several investigators in different countries. Publications so far have been made by Percy (⁶), Trappmann (⁸), and Schaller and Serie (⁷), who cited certain other workers (Chit Yin and U Pe Thein). All of them reported favorable results, and pointed out the excellent tolerance of the drug. The periods of treatment varied from 3 to 24 months, the drug being injected intramuscularly at intervals varying from daily up to one week, in a dose of 400,000 U.

My own previous investigation (⁸) involved 10 patients treated for three months. The results obtained were very satisfying, so that it was decided to start a further trial on a larger number of patients with a longer time of treatment.

MATERIAL AND METHOD

Twenty-nine patients were available for the present trial, the period of which was 9 to 12 months. Of the total, 25 patients were treated for 12 months, 3 for 10 months, and 1 for 9 months. Nineteen patients were of the lepromatous type, and 10 of them were borderline. Among the former there were 4 early cases (L1), 13 slightly advanced (L2), and 2 advanced (L3). The clinical diagnosis in all cases was confirmed by histopathologic examination.

Six of the borderline cases had been treated for 1 to 3 months with sulfones; the other 4 were untreated. Sixteen of the lepromatous patients had not yet been treated, whereas 3 had received sulfone drugs more or less irregularly for quite some time.

All the 29 patients were hospitalized in our clinic. A complete physical examination was performed monthly. Every 3 months the body weight was checked, hemoglobin determinations and red-cell counts were made, and the urine was examined for evidence

¹ Present address: Lisztstrasse 17, Bonn, Western Germany.

of kidney pathology. Photographs were taken as a matter of routine before and after termination of treatment; more were made when considered necessary. The lepromin test, negative in all patients before the beginning of the treatment, was repeated after termination of treatment only in the borderline cases, in which positive conversion of the Mitsuda reaction might be expected.

Material for histologic examination was taken from the earlobe, except in a few cases. This examination was made before and after treatment. Material for bacteriologic examinations, which were made every three months, was taken from the nasal mucosa, one earlobe, and another skin lesion, and was carried out according to a standard procedure of our clinic using the following classification of the findings.

- Negative: no bacilli in the entire preparation;
- ± : 1 or 2 bacilli in the entire preparation;
- 1+a : several bacilli in the entire preparation, or 1 or 2 small clusters;
- 1+b : 5-20 bacilli and a few clusters in a few microscopic fields;
- 1+c : 5-20 bacilli and several clusters in each microscopic field;
- 1+d : 20-50 bacilli and some clusters in each microscopic field;
- 2+a : 50-200 bacilli and numerous clusters in each microscopic field;
- 2+b : more than 200 bacilli and numerous clusters in each microscopic field;
- 2+c : each microscopic field full of bacilli, isolated in clusters.

RESULTS

The essential case data (not including sex, age and duration), and the bacteriologic findings before and after treatment, together with certain other information, are given in Table 1. The results are briefly summarized below, and are discussed in the next section.

Lepromatous cases.—Among the 19 lepromatous patients, 1 showed marked improvement and became bacteriologically negative; in 11 patients distinct but not marked improvement was achieved; in 1 there was slight improvement, and in 6 there was none. Of the 11 distinctly improved patients, 8 showed a definite decrease of bacilli, whereas 3 remained bacteriologically unchanged. In the patient whose clinical improvement was only slight, and in the 6 unimproved cases, the numbers of bacilli remained unchanged. Five patients developed erythema nodosum leprosum (ENL) reactions between the 6th and 8th months of treatment. In 1 of them a slight peroneal paresis was observed. In one patient the lesions showed reinfiltration of short duration in the 5th month of therapy. In another patient there was a slowly increasing anemia with enlargement of the liver and spleen after 6 months' treatment.

Borderline cases.—All of these patients reacted favorably to the medicament. After conclusion of the treatment 7 showed marked clinical improvement, and the 3 others were distinctly improved. Bacteriologically, 9 patients became negative, while 1 remained 1+a positive in the nasal mucosa. In 4 patients, between the 5th and 6th months of treatment, a short reactivation developed. In 2 patients, polyneuritic symptoms were seen. The lepromin reaction became positive in 4

patients, and slightly positive in 4 more, whereas in 2 it remained quite negative.

DISCUSSION

Lepromatous cases.—The prime essential required of an effective antileprosy drug is its ability to make the patient bacillus-free, thus to eliminate him as a source of infection. With sulfone therapy, approximately 2 to 3 years or more are required to achieve this result in moderately advanced (L2) cases, provided the course of treatment is without reactions. Occasionally there are a few cases of early forms which need less time. If the progress of healing is carefully watched, it can be noticed that in general resorption of skin and membrane lesions precedes the reduction of the bacillus content.

