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A REVIEW OF METHYLENE BLUE TREATMENT FOR CARDIOVASCULAR COLLAPSE

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☐ **Abstract—Background: Historically, methylene blue (MB) has been used for multiple purposes, including as an antidote for toxin-induced and hereditary methemoglobinemia, ifosfamide-induced encephalopathy, and ackee fruit and cyanide poisoning; as an aniline dye derivative, antimalarial agent, and antidepressant. Discussion: Most recently, the use of MB has been advocated as a potential adjunct in the treatment of shock states. Our article reviews the role of MB in septic shock, anaphylactic shock, and toxin-induced shock. MB is proposed to increase blood pressure in these shock states by interfering with guanylate cyclase activity, and preventing cyclic guanosine monophosphate production and vasodilatation. Summary: MB may be an adjunct in the treatment of septic shock, anaphylactic shock, and toxin-induced shock.** © 2014 Elsevier Inc.

☐ **Keywords—methylene blue; septic shock; anaphylactic shock; shock due to toxin**

INTRODUCTION

Shock is a condition with the potential for significant morbidity and mortality for patients in the emergency department (ED) and throughout the hospital. Despite multiple causative etiologies, the insufficient delivery of oxygen to organs and tissue results in organ dysfunction and potential organ necrosis. Much effort and attention has been directed at the appropriate treatment of shock in the ED to correct the mismatch between oxygen delivery and oxygen demand, to reverse tissue hypoxia, and limit or prevent organ dysfunction and death. Treatment protocols that emphasize intravascular volume and central venous pressure restoration, optimization of oxygen-carrying capacity via exogenous oxygen delivery and blood transfusion, and vasopressors to improve inotropy, chronotropy, and peripheral vascular resistance have been advocated and implemented with positive results. The use of methylene blue (methylthioninium chloride [MB]) has been advocated as a potential adjunct in the treatment of shock states. This article will review the literature on MB for the treatment of shock.

HISTORICAL BACKGROUND

MB was the first fully synthetic drug used in medicine. This chemical was first developed as an aniline dye derivative for the textile industry by Heinrich Caro in 1876, and Robert Koch used MB as a stain for microscopic visualization of the tuberculosis bacilli in 1870. After observing that bacteria and parasites were seen with MB-containing stains, Paul Ehrlich argued this might suggest a harmful effect on the microorganism by MB that could be used in the prevention and treating of disease (1–3). As a result of these observations and arguments, Ehrlich and Guttman applied MB to the treatment of malaria starting in 1891 (4). MB was used as an antimalarial agent through the end of World War II by U.S. service members but was not well liked, as it resulted in characteristic but reversible blue-green urine and blue sclera (5). More recently, interest has been renewed in MB as an antimalarial agent (6,7). In the 1920s, MB was observed to be a potent treatment for

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cyanide-induced inhibition of oxidative phosphorylation and the electron transport chain. MB has a reduction potential similar to oxygen and can be reduced by members of the electron transport chain (8,9).

Other historical applications for MB have included use as a dye as an indicator of compliance with psychiatric medications (10). This practice indirectly led to the observation that MB has antidepressant and other psychotropic effects. MB served as the lead compound for the development of chlorpromazine and the tricyclic antidepressants (10). More recently, MB has become recognized to be beneficial in the treatment of toxin-induced and hereditary methemoglobinemia (11). MB has been used, in addition, for ifosfamide-induced encephalopathy, and ackee fruit poisoning (12–14). MB has also been described as a treatment for shock states and in calcium channel blocker overdose (15,16).

PHYSIOCHEMICAL CHARACTERISTICS

MB is a heterocyclic aromatic compound with the molecular formula ($C_{16}H_{18}ClN_3S$, $3H_2O$) and the chemical name 3, 7-bis (dimethylamino)-phenazathionium chloride tetramethylthionine chloride (17,18). It is soluble in water and, when oxidized, has a deep blue color; it is colorless in its reduced state (leukomethylene blue). MB is supplied as a 10-mg/mL formulation for intravenous injection with small amounts of sodium hydroxide or hydrogen chloride to adjust the pH to 3–4.5. MB is incompatible with other strong oxidizing or reducing agents (19,20).

PHARMACOKINETICS

Animal and human volunteer studies demonstrate the complex pharmacokinetics of intravenous and oral MB. MB distributes to deeper compartments with a slower terminal elimination estimated at 5.25 h (21–25). Absorption is nearly complete when given orally and has a volume of distribution of 0.02 L/kg (25). Peak oral concentrations after ingestion occur at 1–2 h, but are 100-fold less than concentrations after intravenous administration of an equivalent dose (80–90 nmols/L vs 8000–9000 nmols/L). This substantial difference is attributable to first-pass distribution into the intestinal wall and liver after oral administration (22,23). Metabolism is predominantly (85%) through reduction to leukomethylene blue in peripheral tissue (25). Urinary excretion is 28.6% after intravenous administration and 18.5% after oral administration (25).

Dosing of MB for methemoglobinemia is typically 1–2 mg/kg of a 1% solution intravenously, with a repeat dose given if there is inadequate response to the first dose (2). At higher doses (5–7 mg/kg), electrocardiographic abnormalities (T-wave inversion, diminished R waves), shortness of breath, chest discomfort, nausea, diarrhea, diaphoresis, and abdominal discomfort have been reported (25,26). Similarly, at doses > 4 mg/kg, reversible skin, feces, and urine discoloration occurs. MB can be present in the urine for up to 5 days after dosing, despite a relatively short pharmacological period of activity (27). Paradoxically, at doses between 4 and 15 mg/kg, MB may cause methemoglobinemia.

METHODOLOGY

To review the use of MB in the treatment of shock states, we queried PubMed and the Cochrane Central Register of Controlled Trials Database for relevant English language literature using a methodology consistent with the Cochrane Highly Sensitive Search strategy. Articles in publication or referenced by December 31, 2012 were considered for inclusion. Search terms used were "sepsis and methylene blue," "septic shock and methylene blue," "anaphylaxis and methylene blue," "anaphylactic shock and methylene blue," "drug-induced shock and methylene blue," and "drug-induced hypotension and methylene blue." The articles we selected for review included articles that described MB's role in septic shock, anaphylactic shock, and drug-induced hypotension. Case reports, controlled or observational trials, case series, or review articles referencing case reports, case series, or trials were considered eligible for inclusion. The articles we excluded were those that described MB's role in nonshock states.

Data Collection and Analysis

All identified studies were independently reviewed and consensus reached by two study authors (J.L., M.D.) regarding inclusion criteria. Included studies were assessed independently by the two reviewers for adequacy, blinding, randomization, intervention, primary and secondary outcome measures, and bias, using a standardized form for data abstraction. Disagreements were discussed and arbitrated in meetings to form consensus. Unanimity was reached for all articles included.

Role of MB in Septic Shock

A total of 48 articles were identified using the previously described search terms "sepsis and methylene blue" and "septic shock and methylene blue." After elimination of animal studies and duplicated references, 16 articles were included for review.

Role of MB in Anaphylactic or Drug-induced Shock

A total of 34 articles were identified using the previously described search terms "anaphylaxis and methylene