Methemoglobinemia and dapsone levels in patients with leprosy

ABSTRACT

The objective of this work was to determine the methemoglobinemia and correlate with dapsone levels in multibacillary leprosy patients under leprosy multi-drug therapy. Thirty patients with laboratory and clinical diagnosis of multibacillary leprosy were enrolled. Dapsone was analyzed by high performance liquid chromatography and methemoglobinemia by spectrophotometry. The mean dapsone concentrations in male was 1.42 g/mL and in female was 2.42 g/mL. The mean methemoglobin levels in male was 3.09 µg/mL; 191%, and in female was 2.84 ± 1.67%. No correlations were seen between dapsone levels and methemoglobin in male and female patients. Our results demonstrated that the dosage of dapsone in leprosy treatment does not promote a significant methemoglobinemia.

Keywords: methahemoglobinemia, dapsone, leprosy.

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Dapsone (4-4´-diaminodiphenylsulfone, DDS) is a chemical analogue of sulfapyridine, synthesized in 1908. It is a part of the multidrug regimen recommended for the treatment of leprosy, but it is also used against a number of noninfectious inflammatory diseases.[1]

DDS acts in the same way as sulfonamides, inhibiting the synthesis of dihydrofolic acid through competition with para-aminobenzoate for the active site of dihydropteroate synthetase. The anti-inflammatory action of DDS is associated with the interference in neutrophil chemotactic migration, β2 integrin (CD11b/ CD18)-mediated adherence of human neutrophils in vitro and with the activation or function of the G-protein (Gi type) that initiates the signal transduction cascade common to chemotactic stimuli.[1,2]

DDS is absorbed readily from the gastrointestinal tract with bioavailability of more than 86%. The peak plasma concentration after 100 mg of oral DDS is attained between 2 to 8 hours. The drug shows linear pharmacokinetics within the therapeutic range and the time-course after oral administration fits a 2-compartment model. DDS is distributed for all organs including skin, liver, kidneys and erythrocytes. It is metabolized via acetylation or N-hydroxylation. The latter reaction yields the hydroxylamine, a potentially toxic metabolite produced by cytochrome P-450 enzymes. About 85% of DDS is excreted in the urine, mainly as glucuronide and 10% is excreted in the bile.[3]

Adverse effects associated with DDS include dose-related hemolysis, methemoglobinemia (MeHb), peripheral neuropathy, agranulocytosis, aplastic anemia, and sulfone syndrome (fever, malaise, exfoliative dermatitis or morbilliform rash, hepatic dysfunction, lymphadenopathy, MeHb, and hemolytic anemia).[2] MeHb is the most common side effect of dapsone and is formed by hydroxylamine metabolite, which is capable of being co-oxidized with hemoglobin in the red blood cell. MeHb can occur either in congenital or acquired forms. The first is present at bird and manifests in two distinct forms. Type I is an erythrocyte form with a deficiency of NADHcytochrome b5 reductase gene and Type II is a generalized form that is characterized by a b5 reductase deficiency in all tissues. Acquired forms are usually pharmacokinetically induced responses that result in an increase in rate of oxidation of hemoglobin to methemoglobin and, a number of chemicals have been implicated. The equilibrium between haemoglobin and methaemoglobin is maintained by a particular mechanism. Methaemoglobin is reduced to haemoglobin by the NADHcyto-

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chrome b5 reductase enzyme establishing a steadystate level of about 1% of total haemoglobin.[4-7]

The objective of this work was to determine the MeHb levels and correlate with dapsone plasma levels in multibacillary leprosy patients under leprosy multi-drug therapy.

Were enrolled 15 adult male and 15 adult female patients with laboratory and clinical confirmation of multibacillary leprosy from the State Reference Unit for Leprosy Treatment Dr. Marcello Candia, Marituba, PA, Brazil. Exclusion criteria included incapacitating erythema nodosum leprosum, severe neuritis, SIDA, tuberculosis, and malaria. Their characteristics were as follows (means ± SDs): age, 28 ± 13.1 years (age range; 18 to 37 years); body weight, 64.21 ± 12.1 kg, erythrocyte count, 4.21 ± 0.52 X 10^6/μL; white blood count, 11,300 ± 4,700/μL. Informed consent was obtained from all subjects. This study was approved by the ethics committee of the Tropical Medicine Center of Universidade Federal do Pará.

Each patient received the standard multibacillary leprosy multi-drug therapy of rifampin (600 mg) and clofazimine (300 mg) monthly, supervised, and dapsone (100 mg) and clofazimine (50 mg) daily, unsupervised. At the time of the study, all patients had received dapsone for at least one month.