Among our 19 lepromatous patients treated with HPP, all but 4 for 12 months, we were able to achieve marked or moderate improvement of the skin lesions in 12 patients (63%). In 8 of them (42%) there was definite lessening of the numbers of bacilli; in the remaining cases there was a lack of correspondence between the resorption of skin lesions and the reduction in the numbers of bacilli, which—as already noted—is a recognized phenomenon in the healing process of lepromatous leprosy. The single case which showed marked clinical improvement, an early one, became bacteriologically negative. Among the 11 cases with definite clinical improvement, only 7 revealed reduction of the numbers of bacilli. There were no bacteriologic changes in 4 of the patients who had good clinical responses, or in the 1 who was only slightly improved and the 6 who were unchanged.

These results again confirm our previous experience with this product. After employing a new drug for only one year's treatment of patients who in the main had moderately advanced disease, these results are satisfying and comparable with those achieved by sulfone therapy.

Borderline cases.—All of the borderline cases responded very well clinically, bacteriologically and histologically to the 12-months treatment with HPP. Resorption of plaques, infiltrates, nodules and patches could be observed during the first two months, and was completed in

Key to symbols for Table 1

L1	: lepromatous, early	Ri	: reinfiltration
L2	: lepromatous, slightly advanced	ENL	: erythema nodosum leprosum
L3	: lepromatous, advanced	A	: atrophy
B	: borderline	C	: contraction
NS	: nasal secretion	PP	: peroneal palsy
EL	: earlobe	3+	: improvement, marked
SL	: other skin lesions	2+	: improvement, distinct
Ra	: reactivation	1+	: improvement, slight
		—	: unchanged

TABLE 1.—Case data and findings before and after treatment.

Case No.	Diagnosis	Treatment (months)	Untreated	Pretreated	Bacteriology						Reactions	Neural involvement	Clinical improvement	Mitsuda reaction			
					Before therapy			After therapy						Before therapy	After therapy		
					NS	EL	SL	NS	EL	SL							
1	L2	12	×	×	2+a	2+a	1+d	2+a	1+b	1+a	ENL ENL ENL	PP	2+	Neg.	+5		
2	L2	10	×		2+a	1+c	1+a	2+a	1+c	1+a			Neg.	2+	Neg.	Neg.	
3	L1	12	×		1+a	1+a	1+b	1+a	1+a	1+b			ENL		2+	Neg.	+5
4	L1	12	×		1+b	1+b	1+a	1+b	1+b	1+a	ENL		2+	Neg.	+3		
5	L2	12	×		2+a	2+b	1+a	1+b	1+b	1+a	ENL	A+e	2+	Neg.	Neg.		
6	L2	12	×		1+c	1+b	1+b	Neg.	1+a	Neg.			2+	Neg.	2+	Neg.	+3
7	L2	12	×		2+a	2+a	1+d	1+a	1+b	1+b			ENL		2+	Neg.	+3
8	L2	10	×		1+d	1+c	1+b	1+b	2+a	1+b	Ri	A+e	2+	Neg.	+2		
9	L2	12	×		2+a	2+a	1+b	2+a	1+d	1+b			2+	Neg.	2+	Neg.	+2
10	L2	12	×		1+d	1+b	1+b	1+b	1+a	1+b			2+	Neg.	2+	Neg.	+3
11	L2	12	×		1+a	1+b	1+b	1+b	1+a	1+b	ENL	A+e	2+	Neg.	+3		
12	L3	12	×		1+d	2+b	1+a	1+d	2+b	1+b			2+	Neg.	2+	Neg.	+3
13	L2	12	×		1+d	1+b	1+b	1+b	1+b	1+a			2+	Neg.	2+	Neg.	+5
14	L1	12	×		1+a	1+b	1+b	Neg.	Neg.	Neg.	ENL	A+e	3+	Neg.	+5		
15	L2	12	×		1+b	1+d	1+b	1+b	1+d	1+a			1+	Neg.	3+	Neg.	+5
16	L2	12	×		1+b	1+a	1+a	1+b	1+a	1+a			2+	Neg.	2+	Neg.	+3
17	L1	10	×		1+d	1+b	1+a	Neg.	1+b	1+a	ENL	A+e	2+	Neg.	+3		
18	L3	12	×		2+a	2+a	1+b	2+a	1+b	1+b			2+	Neg.	2+	Neg.	+3
19	L2	9	×		2+b	2+b	1+b	1+a	1+c	1+b			2+	Neg.	2+	Neg.	+5
20	B	12	×	×	1+b	1+c	1+a	Neg.	Neg.	Neg.	Ra	A+e	3+	Neg.	+5		
21	B	12	×		2+a	2+a	1+a	1+a	Neg.	Neg.			2+	Neg.	2+	Neg.	+5
22	B	12	×		1+b	2+a	2+a	Neg.	Neg.	Neg.			2+	Neg.	2+	Neg.	+3
23	B	12	×		1+b	1+a	1+a	Neg.	Neg.	Neg.	Ra	A+e	3+	Neg.	+3		
24	B	12		×	2+a	2+a	1+b	Neg.	Neg.	Neg.			2+	Neg.	2+	Neg.	+3
25	B	12			1+b	1+c	1+a	Neg.	Neg.	Neg.			2+	Neg.	2+	Neg.	+3
26	B	12	×		1+b	1+a	1+a	Neg.	Neg.	Neg.	Ra	A+e	3+	Neg.	+3		
27	B	12		×	1+a	1+a	1+a	Neg.	Neg.	Neg.			2+	Neg.	2+	Neg.	+3
28	B	12	×	×	1+b	1+c	1+a	Neg.	Neg.	Neg.			3+	Neg.	3+	Neg.	+3
29	B	12	×	×	1+b	1+b	2+a	Neg.	Neg.	Neg.	3+	Neg.	3+	Neg.	+5		

