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REVIEW ARTICLE

Methylene blue: from a Victorian-era textile dye to an essential antidote for methemoglobinemia

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Abstract

Introduction: Methylene blue is a drug with a distinctive history spanning more than a century and a half. Developed as an industrial dye in the nineteenth century, its ability to participate in oxidation–reduction reactions led to its medical use and ultimately established it as an essential antidote for methemoglobinemia.

Objectives: To provide a descriptive review of the historical evolution of methylene blue, from its discovery to its current role as the antidote of choice for methemoglobinemia, and to update information on its mechanism of action, indications, dosage, contraindications, and adverse effects.

Results: The main historical milestones that led to the medical use of methylene blue are presented, from its early applications in histopathology and use as an antidote for cyanide poisoning to its introduction in 1933 as an effective treatment for methemoglobinemia induced by oxidizing agents. The pathophysiological basis of both acquired and congenital methemoglobinemia is described. Its mechanism of action as a redox intermediate in the nicotinamide adenine dinucleotide phosphate (NADPH)-dependent pathway, its clinical efficacy, dosing regimens for pediatric and adult patients, and its main contraindications—particularly glucose-6-phosphate dehydrogenase deficiency—are reviewed.

Conclusions: Methylene blue is the first-line treatment for symptomatic or severe methemoglobinemia. Its efficacy and safety, rapid action, low cost, and extensive clinical experience support its continued use as an essential antidote and

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underscore the need for it to be available in emergency and critical care departments.

AZUL DE METILENO: DE TINTE TEXTIL EN LA ÉPOCA VICTORIANA A ANTÍDOTO ESENCIAL EN LA METAHEMOGLOBINEMIA

Resumen

Introducción: El azul de metileno es un fármaco con una historia singular que abarca más de un siglo y medio. Desarrollado como colorante industrial en el siglo XIX, su capacidad para participar en reacciones de óxido-reducción condujo a su aplicación médica y, finalmente, a su consolidación como antídoto esencial en la metahemoglobinemia.

Objetivos: Revisar de forma descriptiva la evolución histórica del azul de metileno, desde su descubrimiento hasta su papel actual como antídoto de elección de la metahemoglobinemia, actualizando su mecanismo de acción, indicaciones, posología, contraindicaciones y efectos adversos.

Resultados: Se presentan los principales hitos históricos que llevaron al uso del azul de metileno en el campo médico, desde sus primeras aplicaciones en histopatología y su empleo como antídoto en la intoxicación por cianuro, hasta su introducción en 1933 como tratamiento eficaz de la metahemoglobinemia inducida por agentes oxidantes. Se describen los fundamentos fisiopatológicos de la metahemoglobinemia, tanto adquirida como congénita. Se analiza su mecanismo de acción como intermediario redox en la vía dependiente de la nicotinamida adenina dinucleótido fosfato (NADPH), su eficacia clínica, las pautas posológicas en población pediátrica y en adultos, y sus principales contraindicaciones, especialmente el déficit de glucosa-6-fosfato deshidrogenasa.

Conclusiones: El azul de metileno es el tratamiento de primera línea para la metahemoglobinemia sintomática o grave. Su eficacia y seguridad, rapidez de acción, bajo coste y amplia experiencia clínica justifican su vigencia como antídoto esencial y la necesidad de que esté disponible en los servicios de urgencias y cuidados críticos.

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INTRODUCTION

The history of some antidotes has a long trajectory, spanning their initial use in industry through their applications in various fields of medicine, ultimately establishing them as essential antidotes. Such is the case of methylene blue (MB), a dye first used in the textile industry in the late nineteenth century that has become the antidote of choice for methemoglobinemia (MHb).

It is of particular interest to provide a descriptive review of this drug's 150-year history, with particular emphasis on its establishment as the antidote of choice for MHb, as well as to update its indications, dosing, adverse effects, and contraindications in the context of current clinical toxicology.

The discovery of methylene blue and its early uses

The synthesis of MB by the German chemist Heinrich Caro in 1876 took place in the context of England's dye industry. Years earlier, William Perkin had accidentally discovered a dye called mauveine by oxidizing aniline. This discovery prompted Caro to experiment with other aniline derivatives, among which he obtained MB, a heterocyclic aromatic chemical compound also known as tetramethylthionine chloride. Thus, the textile industry was its first field of application as a dye[1].

At the beginning of the 20th century, Gordon Wilson reported in 1910 that this dye showed a remarkable affinity for living tissues and, particularly, for nerve cells, leading to the second application of MB, also as a dye but in the field of histopathology[2].

Wilson also observed that neurons took up the dye without initially showing any visible staining, which appeared only after the tissues were exposed to air. This finding demonstrated MB's ability to participate in oxidation–reduction processes. Over time, this chemical property would acquire fundamental clinical significance, as it underlies the mechanism by which MB reverses methemoglobinemia (MHb).

