Acute dapsone exposure and methemoglobinemia in children: treatment with multiple doses of activated charcoal with or without the administration of methylene blue

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Abstract

Objective: to study the changes in methemoglobinemia of 17 children admitted with acute exposure to dapsone complicated by a methemoglobin concentration greater than 20% of the total hemoglobin. The children were treated with multiple doses of activated charcoal with or without the administration of methylene blue.

Patients and Methods: seventeen patients (ages 1-13 y, median 3 y), were admitted 1-72 h after the ingestion of 100-1200 mg (median 350 mg, 10 patients) or an unknown amount of dapsone (7 patients). The methemoglobin blood concentrations upon admission ranged from 23.5%-49.7% (median 37.8%), and the main clinical features were cyanosis (17), tachycardia (17), vomiting (11) and tachypnea (8). All of the children received multiple doses of activated charcoal orally or via nasogastric tube (1g/kg, 10% solution, 4-6 times/day, 3-16 doses with a median of 8 doses). Twelve of the 14 patients with methemoglobin levels greater than 30% were also treated with a single dose of methylene blue (1-2% solution, 1-2 mg/kg) infused IV over 5 min.

Results: there was a progressive decrease in the methemoglobin levels after the beginning of both treatments (multiple doses of activated charcoal alone or associated with methylene blue), and only one dose of methylene blue was necessary. There were no significant statistical differences between the results of the two treatments according to the time-course decrease in methemoglobinemia (p=0.49 Wilcoxon test).

Conclusions: multiple doses of activated charcoal given when methemoglobin levels were greater than 20% can be considered as a possible treatment for pediatric patients, with or without the administration of methylene blue, after acute dapsone exposure.


Introduction

Acquired methemoglobinemia is the most common form of methemoglobinemia, and follows exposure to oxidizing agents, such as sulfones, sulfonamides, aniline and derivatives, nitrates, nitrites, chlorates, metoclopramide, phenazopyridine, local anesthetics and methylene blue (MB).¹⁻³ Of all these substances, dapsone has been reported to be one the main cause of methemoglobinemia, both after its therapeutic use and as a consequence of the ingestion of toxic doses.⁴⁻¹⁶
Dapsone has a powerful anti-inflammatory activity, and has been broadly prescribed for the treatment of leprosy and, sometimes, for some vesicular dermatitis, such as lupus erythematosus and dermatitis herpetiformis. It has also been prescribed as an alternative drug in the treatment of Pneumocystis carinii infection for immunodepressed patients.17-18 Besides methemoglobinemia, the main side effects of dapsone use are hemolytic anemia, allergic dermatitis, reversible peripheral neuropathies and exacerbation of lepromatous leprosy analogous to Jarisch-Herxheimer reaction.18

The standard treatment for symptomatic patients with methemoglobin higher than 20 to 30% of hemoglobin is intravenous infusion of 1-2 mg/kg MB at 1 to 2%.2,19-20 NADPH-erythrocyte methemoglobin reductase converts MB into leukomethylene blue, which then reduces methemoglobin to hemoglobin.1,19-20 As the effect of MB is considerably short and the dapsone half-life is long, it is not unusual to observe the recurrence of methemoglobinemia, which sometimes requires the use of additional MB doses.10,11,13,15 However, doses higher than 7 mg/kg may worsen methemoglobinemia and hemolysis because of the MB oxidizing effect.1,2,19-23 The administration of multiple doses of activated charcoal has also been suggested as an adjuvant therapy to MB administration. Dapsone has some pharmacological characteristics (such as enterohepatic circulation) that would justify its use.5,7,14

The use of expensive, more invasive methods, such as exchange transfusion,11 plasmapheresis and continuous infusion of MB,10 hemodialysis, and hemoperfusion6 have been reported for isolated cases of severe acute dapsone intoxication, most of them intentional and in adults, with recurrent methemoglobinemia and hemolysis. Exchange transfusion has also been prescribed for patients with absolute G6PD deficiency who do not respond to treatment with MB.2,19-20

The objective of this study was to analyze the evolution of methemoglobinemia as a complication of acute exposure to dapsone in 17 children that were treated with multiple doses of activated charcoal, with or without associated administration of MB.

