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Very late relapse of dapsone-induced methaemoglobinemia

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Dapsone, a sulfone active against a wide range of bacteria, is mainly used for *Mycobacterium leprae*. Moreover, because of its immunosuppressive effect, it is used for many auto-immune diseases [1]. Methaemoglobinemia is an expected adverse drug reaction of dapsone, seldom symptomatic. Long-term administration of dapsone at standard doses (100 mg/day) results in methaemoglobinemia in about 15% of patients [2]. When symptomatic

(dyspnea, cyanosis, neurological disorders), methaemoglobinemia is treated with methylene blue (1–2 mg/kg) [3]. Rebounds have been described after dapsone withdrawal, with a maximum delay of 64 h [4]. We report a case of dapsone-induced methaemoglobinemia which relapsed 10 days after drug withdrawal.

A 25-year-old woman was diagnosed with systemic lupus erythematosus in January 2009. Organs involved were skin and joints, and hydroxychloroquine alone was prescribed. In October 2009, she developed a bullous dermatitis and dapsone was added to hydroxychloroquine on 26 October 2009. About 1 month later, on 24 November, she was admitted to the hospital for severe dyspnea. Physical examination was normal except for cutaneous cyanosis. Chest computed tomography and electrocardiogram were normal. Arterial blood gas analysis showed pH: 7.63, PaO₂: 110 mmHg, PaCO₂: 15 mmHg, haemoglobin: 11 g/dL, SaO₂: 99.1%; methaemoglobin: 17%. Methylene blue (2 mg/kg) was injected intravenously. Twenty minutes later, the patient was asymptomatic and arterial methaemoglobin was 4%. Dapsone was discontinued and the patient left the hospital on 26 November. Ten days later, she consulted for relapse of dyspnea. Arterial blood gas analysis showed methaemoglobin at 14%. No symptomatic treatment was done and methaemoglobin rate decreased spontaneously to 5% the next day. Hydroxychloroquine was stopped. The compliance of the patient was not doubtful, and no other cause of intoxication causing methaemoglobinemia was found.

Methaemoglobinemia in dapsone intoxication is due to the ability of dapsone hydroxylamine, a metabolite of the drug, to react with haemoglobin (Fe²⁺) to form methaemoglobin (Fe³⁺) [5]. Methaemoglobin is unable to bind dioxygen, which results in functional anaemia. The clinical

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symptoms depend on the level of methaemoglobinemia: asymptomatic if less than 15%; cyanosis for levels above 15%; headache, dyspnea, nausea, tachycardia, weakness for levels above 20%; coma for levels above 45%; and a high mortality rate is associated with levels above 70% [6]. Methylene blue could act as a cofactor of the enzyme NADPH-methaemoglobin reductase, converting a methaemoglobin molecule into a haemoglobin molecule.

Regarding the relationship with hydroxychloroquine, the delay of onset of methaemoglobinemia seems too long (10 months). To our knowledge, no observation of hydroxychloroquine-induced methaemoglobinemia has been reported in the literature. We only found some cases of chloroquine-induced methaemoglobinemia, generally revealing a genetic deficiency in NADPH-cytochrome b5 reductase [7, 8].

The delay of the methaemoglobinemia relapse after dapsone withdrawal may be explained by the long elimination half-time (20–30 h) [9], which also depends on genetic polymorphisms of cytochrome P450, particularly CYP2E1, which produces the hydroxylamine metabolite [10]. Furthermore, a linear relationship has been demonstrated between hydroxylamine-dependent methaemoglobin formation and reduction of hydroxylamine to dapsone in human red blood cells in vitro [11]. According to these authors, there may be a cycle between hepatic oxidation of dapsone to its hydroxylamine and reduction to the parent amine within the red cells, which may lead to re-oxidation by hepatic cytochrome P450 and thus contribute to the persistence of the drug in vivo.

These pharmacokinetic particularities leading to a late relapse of dapsone-induced methaemoglobinemia should be kept in mind by physicians for appropriate treatment.

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