Prophylactic methylene blue in a patient with congenital methemoglobinemia

[L'administration prophylactique de bleu de méthylène chez un patient atteint de méthémoglobinémie congénitale]

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Purpose: To report the beneficial effect of prophylactic methylene blue administration before induction of anesthesia in a patient with congenital methemoglobinemia.

Clinical features: A 26-yr-old male patient known to have congenital methemoglobinemia was scheduled for turbinectomy under general anesthesia. The patient was clinically cyanotic with a pulse oximetry of 91%. Arterial blood gas analysis showed a partial pressure of oxygen (PaO_2) of 81.3 mmHg associated with a fractional oxyhemoglobin of 80.7%, and a methemoglobin fraction of 0.159. Preoperative iv administration of 1 mg·kg⁻¹ of methylene blue resulted, within five minutes, in a decrease of methemoglobin fraction down to 0.05 associated with an increase of the fractional oxyhemoglobin saturation up to 94.7%. After two hours, the methemoglobin fraction decreased to 0.01 and the fractional oxyhemoglobin concentration increased to 97.7%. Induction of anesthesia as well as intraoperative and postoperative course were uneventful without any episode of hypoxemia. Postoperatively, the methemoglobin fractions remained low for 24 hr, to be followed by a gradual increase up to 0.02 on the second day to reach 0.094 on the fifth day.

Conclusion: The prophylactic preoperative methylene blue administration in a patient with congenital methemoglobinemia significantly decreased the methemoglobin level and increased the fractional oxygen saturation with a consequent increase of the safety margin against perioperative hypoxemia.

Objectif: Signaler l'effet bénéfique de l'administration prophylactique de bleu de méthylène avant l'induction de l'anesthésie chez un patient atteint de méthémoglobinémie congénitale.

Éléments cliniques : Un homme de 26 ans atteint de méthémoglobinémie congénitale devait subir une turbinectomie sous anesthésie générale. Le patient était cyanosé et présentait une sphymo-

oxymétrie de 91 %. L'analyse des gaz artériels a montré une pression partielle d'oxygène (PaO_2) de 81,3 mmHg associée à une oxyhémoglobine fractionnelle de 80,7 % et à une fraction de méthémoglobine de 0,159. L'administration iv préopératoire de 1 mg·kg⁻¹ de bleu de méthylène a donné, en moins de cinq minutes, une baisse de la fraction de méthémoglobine jusqu'à 0,05, et une hausse de la saturation d'oxyhémoglobine fractionnelle jusqu'à 94,7 %. Après deux heures, la fraction de méthémoglobine a baissé à 0,01 et la concentration d'oxyhémoglobine fractionnelle a augmenté à 97,7 %. L'induction de l'anesthésie et l'évolution peropératoire et postopératoire ont été sans incident et sans épisode d'hypoxémie. Après l'opération, les fractions de méthémoglobine sont demeurées basses pendant 24 h et ont été suivies d'une hausse graduelle jusqu'à 0,02 le deuxième jour et 0,094 le cinquième jour.

Conclusion : L'administration prophylactique préopératoire de bleu de méthylène chez un patient atteint de méthémoglobinémie congénitale a significativement réduit le niveau de méthémoglobine et augmenté la saturation en oxygène fractionnée, ce qui a augmenté la marge de sécurité contre l'hypoxémie périopératoire.

