Adverse Drug Reactions

Dapsone-Induced Methemoglobinemia: a Primer for Clinicians

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OBJECTIVE: To present a comprehensive review of dapsone-induced methemoglobinemia and its management.

DATA SOURCES: Literature retrieval was accessed through MEDLINE (1966-March 2011), Cochrane Library, and EMBASE, using the terms dapsone and methemoglobinemia.

STUDY SELECTION AND DATA EXTRACTION: All case reports, small case series, and randomized controlled trials published in English were evaluated. Because of the absence of comprehensive updates on this topic since 1996, publications between 1997 and March 2011 were included in this review.

DATA SYNTHESIS: Between 1997 and March 2011, the majority of publications describing methemoglobinemia associated with dapsone use reported this adverse effect at therapeutic doses. Excluding overdose situations, 18 described symptomatic dapsone-associated methemoglobinemia and clinical presentation ranging from cyanosis to dyspnea. In almost all of the accounts, patients had a concurrent event such as anemia or pneumonia, suggesting an interplay between these comorbidities and the onset of symptomatic methemoglobinemia. Delayed hemolytic anemia was seen in patients with high methemoglobin levels at presentation. Management in most cases consisted of administration of methylene blue. Overall, most reports described a successful outcome, and no mortality resulted from methemoglobinemia associated with therapeutic use.

CONCLUSIONS: Clinicians should recognize methemoglobinemia as an adverse effect associated with dapsone use and the potential factors that precipitate it. They should also know how to promptly and effectively manage this event.

KEY WORDS: dapsone, methemoglobin, methemoglobinemia, methylene blue.

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Dapsone is a sulfone compound commonly used in the prevention of *Pneumocystis jiroveci* pneumonitis (PJP) as well as treatment of conditions such as leprosy and dermatitis herpetiformis.[1-4] PJP is a frequently encountered opportunistic infection in patients with depressed cellular immunity resulting from HIV, leukemia, and drug therapy used in solid organ and hematopoietic stem cell (HSCT) transplantation.[5-7] When used to prevent PJP, dapsone is typically reserved as an alternative agent in patients intolerant of or for whom trimethoprim/sulfamethoxazole is contraindicated.[6] The increase in this population has led to a parallel increase in dapsone use in recent years.[8] A significant adverse effect associated with dapsone use in some patients is the development of Heinz body hemolytic anemia and methemoglobinemia.[1] This review provides a primer for clinicians on the identification and management of methemoglobinemia.

Data Sources

Literature regarding dapsone-induced methemoglobinemia was accessed through EMBASE, the Cochrane Database, and MEDLINE (1966-March 2011). All case reports, small case series, and randomized controlled trials published in English were evaluated. Two publications addressed dapsone-induced methemoglobinemia literature in the period between 1966 and 1996[2,4]; in the absence of comprehensive updates since then, we reviewed publications between 1997 and March 2011.

Pathophysiology of Methemoglobinemia

Methemoglobin (MetHb) develops when heme iron is in the ferric state (Fe^{3+}) instead of the normal ferrous state (Fe^{2+}). Under normal circumstances, erythrocytes produce low levels of MetHb (≤1%) continuously secondary to au-

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tooxidation, with 99% of hemoglobin (Hb) in the ferrous state. Low MetHb levels are achieved through the regulatory actions of nicotinamide adenine dinucleotide (NADH)–dependent cytochrome b5 reductase enzyme (~67-95% of the conversion), nicotinamide adenine dinucleotide phosphate (NADPH)–dependent MetHb reductase (~5% of the conversion), and the nonenzymatic antioxidants ascorbic acid and glutathione (~12-15% of the conversion).[2,9-11] When these control processes are malfunctioning or overwhelmed, high MetHb (>1%) concentrations in erythrocytes develop. In the ferric form, the iron in heme cannot bind oxygen.[10,12,13] Physiologically, the resultant oxygen-dissociation curve of the unaffected Hgb will shift to the left.[9,14] The severity is relative to the patient's Hb level; for example, a patient with anemia who has an Hb level of 7.4 g/dL and a MetHb level of 25% would have only 5.5 g/dL of functional Hb.[9] Cyanosis associated with MetHb results in a brown, pasty appearance of the mucous membranes, unlike the blue color that is associated with cyanosis from other causes.[2] Venous blood samples in methemoglobinemia are brown, typically at levels of 10% or higher.[2,15] Headache, fatigue, tachycardia, weakness, and dizziness appear at levels between 30% and 40%.[10] The latter can lead to acidosis, paralysis, arrhythmias, coma, and seizures when the MetHb level approaches 60%.[2,10,12] Death occurs at levels higher than 70%,[12,16] although survival has been reported with levels as high as 83%.[17] In patients with anemia, significant cardiac or respiratory disease, and other Hb abnormalities (eg, sickle cell anemia), these symptoms occur at lower MetHb levels (eg, 15% or less).[2,16,18,19]

In methemoglobinemia, a discrepancy exists between noninvasive pulse oximeter arterial oxygen saturation (SpO_2) readings and oxygen saturation determined on arterial blood gas testing, a phenomenon known as "saturation gap."[8,11] When MetHb is greater than 20-30%, SpO_2 plateaus at 80-85% and is unaffected by oxygenation status.[16,20] The result is an underestimation of the SpO_2 when the actual values are above 85% and an overestimation of the SpO_2 in patients with hypoxemia below this level.[13] Indeed, the condition of patients with methemoglobinemia will improve little, even at high O_2 concentrations, and worsening hypoxemia may go unnoticed.[11,21] In these circumstances, the presence of cyanosis and low SpO_2 readings with an incongruent normal arterial oxygen pressure (PaO_2) shown on arterial blood gas testing should alert clinicians to the possibility of methemoglobinemia.[22,23] A CO-oximeter, which measures peak light absorbance for MetHb, is a more accurate noninvasive method than pulse oximetry for assessing MetHb levels.[16,23] When CO-oximetry is not available, elevated MetHb concentration determined with arterial blood gas testing typically supports the diagnosis.