most of the cases after the 4th month, the skin lesions either having disappeared completely or leaving behind atrophic areas. The majority at that time were bacteriologically negative, and for them hospital treatment could then have been considered as completed. It was continued with all, however, at a dosage of 400,000 U. per day, so as to discover any possible development of resistance to the drug which we would not have been able to notice in ambulant treatment. One could have expected signs of resistance developing during a treatment with an antibiotic continued in daily doses for months.

Actually, in 4 patients (Cases 23, 26, 27 and 28 of Table 1), in whom the skin lesions had not yet completely subsided, reactivations of lesions occurred during the period of the 5th-6th months. This happened in isolated lesions except in Case 28, in which all lesions became activated. These reactivations, however, were of only short duration, and it should be stressed that the condition regressed again under continued, regular therapy. Thus these reactivations cannot be interpreted as a sign of development of resistance against the drug, since by the end of treatment all patients had become considerably or distinctly improved clinically. Furthermore, all but one had become bacteriologically negative, and the case which did not was only slightly positive. This improvement was also clearly demonstrated histologically, and in some of the cases it was accompanied by conversion of the Mitsuda reaction.

It is a well-known fact that borderline cases respond much more quickly and better to an effective drug than do lepromatous cases. The skin lesions, which at first are dramatic-looking, often disappear within 4 months of treatment. This is not extraordinary, and therefore cannot be considered as definite evidence of the superiority of the new drug.

On the other hand, if its effectiveness is measured in comparison with sulfone therapy as standard antileprosy treatment, I feel justified in saying that in borderline cases the therapeutic activity of HPP equals that of the sulfone products. In support of this view are cited 6 patients who, having been pretreated for 1 to 3 months with DDS or Promin, had developed under sulfone treatment such severe exacerbations that those drugs had to be stopped. Yet the HPP compound was tolerated by all of them, without complications. This advantage was emphasized in my previous report. It therefore appears that in patients showing symptoms of intolerance against sulfones, HPP could be a valuable preparation with the same therapeutic activity but with lesser side effects.

The appearance of neural involvement was observed in 2 patients. In one of them (Case 23), who represented a reactivation, there was thickening of both ulnar nerves with slight atrophy of the interosseous muscles and the thenar and antithenar eminences of both hands, and beginning contraction of the right little finger developed. Immediate

neurolysis on both sides relieved the contraction and prevented progress of the atrophy.

In another case (No. 25), without preceding reactivation, mild atrophy of thenar and antithenar eminences of the left hand appeared, but that was soon arrested and had not advanced any further at the time of writing, a year after the termination of the HPP therapy. An already-existing peroneal paralysis on the left in the same patient, which had appeared during an exacerbation under previous sulfone therapy, was not improved under the HPP therapy.

It is known from experience that only in rare cases has modern antileprosy chemotherapy any influence on neural affections and their sequelae, and that such changes frequently develop even under regular therapy. I have not, therefore, been surprised at being unable to avoid neural phenomena by the influence of the new drug, or at being unable to clear up existing ones.