First antidotal indication for methylene blue: cyanide poisoning

At the beginning of the twentieth century, Otto Warburg's work demonstrated that cyanide inhibits mitochondrial cytochrome oxidase, causing a blockade of oxidative phosphorylation and potentially fatal tissue hypoxia. This laid the pathophysiological foundation for the

search for pharmacological strategies capable of restoring cellular oxidation[3].

Bo Sahlin of Lund University (Sweden) in 1926, Nathan B. Eddy of the University of Michigan (USA) in 1930, and Paul J. Hanzlik of Stanford University (USA) in 1933[4] were the first to demonstrate in animal experiments that MB had an antidotal effect in cyanide poisoning.

The first clinical case documenting MB's antidotal capacity in cyanide poisoning was published in 1932[5]. A young student who had ingested 15 grains of potassium cyanide in a suicide attempt was admitted to a San Francisco hospital in a comatose state. After receiving 50 mL of a 1% aqueous MB solution, he regained consciousness and recovered without sequelae. This effect can be explained by the fact that this dose of MB, seven times higher than the dose currently used to treat methemoglobinemia, paradoxically induced secondary methemoglobinemia; this methemoglobin sequesters the cyanide ion, forming cyanmethemoglobin, thereby freeing mitochondrial cytochrome oxidase to resume its physiological functions[6].

William B. Wendel's studies, conducted in 1934 and 1935, precisely described how MB can induce MHb and be useful in cyanide poisoning[7,8]. This prompted the search for better MHb inducers, such as amyl nitrite and sodium nitrite, and led to the development of the cyanide antidote kit, which was used for many years as first-line treatment[9]. However, beginning in the 1980s and 1990s, methemoglobin-forming agents were progressively supplanted by hydroxocobalamin[10], a safer and more effective drug. After the first quarter of the 21st century, hydroxocobalamin remains the antidote of choice for cyanide poisoning[11].

Methemoglobin: a physiological hemoglobin at low concentrations

Hemoglobin (Hb) consists of two alpha chains and two beta chains, each bound to a heme group containing an iron atom. In its physiological state, this iron is in the ferrous form (Fe^{2+}), which is capable of binding oxygen. Red blood cells are continuously exposed to oxidative stress and have a limited endogenous antioxidant capacity. When these protective mechanisms are overwhelmed, iron is converted to its oxidized ferric state (Fe^{3+}), which cannot transport oxygen, transforming the Hb molecule into MHb. The presence of MHb is therefore physiological at levels below 1–2%, maintained by reductive enzymatic systems; it is considered pathological when it exceeds these values.

An elevated MHb concentration may be acquired or congenital. The acquired form is predominantly iatrogenic or toxic, and is the focus of this review. The most common causes include direct oxidizing agents (benzocaine, prilocaine, and lidocaine, commonly found in topical anesthetic creams)[12], indirect oxidants (nitrates and nitrites found in medications, agricultural products, improperly stored vegetables, or substances of abuse such as *poppers*)[13], and compounds that require metabolism to act as oxidants (sulfonamides, aniline, naphthalene, dapsone, and nitrobenzene)[14,15]. Epidemic outbreaks of MHb, particularly those of foodborne origin, have also been reported[16], as have, more rarely, cases associated with acute paracetamol or valproate poisoning, or secondary to treatment with rasburicase[17].

Infants and young children are particularly susceptible to MHb formation because of their higher proportion of fetal Hb, an immature cytochrome b5-dependent reducing system, increased endogenous nitrite production, and antioxidant mechanisms that are not yet fully developed[18]. In children, foodborne MHb is prevalent and is caused by nitrates in vegetables (spinach, chard, beetroot), cured ham, sausages, or smoked meats[19], as well as by consumption of water with high nitrate concentrations. In this population, particular attention should be paid to the intake of improperly stored vegetable purées: although nitrates are normally present in vegetables, poor storage can promote bacterial growth, converting nitrates into nitrites that cause toxicity when absorbed through the digestive tract. MHb caused by ingestion of the so-called Miracle Mineral Solution has also been described in children[20].

Certain genetic predispositions lead to susceptibility to oxidative stress and to so-called congenital MHb. These congenital forms arise from rare autosomal recessive defects in cytochrome b5 reductase (CYB5R) or from autosomal dominant mutations in globin genes, collectively known as hemoglobin M[21]. Congenital MHb occurs in two distinct clinical forms: type I (erythrocytic form) is the more benign, as it affects only red blood cells and is well tolerated clinically, whereas type II (systemic form) is accompanied, in addition to cyanosis, by severe neurocognitive manifestations, marked psychomotor delay, and a poorer vital prognosis. Genetic analysis of the CYB5R3 gene and/or enzyme analysis is often used for differential diagnosis. Treatment with MB, ascorbic acid, or riboflavin may reduce cyanosis in all cases, but does not improve neurological impairment when present.

