Volume 44, Number 3
Printed in the U.S.A.

INTERNATIONAL JOURNAL OF LEPROSY
And Other Mycobacterial Diseases

VOLUME 44, NUMBER 3 JULY-SEPTEMBER 1976

Long-Term Clinical Toxicity Studies with Clofazimine (B663) in Leprosy [1]

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Clofazimine (B663, Lamprene®), has been used in the treatment of patients with leprosy since 1962 ([12]). It has come to have definite indications in the management of leprosy at Carville, specifically: a) in chronic *erythema nodosum leprosum* (ENL) occurring in females of child-bearing potential in whom thalidomide is contraindicated; b) reactions occurring in borderline to tuberculoid leprosy in which thalidomide is not effective; and c) in patients with sulfone-resistant disease, at least until more experience has been accumulated with rifampin. These indications are sufficient for the relatively widespread use of clofazimine in leprosy. Consequently, detailed analyses of the potential toxicity of this compound are indicated. The present report deals with the results of systematic clinical laboratory testing in search for any long-term toxicity of clofazimine in 51 patients receiving the drug for periods up to eight years.

MATERIALS AND METHODS

From June 1965 through August 1973, 51 patients with leprosy were each continuously treated with clofazimine for at least 24 months. Pertinent clinical characteristics of this group of patients are given in Table 1. The dosages of clofazimine are indicated in Figure 1.

The laboratory tests indicated were performed on each patient at intervals of from one to six months by standard clinical pathology procedures. Normal values for these procedures are indicated in the figures.

Approximately 220 patient-years of observation and an estimated 40,000 total pieces of data have been collected in testing these 51 patients over this eight year period. These data were summarized by determining the average values for each patient per six month period of time. This six month average represented the mean of, from as few as one, to as many as dozens of individual determinations depending on the parameter. Usually routine blood counts and urinalyses were performed routinely every one to two months and blood chemistries, etc., were obtained every two to six months. All available test results were included in the analysis, whether the tests were ordered specifically for clofazimine toxicity or whether they were ordered for other indications, i.e., intercurrent illness.

The summarized data were analyzed as follows: means, standard deviations, and standard errors of the means were calculated for each six month interval for each parameter. Differences in these mean values were tested for statistical significance using the

[1] Received for publication 21 October 1975.

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TABLE 1. *Clinical characteristics of 51 clofazimine treated patients.*[a]

	Mean	Standard Deviation	Range
Year of birth	1920	± 12 yrs.	1894-1942
Year of first symptoms of leprosy	1947	± 12 yrs.	1926-1970
Year of first admission to Carville	1961	± 10 yrs.	1934-1970
Year started on clofazimine	1969	± 1.4 yrs.	1965-1970
Duration of[b] treatment	51.5 mos.	± 16.2 mos.	24-96 mos.

[a] Patient population consist of: males—41 (80.4%); females—10 (19.6%); Caucasian—30 (58.8%); Negro—5 (9.8%); Latin-American—7 (13.7%); Asiatic—9 (17.7%).

[b] Duration of continuous clofazimine treatment as of August 1973.

paired t-test comparing the base line values with values for each patient at each six month interval of clofazimine treatment. Additionally, a paired t-test was performed on the base line values for each patient and the last available value for each patient (after 24-96 months of clofazimine treatment). Finally an overall linear regression line and correlation coefficient were calculated for all values of six month means versus time.

Calculations were performed on a programmable electronic calculator (Hewlett-Packard Model 9810).

RESULTS

The results are presented graphically in Figures 2 through 6. Before receiving clofazimine, a number of patients showed abnormal laboratory findings. Elevations in serum cholesterol (25.5% of the patients), serum glutamic oxaloacetic transaminase (SGOT) (19.6%), thymol turbidity (41.2%), serum globulins (78.4%), uric acid (23.5%), alkaline phosphatase (27.5%), white blood cell count (37.3%), percent neutrophiles (68.6%), and erythrocyte sedimentation rate (ESR) (86.3%) were noted. Lower than normal values were noted for serum albumin (68.6% of the patients), hematocrit (41.2%), hemoglobin (56.9%), percent lymphocytes (56.9%), per-

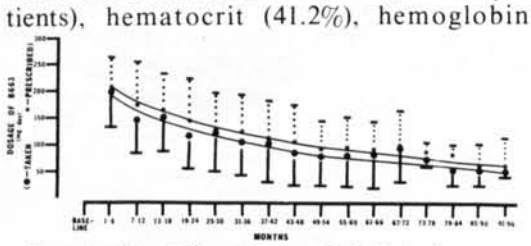

FIG. 1. The daily dosage of clofazimine, prescribed and actually taken by mouth. The data are depicted as means and standard deviations.

