THE VALUE OF THIACETAZONE (TB-1) IN LEPROSY [1]

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INTRODUCTION

A bacteriostatic action of certain thiosemicarbazones against *Mycobacterium tuberculosis* was reported, beginning about 1948, by Domagk ([2]) whose studies on the sulfonamides are well known. This author separated a thiosemicarbazone as an intermediate product in the sulfamido-thiazole synthesis, and observed that the thiacetazone, or TB-1 (also called Tibione, or, originally, Conteben), had a marked effect on the tubercle bacillus. Studies have demonstrated specific effects on *M. tuberculosis* consisting in changes in the morphology and staining power of the organisms and reduction of toxin elaboration; and tuberculous lesions showed regressive changes.

Several leprologists were promptly inspired to try this drug in leprosy treatment. Within a short time there appeared reports such as those of Hohenner ([4]), Ryrie ([5]), Schneider ([6]), Vegas *et al.* ([8]), Gomez Orbaneja *et al.* ([3]), Dharmendra and Chatterjee ([1]), and Schujman ([7]), all reporting good results.

My own experience with this drug dates from January 1951. Since then I have used it in the treatment of about 220 leprosy patients, including 10 borderline cases which are not dealt with in this report. This is the fourth report on the subject to be made.

From the start my impressions of the effects of TB-1 were favorable, and its use has been continued because of the excellent results obtained. TB-1 is not inferior to the sulfones in any way. On the contrary there are some advantages, particularly those relating to the absence of toxic and side effects when the dose employed is not excessive. Consequently, no protective medicaments, such as liver extract and iron compounds, are necessary as is usually the case when the sulfones are used. From this point of view, treatment with thiosemicarbazone is more economical. Furthermore, the drug seems to be relatively more effective than the sulfones against the neural manifestations of leprosy.

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[1] This paper was prepared for presentation at the VII International Congress of Leprology, held in Tokyo, Japan, November 12-19, 1958, but because the author was not present it was not included in the program.

It is my opinion that TB-1 treatment constitutes a first-rate antileprosy therapy, and that this drug should not be relegated to a place of secondary importance. The resolution on therapy of the Madrid congress, in 1953, revealed that the committee which prepared it had had very little experience with this drug, and they were unable to appraise it. A regrettable hesitation is found in their report, in that they recommended the use of thiosemicarbazone only as an alternative treatment for patients who do not tolerate the sulfones. Not understandable is the reference to serious toxic effects, which I have never seen. [2]

For my own part, I have more and more confidence in this drug, the results of whose use are observed in the changes of the clinical, bacteriologic and histopathologic aspects of the patients.

DRUG, DOSAGE AND TOLERANCE

Drug.—Thiacetazone, or TB-1, which has been used entirely in this work until very recently, is *p*-acetylaminobenzoicaldehyde thiosemicarbazone.

Lately another substance of the same group has been under trial, a product of the Wander Laboratory called Tebacyl. Its chemical designation is *p*-ethyloureidobenzoaldehy thiosemicarbazone. It is believed to be even less toxic than TB-1. As yet it has been given to only a few patients.

Dosage.—TB-1 is given by mouth in the dosage of 100 or 150 mgm. daily, in tablets of 25 or 50 mgm., two or three times a day. Higher dosages are not advantageous. It is given without interruption unless some serious occurrence makes it necessary to withdraw it temporarily. Tebacyl is given in the same dosage.

Tolerance.—From this point of view the thiosemicarbazone is, beyond question, superior to the sulfones. No toxic or side effects have been observed in any but one of our 220 patients, and that patient had been subjected to a stomach operation (gastrectomy).

The toxic accidents sometimes reported by others seem to have been due to excessive doses, above 150 mgm. daily, or to some previous organic trouble. Fortunately, we have not had to deal with anemia or leucopenia, or any such disturbance as liver damage. Anemia, with considerable reduction of red blood cells and hemoglobin, is often observed in sulfone therapy, but as said it has not been seen in our cases treated with thiosemicarbazone.

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[2] In the resolutions on therapy of the Tokyo congress, 1958, there is a more definite statement about TB-1. It begins, "This compound has been used fairly widely as an alternative to sulfones in a daily dosage in adults of 100 to 200 mgm. It is effective, but has toxic qualities of about the same order as DDS." No definite recommendations regarding its use were made. [See THE JOURNAL **26** (1958) 342.]—EDITOR.