METHEMOGLOBINEMIA results from the oxidation of the heme moiety in the hemoglobin molecule from the ferrous to the ferric state. In normal individuals, a small amount of the hemoglobin in erythrocytes is oxidized to methemoglobin. The methemoglobin is reduced to hemoglobin enzymatically by nicotinamide-adenine dinucleotide (NADH) dependent cytochrome b5 methemoglobin reductase and hence, methemoglobin concentration remains less than 2%. Other pathways include nicotinamide-adenine dinucleotide phosphate (NADPH) methemoglo-

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TABLE Changes in pulse oximetry, arterial blood gases, and methemoglobin concentrations on room air, after preoxygenation, and after methylene blue administration

		PaO_2 (mmHg)	Spo_2 (%)	SaO_2 (%)	SfO_2 (%)	Methemoglobin (%)
Room air	Room air	81.3	91	96.2	80.9	15.9
After preoxygenation	100% O_2	543	94	99.7	84.1	15.8
Five minutes after methylene blue	100% O_2	519	98	100	94.7	5
Two hours after methylene blue	Face mask O_2	172	99	99.4	97.7	1
Second day	Room air	86	96	96.9	93.4	2.6
Fifth day	Room air	105	95	98.4	88.8	9.4

PaO_2 = arterial partial pressure of oxygen; Spo_2 = pulse oximetry; SaO_2 = functional arterial oxygen saturation; SfO_2 = fractional arterial oxygen saturation.

bin reductase which plays an insignificant role.¹ In acquired methemoglobinemia, exposure to certain oxidant drugs or chemicals may cause oxidation of hemoglobin to methemoglobin to occur faster than the rate of reduction of methemoglobin to hemoglobin by methemoglobin reductase.² A congenital deficiency in the NADH-dependent cytochrome b5 methemoglobin reductase can be inherited in an autosomal recessive pattern. Patients who are homozygous for this enzymatic deficiency have congenital methemoglobinemia and may exhibit lifelong cyanosis.³

The present report presents a patient with congenital methemoglobinemia who previously developed severe oxyhemoglobin desaturation during induction of anesthesia, resulting in the cancellation of surgery.⁴ This report evaluates, for the first time, the beneficial effect of the prophylactic *iv* administration of methylene blue before induction of anesthesia in the same patient when he was rescheduled for surgery four years later.

Clinical features

A 26-yr-old man known to have congenital methemoglobinemia was scheduled on two previous occasions for turbinectomy, but the operation was cancelled because of the development of severe hypoxemia during induction of general anesthesia. Four years later, the patient was rescheduled for the same surgery. The patient was not known to have any cardiovascular problems and was not taking methylene blue or vitamin C orally. The hematocrit was 56.9%; hemoglobin, 17.7 g·dL⁻¹. It was decided to administer prophylactic methylene blue before induction of anesthesia. In the induction room, the patient's fingers and lips were blue, and pulse oximetry on room air revealed an oxygen saturation (Spo_2) of 91%. The patient was continuously monitored by electrocardiogram, pulse oximetry and a non-invasive blood pressure monitor. An 18-gauge *iv* cannula was inserted in the dorsum of the left hand and

an arterial line was inserted in the right radial artery. An arterial blood gas analysis, measured by co-oximetry (ABL 700 series; Radiometer, Copenhagen, Denmark), showed the following results: partial pressure of oxygen (PaO_2), 81.3 mmHg; reduced hemoglobin (RHb) saturation, 3.4%; carboxyhemoglobin (COHb) saturation, 0%; methemoglobin (MetHb) saturation, 15.9%; functional oxygen (SaO_2) saturation, 96.2% [$SaO_2 = (O_2Hb / O_2Hb + RHb) \times 100\%$]; fractional oxygen (SfO_2) saturation, 80.7%, [$SfO_2 = (O_2Hb / O_2Hb + RHb + COHb + MetHb) \times 100\%$].

Following preoxygenation with 100% oxygen for five minutes, the PaO_2 increased from 81.3 mmHg to 543 mmHg, the SaO_2 was 99.7%, while the methemoglobin and the fractional oxyhemoglobin saturation remained unchanged.

Before induction of anesthesia, methylene blue 1% solution (10 mg·mL⁻¹) was administered at a dose of 1 mg·kg⁻¹ intravenously by a slow infusion over three minutes. The *iv* administration of methylene blue was immediately followed by a transient decrease of pulse oximetry down to 75%. However, within five minutes, the pulse oximetry increased up to 98% and the methemoglobin fraction decreased from 0.15 down to 0.05.

