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CLINICAL EXPERIENCE WITH ISOBUTOL: A NEW MOLECULAR COMBINATION OF ETHAMBUTOL-INH

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Introduction

It is estimated that there are approximately seven million cases of infectious tuberculosis in the world today and that the vast majority are in the economically underprivileged countries (Bovornkitti, 1978). Tuberculosis, especially if it affects the lungs and the tracheo-bronchial tree, remains undoubtedly a problematic disease. Despite its great decline in recent years as a cause of death in many countries it has remained a leading killer disease among Filipinos. Since tuberculosis infection occurs more often in the lungs than elsewhere, pulmonary tuberculosis accounts for about 92% of the total deaths from tuberculosis and represents in most instances the source of the disease in other organs.

Tuberculosis control in the Philippines remains a problem of serious proportion despite many years of unrelenting fihgt against the dreaded disease. One difficulty that has been encountered is that the majority of patients cannot afford to pay for treatment and so the disease becomes widespread. This unfortunate situation exists in spite of the advances that have been made in the actual treatment of the disease. Moreover, it is now possible to treat the disease successfully and even to guarantee against relapses (Byrd, 1974).

One of the benefits of modern chemotherapy is most evident in the management of tuberculosis. In all these years during which tuberculosis has been known to have afflicted mankind, it is gratifying to observe that the most significant breakthrough in the control of the disease have occurred during this era (Aquinas, 1977).

Prior to the discovery of Streptomycin by Waksman and associates in 1944, there was no effective agent available for the treatment of pulmonary tuberculosis and this disease was a major public health problem with an extremely high morbidity and mortality rate. The actual treatment of pulmonary tuberculosis in terms of chemotherapy regimens, carried out in any country, has been determined by such factors as cost, drug availability, acceptance, tolerance and toxicity.

For the past 25 years or so, various anti-TB drug regimens have been introduced, capable of obtaining almost 100% favorable results. Chief among these was the Streptomycin-PAS-isoniazid regimen (Leonin, 1976a). However, despite their efficacy, there were difficulties associated with these regimens. Incidence of hepatotoxicity was observed with PAS among Filipino patients and the apparent inconvenience of taking too many tablets led to a high percentage of drug drop-outs with PAS. One of the most significant changes in the mode of therapy of tuberculosis was the complete replacement of PAS as a primary drug by ethambutol in 1960 (Clarke et al., 1972).

For a while the physical combination of INH-ethambutol (Thomas et al., 1961) was a popular regimen until, May 1971, when Dr. C. Xalabarder published his clinical experience with a new drug combination of isoniazid and ethambutol in a single molecule linked by a methyl sulfonic acid bond. This drug, which was known by its generic name Isobutol**(commercially known as ISOETAM® is an anti-tuberculous drug derived by conjugation of isoniazid and ethambutol through a methyl sulfonic bridge. It is a connection of two powerful anti-bacteric agents attached by a disulfide bridge. The purpose of this combination is to keep the strong anti-microbic activity of isoniazid in the manner where ethambutol would delay the appearance of resistance (Xalabarder, 1971).

In isobutol, the physico-chemical properties of isoniazid and ethambutol are modified in such a way that the highest blood level is attained 5 to 6 hours after administration. The therapeutic blood level is maintained for 18 hours and the elimination remained constant. This slowing down of the bio-degradation and the elimination allows

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an increase of the bio-availability of isobutol, that is, there will be a higher concentration of the drug, capable of reaching the injured organ. Thus, this combination became, what is known as the molecular combination. Another significant feature of this new connection was the assimilation of isoniazid not in the form of isonicotinyl-hydrazide but as isonicotinyl-hydrazide methylsulfonic acid since it has already allowed the entry of one sulfur bond, thus incorporating both isoniazid and ethambutol in a single molecule.

The purpose of this paper, therefore, was to show the effectiveness isobutol in the original treatment of pulmonary tuberculosis, including the rate of sputum conversion, incidence of side effects and intolerance, and to detect the appearance of microbial resistance.

Materials

Newly discovered pulmonary tuberculosis cases (without previous chemotherapy). Patients were positive by sputum microscopy before administration of the drug. Extent of the tuberculosis is limited to moderately and far advanced cases, with or without cavity.