The signs and symptoms associated with elevated MHb concentrations result from tissue hypoxia caused by the inability of red blood cells to transport oxygen (Table 1)[22]. Clinical severity is proportional to the blood MHb level, although it is influenced by the patient's comorbidities; conditions such as anemia, heart disease, or pulmonary disease reduce the capacity for hemodynamic compensation in response to hypoxia, increasing the severity of the clinical presentation. At very high MHb levels, the condition may also be accompanied by hemolytic anemia.

TABLE 1.

Approximate correlation between methemoglobin concentration and the patient's clinical manifestations

Methemoglobinemia	Signs and symptoms
< 2 %	No. This is a physiological level
2-9 %	No, except for possible cyanosis. This is a pathological level
10-19 %	Mild cyanosis. Chocolate-brown appearance of arterial blood
20-39 %	Moderate cyanosis. Moderate neurological manifestations (dizziness, headache). Mild lactic acidosis
40-59 %	Marked cyanosis. Severe neurological manifestations (syncope, fainting, seizures) and cardiovascular manifestations (dyspnea, tachycardia, tachypnea, arrhythmias) are added. Marked lactic acidosis
> 60 %	Very severe cyanosis. Risk of cardiocirculatory arrest is added

Historical treatments for elevated methemoglobin levels

Although MHb was characterized in detail in the 19th century, until the mid-20th century therapeutic management was limited to symptomatic measures, among which oxygen therapy was the preferred option in cases of cyanosis. Although this measure does not reduce MHb levels, it increases the fraction of oxygen dissolved in plasma and may partially alleviate tissue hypoxia. However, its efficacy is limited, since dissolved oxygen accounts for only 3% of total oxygen transport. Despite this limitation, high-concentration oxygen therapy remains an adjunctive measure today.

In severe cases, particularly before effective reducing agents were available, whole-blood transfusions or exchange transfusions were used to replace oxidized hemoglobin with functional hemoglobin from donors. This therapeutic indication persists today in exceptional circumstances and may be warranted when severe MHb is also associated with intravascular hemolysis[23].

It was not until 1946 that specific treatments were introduced, such as ascorbic acid (vitamin C), which acts as a reducing agent by promoting the conversion of ferric iron to ferrous iron and the subsequent restoration of oxyhemoglobin[24]. Although its action is slow and of limited potency, it remains indicated when MB is unavailable, in congenital forms of MHb, in mild acquired cases, or in patients with glucose-6-phosphate dehydrogenase (G-6PDH) deficiency, for whom MB is contraindicated[25].

Riboflavin (vitamin B2) was also used as a cofactor to enhance the activity of endogenous reductases, particularly in type I congenital MHb. Although its efficacy is modest, it continues to play a role in congenital MHb[26].

The introduction of methylene blue in the treatment of methemoglobinemia

In November 1933, Williams and Challis described the case of a chemistry student who was handling parabromoaniline while heating it during an experiment. After one hour of exposure, the student noticed changes in skin color, followed by headache and dizziness, and was subsequently admitted to a hospital in Rochester in a comatose state with marked cyanosis. Given the severity of the condition, 100 mL of a 1% MB solution was administered, with prompt improvement in skin color and complete clinical recovery after several hours. This was the first documented case of MHb treated with MB[27]. That same year, Steele and Spink successfully used MB in two patients with MHb secondary to aniline poisoning[28].

From then on, methylene blue began to be used systematically in the management of MHb. Clinical observations confirmed that its intravenous administration rapidly reversed cyanosis and significantly reduced MHb concentrations. These findings preceded the detailed characterization of its biochemical mechanism and laid the groundwork for its increasing adoption in hospital practice during the 1940s and 1950s.

From the second half of the 20th century onward, advances in erythrocyte biochemistry clarified the mechanism by which MB acts as a redox intermediate in the nicotinamide adenine dinucleotide phosphate (NADPH)- and cytochrome b5 reductase-dependent pathway, facilitating the reduction of ferric iron (Fe^{3+}) in MHb to its functional ferrous state (Fe^{2+}). This pathophysiological basis, together with its rapid clinical efficacy, availability, and acceptable safety profile, definitively established MB as the first-line treatment for symptomatic MHb or elevated MHb levels. From the late 20th century to the present, its use has been consistently endorsed in clinical reviews, case series, and emergency treatment guidelines for both adults and pediatric patients, and it remains the antidote of choice, with exceptions limited to specific situations such as G-6PDH deficiency.