Following methylene blue administration, anesthesia was induced with 1 mg·kg⁻¹ lidocaine followed by propofol 2 mg·kg⁻¹ and rocuronium 0.6 mg·kg⁻¹. Anesthesia was maintained with isoflurane 1 to 2% in a mixture of oxygen/air (1/1). The surgery lasted one hour after which the trachea was extubated and the patient was transferred on facemask oxygen to the recovery room. Induction of anesthesia as well as intraoperative and postoperative course were uneventful without any episode of hypoxemia. Postoperatively, the methemoglobin fraction was 0.01, and increased gradually to 0.026 on the second day to reach 0.094 on the fifth day (Table).

Discussion

The diagnosis of congenital methemoglobinemia should be suspected in patients that appear cyanotic and have a low pulse oximetry reading, yet have no apparent respiratory or cardiovascular problems, and have no history of exposure to oxidant agents. Arterial blood gas analysis will reveal a normal PaO_2 that is not consistent with the low pulse oximetry. The absorbency characteristics of methemoglobin are such that the pulse oximetry shows SpO_2 around 85%, regardless of the PaO_2 .^{5,6} The diagnosis is confirmed by measuring methemoglobin levels using co-oximetry, which provides a spectrophotometric analysis of different hemoglobin types.⁷ The patient described has congenital methemoglobinemia, as evidenced by a high methemoglobin fractions of 0.159 associated with a disproportionately low pulse oximetry (91%) and a low fractional oxyhemoglobin saturation (80.9%) compared with the normal partial pressure of oxygen in arterial blood. Symptoms of methemoglobinemia are related primarily to the fractions of methemoglobin; fractions of methemoglobin between 0.15 and 0.20, as in this patient, generally result only in the appearance of cyanosis.

In methemoglobinemia, when the iron in a hemoglobin molecule is oxidized to the ferric state, not only is the heme group incapable of combining with oxygen, but the effect of partial oxidation of one heme group in the hemoglobin tetramer increases the oxygen affinity of the remaining heme groups because of allosteric effects. This causes the oxygen dissociation curve to be shifted to the left, decreasing oxygen unloading to the tissues.⁸ In patients with congenital methemoglobinemia, the decreased fractional oxygen saturation and the leftward shift in the oxyhemoglobin dissociation curve will be associated with an increased hematocrit⁹ as shown in this patient whose hematocrit was 56.9%. In patients with congenital methemoglobinemia, oxygen delivery is already compromised, and hence even a mild degree of respiratory depression, which would go unnoticed in normal patients, can result in serious hemoglobin desaturation.⁴

Preoxygenation increases the oxygen reserve in the lungs' functional residual capacity as well as the plasma oxygen in physical solution, counteracting any decrease of PaO_2 during induction of anesthesia. However, following preoxygenation in this patient, the methemoglobin level remained high and the fractional oxygen concentration low. Therefore, methylene blue was administered in order to decrease the methemoglobin level and increase the margin of safety against hypoxemia throughout the perioperative period.

Methylene blue acts as a cofactor for (NADPH) methemoglobin reductase. In normal patients and in patients with congenital methemoglobinemia, this enzyme remains inactive physiologically, but will be activated by methylene blue when glucose-6-dehydrogenase (G6PD) is normal. G6PD is a key enzyme in the formation of NADPH. In individuals with normal G6PD, sufficient NADPH is generated to efficiently reduce methylene blue to leucomethylene blue which then donates an electron to methemoglobin reducing it to hemoglobin.¹⁰ Known or suspected G6PD deficiency is a contraindication to the use of methylene blue. Such patients have low red cell NADPH concentrations; these low concentrations make augmentation of NADPH methemoglobin reductase by methylene blue limited. Importantly, methylene blue triggers hemolysis in such patients.¹¹