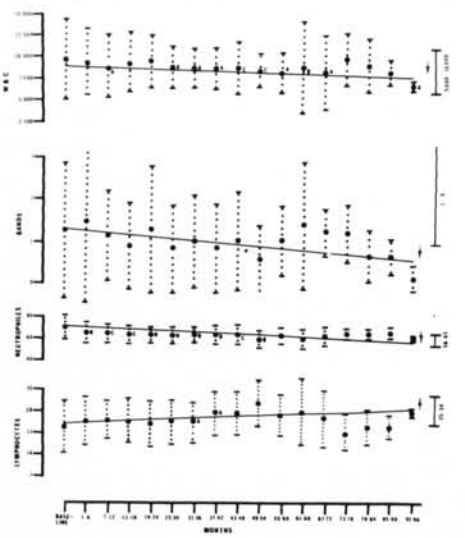

FIG. 2. Changes in white blood cell count (WBC mm^{-3}), neutrophilic bands (as % of white blood cells), neutrophiles (as % of white blood cells) and lymphocytes (as % of white blood cells) with clofazimine.

Values depicted as means ± standard deviations. N=51 for base line, and 51, 49, 51, 50, 50, 48, 39, 33, 21, 11, 8, 6, 3, 4, 4, and 2 respectively for the 16 six month intervals indicated.

↑—indicates an overall significant increase with time by linear regression, $p < 0.01$.

↓—indicates an overall significant decrease with time by linear regression, $p < 0.01$.

A—indicates significant change from base line values, paired t-test, $p < 0.05$.

B—indicates significant change from base line values, paired t-test, $p < 0.02$.

C—indicates significant change from base line values, paired t-test, $p < 0.01$.

D—indicates significant change from base line values, paired t-test, $p < 0.001$.

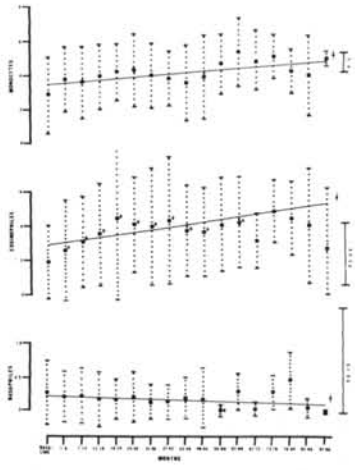

FIG. 3. Changes in monocytes, eosinophiles and basophiles (as % of white blood cells) with clofazimine. Explanation of symbols given in Figure 2.

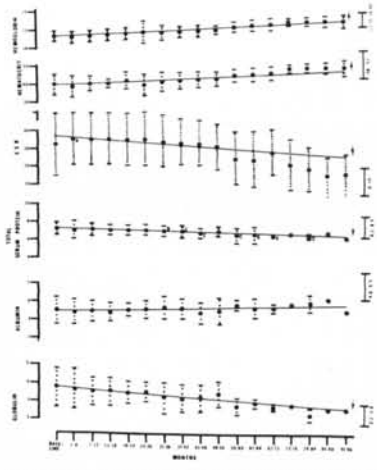

FIG. 4. Changes in hemoglobin (grams %), hematocrit (% packed cell volume), erythrocyte sedimentation rate (ESR in mm hr^{-1}), total serum protein (grams %), serum albumin (grams %), and serum globulins (grams %) with clofazimine. Explanation of symbols given in Figure 2.

cent eosinophiles (25.5%), and percent monocytes (70.6%). It should be noted that overall the calculated absolute counts of each of the types of leukocytes were normal with the exception of an elevated absolute neutrophil count. The abnormal findings before clofazimine was administered must be considered to be a manifestation of these patients' underlying leprosy, and in many patients their concomitant reactions, usually *erythema nodosum leprosum* (ENL).

