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CLINICAL RESEARCH

## Difference of the clinical course and outcome between dapsone-induced methemoglobinemia and other toxic-agent-induced methemoglobinemia

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### ABSTRACT

**Context:** Acquired methemoglobinemia is a potentially fatal condition that leads to tissue hypoxia. Although the clinical features of methemoglobinemia depend on the methemoglobin levels, the clinical course would differ depending on the causative agents.

**Objective:** We attempted to clarify this issue by comparing the clinical course of methemoglobinemia caused by dapsone and that caused by other toxic agents.

**Materials and methods:** A retrospective case–control study was performed. All patients with methemoglobinemia and who were admitted to the emergency department (ED) of our hospital from 1 January 2002 to 31 December 2014 were included.

**Results:** Of the 34 patients with methemoglobinemia, 15 ingested dapsone (14 with acute overdose and one with chronic therapeutic use) and 19 had been exposed to other toxic agents, such as sodium nitrites, indoxacarb, primaquine, and lidocaine. The clinical characteristics and the course of dapsone-induced and other toxic-agent-induced methemoglobinemia were compared. There was no significant difference in clinical presentation and methemoglobin level (38.5% vs. 35.0%,  $p = 0.456$ ) upon their ED arrival between the two groups. However, the methemoglobin level after use of methylene blue and the total dose of methylene blue were higher in patients with dapsone-induced methemoglobinemia than in those with other agent-induced methemoglobinemia (11.9% vs. 1.7%,  $p = 0.001$ , 455 mg vs. 144 mg,  $p = 0.006$ ). The majority of dapsone-induced methemoglobinemia (93.3%) required more than 72 h for normalization of the methemoglobin level, despite the use of methylene blue. Five of the study patients died due to multiorgan failure, and all of whom were inpatients with dapsone-induced methemoglobinemia.

**Conclusion:** The clinical course of dapsone-induced methemoglobinemia was worse than that of other toxic-agent-induced methemoglobinemia despite no significant difference in their initial clinical presentation. Continuous treatment with serial monitoring of the serum methemoglobin is necessary for patients with dapsone-induced methemoglobinemia.

### ARTICLE HISTORY

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Dapsone; methemoglobinemia; poisoning

### Introduction

Methemoglobinemia is a functional hypoxia due to the decreased oxygen-carrying capacity and left-shifted oxygen hemoglobin dissociation curve.[1,2] Symptomatology has been correlated with the methemoglobin levels. Medications are one of the most common causes of methemoglobinemia seen in clinical practice, and, of these, antibiotics (dapsone), local anesthetics (benzocaine and lidocaine), and nitrites (nitroglycerin/nitric oxide) are the most likely causative agents.[2–5] Dietary nitrate in food and water is another major cause of methemoglobinemia in some parts of the world, and pediatricians might see enteritis-associated methemoglobinemia that is usually seen in infants aged younger than six months.[6]

Acquired methemoglobinemia is undiagnosed or diagnosed late in the clinical course of the illness. Treatment begins with discontinuation of the offering agent and the drug of choice is methylene blue as it provides an artificial electron transporter to aid in the reduction of methemoglobin.

It is given in a dose of 1–2 mg/kg IV over five minutes. Serial methemoglobin levels are suggested in order to monitor the adequate response to treatment and repeat methylene blue doses may be necessary.

Previous studies have revealed that the initial methemoglobin concentration, clinical features seen on a patient's emergency department (ED) arrival and the delayed time from intoxication to ED arrival would affect the poor outcomes in patients with methemoglobinemia.[4,5,7] In this study, we compared the clinical course and outcomes of patients who were diagnosed with methemoglobinemia caused by dapsone and other toxic agents.

### Materials and methods

#### Study design and population

We performed a retrospective cohort study. All consecutive patients with methemoglobinemia who presented at the

emergency department (ED) of our hospital between 1 January 2002 and 31 December 2014 were identified retrospectively by using discharge codes according to the 9th International Classification of Diseases (ICD-9 289.7) from the Open Report System of our hospital, a clinical data warehouse. The electronic medical records of all eligible patients were retrieved for evaluation. Our hospital is a university hospital located in an urban area that treats approximately 100,000 patients per year in the ED. Only adult patients ( $\geq 18$  years) with toxicant-induced methemoglobinemia were included in the study. Exclusion criteria were patients whose causative toxic agent was unidentified. Patients were categorized according to a dapsone-induced methemoglobinemia group and other toxic-agent-induced methemoglobinemia group according to the causative agent. The Institutional Review Board of our hospital approved this study.