Dapsone

Dapsone (diaminodiphenylsulfone) is a synthetic sulfone that decreases folate synthesis by inhibiting the enzyme dihydropteroate synthetase.[3,5] It was first used in the 1940s for treatment of leprosy and then in the 1980s for prophylaxis of PJP malaria and treatment of dermatitis herpetiformis.[5,6] The drug's bioavailability is approximately 70-80%, and it reaches peak concentration within 2-6 hours after a dose of 100 mg.[2,3,7,24] Dapsone's elimination half-life is dose-dependent and, in adults, ranges from 20 to 30 hours[19,24]; however, it can be as long as 80 hours (mostly in overdose situations).[3,4,25] In children, the half-life is 15-22.2 hours.[26] Dapsone has a moderately large volume of distribution (1.5 L/kg) and 70-80% protein binding.[2,15,24,27] In the liver, it undergoes reversible acetylation by *N*-acetyltransferase (NAT2) to monoacetyl dapsone and cytochrome P450–mediated *N*-hydroxylation to dapsone hydroxylamine.[19,28,29] The monoacetyl metabolite can also be acetylated back to dapsone or, to a lesser extent, hydroxylated to *N*-hydroxy-acetyl dapsone.[7,29] The acetylated metabolite is 97-100% bound to plasma proteins and has a half-life of approximately 30 hours.[19,24,27] Its proportion in the plasma is dependent on the acetylator phenotype.[27,30] Acetylated metabolites are not excreted in the urine and are pharmacologically inactive.[2,7,29] Dapsone hydroxylamine is generated by CYP2C isoenzymes, with minor contributions from other cytochrome P450 isoenzymes.[31,32] Both hydroxyl compounds undergo glucuronidation (representing 50% excretion of the oral dose[15]) and, in addition to the parent compound dapsone, are excreted in the urine.[30] Indeed, 43 ± 14% of the dapsone dose was recovered in the urine as equal concentration of dapsone and hydroxylamine dapsone.[2,15] The hydroxylamine metabolites are retained in the circulation for a long period as they undergo enterohepatic recirculation.[4] They are quickly taken up by the erythrocytes where they (in particular, dapsone monohydroxylamine[4]) are primarily responsible for the hematologic adverse effects of methemoglobinemia and hemolysis.[30] One hydroxylamine molecule can react with more than 5 molecules of Hb.[33]

Demographically, previous reports have estimated that 4-13% of patients receiving dapsone develop some degree of hemolytic anemia or methemoglobinemia, which is more than other common iatrogenic offenders such as benzocaine sprays.[34] In a study of 2 tertiary care hospitals, 138 cases of methemoglobinemia over 28 months were identified. Dapsone was the most common etiology, accounting for 42% of all cases, followed by benzocaine spray at 20%.[18] Because of its rapid access to the highly vascular pharyngeal mucosa, benzocaine spray is the most common etiology of methemoglobinemia in the perioperative period when used to facilitate upper gastrointestinal endoscopy, laryngoscopy, or bronchoscopy.[35]

Management of Dapsone-Induced Methemoglobinemia

METHYLENE BLUE

Methylene blue (aniline violet, methylthionine chloride) acts in vivo as a cofactor for the NADPH-MetHb reductase enzyme system.[4,14,36] Typically, in the presence of NADPH-MetHb reductase, it accepts an electron from NADPH and is reduced to leukomethylene blue.[14,36] Leukomethylene blue then donates an electron to MetHb, causing the conversion back to oxyhemoglobin.[16,36] The NADPH required for this reaction is generated in erythrocytes from the pentose phosphate shunt, through the action of glucose 6-phosphate dehydrogenase (G6PD).[11] NADPH-reductase enzyme is less efficient in elderly individuals, young children, and neonates.[9]

Methylene blue is given intravenously as 1-2 mg/kg of a 1% solution for the treatment of methemoglobinemia. The dose is repeated if a sufficient response does not occur within an hour following treatment.[2] Methylene blue is eliminated in the bile, feces, and urine as leukomethylene blue.[36] Common adverse effects, such as electrocardiogram abnormalities (inverted T waves and diminished R waves), dyspnea, chest pain, nausea, diarrhea, oral dysesthesia, and diaphoresis are seen, mostly at the 7-mg/kg cumulative dose.[10,36] At doses of 4 mg/kg or more, methylene blue can cause harmless and reversible discoloration of skin, feces, and urine.[36,37] It is present in the urine up to 5 days after an intravenous dose, despite its short-lived pharmacologic action.[14] When methylene blue was used in septic shock treatment, pulmonary vasoconstriction and reduced oxygenation coincided with doses of 3-4 mg/kg in patients with ventilation-perfusion mismatch (eg, acute lung injury, acute respiratory distress syndrome).[37] Recently, an association between the use of injectable methylene blue in patients exposed to serotonin reuptake inhibition properties was described.[38] Cases of serotonin syndrome involved agitation, diaphoresis, hypertonia, hyperpyrexia, tremor, hyperreflexia, and clonus.[38] This may result from the fact that methylene blue has structural properties similar to those of monoamine oxidase inhibitors, known precipitants of serotonin toxicity. Serotonin syndrome has been reported when methylene blue was given at doses as low as 1 mg/kg in patients receiving drugs with serotonin reuptake inhibition properties (eg, duloxetine, venlafaxine, and clomipramine).[38] Several of these patients required admission to the intensive care unit.

Paradoxically, methylene blue may induce methemoglobinemia at doses ranging from 4 to 15 mg/kg by oxidizing Hb to MetHb, although levels rarely exceed 8%.[14,16,36,39] This happens when leukomethylene blue, methylene blue's metabolite, reduces oxygen to hydrogen peroxide, some of which is detoxified through the hexose monophosphate shunt.[14] When this mechanism is overwhelmed, reduced glutathione is depleted and the remaining hydrogen peroxide can oxidize Hb to MetHb.[14] In patients with G6PD deficiency, where NADPH is decreased, methylene blue administration may result in hemolysis.[10] It may exacerbate dapsone-induced Heinz body hemolytic anemia, and this effect can be delayed for several days.[36] It has been suggested that a dose lower than 1 mg/kg can be used in G6PD-deficient patients with methemoglobinemia.[36] However, even with a lower dosage, methylene blue will be ineffective in the treatment of methemoglobinemia in some of these patients, because of the decrease in NADPH concentration.[9,36] In the management of methemoglobinemia, the drug can also alter SpO_2 readings, as it absorbs most light emitted by a pulse oximeter.[37] Although transient, the interference is interpreted as a reduction in circulating Hb and a falsely depressed SpO_2 reading.[36,40] Cyanosis is an unreliable guide to methylene blue's clinical response because the bluish discoloration of skin confounds physical assessment. Elimination of cyanosis may lag behind symptomatic relief; anemia can also disguise cyanosis symptoms despite high MetHb concentration.[4,25]

Table 1 describes reports published between 1997 and March 2011 of methylene blue use in overdose situations.[21,24,27,39,41-46] Some reports suggest that continuous infusion of methylene blue is effective in recalcitrant dapsone-induced methemoglobinemia[27,42]; however, the safety profile of protracted use is unknown. As such, it should be considered with caution.