In a number of parameters there were statistically significant trends noted during the time the patients received clofazimine. In some test results there were significant trends toward normal. Decreases in abnormally elevated values were noted with SGOT (N = 473), thymol turbidity (N = 384), serum globulins (N = 391), uric acid (N = 470), alkaline phosphatase (N = 472), white blood cell count (N = 481), percent (and absolute counts of) neutrophiles (N = 481) and ESR (N = 466). Significant increases toward normal were noted in hematocrit (N = 479), hemoglobin (N = 479), percent lymphocytes (N = 481), percent eosinophiles (N = 481), and

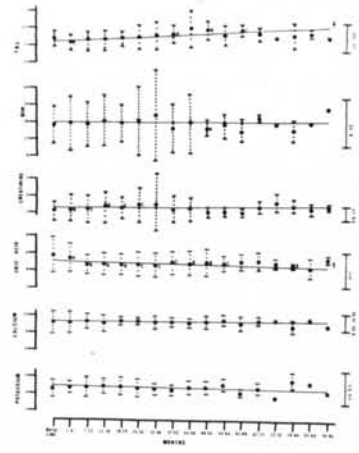

FIG. 5. Changes in fasting blood sugar (FBS in mg % by the ortho-tuluidine method. Glytel®, Pfizer Diagnostics Division, NY, NY), blood urea nitrogen (BUN in mg %), serum creatinine (mg %), serum uric acid (mg %), serum calcium (mEq l^{-1}), and serum potassium (mEq l^{-1}) with clofazimine. Explanation of symbols given in Fig. 2.

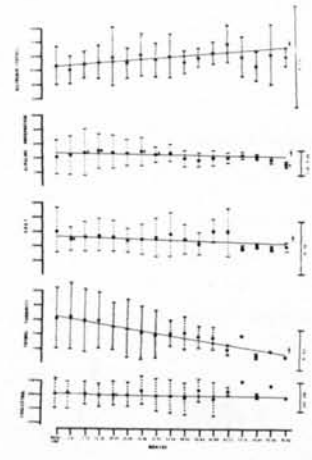

FIG. 6. Changes in total serum bilirubin (mg %), alkaline phosphatase (Bodansky units), serum glutamic oxaloacetic transaminase (SGOT in Transac® units, General Diagnostics, Morris Plains, NJ), thymol turbidity (Shank-Hoagland units), serum cholesterol (mg %) with clofazimine. Explanation of symbols given in Figure 2.

percent monocytes (N = 481).

Although sometimes there were intermediate time intervals which were significantly different by the paired t-test from base line values, as indicated in the figures, no overall statistically significant trends were noted in a number of test results. By paired t-test of base line vs. the last available results, and by overall linear regression, no significant trends were identified in values for blood urea nitrogen (BUN) (N = 409), serum creatinine (N = 470), serum cholesterol (N = 387), serum albumin (N = 391), serum potassium (N = 396), or serum calcium (N = 389). Similarly no changes were identified in the stools for occult blood, routine urinalyses, or reticulocyte counts (data not shown).

Statistically significant increases were noted in values for fasting blood sugar (N = 404). Three patients (5.9%) had abnormally high values before receiving clofazimine and continued to show abnormal elevations afterwards. On the other hand, 12 patients (23.5%) had fasting blood sugars in the normal range at base line and showed elevated values after receiving clofazimine. In seven patients (13.7%) only one abnormally elevated value was seen and in the remaining five patients (10.0%), two or more values were elevated after clofazimine.

A statistically significant increase was noted in total serum bilirubin (N = 474) by the overall linear regression but not by the paired t-test comparing base line with the last available result. One patient showed a value of 1.25 mg% at base line which promptly returned to, and remained within, the normal range after clofazimine. Eight patients (15.7%) showed minor elevations in total serum bilirubin values sporadically while receiving clofazimine.

A statistically significant fall in total serum protein (N = 391) was noted and this was related to the fall in serum globulins associated with no change in serum albumin concentrations. Statistically significant but quantitatively minor decreases were noted in percent neutrophilic bands (N = 481) and percent basophils (N = 481) in the white blood cell differential counts.

DISCUSSION

The antimycobacterial effects of a phenazine group of compounds which later included clofazimine were described in 1948 [8]. A clinical trial of one of these compounds designated B-283 was conducted in leprosy in 1952 [1]. Four of the ten patients treated with B-283 had evidence of liver-damage and this derivative was not used further. Chang [13] found that B663 or clofazimine was effective in *M. lepraemurium* infections in mice. The drug was shown to exert an antibacterial effect in mice infected in the foot pad with *M. leprae* [18, 31, 33]. A pilot trial of clofazimine in leprosy patients was promising [12]. Further studies with clofazimine demonstrated that the drug has an antibacterial effect in leprosy patients [3, 21, 22, 29], although the drug seems to have a slower onset of action than dapsone (DDS) [26]. Significantly, the drug was shown to be active in patients harboring sulfone-resistant organisms [28].