### Data collection

The clinical and demographic characteristics of all patients were collected from our electronic medical records, which included patient age, sex, clinical characteristics on ED arrival such as mental change, dyspnea, and cyanosis, causative toxic agent, timing of their intoxication, timing of their treatment, initial methemoglobin level, clinical course, and outcome. All patients had serial laboratory tests for methemoglobin level and they received standard treatment including mechanical ventilation, vasopressor use, continuous renal replacement therapy, and the use of methylene blue if indicated. The need for mechanical ventilation, vasopressor use, and continuous renal replacement therapy, the total dose of methylene blue during their hospitalization, and the length of their hospitalization were also recorded. For grading the severity of their poisoning, each patient included in this study was evaluated using the poisoning severity score.[8]

Intravenous methylene blue (1 mg/kg) was administered to treat methemoglobinemia at the discretion of the involved clinicians. The definitive criteria for methylene blue administration was for patients with altered mentality or cyanosis, those with vasopressor or mechanical ventilation, and those in asymptomatic and with a methemoglobin level of 30% or greater. Additional methylene blue was administered when patients were still symptomatic or presented with a methemoglobin level of 30% or greater in follow-up test during hospitalization.

### Statistical analysis

Continuous variables are expressed as means with standard deviations or median with the interquartile range (IQR) if the assumption of a normal distribution was violated. Categorical variables were given in terms of the numbers and percentages. We hypothesized that patients in the dapsone-induced group would be different from those in the other toxic-agent-induced methemoglobinemia group in clinical outcomes such as methemoglobin concentration, the total dose of methylene blue, hospitalization days, poisoning severity score, and duration of illness. All of the variables were tested for normal

distribution using the Kolmogorov–Smirnov test. The Student's *t*-test was used to compare the means of normally distributed continuous variables, whereas the Mann–Whitney *U*-test was used to compare noncontinuous variables. The Chi-square or Fisher's exact test was applied for comparing categorical variables. A two-sided *p* value  $< 0.05$  was considered to be statistically significant. All statistical analyses were performed using SPSS for Windows version 21.0 (SPSS Inc., Chicago, IL).

### Results

Between 1 January 2002 and 31 December 2014, a total of 40 patients were retrieved by ICD-9 code for methemoglobinemia. Five were excluded from the study because they were younger than 18 years old ( $n = 3$ ) or their causative agent was unidentified ( $n = 3$ ). Thus, 34 patients were finally included in the study. Fifteen patients (44.1%) ingested dapsone; 11 (73.3%) with acute intentional overdoses; three (20.0%) with acute accidental overdoses; and 1 (6.7%) with chronic prescribed dose. The other 19 patients (55.9%) were exposed to other toxic agents; antifreeze admixtures containing sodium nitrite ( $n = 6$ ); herbicides ( $n = 3$ ); pesticides ( $n = 2$ ); sodium nitrite ( $n = 2$ ); silver nitrate ( $n = 1$ ); lidocaine ( $n = 1$ ); primaquine ( $n = 1$ ); liquefied natural gas ( $n = 1$ ); hair dye ( $n = 1$ ); and Maesilju, Japanese apricot liqueur ( $n = 1$ ).

The demographic findings of the patients in the dapsone-induced and the other toxic-agent-induced methemoglobinemia group were presented in Table 1. The median patient age was 55.5 (19.0–88.0, range) years, and the male-to-female ratio was 1:1. While the majority of the patients in the other toxic agent group (68.4%) had been accidentally exposed to a toxic agent, the majority of the patients in the dapsone group (73.3%) had intentionally ingested dapsone. The patients in the other toxic agent group (68.4%) were unintentionally exposed to the toxic agent from their occupational environment or by environmental contaminants. Mental change, dyspnea, and cyanosis were the common symptoms and signs in both groups (Table 1). The time interval from their intoxication to administration of methylene blue was longer in the dapsone group than in the other toxic agent group (median, 14.0 vs. 4.0, hours).

During hospitalization, the clinical course and outcome of the patients differed between the two groups (Table 2). The severity of poisoning reflected by the poisoning severity score was higher in the dapsone group (median, 8.0; IQR, 7.0–11.0 vs. median, 7.0; IQR 5.0–8.0;  $p = 0.027$ ). All of the patients received a bolus of intravenous methylene blue (1 mg/kg) for treatment of their methemoglobinemia. Although the initial methemoglobin level demonstrated no difference between the patients in the dapsone group and those in the other toxic agent group [38.5% (IQR, 34.0–43.9) vs. 35.0% (IQR, 25.6–48.5),  $p = 0.456$ ], the response to methylene blue differed between the two groups. The methemoglobin level of the patients in the other toxic agent group, which was measured at one hour after the administration of methylene blue, was nearly normalized (1.7%; IQR, 0.5–6.9), however that of the patients in the dapsone group still presented with a higher