METHYLENE BLUE: ITS ROLE IN 2026 AS A TREATMENT FOR PATHOLOGICAL METHEMOGLOBINEMIA

The most recent clinical guidelines, such as those of the European Hematology Society[29] and the American Heart Association[30], establish MB as the treatment of choice for methemoglobinemia, while also recognizing its contraindications and potential adverse effects. This indication is consistent with the recommendations of reference databases such as UpToDate, Poisindex, and DynaMed, as well as with the criteria of the North American Poison Centers[31]. There is broad consensus that MB should be included in the essential antidote stock at hospitals providing emergency toxicology care[32]; it is a drug with proven efficacy in both pediatric and adult populations[33].

Formulations and indications for methylene blue in methemoglobinemia

In Spain, MB has been available since 2018 in 2-mL (10-mg) and 10-mL (50-mg) ampoules[34]. Previously, hospital pharmacy departments dispensed it as a compounded preparation.

According to the Antidote Network of the Societat Catalana de Farmacia Clínica, MB is indicated for symptomatic MHb, usually at concentrations ≥ 20 %[35].

Methylene blue dosing in children and adults

In children, the recommended dose is 1 mg/kg diluted in 50 mL of 5% dextrose solution, administered over 15 minutes. In the absence of a response, the dose may be repeated after 1 hour. It is advisable not to exceed a cumulative dose of 4 mg/kg to prevent the risk of hemolysis. Neonates are more susceptible to adverse effects; therefore, the product information recommends doses of 0.3–0.5 mg/kg in infants younger than 3 months. This regimen may be repeated after 1 hour only if the indication criteria continue to be met.

In adults, 1–2 mg/kg (or alternatively 25–50 mg/m^2) is prescribed in 50–100 mL of 5% dextrose solution, to be infused over 5–30 minutes. If there is no clinical or laboratory response, the dose should be repeated after 1 hour. Additional doses should be considered only when strictly necessary, without exceeding a cumulative dose of 4 mg/kg and avoiding administration of more than 7 mg/kg because of the risk of inducing hemolysis. In patients with moderate or severe renal impairment, dose adjustment should be considered (< 1 mg/kg).

The intravenous route should always be used, and it should be borne in mind that extravasation may cause local necrosis. Therefore, it should not be administered subcutaneously or intramuscularly.

Contraindications

MB is contraindicated in patients with known G-6PDH deficiency. In this case, ascorbic acid is the alternative[36].

Likewise, MB can trigger severe or fatal serotonin syndrome; therefore, concomitant administration with serotonergic drugs is contraindicated, including selective serotonin or norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, antiemetics (ondansetron, granisetron), or opioids, including dextromethorphan[37].

Adverse reactions

Transient chromaturia commonly occurs 15–30 minutes after administration and is a benign manifestation with no clinical consequences. Mild symptoms such as dysgeusia, a sensation of warmth, diaphoresis, and dizziness have also been reported. Administration of high doses may trigger intravascular hemolysis, especially in individuals with G-6PDH deficiency. Newborns are more susceptible to developing hemolytic anemia. Paradoxically, excessive doses of MB may induce methemoglobinemia.

OTHER CURRENT INDICATIONS FOR METHYLENE BLUE UNRELATED TO METHEMOGLOBINEMIA

MB also has another potential indication in the field of toxicology: refractory shock caused by severe calcium-channel blocker or beta-blocker poisoning[38]. In this case, its indication is related to its ability to decrease vascular smooth muscle relaxation by inhibiting guanylate cyclase. Indeed, MB is being used for refractory shock of any origin that does not respond to more conventional measures[39], particularly septic shock in both children[40] and adults[41], although the scientific evidence on this remains limited.

On the other hand, its use in ifosfamide-induced encephalopathy is described and well documented[42]. Methylene blue has also been used in medicine for a wide range of other indications, including fiberoptic endoscopic evaluation of swallowing to improve visualization of pharyngeal bolus transit[43], as an effective, safe, and low-cost tracer for sentinel lymph node biopsy[44], to reduce postoperative pain after hemorrhoid surgery[45], for malaria[46] and infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[47], and for its potential role as a cerebral neuroprotectant[48].

CONCLUSIONS

Throughout its history, methylene blue has demonstrated remarkable therapeutic versatility. This quality, together with its low cost and the extensive clinical experience accumulated, supports its status as an indispensable drug in emergency and intensive care departments, reaffirming it as the first-line antidote for methemoglobinemia in both pediatric and adult patients.

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Santiago Nogué-Xarau: Conceptualization. Project administration. Supervision. Writing—original draft.

Lidia Martínez-Sánchez: Conceptualization. Investigation. Methodology. Visualization. Writing—review and editing.

M Àngels Gispert-Ametller: Conceptualization. Validation. Writing—review and editing.

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Conflict of interest

We declare that there are no commercial or financial conflicts of interest related to this research.

Use of AI

English translation of the Abstract by ChatGPT (version 5.2)

Data availability

The data supporting the results of this study are available upon request from the corresponding author.

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