Clofazimine was shown to have anti-inflammatory effects in laboratory animals [16, 35], in patients with ENL [10, 19, 23], and in patients with reactions in the borderline to tuberculoid types of leprosy [30, 32].

Toxicity of clofazimine has been studied rather extensively in experimental animals. Unchanged drug has been found to accumulate in animals fed clofazimine and crystallization of the drug occurs in various tissues [4–7, 13, 14]. In experimental animals the drug appears to occupy two compartments pharmacodynamically. One compartment is evident with short-term and relatively low doses which has a half-life of elimination of approximately one week [24]. A second compartment is evident on long-term high dose administration which probably represents crystals of the compound in various organs, and this second compartment has a half-life of elimination on the order of two to three months [4, 35].

Foreign body reactions have been described to the clofazimine crystals in tissues [7, 13], and focal hepatic lesions have been noted in mice treated long-term with clofazimine [33]. There is selective uptake of the drug by fat cells in laboratory animals as well as cells of the reticuloendothelial system [9, 14, 35]. Since 1969, reports have appeared indicating that clofazimine induces decreases in reticuloendothelial system clearances [5, 15].

In humans, as in experimental animals, accumulation and crystallization of clofazimine occurs in various organs. This is associated with skin discoloration secondary to drug deposition [11, 37], which in some pa-

tients is cosmetically unacceptable [29]. Other sites of accumulation, in addition to the skin, in humans include subcutaneous fat, adrenals, heart, liver, lungs, lymph nodes, kidneys, pancreas, and spleen [27]. Crystals of clofazimine have been described in human bone marrow [2], sputum [6], the lamina propria of the jejunum [2], and the cortical tubules of the kidney [32].

Clinical side effects of clofazimine have been primarily observed in the skin and gastrointestinal tract. Besides the skin pigmentation related to deposits of clofazimine itself, there is an increase in melanin in the skin [11, 25, 29], and phototoxicity has been observed [17, 20]. General dryness of the skin [22, 30], pruritis [37] and ichthyotic changes [3, 32] have been noted in patients receiving clofazimine. Acneiform eruptions [30, 32] and nonspecific skin rashes [32] have been described as well as one possible case of exfoliative dermatitis [37]. The drug apparently crosses the human placenta, and infants born to females who take clofazimine during pregnancy are somewhat pigmented at birth [37]; however, no evidence of teratogenicity has been found [32, 37].

Other than symptoms of "giddiness" and one report of transient hematuria associated with a decrease in creatinine clearance [37], the principle other clinical side effects of clofazimine have involved the gastrointestinal tract. These have consisted of various signs and symptoms including dyspepsia [3], anorexia, nausea, vomiting [2, 32], abdominal pain [2, 29, 30, 32, 36], constipation [32], diarrhea [29, 30, 32, 36], weight loss and a coarsened mucosal pattern in the distal small bowel seen radiographically [2].

On the other hand, despite the pharmacologically disturbing accumulation of relatively massive amounts of the drug in various tissues in humans [27], clofazimine is relatively free of serious side effects when used clinically [2, 20, 22, 23, 32, 34, 36]. The present results have failed to demonstrate any clinically significant toxic effects of clofazimine on the kidneys, liver, or bone marrow as measured by the clinical laboratory tests employed. The trend towards increased values in fasting blood sugar may be a manifestation of clofazimine toxicity. On the other hand, it may well be a reflection of the age of these patients (mean age of 49 years at the beginning of clofazimine therapy) and the tendency for naturally occurring maturity-onset diabetes mellitus to manifest itself with advancing age. A more practical explanation, especially for those patients who had only sporadic values which were higher than normal, might be that over the course of years of periodic testing there were occasions when blood was drawn when the patients were not actually fasting.

Although the skin and gastrointestinal side effects of clofazimine obviously limit its usefulness, it may be concluded that on the evidence to date the drug is remarkably free of serious or life-threatening toxicity. When its use is limited to: a) female leprosy patients of child-bearing potential requiring corticosteroids to control chronic ENL; b) patients having reactions in borderline to tuberculoid leprosy requiring long-term corticosteroids to control; and c) patients with sulfone-resistant disease, the advantages of clofazimine, in our opinion, continue to outweigh any of its presently known disadvantages.