Methods

Isobutol per tablet consists of 110 mg of isoniazid and 110 mg athembutol. Dose was 11 mg per kilogram body weight or one tablet per 10 kilograms body weight given in two divided doses, after meals.

The regimen was maintained for 6 months, but the regimen could be interrupted if there would be failure to improve or toxic manifestations appear.

Sputum examinations by microscopy were done prior to administration of the drug, and 3 consecutive times, every 15 days for the first 2 months and monthly thereafter for 6 months.

No other anti-TB drugs were given. Clinical improvement was noted. Laboratory examinations were done monthly including renal tolerance, liver profile tests, and CBC. Fundoscopy and color discrimination tests were done initially and monthly. Acceptance and tolerance to the drug was observed.

Results and Observations

There were 19 patients who initially started the clinical study. The age range was 18–59 years old. There were 11 males and 8 females. All were positive by sputum microscopy initially. There were 7 cases of moderately advanced non-cavitary cases.

However, after 3 months, for reasons other than toxicity and intolerance, 5 dropped out, and 14 were able to finish the clinical study. There were no deaths among all the patients who were able to finish the three-month as well as the six-month clinical study.

Ten were hemoptic, but none manifested any other complications.

After 1 month, only six (31.58%) patients were still positive, and the rest (68.42%) were already negative. Among the patients who converted in the 1st month, 5 converted on the 2nd week, and 8 in the 4th week. Among the six who were positive after the 1st month, 4 converted in the 6th week and 2 converted in the 8th week, so that by the end of 2nd month, all were already negative. The most notable conversion rate occurred during the first six weeks of therapy with 17 patients (89.4%) already negative (Table 1).

The extent of regression of lesions and cavities on the chest films were interpreted based on approximate total average percentage among all the patients. Interpretation of regression of lesions was done exclusive of the interpretation of regression of cavities.

Table 1. Results of Sputum Microscopy

	1st month (%)	2nd month (%)	3rd month (%)	4th month (%)	5th month (%)	6th month (%)
Conversion	68.4	100	100	100	100	100
Non-conversion	31.6	0	0	0	0	0
Relapse-re-conversion	—	0	0	0	0	0

Table 2. Chest X-ray Evaluation

	Lesions			Cavities		
	1st month (%)	3rd month (%)	6th month (%)	1st month (%)	3rd month (%)	6th month (%)
Regression	26.6	82.4	88.6	17.3	73.6	89.2
Pregression	0	0	0	0	0	0

After the first month, 26.6% of the lesions regressed and 73.4% remained unchanged. By the end of the 3rd month, further regression up to 82.3% was noted and by the end of the 6th month, with 5 patients already out of the clinical trial, 88.6% of the total average lesions regressed. It is significant that most of the lesions regressed between the 1st and 3rd month.

Interpretation of regression or reduction in the sizes of the cavities was also based on total average percentage. After the 1st month, 17.3% regression of the sizes of the cavities was noted. After the 3rd month, there was 73.6% regression. Among the eleven cavitary cases, 2 did not continue with the trial, and at the end of the 6th month, the total average percentage of regression among the patients who remained, was 89.2%. Reduction of the sizes of the cavities occurred between the 1st and 3rd months, but further reduction up to the 6th month, was observed. (Table 2).

Clinical evaluation:

Twenty-four hour average sputum output was measured and after the 1st month, an average decrease of 25–35 m*l* which further decreased to 40–45 m*l* on the 3rd month and down to 80 m*l* after 6 months. Frequency of cough decreased. After the 1st month, 68.4% of the patients showed a weight gain of 10–15 lbs., 26.3% had weight gains of 15–18 lbs. while one patient (5%) showed no change in weight. After the 3rd month, almost half of the patients (47.4%) showed a weight gain of 15–20 lbs. and one patient who had on weight gain after the 1st month showed an increase of 7 lbs. After the 6th month, 57.9% of the remaining patients had an average weight gain of 15–20 lbs. There was marked improvement in appetite in majority of the patients.

