Decreased Counts of Blood Neutrophils, Monocytes, and Platelets in Human Immunodeficiency Virus-Infected Children and Young Adults Treated with Diethylthiocarbamate

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Nineteen young human immunodeficiency virus-infected patients were randomized to receive 400 mg of oral diethylthiocarbamate (DTC) per m² or placebo weekly for 12 weeks. Changes in blood CD4+ lymphocytes were not significantly different between groups. However, neutrophil, monocyte, and platelet counts consistently decreased during DTC treatment, suggesting DTC-mediated myelosuppression.

A report that diethylthiocarbamate (DTC) recruited functional T lymphocytes in children undergoing immunosuppressive treatment for cancer (7) has prompted several clinical trials of this drug as a possible therapy for human immunodeficiency virus (HIV)-infected adults. To assess the safety and estimate the efficacy of DTC in HIV-infected children, adolescents, and young adults, we conducted a double-blind, randomized, placebo-controlled clinical trial. Patients aged 6 through 25 years and with HIV infection were eligible for the study if they had blood CD4+ lymphocyte counts of <400/µl or serum HIV p24 antigen detectable by enzyme-linked immunosorbent assay (Abbott Laboratories, Abbott Park, Ill.). Patients who had received antiviral therapy within the 2 months before the study were not eligible. Informed consent was obtained from all subjects or their parents.

The study opened on 19 April 1988 and closed on 21 January 1992. Eligible patients were randomized evenly between DTC and placebo treatment groups by use of assignment cards. The blind nature of the study was maintained until preliminary analyses and interpretation of the results were completed.

Under medical supervision, patients received 400 mg of DTC (Imuthiol; Pasteur Mérieux Serums and Vaccins S. A., Lyon, France) per m² or placebo orally once a week for 12 weeks. The combination of 50- and 125-mg capsules that most closely approximated the calculated dose was prescribed. Patients were not permitted to use anti-HIV drugs during the study.

The demographic, clinical, and laboratory characteristics of the 19 patients who participated in the trial are summarized in Table 1. The primary endpoint of the study was the change in blood CD4+ lymphocyte counts from baseline to week 12. Among the patients who met the CD4+ count entry criterion and completed 12 weeks of therapy, those treated with DTC (n = 7) had a median decrease of 10 CD4+ cells per µl, whereas the placebo-treated patients (n = 8) had a median increase of 60 CD4+ cells per µl (P = 0.06; rank sum test). The difference in the mean count changes from baseline to week 12 between DTC- and placebo-treated patients was -48 CD4+ cells per µl (95% confidence interval, -98 to +2 CD4+ cells per µl). There was no apparent pattern of change in either group with regard to the percentage of CD4+ lymphocytes or the total, total B, total T, CD4+ helper, CD4+ inducer, CD8+, CD8- cytotoxic natural killer, or activated T lymphocyte counts.

In contrast to the lack of effect of DTC on lymphocyte subsets, median leukocyte, neutrophil, absolute monocyte, and platelet counts were lower than those at baseline for all 24 sampling intervals in DTC-treated patients, whereas no consistent change in these cellular subsets was evident in placebo-treated patients (Table 2) (P < 0.0001; Fisher's exact test). Despite the small sample size, differences between the DTC and placebo treatment groups achieved statistical significance for 3 of the 24 individual testing points during treatment (Table 2).

In DTC-treated patients, the median serum glucose, alkaline phosphatase, and magnesium concentrations were generally higher throughout the study period than those at baseline. These values remained relatively unchanged in placebo-treated patients. DTC had no effect on serum creatinine, total bilirubin, aspartate aminotransferase, alanine aminotransferase, sodium, potassium, bicarbonate, chloride, calcium, phosphate, albumin, total protein, blood urea nitrogen, hemoglobin, or serum immunoglobulin G (IgG), IgM, or IgA levels. Consistent with the potent copper-chelating activity of DTC and animal studies (1, 10), the median serum copper levels increased in patients receiving DTC (+0.04 µg/ml) but decreased in those given placebo (-0.085 µg/ml) (P = 0.04; rank sum test).

Among 83 skin test batteries performed (seven antigens per battery; Multitest; Connaught Laboratories, Inc., Swiftwater, Pa.), there were only eight reactions. Seven of these eight reactions were in a single patient who was treated with placebo, and none exceeded 6 mm. Two other patients reacted to histoplasmin (10 and 20 mm). Thus, 15 (79%) of 19 patients were anergic, and DTC had no effect on the skin test reactivity status.

The levels of p24 antigen increased progressively during the study for patients in both groups, with no significant between-group difference after 12 weeks. Opportunistic infections occurred in one DTC-treated patient (cryptococcal meningitis at...
The mechanism for the increased progression to AIDS was not identified.

Invariably, we observed decreases in leukocyte, neutrophil, monocyte, and platelet counts in DTC-treated subjects in our study. This apparent effect of DTC persisted for up to 4 weeks after discontinuation of the drug. Although the serum DTC half-life is only about 20 min (4), DTC produces sensitivity to alcohol for up to 2 weeks (package insert for Antabus; Wyeth-Ayerst Laboratories, Philadelphia, Pa.) and prevented retrovirus-induced lymphoproliferation in mice for up to 6 weeks after the cessation of therapy (4). In frequent blood sampling and the introduction of open-label DTC and zidovudine for several patients 4 weeks after the discontinuation of DTC or placebo precluded further analysis of the posttreatment effects of DTC. Although not the primary end point of the study, the definitiveness of these findings for all three myeloid cell lines evaluated diminished the possibility that the decreases in myeloid cell counts occurred by chance alone. Moreover, concordant with our results, ex vivo studies have reported that DTC is toxic for human neutrophils, monocytes, and macrophages at clinically relevant concentrations (2, 9). Nonetheless, these novel clinical findings should be confirmed by an independent study designed specifically for this purpose.

Our results evoke concerns that DTC could decrease myelopoiesis and, consequently, immune system function, leading to increased opportunistic infections. In this regard, one could speculate that the increased progression to AIDS (5) and decreased lymphadenopathy (6) observed in DTC-treated patients in the previously published trials reflected a DTC-induced decrease in the counts of neutrophils, monocytes, and macrophages, including those in lymph nodes.

In conclusion, our findings contradict the purported ability of DTC to recruit functional lymphocytes, the principal rationale for the use of this compound in HIV infections. Moreover, future trials of DTC should include monitoring for drug-induced leukopenia, neutropenia, monocytopenia, and thrombocytopenia, especially in patient populations already at increased risk of infection.

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REFERENCES


