

Clinical Review:

Methylene Blue

Dosing Pearls

Methylene Blue, currently available as an injectable FDA approved for the treatment of methemoglobinemia, is currently under investigation for a variety of conditions including treatment for Lyme disease as well as treatment for neurodegenerative conditions such as Alzheimer's.

Max Dose^{1,2}

Experts recommend no more than 5mg/kg/day and some studies have safely used up to 4mg/kg orally. Short term treatment with much higher quantities has been explored for some treatment protocols.

Lyme Disease (*Borrelia burgdorferi* infection)³⁻⁶

Mechanism of Action: Methylene blue is used in some Lyme disease protocols in combination with Dapsone to help lower methemoglobin levels, which can be elevated with pulsed high dose or double dose dapsone protocols used to manage Lyme disease. Methylene blue may also exhibit some effect on its own against biofilms that can be formed from by *B. burgdorferi*.

Dosing: Dosing for Lyme disease protocols varies. Some protocols have evaluated 50mg orally twice daily working up to 100mg orally twice daily and even higher doses in some cases if indicated based on elevated methemoglobin levels, with one protocol noting a temporary maximum dose of up to 300mg BID orally. Methylene blue was decreased if a drop in hemoglobin was noted as high dose methylene blue can be associated with hemolysis.

Duration: Duration of treatment varies, some studies, such as one using a double dose of dapsone for 1 month protocol, escalated the methylene blue dose while taking double dose dapsone before tapering off over 6 days after dapsone was discontinued.

Malaria (*Plasmodium* Parasites)⁷⁻⁹

Mechanism of Action: The mechanism of action has not been fully elucidated, it is thought that methylene blue may increase the concentration of toxic products and oxidants in the cells in part through competitive inhibition of glutathione reductase, which also results in sensitization of the parasite to some other antimalarial drugs.

Dosing: Dosing for management of malaria is variable. One study in patients 6-59 months old dosed methylene blue at 15mg/kg/day divided into 2-4 doses per day for 3 days and added it to standard of care. The study did note significantly lower hemoglobin levels in the methylene blue treatment arm, but clearance of *P. falciparum* was more rapid in the methylene blue group. Other studies looked at a much lower 4mg/kg dose in patients in the same age range vs treatment with chloroquine alone and did note adequate clinical and parasitological response more often in the methylene blue group than the chloroquine alone group. A study in adults evaluated 780mg methylene blue in two divided doses as monotherapy for 3, 5, or 7 days and noted better efficacy with the 7 day treatment.

Duration: Most studies evaluate short duration of treatment, about 3 days up to 14 days in some studies

Neuroprotection (Alzheimer's, Traumatic Brain Injury etc.)¹⁰⁻¹³

Mechanism of Action: Methylene Blue has been noted to have a stabilizing effect on mitochondrial function and has been noted to mitigate production of reactive oxygen species. Mitochondrial dysfunction and oxidative stress are often implicated in progressive neurodegenerative disorders such as traumatic brain injury, Alzheimer's disease, and Parkinson's disease.

Dosing: One dose finding study evaluated doses of 30mg and up per day orally in patients with mild to moderate Alzheimer's and found 138mg/day in divided doses to be beneficial. Another study evaluating postoperative delirium in elderly patients noted that patients who received 2mg/kg IV methylene blue within 60min of anesthetic induction were significantly less likely to suffer from postoperative delirium and post operative cognitive dysfunction. Studies in humans for management of acute traumatic brain injury are limited, but rat trials evaluating 1mg/kg 30min post injury and then again once monthly for 6 months noted superiority over single treatment with methylene blue.

Duration: Duration varies between single dose for some conditions to continuous dosing for others. Existing trials evaluating methylene blue for Alzheimer's Disease have spanned up to 50 weeks.

Drug Interactions^{4,13-17}

Methylene Blue is a potent reversible inhibitor of monoamine oxidase, an enzyme involved in the breakdown of neurotransmitters including norepinephrine, serotonin, dopamine, and tyramine. Patients on selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), or drugs known to increase serotonin levels such as bupropion should be evaluated for the appropriateness of methylene blue therapy. The FDA has released Drug Safety Communications specifically regarding the risks of coadministration of serotonergic medications and methylene blue for injection.

Methylene blue may also produce hypertensive effects in the presence of certain foods high in tyramine. Some Lyme disease protocols provided the below list of foods to avoid with concurrent methylene blue administration: "aged cheese, aged chicken or beef liver, air-dried sausage and similar meats, avocados, beer, and wine (in particular, red wine), canned figs, caviar, fava beans, meat tenderizer, overripe fruit, pickled or cured meat or fish, raisins, sauerkraut, shrimp paste, sour cream, soy sauce, and yeast extracts". Other supplements to watch out for could include protein, body building, or weight loss supplements, which sometimes contain tyramine.

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