Prior to the treatment, 52.6% were non-ambulatory because of marked pulmonary symptoms. A month after treatment most of the symptoms were relieved. The patients could ambulate and remained ambulatory throughout the rest of the clinical study. Almost the 1st month, all the patients were afebrile and remained afebrile throughout. Although, all of the patients had chest symptoms prior to treatment, 89.5% were relieved after the 1st month.

Laboratory results:

Laboratory examinations consisting of renal studies, liver profile tests, hematology and Snellen's test of visual acuity were performed on all patients prior to the administration of the drugs and monthly, thereafter, for six months. Values were normal prior to treatment and remained normal throughout.

Adverse reactions:

One patient complained the slight nausea and vomiting during the 1st week. The symptoms were treated symptomatically and was relieved. One patient complained of mild and transient pruritus on the 3rd day of therapy. The symptoms were relieved after a day and in both instances the drug was not altered or discontinued. There was good tolerance and acceptance to the drug.

Discussion

The importance of ensuring that every patient with active pulmonary tuberculosis receives adequate therapy is obvious. To achieve such an objective, a method should be established which can offer effective, adequate, non-toxic and tolerable anti-TB regimen. The treatment of PTB in general through the use of various combinations of anti-tuberculous drugs has reached the stage of maximum effectivity. With adequate duration of therapy and proper selection of drug regimen in the management, a very high cure rate has been achieved among the virgin cases which can provide an early return of patients to active and productive lives. The treatment period and regimen for original cases must be definitely established to be highly successful. Conversely, patients who received inadequate and ill-supervised treatment, most often lead to failures and the disease will eventually progress to a stage of more

widespread lesions.

For quite sometime, the physical combination of INH-ethambutol has been accepted as truly effective in minimal and moderate cases, but in cavitary and far advanced cases when the bacillary population has been presumed to be great, the use of a third drug, either rifampicin or streptomycin may become necessary. Although streptomycin is a popular drug among the low income group, a high percentage of auditory complaints has been attributed to its use. Rifampicin, on the other hand, is an effective anti-TB drug but it is so expensive that it is beyond the reach of most TB patients (Raleigh et al., 1972).

The search for an ideal and practical regimen which is economical, effective, safe, and acceptable resulted in the introduction of a molecular combination of INH-ethambutol known as Isobutol for oral administration with a convenient dose form. The effectiveness of isoniazid is already well established and the clinical activity of ethambutol, a bacteriostatic drug, molecularly combined with INH has been investigated in the original treatment of advanced pulmonary tuberculosis in numerous controlled studies and foremost of which was the report of Pastor et al., 1974. In the Philippines, Isobutol was first introduced in 1976, and was the subject of a clinical trial by Quezon Institute on Filipino subjects with newly diagnosed PTB (Santos et al., 1977) followed later by our clinical investigation conducted at the Veterans Memorial Medical Center. Chavez, from UP-PGH initiated a study for retreatment cases (Chavez et al., 1979).

Quezon Institute reported a sputum conversion of 82% after the first month and 100% conversion after the 2nd month in contrast to the results of our present investigation of 68.4% sputum conversion after the 1st month, with a 100% conversion after the 2nd month.

A study conducted by Leonin et al. using the physical combination of INH-ethambutol compared with INH-rifampicin for new cases published in 1974 (Leonin et al., 1974b) showed that sputum conversion in INH-rifampicin was 21% after the 1st month, 80% after the 2nd month and 100% after the 3rd month. The physical combination showed a sputum conversion of 5% after the 1st month and 70% after the 3rd month.

92.3% after the 3rd month and 86.7% after the 6th month regression of lesions on chest roentgenograph were noted in the Quezon Institute trial while our present study showed an 82.4% regression after the 3rd month and 88.6% after the 6th month. In the same 1974 study by Leonin et al., 64% after the 3rd month, and 93% regression of lesions after the 6th month was observed among the group who received INH-rifampicin and 40% after the 3rd month and 70% after the 6th month among the INH-ethambutol physical combination users.

In our clinical study, there were 11 cavitary cases and 11 far-advanced cases. And following the established principles, a triple drug combination or an isoniazid-rifampicin dual-drug combination should have been used to insure better results (Fox et al., 1975), but our study made use only of two basic effective anti-TB drugs, combined in a single molecule, isoniazid which is a complete bactericidal drug and ethambutol, a bacteriostatic drug. The results obtained were almost comparable but slightly inferior to isoniazid-rifampicin combination.

