CLINICAL EVALUATION STUDIES IN LEPROMATOUS LEPROSY: A 24-WEEKS' STUDY OF PYRAZINAMIDE-ISONIAZID THERAPY

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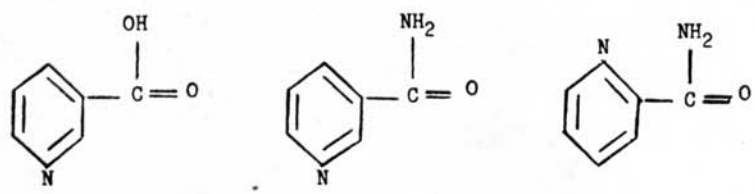
Pyrazinamide[2] was synthesized at the Lederle Laboratories by Kushner *et al.* ([5]) in the search for synthetic compounds with possible antituberculosis activity. It is a diazine carboxamide related to nicotinic acid, differing from nicotinamide in chemical structure in that a carbon atom in the para position is replaced by one of nitrogen.



Nicotinic acid **Nicotinamide** **Pyrazinamide**

The tuberculostatic activity of pyrazinamide (PZA) was estimated ([5]) to be about three times greater than that of *p*-aminosalicylic acid (PAS) or nicotinamide, but substantially lower than that of streptomycin. Malone *et al.* ([6]) demonstrated that in experimental tuberculosis in mice there was a significant prolongation of survival time and considerably less lung involvement in animals treated with PZA than in the untreated controls. Dessau *et al.* ([3]) tested PZA against experimental tuberculosis in the guinea-pig. When given in the diet, it was slightly less effective than 4-4'-diaminodiphenyl sulfone (DDS) but more effective than PAS and nicotinamide. When injected subcutaneously it was less effective than streptomycin. Toxic effects were absent although the guinea-pigs received from 30 to 900 mgm./kgm. daily.

Yeager *et al.* ([10]) treated with PZA 43 patients suffering from active pulmonary tuberculosis. The administration of the drug was promptly followed by a rapid reduction of temperature, and lessening of severity of cough and quantity of sputum. Its effective-

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[2] The proprietary name of the Lederle Laboratories, American Cyanamid Co., for this drug is Aldinamide.

ness was apparently unaffected by resistance of the tubercle bacilli to streptomycin. The usefulness of PZA was found to be limited, however, by rapid emergence of drug-resistant bacilli. The toxic reactions that were noted were all mild. Jaundice occurred in two patients, preceded by anorexia and lassitude, one after 142 gm. of PZA had been given over a period of 42 days; the other after 159 gm. in a period of 87 days. Recovery followed discontinuance of the drug and there was no evidence of hepatic disease in these patients, six and eight months later.

A combination of PZA and isoniazid (INH) was shown by McDermott *et al.* [7] to be highly effective in experimental tuberculosis of mice. Favorable results with this combination in human tuberculosis were also reported by Schwartz and Moyer [9], Campagna *et al.* [1], and Philips *et al.* [8].

Chang [2] studied the suppressive activity of PZA in experimental murine leprosy and found that the drug had a degree of activity similar to that of INH and nicotinamide and superior to that of streptomycin. He suggested clinical trial of PZA and of nicotinamide in human leprosy.

PRESENT STUDY

The therapeutic activity of PZA in tuberculosis and in murine leprosy made it obviously desirable to test this drug in human leprosy. The emergence of resistant strains in tuberculosis and the favorable results with combined PZA-INH therapy suggested the advisability of using this combination of drugs. Studies of the combined effect of PZA and INH were therefore carried out at two leprosaria in the Philippines, the Central Luzon Sanitarium in Tala, Luzon, and the Eversley Childs Sanitarium in Mandawe, Cebu.

Treatment was given for 24 weeks; at Central Luzon from November 14, 1955, to April 30, 1956, and at Eversley Childs from October 31, 1955, to April 16, 1956.

Selection of patients.—At each institution 30 patients were selected, all suffering from the lepromatous type of the disease, bacteriologically positive and lepromin negative. The patients at each institution were divided into two groups which were matched carefully in respect to characteristics that might affect prognosis. This matching was done at the Washington, D. C., office of the Leonard Wood Memorial. The characteristics that were given principal weight were sex, age, stage of disease, and prior sulfone treatment. At Eversley Childs only 4 of the 30 had had sulfones, and at Central Luzon only 5. By coin tossing it was decided that Group A at each institution would be given PZA and INH and Group B the reference drug, DDS.