CIMETIDINE INTERACTION WITH DAPSONE

In an analysis of 8 patients receiving dapsone for dermatologic conditions, Rhodes et al. studied cimetidine's effect on MetHb and dapsone kinetics.[30] Daily dosages of oral dapsone were 100 mg (n = 6), 75 mg (n = 1), and 50 mg (n = 1). Cimetidine 800 mg was given 1 hour prior to dapsone (to inhibit dapsone hydroxylation at peak concentration) followed by 400 mg (8 hours after the 800-mg dose) for 12 weeks. At week 3 of cimetidine, mean dapsone concentrations increased by 30% versus baseline ($p < 0.01$). No effect on dapsone acetylation ratio was seen during the study. Basal MetHb fell from a mean of 5.5 ± 2.2% at baseline to 3.9 ± 1.1% at week 3 of cimetidine administration ($p < 0.01$) and remained low up to week 9. At week 12, MetHb increased to 5.3 ± 2.2%, despite the continuation of cimetidine. Skin disorder control was not lost, suggesting a neutral effect of cimetidine on the parent drug dapsone, with its neutrophil inhibitory properties.[30] Previous work from the same group showed that a 2-week course of cimetidine, by virtue of its inhibitory action on cytochrome P450 (chiefly 2C19) isoenzymes, decreased dapsone's metabolism to its toxic hydroxylamine metabolite with an attendant 27% reduction in the baseline MetHb level.[28] An el-

Table 1. Methylene Blue Use in Dapsone Overdose–Induced Methemoglobinemia

Reference	Publication Type	Baseline Demographics	Results	Comments
Ferguson (1997)[39]	Case report (N = 1)	Age 14 years; intentional overdose (8-9 g) MetHb level >55%, SpO_2 83-84%, reduced mental status, incoherent speech, cyanosis, seizures	MetHb level decreased to 5.9% 1 hour later; delayed MetHb peaks of ~30% over the next 48 hours mandated multiple MB administration (total cumulative dose 8 mg/kg)	Gastric lavage and nasogastric-administered activated charcoal given with MB Delayed-onset hemolytic anemia required prolonged hospital stay
Southgate (1999)[42]	Case report (N = 1)	Age 29 years; accidental overdose (6 g over 25 days) MetHb level 36%, SpO_2 89%, chocolate brown arterial blood, 3 days of malaise, fatigue, shortness of breath on exertion, cyanosis, darkened urine	2 Doses of MB reduced MetHb to 2.3% without clinical improvement; rebound MetHb level peaked at 45%, requiring MB continuous infusion at 7 mg/h with oral ascorbic acid; MetHb dropped to 10-12%, concurrent physical and mental condition improvement	Initial bolus MB with exchange transfusion unsuccessful; random serum dapsone level 58 mg/L (normal <10 mg/L) Severe hemolytic anemia 7 days after MB initiation (felt to be due to dapsone overdose and continuous-infusion MB) Pt. recovered with residual mixed sensorimotor axonal neuropathy
Bucaretchi (2000)[41]	Retrospective case series: single MB + activated charcoal (n = 12) vs activated charcoal alone (n = 5)	Age 1-13 years; overdose (100-1200 mg); pts. presented within 72 hours of exposure Median MetHb level 37.8% (23.5-49.7%); cyanosis and tachypnea most common presenting symptoms	Faster, but statistically nonsignificant, reduction of MetHb level in first 6 hours in the combination group No significant difference in MetHb decay over 72 hours between treatment arms (p = 0.49)	Activated charcoal: median 8 doses; MB 1 mg/kg Most pts. had reduced, but still above normal, MetHb concentrations
Carrazza (2000)[46]	Retrospective chart review (N = 266)	Age 1 month-50 years; mostly accidental intoxication (300-2000 mg) MetHb 3.2-94%, cyanosis, vomiting, mental confusion, tachycardia, dyspnea	Significant negative correlation between methemoglobinemia and time after intake (r = –0.134, p < 001)	Cyanosis in all pts. <5 years (n = 147) MetHb level 17% with dapsone 100 mg/day in 17-year-old pt.
Falkenhahn (2001)[21]	Case report (N = 1)	Age 29 years; unknown amount MetHb 47%, SpO_2 80% on 10 L O_2, dark brown arterial blood, cyanosis, dyspnea, anxiety, tachycardia, tachypnea	MetHb levels 13.8-31% over the first 72 hours, requiring 6 MB doses; MetHb level dropped to <15% by day 4, with clinical recovery	MB given with oral vitamin C 1 g/day Gas chromatography/mass spectrometry urine analysis positive for dapsone Blood MetHb reductase activity and G6PD level normal
Shadnia (2006)[44]	Case report (N = 1)	Age 18 years; overdose (2000 mg) MetHb 38%; cyanosis and tachypnea necessitating mechanical ventilation	MB given on day 3; MetHb level normalized by day 8 to 2%	Gastric lavage, ascorbic acid, repeated doses of activated charcoal/sorbitol 70% for 2 days without improvement Concurrent severe hemolysis
Prasad (2008)[27]	Phase 2 two-arm trial; MB 2-mg/kg bolus every 6 hours (n = 5) vs 6-hour infusion in normal saline (n = 6)	Age 38-61 months; pts. presented within 4-6 hours of dapsone ingestion (350-600 mg) Average MetHb 52% on admission; tachypnea and cyanosis in all pts., severe anemia in 2, seizures and altered sensorium in 6	Mean MetHb on last measure (at 72 hours) 20% (bolus) vs 11.2% (continuous infusion) (p = 0.001)	Faster MetHb level decline with continuous infusion over 3 days 2 Pts. in continuous infusion arm developed sulfhemoglobinemia
Thunga (2008)[24]	Case report (N = 1)	Age 19 years; overdose (4-4.5 g) MetHb 51% (~6 hours after ingestion) and Heinz bodies on peripheral blood smear; drowsiness and hypoxemia	MB (with other interventions) lowered MetHb by day 3	Pt. also received gastric lavage, activated charcoal slurry, and hemodialysis for 3 days Multiple doses of 100-mg MB Severe delayed-onset (day 7) hemolytic anemia
Narayanan (2010)[43]	Case report (N = 1)	Age 34 years; intentional overdose MetHb 44.4%; SpO_2 83% (with 15 L O_2 via a non-rebreather mask); sudden onset of dyspnea, decreasing level of consciousness (GCS = 3), tachypnea, cyanosis	MB 1.5 mg/kg provided immediate improvement of the pt.'s color and rise in the SpO_2 to 100%	Full recovery over "few" days (number not mentioned) Large saturation gap between SpO_2 between admission pulse oximeter and ABG, raising the author's suspicion for methemoglobinemia