Patients and methods

We reviewed the medical records of 29 children up to 14 years old admitted to the Hospital de Clínicas, Universidade Estadual de Campinas, from January 1988 to December 1996, with a diagnosis of acute exposure to dapsone and methemoglobinemia (methemoglobin level higher than 1.5% of total hemoglobin). Only 17 of these children met this study’s selection criteria: methemoglobinemia higher than 20% of total hemoglobin at admission, and treatment with at least 3 sequential doses of activated charcoal (1 g/kg, 10% solution) at 4 to 6-hour intervals, orally or via nasogastric tube, with (group II, 12 patients) or without (group I, 5 patients) associated intravenous administration of MB infusion (1-2 mg/kg, 1-2% solution) for approximately 5 minutes. Methemoglobinemia was measured by spectrophotometry at a wavelength of 632 nm24, and/or by direct readings from the CO-oximeter IL282 (Instrumentation Laboratory INC.).

The Wilcoxon25 non-parametric test was used to calculate statistical differences between the two groups according to the evolution of methemoglobinemia in time. The objective was to compare the area measurements below the curve, considering α = 0.05 (SAS, 6.12 version, SAS Inc., Cary, NC, USA, 1996). The curves for both groups were adjusted by non-linear regression of the repeated measurements of methemoglobin dosages (Origin 5.0, Microcal™, Northampton, MA, USA, 1997).

Results

The age of the 17 children studied ranged from 1 to 13 years (median = 3 years), and they were admitted to our service 1 to 72 hours after exposure to dapsone (median = 8 hours). This information was not available for three patients. The amount of ingested dapsone ranged from 100 to 1200 mg (median = 350 mg). The amount ingested could not be determined for seven patients. Methemoglobin at admission ranged from 23.5 to 49.7% (median = 37.8%) and 14 patients presented with values higher than 30%. The treatment for all the cases was administration of multiple doses of activated charcoal, 3 to 16 doses for each patient (median = 8 doses). A single dose of MB associated with multiple doses of activated charcoal was used for 12 patients. These data are summarized in Table 1.

The following clinical features were observed at admission: cyanosis (17/17), tachycardia (17/17), vomiting (11/17), tachypnea (8/17), dyspnea (4/17), restlessness (4/17), and diarrhea (2/17).

Figure 1 shows methemoglobinemia decrease according to time and group of treatment. There was a trend of faster initial methemoglobinemia decrease in group II (Figure 1B) when compared with group I (Figure 1A), especially in the first 6 hours. However, levels remained above normal for 3 days in both groups. When both groups are compared, no statistically significant difference is observed in the evolution of methemoglobinemia according to the treatment used (Figure 1C, P=0.49).

Discussion

Acquired methemoglobinemia is not infrequent in children. It has been described more often in countries where water and food contain a high content of nitrates and nitrites,1,2,27,28 in newborns and in young infants during
Acute diarrhea episodes usually caused by classic enteropathogenic Escherichia coli, associated with metabolic acidosis, and in places where leprosy is highly prevalent, due to the high use of dapsone. In this study, clinical features were closely associated with level of methemoglobinemia and did not differ from those previously described in medical literature. However, we did not observe any apparent correlation with the amount of dapsone ingested (Table 1). No child studied was younger than 6 months, and it should be considered that this age group is at higher risk of developing methemoglobinemia due to the low activity of NADH-erythrocyte methemoglobin reductase.

Although reticulocyte count and haptoglobin estimation were not checked, four patients (1, 7, 8 and 16) presented a significant hemoglobin decrease, ranging from 3.0 to 7.6%, which suggests the presence of hemolysis in this group. MB was administered to all these patients. Both MB and dapsone can alone cause hemolysis due to their oxidizing effect. Serum dosages of dapsone and its metabolites were not carried out in this study, and sulfhemoglobinemia was not measured either. The criteria for therapeutic control were the profile of methemoglobinemia decrease and the clinical evolution. For both groups, methemoglobinemia and clinical improvement were progressive, and new doses of MB were not necessary (group II) (Figure 1). These observations concur with the results reported by Neuvonen et al. (1983), and show that the continuous action of activated charcoal in the intestinal lumen may increase dapsone elimination due to the adsorption of the actively secreted drug in the intestinal lumen. This would prevent both dapsone absorption and recirculation through the enterohepatic tract, and avoid the recurrence of methemoglobinemia. Another study also reports good results with multiple doses of activated charcoal for an isolated case of dapsone intoxication in an 18-month-old infant.