**Table 1.** Demographic and hospital course of the study patients.

	Total	Dapsone-induced	Other toxic agent induced
Number of patients	34	15	19
Age, years (range)	55.5 (19.0–88.0)	58.0 (19.0–88.0)	51.0 (19.0–83.0)
Male	17 (50.0%)	6 (40.0%)	11 (57.9%)
Systolic blood pressure (mmHg)	130.7 ± 22.1	126.5 ± 24.1	134.6 ± 20.4
Diastolic blood pressure (mmHg)	78.8 ± 18.4	72.5 ± 22.2	84.7 ± 16.0
Mean arterial pressure (mmHg)	96.1 ± 19.5	90.5 ± 21.4	101.3 ± 15.8
Intentional intoxication	17 (50.0%)	11 (73.3%)	6 (31.6%)
Alcohol co-ingestion	9 (26.5%)	6 (40.0%)	3 (15.8%)
Initial symptoms and signs			
Mental change	15 (44.1%)	9 (60.0%)	6 (31.6%)
Dyspnea	21 (61.8%)	7 (46.7%)	14 (73.7%)
Cyanosis	25 (73.5%)	13 (86.7%)	12 (63.2%)
Irrigation	13 (38.2%)	5 (33.3%)	8 (42.1%)
Charcoal use	8 (23.5%)	5 (33.3%)	3 (15.8%)
Elapsed time of antidote use after exposure (hours) <sup>a</sup>	8.0 (3.3–14.8)	14.0 (8.0–20.3)	4.0 (2.0–10.0)
Vasopressor use	4 (11.8%)	3 (20.0%)	1 (5.3%)
Mechanical ventilation	7 (20.6%)	4 (26.7%)	3 (15.8%)
Continuous renal replacement therapy	2 (5.9%)	1 (6.7%)	1 (5.3%)

Values are expressed as the mean with standard deviation, the median with the interquartile range or as *n* (%).

<sup>a</sup>The exposure time was not identified in two patients (1 in the dapsone-induced methemoglobinemia group and 1 in the other toxic-agent-induced methemoglobinemia group).

**Table 2.** The main outcomes of the study patients.

	Total ( <i>n</i> = 34)	Dapsone induced ( <i>n</i> = 15)	Other toxic agent induced ( <i>n</i> = 19)	<i>p</i> Value
Poisoning severity score, total	7.0 (6.0–9.0)	8.0 (7.0–11.0)	7.0 (5.0–8.0)	0.027
Initial methemoglobin concentration (%)	36.7 (30.6–44.3)	38.5 (34.0–43.9)	35.0 (25.6–48.5)	0.456
Methemoglobin concentration after the use of methylene blue (%)	7.0 (1.2–18.6)	11.9 (7.5–22.7)	1.7 (0.5–6.9)	0.001
Hospitalization days	3.5 (3.0–7.0)	6.0 (3.0–8.0)	3.0 (3.0–5.0)	0.138
Duration for normalization of methemoglobinemia				<0.001
within 12 h	14 (41.2%)	0 (0%)	14 (73.7%)	
12 h to 24 h	1 (2.9%)	0 (0%)	1 (5.3%)	
24 h to 72 h	1 (2.9%)	1 (6.7%)	0 (0%)	
more than 72 h	18 (52.9%)	14 (93.3%)	4 (21.1%)	
Rebound phenomenon	16 (47.1%)	13 (86.7%)	3 (15.8%)	<0.001
Total dose of methylene blue in use during hospitalization (mg)	184 (100–499)	455 (155–984)	144 (100–201)	0.006
28-day mortality	5 (14.7%)	5 (33.3%)	0 (0.0%)	0.011

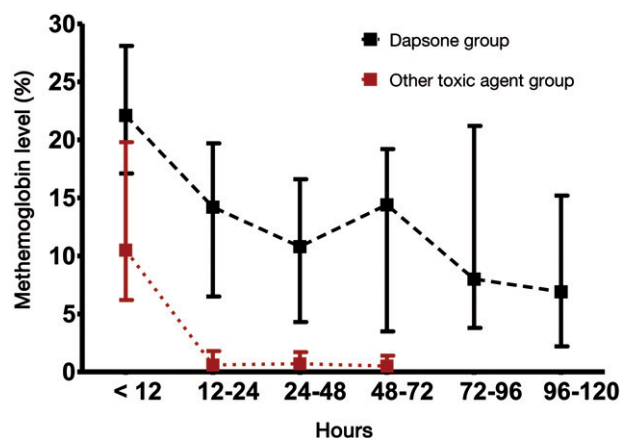
Values are expressed as the median with the interquartile range or as *n* (%).

level after administration of methylene blue (11.9%; IQR, 7.5–22.7; *p* = 0.001).