Park (2010)[45]	Retrospective observational study (N = 46)	Mean age 60.91 years; mostly intentional overdoses (mean 43.97 g) Mean MetHb 30.80 g/dL (mean 543.9 minutes after ingestion); cyanosis, dyspnea, mental status changes (more in older patients), abdominal pain, hypoxemia	9 (19.6%) Pts. died; interval between ingestion and ED presentation longer in pts. who died (p = 0.003); mortality higher in older pts. (p = 0.009)	MB bid, gastric lavage, activated charcoal administered MetHb >30% in 2 elderly pts. who took dapsone 200 mg/day

ABG = arterial blood gases; ED = emergency department; G6PD = glucose-6-phosphate dehydrogenase; GCS = Glasgow Coma Scale; MB= methylene blue; MetHb = methemoglobin; SpO_2= pulse oximeter arterial oxygen saturation.

derly patient developed methemoglobinemia with mild cyanosis when dapsone therapy was initiated for pemphigus.[47] After 4 weeks of cimetidine treatment (400 mg 3 times a day), his MetHb level and cyanosis improved without interference with dapsone's effectiveness. In general, most case series describing cimetidine use for the treatment of dapsone-induced methemoglobinemia reported a positive outcome.[11,13,16,18,47] Almost all of these reports were in patients receiving dapsone for dermatologic indications in which protracted cimetidine administration did not hinder dapsone's effectiveness.[13,28,47] Although unlikely in theory, its interference with dapsone's antiinfective indications (eg, PJP prophylaxis) is unknown. Cimetidine use was advocated in patients receiving dapsone preoperatively to reduce the risk of intraoperative methemoglobinemia.[40] Conversely, some authors recommended against cimetidine use in the acute setting, citing its slow onset of action as a shortcoming.[18] Cimetidine's effect on dapsone-induced hemolytic anemia has been inconsistent.[13,30,47]

OTHER REMOVAL COMPOUNDS OR PROCEDURES

Because dapsone undergoes enterohepatic circulation, multiple doses of active charcoal have been attempted, especially in the acute overdose setting.[2,4,48] The hypothesis for this treatment is that activated charcoal will interrupt dapsone's (and its metabolite) enterohepatic circulation.[24] Repeated charcoal administration resulted in a decrease of both dapsone's and monoacetyldapsone's mean half-life from 77 ± 23 hours to 12.7 ± 0.7 hours and 51 ± 10 hours to 13.3 ± 1.0 hours, respectively.[4,15] Activated charcoal use is typically limited by gastrointestinal intolerance and is reserved for conscious patients.[2,4] As a source of NADH to red blood cells from glycolysis, dextrose administration was advocated for treatment of acute methemoglobinemia.[49] Gastric lavage, combined with oral charcoal therapy, has been attempted in acute overdose.[15] Its benefit is short-lived and limited to the early phase of the acute ingestion.[15] Charcoal hemoperfusion has been used; however, the procedure's benefits remain ill-defined.[2] It successfully reduced dapsone's half-life, with clinical resolution, but adverse effects such as hypoglycemia, hypotension, and thrombocytopenia developed.[15] Ascorbic acid, which increases nonenzymatic reduction of MetHb, has been tried but, because of its slow onset of action, is not recommended as monotherapy for acute symptomatic methemoglobinemia.[15] Vitamin E has been evaluated, with inconsistent results.[9] In refractory acute overdose cases, hyperbaric oxygen therapy, hemodialysis, and plasma exchange have been attempted, with equivocal results.[2,16] The lack of response with the latter 2 strategies was attributed to dapsone's large volume of distribution. Indeed, when initiated 3 days after massive dapsone ingestion, plasma exchange removed only 2% of the ingested drug.[25]

Literature Review

Ash-Bernal et al. reviewed the charts of 138 patients who acquired methemoglobinemia in 2 teaching hospitals in Maryland.[18] They found that the majority (58) of cases were caused by dapsone. Discontinuation of dapsone occurred in 18 of the 42 documented mild cases; 2 were treated with methylene blue. In fact, 1 patient with hemolytic anemia had symptoms at a MetHb level of 4.67%. The majority of patients in the series were anemic (2 patients with MetHb levels of 3.6% and 6.5% were treated with a reduced dapsone dose and cimetidine). In 1 sample case, a 34-year-old HIV-positive patient presented with dyspnea on exertion, cyanotic extremities, and an SpO_2 of 89% on room air. His MetHb level was 12.1%. He had been on dapsone for 3 months. The drug was stopped and the patient improved within 24 hours. In a study of HIV-positive children receiving either weekly (4 mg/kg; n = 46) or daily (1-2 mg/kg; n = 48) dapsone, changes in methemoglobinemia were similar with all dosing regimens: 15 and 2 had MetHb levels above 5% and 10%, respectively.[50] All patients were asymptomatic. The authors surmised that the lack of differences may be the result of the high dosage with the weekly regimen.

Williams et al. assessed the incidence of MetHb in children with acute lymphoblastic leukemia receiving dapsone.[26] Symptomatic MetHb was defined as above the normal level of MetHb, as measured by venous blood CO-oximetry, coupled with hypoxemia with or without cyanosis or respiratory distress. Twenty percent of patients (3/15) had symptomatic methemoglobinemia, with a mean MetHb level of 11.67%. The remaining 12 patients with asymptomatic methemoglobinemia had a mean MetHb level of 1.37% (range 0.02-3%). The mean blood cytochrome b5 reductase level was lower in symptomatic patients than in asymptomatic patients. The low levels were borderline statistically nonsignificant ($p = 0.06$), largely due to a small sample size. To eliminate leukemia as a cause of MetHb,[51] the authors analyzed 10 pediatric patients with leukemia who were receiving trimethoprim/sulfamethoxazole as control. Their MetHb level was normal at 0.54% (range 0.1-9.8%) and also significantly lower than that of the 12 asymptomatic patients on dapsone ($p < 0.001$). Sulfamethoxazole is associated with less methemoglobinemia than dapsone because of the preferential trapping of dapsone's hydroxylamine metabolite in red blood cells.[52]