Dosage.—The dosage of PZA was 30 mgm. per kgm. body weight and of INH 5 mgm. per kgm. throughout the period. The dosage of DDS commenced at 50 mgm. daily and increased to a maximum of 200 mgm. daily at the beginning of the tenth week. All drugs were given by mouth, and none was given on Sundays.

Tests of liver function.—At Central Luzon, the urine of every patient of both groups who completed therapy was negative for urobilin by Ictotest[3] and within normal limits for urobilinogen by the Wallace-Diamond method in examinations made before therapy, and at the end of the 8th, 16th and 24th weeks. Catarrhal jaundice was noted at the end of the 16th week in one patient of Group B (DDS), but the results of the urine tests were normal at that time. Unfortunately, this patient left the institution shortly thereafter without permission.

At Eversley Childs the urine of every patient was negative for urobilin by Ictotest on preliminary examination, and that of every patient of Group A who completed treatment was negative also at the end of the 8th, 16th and 24th weeks. The patients of

[3] Ictotest is a brand name of the Ames Company, Elkhart, Indiana, for a tablet containing *p*-nitrobenzene diazonium *p*-toluene sulfonate ("Bilazo"). The reaction of bilirubin in the urine with the diazo compound produces a purple color within 30 seconds. After that time negative urines may give a pink color which should be disregarded.

Group A were not tested during therapy. Quantitative serum bilirubin estimations were made on the blood serum of each patient of Group A at the end of the 8th and 16th weeks. In all cases the quantity was less than 1.0 mgm. per 100 cc. Jaundice was not observed in any patient of either group.

Other laboratory tests.—Other laboratory tests were performed before and during therapy, including hemoglobin estimations, red cell counts or packed cell volume, sulfone determinations and routine urine examinations.

Eight sites were examined for *M. leprae* before treatment, at the end of the 12th week and at the end of the 24th week. These sites were selected and the smears stained, examined and graded in the same way as in the Clinical Evaluation Studies, First Series, as described by Doull *et al.* (4). One site on each side of the nasal septum, one on each earlobe, and four optional sites elsewhere were included.

Physical examinations.—Dermatologic and neurologic examinations were made at monthly intervals by the research leprologists (J. V. F. at Central Luzon and J. G. T. at Eversley Childs). Serving as consultant leprologist, one of us (J. G. T.) examined the patients at Central Luzon before commencement of therapy and at the end of 24 weeks. Another of us (J. N. R.) in a similar capacity, made those examinations at Eversley Childs. The nature of the treatment given to a patient was not disclosed to the consultant until the final examination was completed.

Photographs.—Color and black-and-white photographs were made during the preliminary period and at the end of therapy.

Record keeping.—Records of clinical and laboratory results were kept on forms similar to those used in the first series (4). After completion of therapy these records were sent to the Washington office of the Memorial for analysis.

Dropped patients.—At Central Luzon, 7 patients, 3 of Group A and 4 of Group B, left the institution without permission during the study. At Eversley Childs, 1 patient of Group A left without permission. All other patients completed therapy.

RESULTS

Clinical changes.—At the conclusion of therapy the consultant made a complete review of the clinical findings for each patient. Basing his opinion on these findings only, he then entered his final judgment on the record as improved, stationary, or worse. Degrees of improvement or worsening were defined as slight, moderate or marked. These opinions are summarized in Table 1.

TABLE 1.—*Clinical status after 24 weeks therapy with pyrazinamide-isoniazid (Group A) and DDS (Group B) at Central Luzon and Eversley Childs Sanitaria.*

Status	Central Luzon		Eversley Childs		Both institutions	
	A	B	A	B	A	B
Improved	4	2	2	7	6	9
Stationary	7	8	6	8	13	16
Worse	1[a]	1[a]	6[b]	0	7	1
Total	12	11	14	15	26	26
Absconded	3	4	1	0	4	4
Grand total	15	15	15	15	30	30

[a] Slightly.
[b] Slightly, 5; moderately, 1.