Parenteral methylene blue is available as a 1% solution ($10 \text{ mg}\cdot\text{mL}^{-1}$); it should be administered intravenously over three to five minutes at an initial dose of 1 to $2 \text{ mg}\cdot\text{kg}^{-1}$. Resolution of cyanosis usually occurs within 15 to 20 min. If the patient is seriously symptomatic and no response occurs within 15 min, or if the patient remains moderately symptomatic without any improvement after 30 to 60 min, then repeat doses of $1 \text{ mg}\cdot\text{kg}^{-1}$ may be given. The total dose of methylene blue administered during the first few hours should not exceed 5 to $7 \text{ mg}\cdot\text{kg}^{-1}$. Methylene blue discolours skin and mucous membranes, making visual interpretation of cyanosis inaccurate; it may also interfere with pulse oximetry readings. Repeat determinations of methemoglobin fractions should be performed before repeat doses of methylene blue are administered.¹²

Methylene blue is excreted primarily by the kidneys. Although side-effects are uncommon, large, rapidly administered doses have been associated with nausea, vomiting, retrosternal chest pain, dyspnea, tachycardia, hypertension and, rarely, anaphylactoid reactions. Methylene blue may even contribute to methemoglobinemia in higher than recommended doses, but this complication is unproven in clinical practice. Methylene blue may also add to oxidative hemolysis, and young infants without G6PD deficiency have developed Heinz body hemolytic anemia at doses as low as $4 \text{ mg}\cdot\text{kg}^{-1}$.¹⁰

Patients who do not respond to methylene blue therapy may have hemoglobin M diseases or congenital lack of NADPH methemoglobin reductase, or unrecognized G6PD deficiency. Also, patients exposed to large amounts of drugs or chemicals that, even with methylene blue therapy, produce methemoglobin at a rate greater than the rate of reducing

capacity, do not show clinical improvement. Failure of methylene blue treatment occurs also in patients with sulfhemoglobinemia which can be mistaken with methemoglobinemia and in those treated with repeated doses of methylene blue which results in blue discolouration of the skin.¹⁰

Treatment options for the patient who cannot receive or who fails to respond to methylene blue therapy remain somewhat limited. Ascorbic acid, 300 to 1000 mg·day⁻¹ intravenously in three to four doses provides nonenzymatic methemoglobin reduction but is slow and is considered ineffective for the treatment of acute methemoglobinemia. Additional therapies to increase oxygen delivery include blood transfusions, exchange transfusions, and hyperbaric oxygen therapy.^{11,12}

The preoperative administration of methylene blue in this patient with congenital methemoglobinemia decreased the methemoglobin fraction from 0.159 to 0.05 after five minutes and to 0.01 after two hours. Also, it increased the fractional oxyhemoglobin saturation from 80.9% up to 97.7%. The decrease of methemoglobin level lasted for 24 hr, followed by a gradual increase to reach 0.094 on the fifth day. Our observation is at variance with the critical severe rebound of methemoglobin concentration reported after methylene blue administration in cases of acquired methemoglobinemia.¹³ Oxidant agents directly accelerate the rate of heme oxidation by 100 to 1,000-fold, overwhelming the normal enzymatic capacity of red blood cells. In acquired methemoglobinemia, after exposure to the offending agent ceases, methemoglobin concentrations usually return to normal within 36 hr.¹² The biologic fate and the long half-life of some direct-acting or bioactivated oxidant agents may overlast the duration of action of methylene blue, and hence can result in recurrence or even rebound of the increased methemoglobin levels.^{13,14}

In conclusion, our report describes, for the first time, the prophylactic preoperative administration of methylene blue in a patient with congenital methemoglobinemia. Preoperative methylene blue significantly decreased methemoglobin levels and increased the fractional oxygen saturation during 24 hr, increasing the margin of safety against perioperative hypoxemia.

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