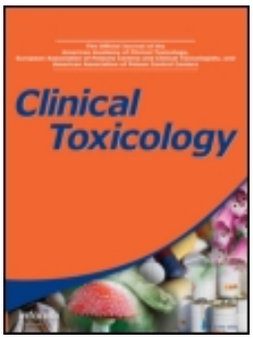

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LETTER TO THE EDITOR

Very late recovery of dapsone-induced methemoglobinemia

To the Editor:

We report a case of dapsone-induced methemoglobinemia with a severely prolonged recovery period of 374 days.

A 47-year-old woman was referred for 3 months of progressive nausea, fatigue, palpitations, and dyspnea. Three years earlier linear IgA bullous dermatosis was diagnosed, at that moment dapsone 100 mg twice daily was prescribed. Six months later additional treatment with adalimumab was started because of insufficient disease control, but stopped after 1.5 years due to pulmonary toxicity and prednisolone was introduced. At presentation she received 25 mg prednisolone daily, calcium carbonate and risedronic acid. She had Cushingoid features, a body mass index (BMI) of 37 (weight: 107 kg and length: 170 cm).

On examination patient had cyanotic signs at lips, ears and fingers, low peripheral oxygen saturation (87%), methemoglobin (MetHb) 17% (normal $\leq$1%), reticulocytes 305‰ (normal 3–18‰), haptoglobin $<$0.10 g/L (normal: 0.3–2.0 g/L), Lactate dehydrogenase 501 U/L (normal $<$250 U/L), a negative direct antiglobulin test and normal renal function (creatinine 72 µmol/L) Arterial blood gas showed hypoxemia, most probably due to areas with low ventilation–perfusion ratio in basal parts of the lungs (pO_2: 57 mm Hg, pCO_2: 36 mmHg, pH 7.47, calculated O_2 saturation 88%). On supplemental oxygen, the hypoxemia could be corrected without resolving the central cyanosis. Dapsone-induced hematotoxicity was suspected and dapsone was stopped.

To reduce MetHb to hemoglobin methylene blue was administered. Charcoal was given to interrupt dapsone's enterohepatic cycling, but stopped because of nausea. Ascorbic acid was introduced to enhance non-enzymatic MetHb elimination.[1,2] Cimetidine was given to reduce formation of hematotoxic hydroxylamine-dapsone.[3] Despite therapy dapsone and MetHb levels remained high for over 315 days (Fig. 1). In the 2 months following normalization of MetHb and dapsone levels patient experienced a complete recovery in daily performance.

Pharmacogenetic analysis showed patient was wild-type CYP2C19, CYP3A4, poor metabolizer CYP2C9 (*2/*2), and intermediate metabolizer N-acetyltransferase 2 (*4/*5A). There was no G6PD or cytochrome B5 reductase deficiency. The

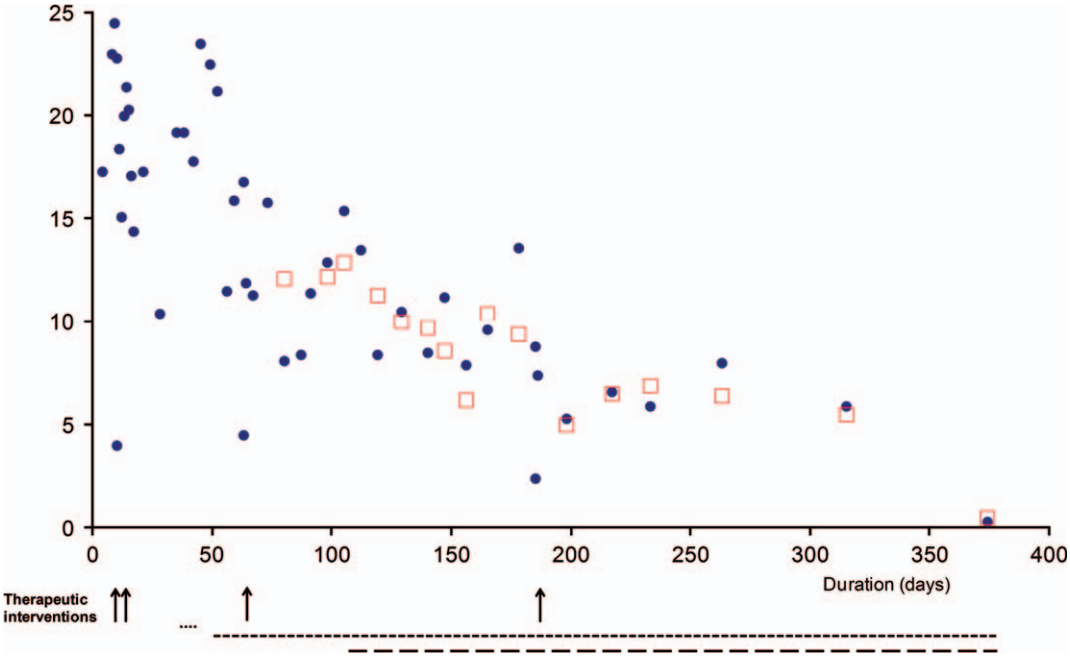

Fig. 1. Methemoglobin and dapsone serum levels after cessation of dapsone therapy. Day 0 = day of clinical presentation and cessation of dapsone therapy; ●: Methemoglobin (%); □: Dapsone concentration (mg/L); ↑: Methylene blue 1 mg/kg intravenously [Day 10 (twice), 11, 63, 185]; ····: Charcoal 50 g in 500 ml sodium sulfate (Carbomix®) twice daily orally (day 39–46); ---: Ascorbic acid 500 mg tablet thrice daily (Day 49 – end); −−−: Cimetidine 400 mg tablet thrice daily (Day 106 – end).

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Naranjo score of 7, indicated dapsone probably caused the hematotoxicity.[4]

Dapsone's half-life ranges from 10 to 80 h. Dapsone and metabolites are mainly excreted renally and also undergo enterohepatic circulation. Dapsone is distributed in most tissues with concentrations that equal with those in blood. Dapsone is fat soluble with an octanol water partition coefficient (log P) of 0.97 and a volume of distribution of 1.5 L/kg.[1,2]

Dapsone's elimination half-life was severely prolonged, but in our case renal function was normal suggesting intact renal elimination of dapsone and metabolites. Pharmacogenetic analysis gave no definitive answer in this case. Munchhausen syndrome seems unlikely, because no psychiatric risk factors existed and no refill of dapsone prescriptions in local pharmacies was noted. To our knowledge the longest recovery period, documented in the literature, of dapsone-induced methemoglobinemia in therapeutic dosage is 44 days.[5]

We hypothesize redistribution of dapsone from peripheral tissues to the blood compartment as explanation for the prolonged high concentrations. Arguments in favor of redistribution are a) the BMI of 37 indicating a large (adipose) tissue compartment for storage of dapsone; b) a high dosage used for 3 years; and c) the sudden rapid clearance of dapsone from the blood compartment after 315 days, suggesting empty peripheral depots.

In absence of other explanations, we hypothesize that patient extremely prolonged dapsone-induced methemoglobinemia of 374 days was due to massive storage of dapsone in peripheral (adipose) tissue.

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Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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