SUMMARY

Fifty-one leprosy patients receiving long-term clofazimine have undergone systematic clinical laboratory testing in a search for any toxicity secondary to the drug. In approximately 220 patient-years of observation and in analyzing approximately 40,000 test results, no statistically significant changes in the direction of abnormality have been observed in SGOT, thymol turbidity, serum globulins, uric acid, alkaline phosphatase, white blood cell count or differential, hematocrit, hemoglobin, BUN, serum creatinine, serum cholesterol, serum albumin, serum potassium, serum calcium, stool for occult blood, routine urinalysis, or reticulocyte count. Statistically significant changes toward abnormality were found in fasting blood sugar and total serum bilirubin. These statistically significant changes in the direction of abnormality were of small magnitude, were not associated with related clinical signs or symptoms, and do not seem to be of major clinical significance. Despite the accumulation of relatively massive amounts of the drug in various tissues, clofazimine appears remarkably free of serious or life-threatening toxicity clinically. Although the skin and gastrointestinal side effects of clofazimine limit its usefulness, on the evidence to date, its advantages outweigh its disadvantages in those leprosy patients for whom it is indicated.

RESUMEN

En este estudio se presentan los resultados de laboratorio clínico efectuados en 51 pacientes leprosos tratados por períodos prolongados con clofazimine, con el objeto de determinar la posible toxicidad secundaria de la droga.

En un módulo de observación de aproximadamente 200 año/paciente y en el resultado de 40.000 análisis, no se observaron cambios estadísticamente significantes en SGOT, turbidez timólica, globulinas séricas, ácido úrico, fosfatasa alcalina, recuento y fórmula diferencial de leucocitos, hematocrito, hemoglobina, BUN, creatinina sérica, colesterol sérico, albúmina sérica, potasio sérico, calcio sérico, sangre oculta en materias fecales, análisis de orina de rutina, o en el recuento de reticulocitos. Cambios anormales estadisticamente significantes fueron hallados en los niveles glucémicos en ayunas y en la bilirrubina total sérica. Sin embargo estos resultados anormales fueron de pequeña magnitud, no estaban asociados con correspondientes signos y simptomas clínicos, y parecian no tener significación clínica. A pesar de la cantidad relativamente masiva de la droga en diferentes tejidos, clofazimine parece estar libre de serios efectos tóxicos.

Aunque los efectos laterales cutaneos y gastrointestinales limiten su uso, resulta evidente que las ventajas exceden a las desventajas en aquellos pacientes en los que la droga está indicada.

RÉSUMÉ

En vue de mettre en évidence une toxicité éventuelle de la clofazimine, on a procédé à des épreuves cliniques et à des épreuves de laboratoire systématiques chez 51 malades de la lèpre qui ont été soumis à ce traitement pendant une longue durée. L'étude a porté sur environ 220 personnes-années d'observation, ayant fourni approximativement 40.000 résultats d'épreuves diverses. Aucune épreuve n'a fourni de valeurs anormales statistiquement significatives quant aux épreuves suivantes: SGOT, turbidité au thymol, globulines du serum, acide urique, phosphatase alcaline, numération de globules blancs, formule sanguine, hématocrite, hémoglobine, BUN, créatinine du serum, cholestérol sérique, albumine sérique, potassium sérique, calcium sérique, présence de sang occulte dans les selles, examen urinaire de routine, ou numération des réticulocytes. Des modifications aussi statistiquement significatives, avec valeurs anormales, ont été relevées dans la glycémie chez des sujets à jeun, et dans la bilirubine totale du serum. Ces modifications statistiquement significatives dans le sens de valeurs anormales étaient de la même ampleur, n'étaient pas associées avec des signes ou symptômes cliniques, et ne paraissaient pas présenter une signification clinique importante. Malgré une accumulation relativement massive de médicaments dans différents tissus, la clofazimine apparaît remarquablement dépourvue de toxicité clinique grave ou menaçant la vie. Quoique les effets secondaires de la clofazimine au niveau de la peau et du système gastro-intestinal restreignent son emploi, il semble d'après les données recueillies jusqu'à présent que ses avantages compensent et au-delà ses désavantages chez les malades de la lèpre pour lesquels elle est indiquée.

Acknowledgments. The authors wish to express their gratitude to Dr. W. Vischer and CIBA-GEIGY, Basel, Switzerland, who for many years donated clofazimine for these studies; to the many dedicated technicians and technologists of the Clinical Laboratory Service who have performed these tests over the last ten years; and to the staff of the Pharmacology Research Department who have laboriously collected, organized, summarized, and analyzed the estimated 40,000 individual pieces of data which make up the present report.

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