A retrospective analysis of patients who had undergone HSCT at a single institution found an incidence of approximately 3% (5 of 155 patients with dapsone adverse events) of methemoglobinemia associated with dapsone given as 50 mg twice daily.[1] All patients had concurrent hemolytic anemia. Another retrospective study in 327 patients who received HSCT noted that, in the subset of patients who received dapsone 100 mg daily (n = 114), methemoglobinemia occurred in 3 individuals (2.6%).[6] In both reports, details about these patients were not provided. A male patient who received HSCT presented with mild aphasia, difficulty with coordination, paresthesia, and slurred speech.[8] A faint bluish tinge on the patient's nail beds was also noted. The SpO_2 dropped into the high 80s, and he become progressively short of breath. Dapsone was stopped when a MetHb level of 10.2% was determined, and methylene blue was administered. In less than an hour, the SpO_2 rose to approximately 97% and his mental status returned to baseline. A second patient had severe chest congestion, discomfort, and shortness of breath. The patient also had left lobe crackles, tachypnea, and cyanosis. The MetHb level was 9.7%; improvement occurred upon methylene blue administration. Concomitantly, the patient was diagnosed with pneumonia. In this report, the authors stated that dapsone-induced methemoglobinemia is not dose-related, a statement that is contrary to the body of evidence in the literature.[9,28,30,53] In a study evaluating the effect of cimetidine on dapsone kinetics, the daily dapsone dosage exhibited linear correlation with the methemoglobinemia ($r = 0.91 \pm 0.04$).[28] Non–dose-related methemoglobinemia has been documented as part of dapsone-associated sulfone syndrome, an uncommon but potentially fatal hypersensitivity reaction characterized by fever, malaise, exfoliative dermatitis, or a morbilliform rash, hepatocellular damage or cholestasis, lymphadenopathy, hepatosplenomegaly, and hemolytic anemia.[54] Conversely, a study evaluating dapsone 100 mg daily use in patients with leprosy found no correlation between steady-state trough plasma concentrations and MetHb levels.[55] A weak correlation was seen between dapsone and MetHb levels in overdose situations.[46]

Zosel et al. reported a case of a 37-year-old patient receiving dapsone for lupus.[12] Dapsone was initiated 8 months before her admission, with a dose increase 2 months prior. On presentation, the patient experienced cough and shortness of breath for the last 3 days with a SpO_2 of 94% on 2 L of O_2. A bluish hue to her fingertips and lips was noted the day before admission. At the time, methemoglobinemia was not suspected and the patient was treated for pneumonia, as pulmonary infiltrates were seen on chest computed tomography. The patient's condition worsened and, after 10 days of hospitalization, she developed respiratory alkalosis shown on arterial blood gas testing, with a 94-97% SpO_2 on 5 L of O_2. Her blood was dark purple, and dapsone-induced methemoglobinemia was suspected; a MetHb level of 25% confirmed the diagnosis. Methylene blue was administered twice: the first dose resulted in a MetHb level of 7%, only to rise to 13.6% within 6 hours. The second dose normalized the MetHb (values not reported). With resolution of the dyspnea, the patient

was discharged on hospital day 15 (5 days after dapsone was stopped).[12] Choi and Sarang reported the case of a 57-year-old woman on dapsone for granuloma faciale who, 3 days following elective coronary artery bypass graft, developed methemoglobinemia.[23] She suddenly became drowsy and was roused only by persistent verbal commands, with no focal neurologic signs. The SpO_2 ranged from 72% to 88%. The MetHb level determined on arterial blood gas tests rose from a preoperative baseline of 4.4% to 13%. Her condition improved within 24-48 hours after stopping dapsone and initiating oral ascorbic acid therapy.

Esbenshade et al.[53] undertook a 15-year retrospective cohort study of pediatric patients with hematologic diseases receiving dapsone. The primary endpoint was time to the development of symptomatic methemoglobinemia. The prevalence of confirmed methemoglobinemia was approximately 20% (32 of 167 patients). Median MetHb level was 8.95% (range 3.5-22.4%), with the majority of patients presenting with cyanosis and hypoxia (SpO_2 <95%). These patients received dapsone for a median of 67 days versus 427 days in patients without methemoglobinemia ($p < 0.001$). In the multivariate model, dapsone dose was associated with risk of methemoglobinemia (hazard ratio 6.25; 95% CI 2.45 to 15.93; $p < 0.001$). Sex, age, and body mass index were not associated with an increased risk of methemoglobinemia. A cross-sectional analysis of a subset of patients with methemoglobinemia (n = 20) with a matched control without methemoglobinemia (n = 20) did not find a correlation between cytochrome b5 reductase levels and MetHb levels. The highest MetHb level was seen in a symptomatic patient who subsequently was found to be the only G6PD-deficient subject of the cohort. A recent case report described a patient receiving dapsone 200 mg daily for dermatitis herpetiformis with chronic methemoglobinemia and SpO_2 of 87-89% on room air.[13] Cimetidine was started and the MetHb level decreased to 6%, eventually normalizing to 2.1% after the dapsone dose was halved to 100 mg daily.

The above, as well as additional reports describing dapsone-induced methemoglobinemia at therapeutic doses, are listed in Table 2.[2,8,10-13,16,18,20,22,23,26,31,34,35,47,49,53,56-62]

Discussion

Contrary to earlier findings,[2,4] most of the published dapsone-induced methemoglobinemia reports spanning the last decade describe this adverse effect as occurring at therapeutic doses (Table 2). We were able to find only 10 accounts of methemoglobinemia caused by overdose exposure over the same time span.[21,24,27,39,41-46] This largely mirrors modern-day practices in which dapsone is used in many indications, especially in immunocompromised hosts.

