

CORRESPONDENCE

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Dapsone-Induced Methemoglobinemia in
Leprosy Patients

TO THE EDITOR:

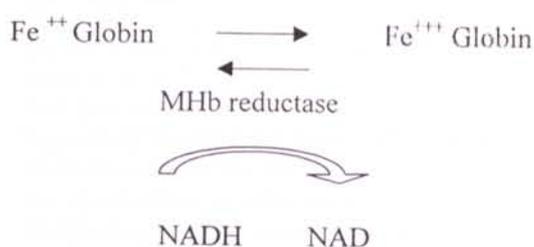
Diaminodiphenylsulfone (dapsone) is one of the most widely used drugs being given to millions of leprosy patients for the last six decades. Considering the enormous number of persons receiving dapsone, severe toxic reactions are rare (⁴). Methemoglobinemia as a toxic effect with dapsone in high doses has been well documented (³). However, clinically significant methemoglobinemia as a hematological side effect of dapsone is rare at therapeutic doses (⁴).

Methemoglobin is an oxidized product of hemoglobin in which heme iron becomes Fe³⁺ and is incapable of binding oxygen. Normally, a low level of methemoglobin is maintained in the blood due to activity of the cytochrome b₅ reductase (methemoglobin reductase) enzyme (⁵). Malaria prophylaxis has been reported as provoking methemoglobinemia in unsuspected heterozygous individuals deficient in NADH-cytochrome b₅ reductase enzyme (¹). The present study was designed to investigate the role of cytochrome b₅ reductase activity in dapsone-induced methemoglobin production in leprosy patients.

Twenty, untreated, newly diagnosed patients with leprosy (8 BL/LL, 12 BT/TT) and 10 healthy age- and sex-matched controls attending Nehru Hospital, Postgraduate Institute of Medical Education and Research, Chandigarh, India, were enrolled in

the study. Blood samples were collected from all leprosy subjects prior to and after treatment with the 1982 World Health Organization (WHO) multidrug therapy (WHO/MDT). All samples were tested for oxyhemoglobin and methemoglobin levels using standard (biochemical) methods. NADH-methemoglobin reductase enzyme activity was estimated by a slightly modified technique of Scott, *et al.* (⁶), using erythrocytes of blood conserved in ACD, removing excess nitrite, 10 ml of double distilled water was added to 0.05 ml of packed cells. Finally, absorbance was determined at 600 nm against distilled water. Then to 3 ml of hemolysate, 0.2 of 0.012 M 2, 6-dichlorobenzene indophenol (DCIP) in 1 M Tris-HCl buffer (pH = 7.6) containing 0.011 M disodium EDTA was added. The enzyme activity was studied using 0.008 M NADH, and the enzyme activity expressed in change in absorbance per minute at 600 nm ($A \times 600/\text{min} \times 10^4$). All patients were also screened for glucose 6-phosphate dehydrogenase (G-6-PD) deficiency.

There were 12 male and 8 female leprosy patients with ages ranging from 12 to 47 years. Mean hemoglobin levels were found to be significantly decreased ($p < 0.05$) in leprosy patients after therapy (WHO/MDT) compared to before therapy. After treatment, a slight but significant increase ($p < 0.01$) in methemoglobin levels was ob-



THE FIGURE. The interconversion of hemoglobin and methemoglobin.

served in leprosy patients as compared to control subjects. There was a statistically significant decrease in the activity of the methemoglobin reductase enzyme after treatment in patients compared to controls ($p < 0.01$). Similar observations have also been made in another two studies of leprosy patients in the past (^{6,8}). None of our patients had significantly raised methemoglobin levels to manifest clinically. All patients screened for G-6-PD deficiency were found to be normal. Manfredi, *et al.* (⁷) also concluded that hemolytic anemia and methemoglobinemia in patients taking dapsone is not due to functional impairment of the G-6-PD enzyme.

Acquired methemoglobinemia results from exposure to certain drugs and chemicals, such as nitrite, chlorate, and sulfonamide compounds capable of oxidizing hemoglobin directly or indirectly. The exact mechanism by which dapsone induces methemoglobinemia *in vivo* is not known, but the drug metabolite 4-amino-4-hydroxyaminodiphenylsulfone is said to be responsible for oxidation (⁹).

The NADH-dependent reductase system associated with cytochrome b_5 represents one of the major electron transport systems in the body which convert methemoglobin to hemoglobin (The Figure). So, we propose that a decrease in activity of the NADH-methemoglobin reductase enzyme, as observed in our study, might be one of the major factors responsible for dapsone-induced methemoglobinemia in leprosy patients. The growing numbers of immunosuppressed patients due to the spread of HIV infection may result in increased dapsone use for *Pneumocystis carinii* pneumonia (PCP) prophylaxis (¹⁰). Although methemoglobinemia occurring at therapeutic doses of dapsone is generally asymptomatic, clinicians should be aware of this adverse ef-

fect, and patients presenting with respiratory distress of unknown etiology should be evaluated for methemoglobinemia.

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