Prolonged methemoglobinemia, despite the additional use of methylene blue, was demonstrated in the patients in the dapsone group as nearly all of the patients in the dapsone group (93.3%) required more than 72 h for normalization of their methemoglobin level, while the methemoglobin level in more than two-thirds of the patients in the other toxic agent group (73.7%) was normalized within 12 h (Figure 1). The rebound phenomenon occurred more frequently in the patients in the dapsone group (86.7% vs. 15.3%, *p* = 0.000) and resulted in the administration of a much larger dose of methylene blue in for the patients in the dapsone group (455 mg vs. 144 mg, *p* = 0.006). Five patients (14.7%) of our study died of multiorgan failure and all of these patients presented ED after intentional dapsone overdose.

## Discussion

We compared patients with methemoglobinemia according to the causative agent (dapsone and others) as the initial clinical symptoms and initial methemoglobin level were similar in the two groups. However, the clinical course and outcome of patients in the dapsone group were obviously worse as those patients demonstrated more prolonged methemoglobinemia



**Figure 1.** Serial changes of the methemoglobin level (%) in methemoglobinemia patients, as caused by dapsone and other toxic agents. The graph represents the median with the interquartile range of the methemoglobin level.

which required multiple administrations of methylene blue and five of these patients (14.7%) eventually died.

Our patients in the two groups had no statistical differences in the methemoglobin level, and as a result, the presented clinical symptoms and signs did not differ in either group. The most common symptom and sign at ED admission was dyspnea (61.8%) and cyanosis (73.5%), respectively. However, the clinical course during hospitalization differed significantly different in both groups, and the physicians

should consider this when evaluating and managing patients with acquired methemoglobinemia.

All of the patients in our study received intravenous methylene blue. The majority of the patients in the dapsone group received multiple doses of intravenous methylene blue due to their rebound phenomenon of methemoglobinemia (86.7%). On the other hand, the majority of the patients in other toxic agent group (84.2%) recovered from their methemoglobinemia after receiving one dose of intravenous methylene blue. If the causative agent of methemoglobinemia was not identified, the patient response to methylene blue might provide a clue, such as dapsone, benzocaine, and aniline, which were well known to cause rebound phenomenon.

In our study, all of the methemoglobinemia fatalities were caused by dapsone ingestion. The five patients arrived comatose at the ED after intentional dapsone overdose, and hypoxic brain damage was already documented by diffusion-weighted magnetic resonance imaging (MRI). During hospitalization, persistent methemoglobinemia (rebound phenomenon), hemolysis, and pneumonia occurred in those patients, and despite continued treatment patients subsequently developed renal and respiratory failure and finally died. The pharmacological characteristics of dapsone, itself, as well as the characteristics of patients in the dapsone group might affect the fatality rate. The principal metabolite of dapsone is mono-*N*-acetyl dapsone, which is not associated with toxicity.[9] However, another metabolic pathway is the *N*-hydroxylation of dapsone (DDS-NHOH), which is mainly responsible for the hematological toxicity. This is formed by hepatic cytochromes P450, particularly CYP2C9 and CYP2C19.[10] Elimination of the half-life of dapsone is dose-dependent and ranges from 20 to 30 h in adults.[11] Dapsone is also fat soluble and is distributed in most tissues. This elongated the elimination half-life and might contribute to relapse of methemoglobinemia.[12,13] The prolonged time interval from intoxication to administration of methylene blue in the dapsone group would also affect the outcome.[5]

Our study is limited by its retrospective design, with all of the potential biases inherent to this type of study, including data gathering, analysis, and interpretation. Also, the accurate comparison between two groups could not be made because we could not control the variables which possibly affect the outcome. Second, this is a single-center study with a relatively small sample size, which limits the generalization of our findings. Third, the patients in the study sample were identified by using ICD-9 code for methemoglobinemia; patient eligibility may therefore be subject to study selection biases due to coding procedures. Fourth, the risk factors for methemoglobinemia, such as anemia and G6PD deficiency, were missing, which affect the outcome, Another major concern is that other agents which were known to cause of persistent methemoglobinemia, such as benzocaine and aniline, were not included in our study due to not using 20% benzocaine spray during an echocardiogram or bronchoscopy in our institution.

Additionally, the dose of dapsone could not be identified in our study, which could affect the clinical outcome.

## Conclusions

The clinical course of dapsone-induced methemoglobinemia was worse than that of other toxic-agent-induced methemoglobinemia particularly longer duration of hospitalization and more frequent complications. This emphasized the importance of identifying the causative agent of methemoglobinemia. Continuous treatment with serial monitoring of serum methemoglobin levels is necessary for patients with dapsone-induced methemoglobinemia.

## Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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