One patient (No. 28) deserves special mention from the diagnostic point of view, beyond the special scope of this report. The initial clinical diagnosis was undecided between borderline and a tuberculoid exacerbation. Before the histologic preparations were completed the patient was given methylene blue, using the technique of Montel ⁽⁴⁾ as recommended by Wade ⁽⁹⁾. A 1 per cent solution was injected according to the schedule employed by Convit *et al.* ⁽¹⁾. A lepromatous patient (Case 2) and a tuberculoid patient served as controls. After the 3rd injection the lepromatous patient presented a diffuse bluish coloration almost all over his body, whereas the tuberculoid case did not show any blue coloration even after the 15th injection. The borderline case showed bluish patches on both earlobes and behind the auricle after the 8th injection. The diagnosis of borderline was later confirmed by histology (biopsy of the left earlobe). There were tuberculoid as well as lepromatous structures in the same specimen, together with numerous lepra cells in the region of the lepromatous tissue.

Erythema nodosum leprosum (ENL).—Many authors do not think the appearance of ENL, which occurs only in lepromatous cases, results from drug intolerance, as it occurs under various forms of treatment. Some authors, as Pepler *et al.* ⁽⁵⁾, even hold that its appearance is in direct relation to the efficacy of the drug employed. Wolcott ⁽¹⁰⁾ reported frequent bacteriologic and clinical halting of the disease after repeated intensive attacks of ENL, and he considered them to be a sign of growing resistance. At the Madrid congress ⁽³⁾ the general opinion appeared to be that ENL is indicative of a favorable prognosis. Davison ⁽²⁾, on the contrary, considers ENL to be disadvantageous for the patient and recommends that particular attention should be paid to the treatment of this reaction.

The 5 cases of ENL in my patients (see Table 1) comprised of 4 with acute episodes in which the reaction occurred for the first time

between the 6th and 8th months of treatment, and 1 chronic case of 2 years duration in which reactions had begun under DDS treatment and had made it necessary to discontinue the use of that drug. Before this patient was transferred to my ward he had been under treatment with antimony and corticosteroids for 6 months, without lasting effect. When under the HPP treatment he remained free from ENL for the first 6 months. His temperature became normal and there was a marked improvement in his general condition. Other ENL episodes occurred later, however, with more relapses until the end of treatment, but never reaching the severity of the previous attacks. One of the 4 other cases showed impairment of his general condition and fever up to 40°C when suffering from ENL, whereas the other 3 patients only had occasional attacks without fever and their general condition remaining unchanged.

In all these patients the ENL episodes occurred after their skin lesions had subsided considerably. There was no interruption of therapy, nor reduction in dose. Four of the 5 patients showed marked clinical improvement at the end of the treatment, and 3 of them had definite reduction of bacilli. One patient was only slightly improved clinically, and his bacteriologic status remained unchanged.

Because of the small number of patients concerned in this study and the few ENL cases observed in the year of treatment, it is not possible to evaluate ENL as favorable or unfavorable with respect to prognosis. Considering, however, the good results achieved, its occurrence seems not to have lessened the effectiveness of the drug in these cases.

Other side effects.—The patient with reinfiltration of all lesions (Case 12) need not be mentioned in detail, as the relapse was only of short duration and disappeared under continued therapy with the same dosage; after conclusion of the treatment he was clearly improved. The cause of the transient deterioration remained unknown.

Apart from the two borderline cases already mentioned, there was a left peroneal palsy in a lepromatous patient with chronic ENL while under treatment with HPP.

One patient who showed considerable resorption of the acute skin lesions during the first 4 months of treatment, with corresponding reduction of bacilli, developed a gradually-increasing enlargement of the liver and spleen after 6 months, with hemoglobin down to 40 per cent and septic temperatures around 40°C. The patient was under observation in the medical department of the Central Hospital for 2 months, but clinical investigations provided no clues as to the cause of the condition. The possibility of a leprosy reaction manifested only in the internal organs was considered, as active lesions of the skin or mucous membranes could no longer be found. Study of this patient has not yet been concluded, and biopsies of the liver and spleen are awaiting improvement of his general condition.

Apart from this patient, whose final assessment is still to be made, no actual untoward effect of the drug could be seen. The patients never made any complaints during the examinations performed at frequent intervals. Laboratory tests showed no harmful effect upon hemoglobin or the red-cell count. No signs of pathology were elicited by the urinalyses. In spite of daily injections, HPP was tolerated well.