EFFECTS OF THIOSEMICARBAZONE TREATMENT

EFFECTS ON CUTANEOUS LESIONS

1. *Lepromatous type.*—The results seen after four to six months of treatment are convincing of effectiveness. Among 85 patients of this type, only 1 did not show constant benefit; the other 84 have shown unquestionable amelioration. The exceptional case did not show improvement under sulfone treatment, either.

The lesions of the lepromatous type—erythematous and pigmented-erythematous macules, infiltrations, tubercles and nodules—are promptly influenced for the better, with reduction in their volume and gradual fading of their color until they disappear.

Diffuse infiltrations may subside within as little as three months. In many cases tubercles flatten without leaving traces of their existence, sometimes after only five months of treatment but usually after longer periods—one, two, or three years.

Many patients improve so markedly in a relatively short time that the disease is no longer revealed on their faces. The time periods in representative cases were five months (Case 131), nine months (Case 213), ten months (Case 95), fifteen months (Case 78), and eighteen months (Case 83).

Reactions of the erythema nodosum leprosum type are observed with about the same frequency as in sulfone treatment. About 65 per cent of the lepromatous patients have shown this manifestation.

2. *Tuberculoid type.*—In the 75 cases of this type the results obtained have been entirely satisfactory. Clinical regression often occurs with astonishing rapidity. Marked amelioration is usually seen after one month of treatment, and there are few cases without marked regression—short of clearing up—within six months. The time required for complete clearing varies greatly from case to case, but on a general average it takes about one year.

Hypochromic macules recover their pigmentation usually within three months or so, but there are occasional cases—only about 2 per cent—in which repigmentation is rather slow, not complete until after two years or so of treatment.

The most interesting results have been the following: clearing within three months (Case 102), clearing of extensive lesions after about one year (Case 146), recovery of pigmentation within three months (Case 119).

3. *Reactional tuberculoid cases.*—This group is composed of 15 cases. As a general rule, they begin to improve before the end of three months. Most impressive is the fact that 3 of these patients showed striking amelioration after only one month, and in 5 other cases the same degree of improvement was seen within three months.

The most striking results were obtained in 4 cases which, because improvement began early, became completely cleared in a short period in spite of extensive lesions. Two other cases, also with large lesions, became cleared within one and two years, respectively.

4. *Indeterminate form.*—This group is composed of 35 patients. Amelioration in such cases may be noticeable after the first month of treatment, and generally the lesions are cleared in less than one year.

EFFECTS ON MUCOUS MEMBRANES

The effects on lesions of the nasal mucosa membranes are quite satisfactory. Complete clearing of nasal obstruction usually occurs within two to four weeks. One case, the slowest one to get regression of this sort, took two months to clear up. Nasal ulcers usually heal in less than seven months, and in no case did it take longer than one year to get complete healing.

EFFECTS ON NEURAL MANIFESTATIONS

Some cases recover from manifestations of nerve involvement in a surprising manner. The most interesting example is that of a patient (Case 102) with muscular atrophies whose right hand got better within three months, and who by about the fourteenth month had recovered completely so that the atrophies were no longer distinguishable. Similar results have been obtained in 4 other patients, although they took a little longer.

In this matter thiosemicarbazone seems to be superior to the sulfones, as Ryrie remarked. Unfortunately, this is not to be observed in all cases. Of course, favorable results may be obtained only before the nerve lesions have reached the irremediable stage.

EFFECTS ON THE BACTERIOLOGY

The effects of thiosemicarbazone on the bacillus content of the lesions are, in general, comparable to those of the sulfones, although there have been a few cases which seemed to be in favor of the thiosemicarbazone. In 30 per cent of the lepromatous cases in this series, the numbers of bacilli had diminished after the first year of treatment. Degenerative forms—faded and broken bacilli, and bacilli of granular aspect—are usually found in lepromatous patients who have been under treatment for more than one year.

In several noteworthy cases negativization occurred within periods shorter than is usual in similar patients under sulfone treatment: one year (Case 108), twenty months (Case 162), two years (Case 16), two years and four months (Case 32), two years and six months (Case 89), and three years (Case 24).

Reactional tuberculoid and borderline cases become bacteriologically negative more readily than do lepromatous cases—usually after three months. One reactional tuberculoid case (Case 38) became negative in only one month.

My own experience does not permit me to share the opinion of certain authors who have reported that thiosemicarbazone was inferior to the sulfones from the viewpoint of producing bacteriologic negativization. Unfortunately, bacteriologic negativization of lepromatous cases is slow, whichever of these drugs be used. Leprologists are still waiting for an ideal drug to make such cases negative in a short time, to lessen the possibilities of their causing new contagions while under treatment.