The review also sheds light on important clinical aspects of dapsone's ability to cause methemoglobinemia. First, it is clear that, when receiving therapeutic doses, patients can become symptomatic at MetHb levels greater or less than 10% and that the existing MetHb level cut-offs for symptoms,[2] derived from overdose cases in otherwise young healthy individuals, are not representative of what is seen in present-day clinical practice.[18] In general, the MetHb level is useful to confirm diagnosis, but it is not as important as the patient's clinical status for determining early treatment.[44] Symptoms have occurred at MetHb levels ranging from 1.9% to 26.8%, mostly at the 100-mg dose (Table 2). In most cases, patients' conditions tended to decompensate at these MetHb levels because of concurrent cardiopulmonary risk factors such as active coronary artery disease,[23,57,62] blood loss or anemia,[10,16,18,20,23,34,49,57,59,62] and pneumonia or lung disease.[8,12,20,47,58] In other accounts, overexposure to dapsone due to renal failure[2,31] and a pharmacodynamic interaction with another methemoglobinemia-inducing compound[16] were believed to be potential contributors. Those inciting factors may also explain the wide variability in time to onset of methemoglobinemia from dapsone therapy initiation as well as, in part, the variability in time to symptom resolution (Table 2). These findings are congruent with our clinical experience where we observed symptomatic methemoglobinemia at the range shown in Table 2 in patients with cardiopulmonary compromise or in patients stable on dapsone who began receiving an agent known to cause methemoglobinemia (eg, the aniline-like derivative phenazopyridine)[63] (RBI, unpublished observation). It is well known that the combination of 2 or more drugs known to cause methemoglobinemia increases its risk greatly.[7]

Second, protracted, or rebound methemoglobinemia is uncommon at therapeutic dose–associated dapsone methemoglobinemia.[1,8,10,11,16,20,22,23,26,34,35,49,56,58] In fact, only 4 reports, each on 1 patient, have described a second MetHb peak following appropriate interventions.[2,12 59,61] Two of these patients had confounding factors: compromised renal failure in 1[2] and a dosage higher (ie, 200 mg/day) than usual in the other,[12] suggesting increased dapsone exposure in both patients. The third patient had a 10-year history of grayish lips and fingers, hinting at a heightened sensitivity to methemoglobinemia-precipitating factors.[59] MetHb levels on presentation were between 15% and 20% in all 4 reports. Consistent with previously published overdose literature,[15] 2 overdose cases in our review displayed a delayed or rebound MetHb peak.[21,42] In our review, hemolytic anemia was reported in all cases describing methemoglobinemia overdose[24,39,41,42,44,45] and, to a lesser extent, at therapeutic doses.[1,11,13,18,31,58,59] Hemolytic anemia secondary to dapsone overdose developed over 5-9 days.[44] In therapeutic cases, it tended to be mild[1,13,31]; however, a more severe presentation with the administration of 2 doses of methylene blue was also reported.[11] In the majority of overdose cases, the hemolytic anemia was severe.[24,27,39,41,42,44] Collectively, the reviewed publications suggest that the higher the

Table 2. Dapsone-Induced Methemoglobinemia in Nonoverdose[a]

Reference	Publication Type	Symptoms (MetHb level)[a]	Time to Onset/Clinical Resolution	Comments
Plotkin (1997)[10]	Case report (N = 2)	Cyanosis, decreased mentation, hypoxemia (pt. 1, 18%; pt. 2, 22%)	3-4 days; 36-48 hours	MB 2 mg/kg (1 dose); GI bleeding at anastomosis suture line in 1 pt.
Ward (1998)[2]	Case report (N = 1)	Dyspnea and oxygen desaturation (peak 15.9%)	9 days from reexposure; MetHb normalized within 4 days	MB and 1 dose of activated charcoal; coexisting chronic renal failure (CrCl = 8-11 mL/min)
Craig (2000)[20]	Case report (N = 3)[b]	Pt. 1: asymptomatic (5.6%) Pt. 2: mild cyanosis and hypoxemia (1.3%) Pt. 3: cyanosis, tachypnea hypoxemia, epigastric tenderness (21%)	Pt. 1: NR; 12 days Pt. 2: NR Pt. 3: NR; 11 days	Dapsone continued in pt. 1; potential exacerbating factors uncontrolled menorrhagia (pt. 2) and right basilar pneumonia (pt. 3)
Mandrell (2001)[56]	Case report (N = 4); pediatric	Pt. 1: cyanosis (12.6%) Pt. 2: dusky appearance, hypoxemia (10.4%) Pt. 3: dusky appearance, hypoxemia (11.6%) Pt. 4: cyanosis, hypoxemia (NR)	Pt. 1: NR; 48 hours Pt. 2: 3 months; NR Pt. 3: NR; 1week Pt. 4: NR; within days	Dapsone discontinuation the only intervention
Salamat (2003)[57]	Case report (N = 1)	Angina, breathlessness, central cyanosis (17.5%)	4 months; NR	MB (1 dose); coexisting ischemic 3-vessel heart disease; MetHb reductase level normal
Ash-Bernal (2004)[18]	Retrospective chart review (n = 58/N = 138)	Hypoxia, cyanosis, change in mental status, headache (7.6%; range 2.1-34.1%)	NR; NR	Total of 138 pts. with methemoglobinemia
Lee (2005)[34]	Retrospective chart review (n = 5/N = 16)	NR (7.2%; range 5.1-10.7%)	48 days (7-809);13 (1-44)	4/5 Pts. had anemia or cardiopulmonary disease; 3/5 pts. had lung transplant; methemoglobinemia diagnosis delayed (median 17 days; range 3-573)
Talarico (2005)[35]	Case report (N = 1)[c]	Dyspnea and oxygen desaturation (11.6%)	NR; 48 hours; MetHb decreased to 2.2%	Intraoperative anemia
Williams (2005)[26]	Retrospective chart review (n = 3/N = 15); pediatric	NR (mean 11.67%; range 7-18%)	24-70 Days; hypoxia improved within 3-5 days; MetHb normalized 4-6 days after stopping dapsone	Dapsone dosage 5-10 mg/kg/week 3 times a week
Dunford (2006)[8]	Case report (N = 2)	Pt. 1: neurologic symptoms, bluish tinge of nail beds (10.2%) Pt. 2: cardiopulmonary symptoms (9.7%)	Pt. 1: 28 days; respiratory status improved <1 hour post-MB Pt. 2: 10 weeks; NR	Pt. 2 had suspected pneumonia
Schiff (2006)[58]	Case report (N = 1); pediatric	Nail bed and perioral cyanosis, hypoxemia (9.6%)	24 hours; 3 days	Concurrent pneumonia and suspected hemolysis; results of cytochrome b5 reductase and G6PD tests normal
Turner (2007)[16]	Case report (N = 1)[c]	NR (18%)	NR; 10 minutes; MetHb decreased to 4.7%	MB 1 mg/kg (1 dose); intraoperative lidocaine administration thought to play a role
Zosel (2007)[12]	Case report (N = 1)	Cough, shortness of breath, bluish fingertips/lips, hypoxemia (18%)	Occurred 2 months from dose increase[d]; NR	Concurrent pneumonia; MB 1 mg/kg (2 doses); dapsone dose 200 mg/day
Choi (2007)[23]	Case report (N = 1)[b]	Drowsiness, hypoxemia (13%)	NR; 24-48 hours	Intraoperative acute anemia; history of CAD and COPD
Arrivabene-Caruy (2007)[49]	Case report (N = 1)	Brown blood, cyanosis, tachypnea, somnolence and hypoxemia (10.4%)	NR; 15 minutes; MetHb 2.7% 24 hours post-MB	Intraoperative event involving general anesthesia; MB 1 mg/kg (1 dose)
O'Dwyer (2008)[22]	Case report (N = 1)	Cyanosis, dyspnea, headache, tachycardia, hypoxemia (22.9%)	3 weeks; 5 days	MB 1 mg/kg (1 dose); dapsone dose 50 mg/day
Walker (2009)[11]	Case report (N = 1)	Back pain, tachycardia, dyspnea (16%)	4 days; NR; MB; MB with cimetidine reduced MetHb to 1.9% and improved respiratory status	MB 100 mg daily (2 doses) with cimetidine; onset of severe hemolytic anemia 4 days after MB Pt. of Mediterranean descent; suspected G6PD deficiency