The necessity of daily injections to obtain an active effect in such a chronic disease as leprosy—which requires years of treatment—restricts the use of this product for mass treatment. Schaller and Serie, however, mention a depot effect of HPP, and it can be seen from Table 2 of their report—although it was not explicitly reported—that injections had been given at intervals which in a few cases amounted to weeks. These intervals between the injections seemed to be of no account, as demonstrated by the good results achieved.

Having injected the product daily, I have not been able to collect any relevant data of my own. I would think it necessary, however, to test the efficacy of the preparation given in an increased single dose every week, or every second week, and thus ascertaining its possible usefulness in a much larger field.

No control series of sulfone-treated cases was set up for comparison with the HPP-treated cases, because knowledge of sulfone therapy is now so abundant as to make such an additional group appear unnecessary. Moreover, it would been very difficult to obtain the same number of suitable lepromatous and borderline cases for such an extended hospital treatment. Therefore the data and results of sulfone therapy referred to in this report are taken from generally-known experience.

SUMMARY AND CONCLUSIONS

The use of a new antileprosy product called hydroxyprocaine-penicillin in 29 leprosy patients, 19 lepromatous and 10 borderline, for an average of 11.5 months is reported.

All of the borderline cases showed very marked or marked clinical improvement at the end of treatment. Nine of them became bacteriologically negative, while 1 remained weakly positive in the nasal mucosa; 4 became Mitsuda-positive, 4 weakly positive, and 2 remained unchanged.

Of 19 lepromatous cases, 1 improved quite markedly, 11 showed distinct clinical improvement, and 1 patient cleared only to a minor degree; 6 cases remained unchanged.

The appearance of transient reactivations of the disease among the borderline cases, and of ENL reactions in lepromatous patients, did not affect the good overall results. These reactions were not considered to be symptoms of intolerance toward the drug. Neural affections which appeared in 3 patients, resulting in minor atrophies and mus-

cular contractions, or a peroneal palsy in one case, could not be prevented.

The value of the methylene blue test for differentiation of various forms of leprosy is illustrated.

Experience gained so far shows that hydroxyprocaine-penicillin is a product which is effective in the treatment of leprosy. It appears to be of great value in the treatment of borderline cases. Its good tolerability in patients allergic to sulfones is of particular significance. Its favorable effect upon the lepromatous form, resulting in quick resorption of lepromatous skin lesions and in distinct reduction of bacilli, equals that of sulfone therapy. Hydroxyprocaine-penicillin is regarded as a product suitable for use on a broader scale in the treatment of leprosy. Its therapeutic value as a depot product should therefore be clearly assessed.

RESUMEN Y CONCLUSIONES

Describese el empleo de un nuevo producto antileproso llamado hidroxiprocaína-penicilina en 29 leprosos, 19 lepromatosos y 10 limítrofes, durante un promedio de 11.5 meses.

Todos los casos limítrofes mostraron mejoría muy notable o notable al cabo del tratamiento. Nueve de ellos se volvieron bacteriológicamente negativos mientras que 1 permaneció débilmente positivo en la mucosa nasal; 4 se volvieron Mitsuda-positivos, 4 débilmente positivos y 2 permanecieron inalterados.

De los 19 casos lepromatosos, 1 mejoró bastante decididamente, 11 mostraron indudable mejoría clínica y 1 enfermo no se despejó más que en poca escala; 6 casos permanecieron inalterados.

La aparición de reactivaciones pasajeras de la dolencia entre los casos limítrofes y de reacciones ENL en los lepromatosos no afectó los buenos resultados obtenidos en conjunto. No se consideró que estas reacciones fuesen síntomas de intolerancia hacia la droga. Las afecciones neurales que aparecieron en 3 enfermos, dando por resultado pequeñas atrofas y contracturas musculares, y una parálisis peronea en un caso, no pudieron prevenirse.

Queda ilustrado el valor de la prueba del azul de metileno para la diferenciación de varias formas de lepra.

La experiencia obtenida hasta ahora demuestra que la hidroxiprocaína-penicilina es un producto eficaz en el tratamiento de la lepra, que parece ser de mucho valor en los casos limítrofes. Su tolerabilidad en los enfermos alérgicos a las sulfonas es en particular de importancia. Su efecto favorable sobre la forma lepromatosa, dando por resultado la rápida reabsorción de las lesiones cutáneas lepromatosas y una reducción bien definida de bacilos, iguala el debido a la sulfonoterapia. Se considera que la hidroxiprocaína-penicilina es un producto apropiado para empleo en mayor escala en el tratamiento de la lepra, cuyo valor terapéutico como producto de depósito debe por lo tanto ser justipreciado claramente.

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