Blood samples were taken in the steady-state; i.e., three days after the administration of supervised dose. All samples were taken before dapsone intake; i.e., trough levels were measured. MeHb was determined according Heggesh *et al.* (1970).[8] Dapsone was analyzed by high performance liquid chromatography with ultraviolet detection (Pro Star – Varian, Walnut, CA-USA), as described previously.[9] The column was an ODS C18 4.6 X 250 mm (Supelco Inc. Bellefonte PA, USA). The method involved liquid-liquid extraction of drug from plasma samples with diethyl-ether. The mobile phase consisted of 20% acetonitrile v/v. Phenacetin (100 μg/mL) was used as internal standard. The analytical procedure validated in our laboratory demonstrate that within-day and day-to-day coefficients of variation were 10.7 and 14.1%, respectively. Mean extraction recovery of dapsone was 90%. The stability of blank plasma spiked with dapsone was 60 days. Rifampin, clofazimine, prednisone and thalidomide do not interfered in the detections of dapsone.

Data are presented as mean ± SD. The concentrations of dapsone between patients were compared by Student's t, with p-values of < 0.05 considered to indicate significant differences, and Pearson coefficient to estimate the correlation between the variables. Statistical evaluations were conducted using the statistical computer package STATISTICA (Statsoft, Tulsa, Okla., USA).

The mean concentration of dapsone in male plasma samples in the steady state was 1.42 ± 1.65 μg/mL, ranging from 0.22 to 6.9 μg/mL, and in the female samples was 2.42 ± 2.28 μg/mL, ranging from 0.24 to 8.0 μg/mL. These results are consistent with previous work in healthy volunteers after 100 mg of oral dapsone, which show dapsone levels ranging from 1.10 to 2.33 μg/mL, and demonstrated that the bioavailability of dapsone is similar between healthy volunteers and leprosy patients. No difference was observed between male and female dapsone plasma levels.[10]

It has been demonstrated that the compliance with prolonged leprosy therapy was enhanced when dapsone was associated with others drugs and, in this study, 90% of patients presented therapeutic levels of dapsone for leprosy multi-drug therapy of 0.5 to 5.0 μg/mL, and correlated with previous report of adherence in leprosy multi-drug therapy studies where the compliance was above of 85%.[1]

The MeHb levels of male patient was 3.09 ± 1.91 %, ranged from 1.14% to 8.33%, and in female patients was 2.84 ± 1.67%, ranged from 0.28% to 5.89%. No difference was observed between male and female patients. 73% of patients presented MeHb levels above the values of unexposed population, but no signs or symptoms of MeHb were observed.[2,4] It has been demonstrate that the symptoms of MeHb generally correlate with MetHb levels. At levels above 10%, cyanosis becomes clinically apparent. Exertion dyspnea, tachycardia, dizziness, chest pain, and headache occur with levels up 20%. At levels > 50%, arrhythmias, seizures, and depressed consciousness may be seen, levels above 85% are life threatening. Our results are consistent with previous work that show the risk of dapsone-dependent side effects is very low if plasma concentration is below 5 mg/L.[2,4-7]

No significances were seen in Pearson coefficients between dapsone concentrations and MeHb levels in both groups. In male patients was -0.3419 and 0.355 in female patients. This finding does not support the evidence of a good relationship between these variables in the therapeutic use of dapsone. Our results provide evidence suggesting that the dosage of dapsone in leprosy treatment does not promote an important MeHb.

REFERENCES

1. Zhu IY, Stiller MJ. Dapsone and sulfones in dermatology: overview and update. J Am Acad Dermatol. 2001; 45:420-34.
2. Coleman MD. Dapsone toxicity: some current perspective. Gen Pharmacol. 1995; 26:1461-7.
3. Zuidema J, Hilbers-Modderman ESM, Merkus FWHM. Clinical pharmacokinetics of dapsone. Clin Pharmacokinet 1986; 11:299-315.
4. Halim NKD, Ogbeide E. Haematological alterations in leprosy patients treated with dapsone. East Afr Med J. 2002; 79:100-2.
5. Kaur I, Metha M, Agnihotri N *et al.* Dapsone-induced methemoglobinemia in leprosy patients. Int J Lepr 2001; 69:247-9.
6. Vage C, Saab N, Woster PM, Svensson CK. Dapsone-induced hematologic toxicity: comparison of the methemoglobin-forming ability of hydroxylamine metabolities of dapsone in rat an human blood. Toxicol Appl Pharmacol 1994; 129:309-16.
7. Reilly TR, Woster PM, Svensson CK. MMethemoglobin formation by hydroxylamine metabolites of sulfamethoxazole and dapsone: implications for differences in adverse Drug Reactions. J Pharmacol Exp Ther 1999; 288: 951-9.
8. Hegesh E, Gruener RN, Bockwosky R, Shuvat HJ. A sensitive micromethod for the determination of methemoglobin in blood. Clin Chim Acta 1970; 30: 679-82.
9. Kwadijk S, Torano JS. High-performance liquid chromatographic method with ultraviolet detection for the determination of dapsone and its hydroxylated metabolite in human plasma. Biomed Chromatogr 2002; 16:203-8.
10. Ab G, Brocavich JM, Etzel JV *et al*. Evaluation of effects of altered gastric pH on absorption of dapsone in healthy volunteers. Antimicrob Agents Chemoter 1994; 38:2227-9.