Sulfhemoglobinemia has rarely been reported as a complication of acute exposure to dapsone. Similarly to methemoglobinemia, sulfhemoglobinemia may cause tissue hypoxia and cyanosis. Sulfhemoglobin is an extremely stable compound whose spectrophotometry readings peak at around 620 nm. It is eliminated from circulation only when erythrocytes are renewed. Differently from methemoglobinemia, it does not respond to the administration of MB, and it may cause prolonged cyanosis.

Table 1 - Data of 17 children with acute dapsone exposure and methemoglobinemia higher than 20% of total hemoglobin

<table>
<thead>
<tr>
<th>Patient*</th>
<th>Age (years)</th>
<th>Dapsone (mg)</th>
<th>Admission (hours) †</th>
<th>Methemoglobinemia at admission</th>
<th>Methylene (number of doses)</th>
<th>Activated (number of doses)</th>
<th>Hemoglobin variation (g%)</th>
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<tr>
<td>1</td>
<td>9</td>
<td>100</td>
<td>24</td>
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<td>7</td>
<td>13.9-9.7</td>
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<td>2</td>
<td>2.8</td>
<td>?</td>
<td>3</td>
<td>43.0%</td>
<td>-</td>
<td>11</td>
<td>10.8 ‡</td>
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<tr>
<td>3</td>
<td>3</td>
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<td>3</td>
<td>49.7%</td>
<td>1</td>
<td>10</td>
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<tr>
<td>4</td>
<td>6</td>
<td>1,000</td>
<td>?</td>
<td>29.8%</td>
<td>-</td>
<td>9</td>
<td>10.5-10.7</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>?</td>
<td>72</td>
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<td>-</td>
<td>8</td>
<td>11.3-10.7</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>500</td>
<td>1</td>
<td>44.5%</td>
<td>1</td>
<td>3</td>
<td>9.3-9.7</td>
</tr>
<tr>
<td>7</td>
<td>9</td>
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<td>9</td>
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<td>?</td>
<td>?</td>
<td>46.5%</td>
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<td>10</td>
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<tr>
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<td>4</td>
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<td>36.0%</td>
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<td>2.5</td>
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<td>-</td>
<td>6</td>
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<tr>
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<td>29.7%</td>
<td>-</td>
<td>8</td>
<td>13.3 ‡</td>
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</tbody>
</table>

*Patients 1-16: accidental ingestion; patient 17: intentional ingestion; †: time from ingestion to admission; ‡: isolated measurement of hemoglobin; ?: not determined.
Figure 1 - Methemoglobinemia concentrations according to time and treatment regimen of 17 children with acute exposure to dapsone, complicated by methemoglobinemia higher than 20% of total hemoglobin. A - Group I: Five patients treated with multiple doses of activated charcoal only; B - Group II: Twelve patients treated with multiple doses of activated charcoal and intravenous administration of a single dose of methylene blue. C - Comparison of methemoglobinemia according to time and group of patients: Group I (■) and Group II (●). The curves were adjusted by non-linear regression for repeated measurements of methemoglobinemia dosage. F=0.49 (Wilcoxon method, comparison of measurements of areas under the curve)

The results of the present study suggest that the administration of multiple doses of activated charcoal may be a relatively safe and low-cost therapeutic alternative in the treatment of children with acute exposure to dapsone, complicated by methemoglobinemia higher than 20% of hemoglobin. MB should be the treatment of choice in urgencies of severe methemoglobinemia caused by acute exposure to dapsone. However, the therapeutic association with multiple doses of activated charcoal may reduce the chances of methemoglobinemia recurrence, thus reducing the need for repeated administration of MB and avoiding its possible complications.

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References


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