EFFECTS ON HISTOPATHOLOGY

1. *Lepromatous type.*—The lesions show evident alterations, which demonstrate undoubted action of thiosemicarbazone, as a diminution of the infiltrate at the time when the bacilli are becoming converted into acid-fast granulations. Such alterations may be seen within six to twelve months of the treatment. Later on, when the bacilli disappear, the lesions take on the aspect of the "leproma in regression," before changing to the banal chronic inflammatory infiltration of nonspecific nature.

Two of the lepromatous cases treated changed in their histology to the reactional tuberculoid picture. It may be that this occurrence signifies that they were of the borderline form, wrongly taken at the beginning for lepromatous.

2. *Tuberculoid type.*—Although most of the tuberculoid patients show clinical amelioration very rapidly, giving the impression of complete subsidence within a few months, the histologic examination shows more persistent abnormality. Usually the tuberculoid structure has disappeared, leaving only residual simple chronic inflammatory infiltration, but sometimes the tuberculoid structure persists. In about 85 per cent of tuberculoid cases the characteristic picture disappeared during the second year of treatment.

3. *Reactional tuberculoid cases.*—In these cases the lesions may change, and show only the chronic inflammatory exudate, after only a few months of treatment. This rapid involution was seen in two instances (Cases 30 and 71). On the other hand, in one patient (Case 111) it was expected that that conversion would be found because of the apparent state of the lesions after six months of treatment, but actually the histologic picture was tuberculoid.

In borderline cases the lesions may lose their special histology, with only the banal chronic exudate remaining, after a few months of treatment. Two such cases changed to reactional tuberculoid.

4. *Indeterminate form.*—As the general rule, patients of the indeterminate form, with lesions showing only the simple inflammatory exudation at the outset, continue to show the same histologic picture after as much as three years of treatment, although the amount of exudate is reduced, and the clinical appearance is of complete cure.

SUMMARY

The author has employed TB-1 in the treatment of leprosy since 1951, and in that period 220 patients have been submitted to this therapy. The results obtained have convinced him that TB-1 is a first-rate drug which merits more consideration than it has been given. To relegate TB-1 to a secondary rank denotes lack of experience or error in judgment. Continued experience has been convincing of its value because of the results obtained from the clinical, bacteriologic and histologic points of view.

The dosage to be used is from 100 to 150 mgm. a day; there is no advantage in using higher doses. Within this limit all of the patients have tolerated the drug quite well, without toxic effects. It is superior to the sulfones principally in the matter of tolerance. As yet neither anemia nor liver disturbance has been observed. Treatment becomes easier, for it is unnecessary to control the patients by blood examinations or urinalyses.

The drug is effective in any form of the disease: lepromatous, tuberculoid, borderline, or indeterminate. Its success with respect to skin and mucosa lesions is very similar to that of the sulfones. For neural disturbances it seems to be better than the sulfones, although it is still not the ideal treatment for those difficult conditions.

RESUMEN

El A. ha empleado la TB-1 en el tratamiento de la lepra desde 1951 y en ese período de tiempo se han sometido 220 enfermos a dicha terapéutica. Los resultados obtenidos lo han convencido de que la TB-1 es una droga de primera fila que merece mayor consideración que la que ha recibido. La relegación de la TB-1 a un puesto secundario denota falta de experiencia o error de criterio. El uso continuo demuestra el valor de esta droga por virtud de los resultados obtenidos desde los puntos de vista clínicos, bacteriológicos e histológicos.

La dosis que debe usarse es de 100 a 150 mgms. al día; no se gana nada con el uso de dosis mayores. Dentro de dichos límites, todos los enfermos han tolerado la droga bastante bien, sin efectos tóxicos. La misma es superior a las sulfonas, principalmente en la cuestión de tolerancia. Hasta la fecha no se han observado ni anemia ni trastornos hepáticos. El tratamiento se vuelve más fácil, pues no hay que fiscalizar a los enfermos con hemanálisis o uranálisis.

El medicamento resulta eficaz en cualquiera forma de la dolencia: lepromatosa, tuberculoidea, limítrofe o indeterminada. El éxito con respecto a las lesiones cutáneas y mucosas es muy semejante al logrado por las sulfonas. Para los trastornos neurales, parece ser mejor que las sulfonas, aunque no es todavía el tratamiento ideal para estados tan difíciles.

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