It is evident from inspection of Table 1 that as far as could be judged on clinical grounds at the end of 24 weeks, combined therapy with PZA and INH did not give results superior to those obtained with DDS. There is in fact a suggestion that the PZA-INH results were in-

ferior. At both institutions taken together, 6 patients of Group A improved as compared to 9 of Group B. For the cases in Group A the signs of worsening were increase in infiltrations, or the appearance of new plaques, or both. In the single patient recorded as moderately worse, a lepromatous ulcer of the skin occurred, in addition to increase in infiltrations and plaques.

The patient of Group B who became worse showed new reactional plaques on the extremities, and lepromatous ulcers on the legs which were not present on the preliminary examination.

Bacteriologic changes.—No patient became bacteriologically negative at all of the eight sites regularly examined. The proportions of sites that were negative, or slightly or moderately positive (VS, 1+, 2+) and heavily positive (3+, 4+) on preliminary examination were maintained at about the same levels at the final examinations. That is, there is no evidence that significant bacteriologic improvement or worsening occurred in either group at either institution. The percentage distribution of sites according to bacteriologic findings before and after therapy is given for each institution in Table 2.

TABLE 2.—*Percentages of sites negative; VS, 1+ or 2+ positive, and 3+ or 4+ positive, on preliminary examination and after 24-weeks treatment, for patients of Groups A and B at each institution who completed therapy; eight sites on each patient.*

Results of smears	For all 8 sites							
	Group A (PZA-INH)				Group B (DDS)			
	Central Luzon		Eversley Childs		Central Luzon		Eversley Childs	
	Prelim.	24-wk.	Prelim.	24-wk.	Prelim.	24-wk.	Prelim.	24-wk.
Negative	1.0	4.2	7.1	5.3	—	—	3.3	6.7
VS, 1+, 2+	41.7	45.8	44.6	56.3	30.7	44.3	46.7	57.5
3+, 4+	57.3	50.0	48.2	38.4	69.3	55.7	50.0	35.8
Total	100.0	100.0	99.9	100.0	100.0	100.0	100.0	100.0

SUMMARY

The therapeutic value of combined therapy with pyrazinamide (Aldinamide) and isoniazid (INH) was compared with that of 4,4′-diaminodiphenyl sulfone (DDS) in a 24-weeks' study. Only lepromatous patients were treated, and duplicate experiments were carried out, one at the Central Luzon Sanitarium and the other at the Eversley Childs Sanitarium in the Philippines.

Of 26 patients completing therapy with pyrazinamide and isoniazid, 6 showed clinical improvement, 13 had remained stationary and 7 had become worse. Of 26 treated with DDS, 9 showed clinical improvement, 16 had remained stationary and 1 had become worse.

No significant bacteriologic changes occurred in either group at either institution.

For the dosages used, that is, 30 mgm. per kgm. body weight of pyrazinamide and 5 mgm. per kgm. of isoniazid, treatment with pyrazinamide and isoniazid was well tolerated, no evidence of toxicity having been noted.

RESUMEN

En un estudio que duró 24 semanas se comparó el valor terapéutico del tratamiento combinado con piracinamida (Aldinamida) e isoniacida con el de la 4,4′-diaminodifenil-sulfona (DDS). No se trató más que a enfermos lepromatosos, y los experimentos se llevaron a cabo en duplicado: uno en el Sanitario Central de Luzón y el otro en el Sanitario Eversley Childs, ambos en las Filipinas.

De 26 enfermos que terminaron el tratamiento con piracinamida e isoniacida, 6 revelaron mejoría clínica, 13 permanecieron estacionados y 7 empeoraron. De 26 tratados con DDS, 9 mostraron mejoría clínica, 16 permanecieron estacionados y 1 empeoró.

No hubo importantes alteraciones bacteriológicas en ninguno de los dos grupos en uno u otro establecimiento.

A las dosis usadas, es decir, 30 mgm. de piracinamida por kg. de peso vivo y 5 mgm. de isoniacida por kg. de peso, el tratamiento con piracinamida e isoniacida fué bien tolerado, sin que se notaran signos de toxicidad.

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