Goolamali (2009)[47]	Case report (N = 1)	Mild cyanosis (9.4%)	4 weeks; at 4 months, MetHb 3.7%, hemolysis improved	History of oxygen-dependent COPD; cimetidine treatment; dapsone dose 75 mg/day
Cho (2010)[62]	Case report (N = 1)	Asymptomatic; lips and fingernail cyanosis (18.3%)	Shortly after anesthesia induction; on the same day, MetHb decreased to 2.3% with MB and ascorbic acid[e]	Concurrent anemia; pt. on dapsone for 30 years; received MB 1 mg/kg (1 dose) and ascorbic acid 600 mg
Subramaniam (2010)[60]	Retrospective observational (n = 13/N = 34)	4 Symptomatic pts. with hypoxemia (mean 3.6%; range 1.9-26.8%)	Mean 11.8 days (range 4-18); NR; all 4 pts. improved	MB administered to 3 pts.; all pts. anemic; 1 symptomatic pt. had stable ischemic heart disease
Moulis (2010)[59]	Case report (N = 1)	Dyspnea and cyanosis (17%)	1 Month; 20 minutes post-MB, MetHb 4%; discharged within 48 hours Symptomatic MetHb 14% 10 days later	MB 2 mg/kg (1 dose) Second event, no intervention; MetHb decreased to 5% the next day
Ashurst (2010)[61]	Case report (N = 1)	Shortness of breath, chills, weakness, hypoxia, central and peripheral cyanosis (6.3%)	NR; MetHb decreased to 3.8%; hypoxia improved on admission day 2	Dapsone cessation and O_2 were the only interventions
Esbenshade (2011)[53]	Retrospective cohort (n = 32/N = 167)	Cyanosis and hypoxia (median 8.95%; range 3.5-22.4%)	Median time to onset 67 days; NR	All pts. (except 1 who received MB) improved with dapsone discontinuation; no comorbidities
Pallais (2011)[13]	Case report (N = 1)	Chronic low SpO_2 (chronic level 9.7-16.5%)	8 Years; improvement in MetHb level at 1 year	Mild hemolysis; dapsone dose 200 mg/day
Abouraya (2011)[31]	Case report (N = 1)	Progressive shortness of breath, fatigue, tachypnea, cyanosis, hypoxemia (NR)	NR; NR	Pt. had renal failure (SCr 3-4 mg/dL); responded to single-dose MB; normal G6PD level; concomitant mild hemolysis; dapsone dose 100 mg 3 times/week

CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CrCl = creatinine clearance; G6PD = glucose-6-phosphate dehydrogenase; MB = methylene blue; MetHb = methemoglobin; NR = not reported; SCr = serum creatinine; SpO_2 = pulse oximeter arterial oxygen saturation.

[a]Unless otherwise stated, all adults received dapsone 100 mg/day and methylene blue was given over 5 minutes.

[a]At the onset of the adverse event.

[b]One patient (aged 16 years) received dapsone 50 mg/daily.

[c]Dapsone dose NR.

[d]Started 8 months.

[e]MetHb decreased to 11.2% with vitamin C and then to 2.3% with methylene blue. MetHb later rose to 8.5-11% later, but the patient did not require treatment.

MetHb level on presentation, the greater the chances for a delayed MetHb rebound and hemolytic anemia. The latter entity is likely related to overexposure to dapsone's hydroxylamine metabolites and subsequent recourse to multiple doses of methylene blue to control the high MetHb levels. As discussed earlier, the use of high doses of methylene blue carries the risk of hemolytic anemia, especially in G6PD-deficient patients.[11,42]

While methemoglobinemia is clearly a dose-related adverse effect,[9,28,53] attempts to decrease the dapsone dose (ie, from 100 mg/day to 50 mg/day) are not recommended in patients taking the drug for antiinfective indications, as this has been associated with higher incidence of breakthrough infections.[64] Indeed, PJP rates increased from 2.6% to 11.3% when the dapsone dose was decreased from 50 mg twice a day to 50 mg daily.[64] In another report, dapsone 50 mg twice daily 3 times a week was suboptimal in PJP prevention in adults who received HSCT.[65] A retrospective single-institution study reported no adverse events and acceptable effectiveness when a weekly dapsone dose of 50 mg/m^2 was given to a pediatric population, although breakthrough *Toxoplasma gondii* was a concern.[66] Dapsone, when combined with pyrimethamine, is active against PJP and *T. gondii*.[3,7] While the intent of this regimen is to use lower doses of dapsone, it was found that the combination may cause more methemoglobinemia than dapsone alone.[3,7]

With the exception of 2 studies,[26,53] most of the reviewed publications lacked a rigorous scientific analysis of risk factors for dapsone-induced methemoglobinemia. Naik et al. showed that, in lung transplant recipients, the incidence of dapsone-induced hemolytic anemia correlated with renal function and low ideal body weight when the drug was given at the fixed dose of 100 mg daily, suggesting a relation to total drug exposure.[5] Because methemoglobinemia and hemolytic anemia share the same offending agent, dapsone's hydroxylamine metabolites,[30] the contribution of these risk factors to methemoglobinemia is possible and warrants study. We suspect that a significant number of patients receiving dapsone have a borderline elevated MetHb but remain asymptomatic until the advent of a trigger, as illustrated in the case report by Choi and Sarang.[23] A study evaluating patients on dapsone with MetHb levels obtained at baseline and at the onset of symptomatic methemoglobinemia will help to ascertain these observations. In our review, few reports assessed the patient's G6PD[21,31,47,53,58,62] and cytochrome b5 status,[21,26,31,53,57,58] with the majority being descriptive. Esbenshade et al.[53] and Williams et al.[26] studies were the only evaluations in which a statistical correlation between methemoglobinemia and cytochrome b5 reductase level was undertaken. The presence of impaired cytochrome b5 reductase activity, along with a slow acetylator NAT2*5B haplotype, in an adult with methemoglobinemia was recently described.[31] This is important because, excluding overdose scenarios, toxic methemoglobinemia may result from ingestion of appropriate dapsone doses in individuals with partial deficiencies of cytochrome b5 reductase.[35,57] The impact of CYP2C polymorphisms on dapsone-associated methemoglobinemia has yet to be addressed.[32]