The study by Chavez on retreatment cases with the molecular combination showed that for minimal cases, an 82% sputum conversion rate after 8 weeks and 100% after 36 weeks. For the moderately advanced cases, the sputum conversion rate was 80% after 8 weeks and 96% after 36 weeks and the far-advanced cases, 70% after 8 weeks and 86% after 36 weeks. On chest roentgenograph, 90% regression was observed in minimal cases but only 40% for the moderately and far-advanced cases.

Based on the finding for retreatment cases, it can be deduced that radiologically, the response was closely related to the intensity of pulmonary lesions. Chavez, in his conclusion, had widely acclaimed the excellent response of minimal retreatment cases to isobutol therapy alone but has reservations as to the wisdom of using either the molecular or the physical combination alone for the moderately advanced and far-advanced cavitary retreatment cases.

The molecular combination is a sulfurated compound, and it is known that even during the time of Homer and Galen some stimulus capacity of defense for the organism has been ascribed to sulphur, and at that time, it was confirmed that patients suffering from tuberculosis have a deficit in sulphur. Their deficit is caused by their incapacity to incorporate the sulfurated amino acids and glutation to their proteins. With sulfurated compounds, the defenses of the organisms increase against infection. Many authors have stressed the fact that isobutol has a fine mechanism of penetration and concentration in the level of the lungs and its sulphur content prevents a production of fibrous

residues and leads to restituto ad integrum (anti-sclerosis effect) (Civil, 1973).

Following the Jawetz concept of synergistic bactericidal activity of drug combination (Jawetz, 1952), a dual chemotherapy of INH-rifampicin, being both complete bactericidal drugs may be as effective as a triple anti-TB drug regimen consisting of streptomycin (considered only as a half bactericidal drug because it is effective only on alkaline pH), isoniazid and PAS or streptomycin plus a physically combined ethambutol-INH. Since any regimen containing rifampicin may not be practical in a country like the Philippines where drug therapy could be expensive, the results of our study using a molecularly combined INH-ethambutol may prove to be the answer to the search for a practical, economical, non-toxic, effective and tolerable drug regimen.

It should be emphasized that while chemotherapy is an important factor in the treatment of tuberculosis, there is an essential element in the host-parasite relationship or the immune defense system of the host also plays an important role in therapy. One outstanding feature of the sulfurated compound is its ability to stimulate and increase the immunological defense mechanism of the host, thereby permitting the host to contain infection more effectively.

The latest mode of therapy calls for the administration of a rifampicin-INH-PZA-streptomycin regimen for 6 months and the initial report found the regimen effective with minimal percentage of relapse (East African/British Medical Research Councils, 1972). PZA is known to be hepatotoxic among Filipino patients and streptomycin is ototoxic. These findings prompted a multicenter clinical studies instituted by the Philippine College of Chest Physicians using ethambutol instead of SM and PZA. Pilheu from Buenos Aires (Pilheu, 1977) reported encouraging results using a rifampicin-INH-ethambutol regimen for short-course chemotherapy. Felipe et al. (unpublished data) from UP-PGH, submitted initial findings that a short-course regimen of rifampicin-isobutol, has so far, shown no evidence of relapse. A better future and a favorable prognosis await the tuberculous patients with an effective anti-TB drug already within their reach and the time is not far when complete eradication can be achieved (Sbarbaro, 1975).

Summary

Isobutol, a molecular combination of INH-ethambutol linked by a sulfur bond was clinically studied on Filipino subjects at the Quezon Institute and VMMC on primary cases and at the UP-PGH for retreatment cases.

Based on its fast sputum conversions and marked regression of lesions on chest roentgenograph, isobutol was found to be effective as the sole anti-TB drug in primary TB as reported by studies separately conducted at QI and VMMC from minimal to far-advanced cavitary and non-cavitary cases. At the UP-PGH, isobutol was likewise used as the sole medicine in retreatment cases from minimal to moderately advanced non-cavitary cases.

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