DAPSONE INDUCED METHAEMOGLOBINEMIA

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A 33-year-old female developed methaemoglobinemia manifesting as cyanosis, fatigue, malaise and headache 3 weeks after being put on 100 mg of dapsone daily for borderline tuberculoid leprosy. Similar manifestations developed in a 15-year-old boy, 9 days after he was put on 50 mg of dapsone daily for suspected indeterminate leprosy. Withdrawal of dapsone resulted in reversal of methaemoglobinemia.

Key words : Dapsone, Methaemoglobinemia.

Diaminodiphenylsulphone (dapsone) is being used for the treatment of leprosy since the last five decades. It is a relatively safe drug in the dosages used for leprosy. Haematological side effects of the drug include haemolytic anemia,[1] methaemoglobinemia,[2] sulphaemoglobinemia and agranulocytosis.[3] Methaemoglobinemia as a toxic effect with dapsone in high dosages has been well documented.[4] Clinically significant methaemoglobinemia occurring with therapeutic dosages of dapsone is rare. We report two cases of clinically manifest methaemoglobinemia induced by dapsone in dosages of 100 mg and 50 mg respectively.

Case Reports

Case 1

A 33-year-old female developed an ill-defined, hypopigmented, atrophic, hypoaesthetic patch, 5 cm $\times$2.5 cm in size, below the left knee for the past 6 weeks. The left lateral popliteal nerve was thickened and non-tender. Bacteriological examinations were negative for *M. leprae*. A diagnosis of borderline tuberculoid leprosy was confirmed by histopathology. General physical and systemic examinations were normal. The patient was started on dapsone 100 mg daily and rifampicin 600 mg once a month. Three weeks later, the patient reported back with fatigue, malaise, headache and bluish discoloration of the tips of the fingers and lips. Examination revealed cyanosis affecting the nail beds, lips and tongue. The patient was otherwise normal. History did not reveal intake of any other drug in the previcus 3 weeks. There were no similar episodes in the past. There was no family history of similar illness.

Dapsone was discontinued and within a week the patient felt better and the cyanosis disappeared totally. A fortnight later, the patient was restarted on 100 mg of dapsone and all the symptoms including the cyanosis recurred within the next 24 hours. On the third day, methaemoglobin estimation using spectroscopic method[5] was 12.9%. Her haemoglobin was 13 gm%. Blood cell counts, peripheral smear examination, urinalysis and liver function tests were normal.

Case 2

A 15-year-old boy was put on dapsone 50 mg/day at a primary health centre for a hypopigmented patch on the left thigh. Nine months later, he presented to us with gradually progressing bluish discoloration of the hands and lips and breathlessness on exertion for the same period. There was no family history of similar complaints. Examination revealed marked cyanosis of nail beds, lips and tongue. Cardiovascular examination revealed a functional short systolic murmur in the mitral area. Respiratory system was normal. X-ray chest and electrocardiogram were within normal

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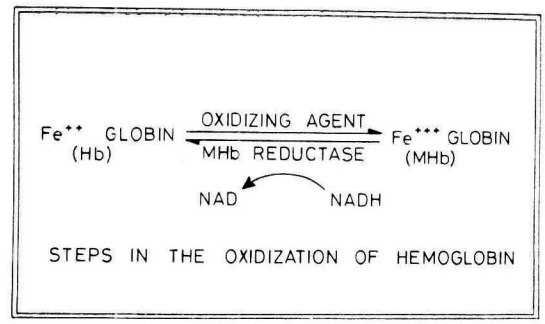
limits. Detailed examination did not reveal any evidence of leprosy in the patient.

Methaemoglobin level was found to be 29.9%. His haemoglobin was 12.5 gm%. Other investigations were within normal limits. Cyanosis and exertional dyspnoea improved within a week after stopping dapsone.

Comments

Methaemoglobinemia describes the clinical situation in which more than 1% of the haemoglobin within the circulating erythrocytes has been oxidized to the ferric form (Fig. 1).[6] In the ferric form the iron does not combine with oxygen, thus reducing the oxygen carrying capacity of blood. If methaemoglobin levels exceed 1.5 gm/ml (10% of the total haemoglobin), the affected individuals will have clinically obvious cyanosis. With higher levels, other symptoms of hypoxia like headache, weakness, dizziness, dyspnoea and tachycardia will appear. Concentrations of 70% and above may prove fatal.

Methaemoglobinemia can be either hereditary or acquired.[7] Hereditary methaemoglobinemia is either due to the presence of one of the M-haemoglobins or the deficiency of the enzyme methaemoglobin-reductase (Cytochrome b reductase), which plays a major role in methaemoglobin reduction under physiologic conditions. In these conditions, the cyanosis is present since birth or early childhood. Acquired methaemoglobinemia results from exposure to drugs or chemicals which accelerate the oxidation process in the erythrocytes beyond the reductive and protective capabilities of the cell. Nitrites and nitrates like amyl nitrite, sodium nitrite, nitro-glycerine, bismuth subnitrite and nitroprusside, sulfonamides like sulfanilamide, sulfapyridine, sulfamethizole and dapsone, quinones, aniline dyes, phenacetin, acetanilid and local anaesthetics like lidocaine are some of the compounds which can produce clinically significant methaemoglobinemia.[7,8]



STEPS IN THE OXIDIZATION OF HEMOGLOBIN

Fig. 1. Steps in the oxidization of hemoglobin.

Dapsone is well known to produce a minimal degree of methaemoglobinemia in normal subjects at therapeutic doses but generally this does not cause a major problem.[9] Methaemoglobinemia as a toxic effect with dapsone in high dosages has been well documented.[4] It depends not only on the dose of the drug but also on individual susceptibility. This might explain the clinically significant methaemoglobinemia which developed in our patients with therapeutic dosages of 100 mg and 50 mg respectively. The exact mechanism by which dapsone induces methaemoglobinemia in vivo is not known, but the drug metabolite aminohydroxylaminodiphenylsulfone is said to be responsible for the oxidation of haemoglobin.[9]

Severe toxic methaemoglobinemia is to be treated as a medical emergency. Methylene blue 1-2 mg/kg body weight given as a 1% aqueous solution intravenously will result in a marked reduction in the level of methaemoglobin. Ascorbic acid orally as 500 mg tablets every 6 hours is also useful.[7] Oxygen inhalation may be required. Mild methaemoglobinemia as was seen in our patients can be reversed with mere withdrawal of the offending agent. Lastly, it is suggested that methaemoglobinemia should be considered in any cyanotic patient with no evidence of heart or lung disease.

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