It is known that children younger than 6 years are at an increased risk of methemoglobinemia in the setting of gastroenteritis, dehydration, and sepsis because of the low activity of erythrocyte NADH-MetHb reductase.[18,41] This is more pronounced in neonates because fetal Hb, which is unstable, is more easily oxidized to MetHb.[9,57] In the pediatric literature reviewed here, patients younger than 6 years, but not neonates, were examined with other children; however, no separate analysis was conducted for this age group.[1,26,53,66] An exception was a retrospective review of dapsone overdoses from Brazil in which a separate analysis of children younger than 5 years was conducted (Table 1).[46] The authors noted that cyanosis was the presenting symptom in all children of this age group. In all, children exhibited no excess or unusual morbidity to dapsone-induced methemoglobinemia and appropriate response to methylene blue intervention.[27,41,53]

Summary

Clinicians caring for patients receiving dapsone should be aware of methemoglobinemia as a not uncommon adverse effect of this antiinfective compound at therapeutic doses. They should be aware of factors that may precipitate dapsone-induced methemoglobinemia and, should it happen, know how to promptly and effectively manage it.

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Metahemoglobinemia Inducida por Dapsona: un Manual para Facultativos

JA Barclay, SE Ziemba, y RB Ibrahim

Ann Pharmacother 2011;45:xxxx.

EXTRACTO

OBJETIVO: Presentar una revisión exhaustiva de la metahemoglobinemia inducida por dapsona y su tratamiento.

FUENTES DE INFORMACIÓN: Se accedió a la recuperación de literatura a través de las bases de datos MEDLINE (1966-marzo de 2011), la biblioteca Cochrane, y EMBASE mediante los términos de búsqueda dapsone (dapsona) y methemoglobinemia (metahemoglobinemia).

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE DATOS: Se evaluaron todos los artículos identificados en inglés de las fuentes de datos. Se evaluaron todos los casos clínicos en humanos, los ensayos de series de casos de tamaño reducido y los ensayos aleatorizados y controlados que se publicaron en inglés. Debido a la ausencia de actualizaciones exhaustivas sobre este tema desde 1996, en esta revisión se incluyeron las publicaciones entre 1997 y marzo de 2011.

SÍNTESIS: Entre 1997 y marzo de 2011, la mayoría de las publicaciones que describen la metahemoglobinemia asociada con el uso de dapsona notificaron este efecto adverso a dosis terapéuticas. Si excluimos las situaciones de sobredosis, se identificaron 18 casos clínicos de metahemoglobinemia sintomática asociada con dapsona y la presentación clínica del trastorno oscila desde cianosis a dificultad para respirar. En casi todos los casos, los pacientes presentaron un evento concurrente como anemia o pneumonía sugerente de una interacción entre estas comorbilidades y el inicio de la metahemoglobinemia sintomática. Se ha observado la aparición de anemia hemolítica tardía en casos con un nivel alto de metahemoglobinemia en la presentación. El tratamiento consiste en la administración de azul de metileno en la mayoría de los casos. En general, la mayoría de los casos clínicos tuvieron un resultado favorable y no hubo fallecimientos resultantes de la metahemoglobinemia asociada con el uso terapéutico del fármaco.

CONCLUSIONES: Los facultativos deben conocer la metahemoglobinemia como un efecto adverso asociado con el uso de dapsona y los factores potenciales que favorecen su aparición. Asimismo, deben conocer cómo tratar este evento de forma rápida y eficaz.

Traducido por Enrique Muñoz Soler

Méthémoglobinémie Induite par le Dapsone: une Mise à Jour Pour les Cliniciens

JA Barclay, SE Ziemba, et RB Ibrahim

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RÉSUMÉ

OBJECTIF: Présenter une revue détaillée de la méthémoglobinémie induite par le dapsone et sa prise en charge.

SOURCES DE DONNÉES: Une revue de la documentation scientifique a été effectuée par le biais d'une recherche MEDLINE (1966 à mars 2011), la Librairie Cochrane, et EMBASE avec l'utilisation des termes dapsone et méthémoglobinémie.

SÉLECTION DES ÉTUDES ET EXTRACTION DES DONNÉES: Tous les articles de langue anglaise identifiés par le biais de la recherche ont été évalués. Tous les rapports de cas, les séries de cas et les essais cliniques randomisés publiés en anglais ont été analysés. En l'absence d'une mise à jour détaillée sur le sujet depuis 1996, les publications disponibles de 1997 à Mars 2011 ont été inclues dans la revue.

SYNTHÈSE DES DONNÉES: Entre 1997 et Mars 2011, la majorité des publications concernant la méthémoglobinémie à l'utilisation du dapsone ont rapporté cet effet indésirable à des doses thérapeutiques. En excluant les situations de surdose, 18 rapports ont été identifiés avec une méthémoglobinémie symptomatique associée à la prise de dapsone et une présentation clinique attenante allant de la cyanose à des difficultés respiratoires. Dans la majorité des cas, les patients présentaient un

événement concomitant tel que de l'anémie ou une pneumonie suggérant une relation entre ces comorbidités et le début de la méthémoglobinémie symptomatique. Une anémie hémolytique retardée a également été recensée pour les cas où la méthémoglobine était élevée initialement. La prise en charge consistait en l'administration de bleu de méthylène pour la plupart des événements. En général, la majorité des rapports faisaient état d'une résolution adéquate de la situation et aucune mortalité n'est documentée à la suite d'une méthémoglobinémie associée à un usage thérapeutique du dapsone.

CONCLUSIONS: Les cliniciens doivent être à même de reconnaître une méthémoglobinémie, comme effet indésirable associé à la prise de dapsone et les facteurs de risque qui favorisent son apparition. Ils doivent également pouvoir réagir rapidement et efficacement pour prendre en charge cette situation.

Traduit par Chantal Guévremont