International Journal of Medical Science and Clinical Research Studies

ISSN(print): 2767-8326, ISSN(online): 2767-8342

Volume 03 Issue 10 October 2023

Page No: 2281-2283

DOI: https://doi.org/10.47191/ijmscrs/v3-i10-32, Impact Factor: 6.597

Role of Methylene Blue in Refractory Anaphylaxis -A Case Report

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ABSTRACT

Refractory anaphylaxis is defined as anaphylaxis which, after treatment with at least 2 doses of minimum 300 microgram epinephrine, does not achieve normalization of symptoms. Dysregulation of NO synthesis and vascular smooth cell guanylate cyclase activation may have a role in refractory vasoplegia. Methylene blue is competitive inhibitor of NO synthase and guanylate cyclase. Thus, blocking the effects on cGMP mediated smooth muscle relaxation and vasodilation and mast cell mediator release. Thus, methylene blue has been implicated as a treatment option for refractory vasoplegia. We present the case of a 21-year-old male who presented with anaphylactic shock that was unresponsive to epinephrine. After administration of methylene blue, his blood pressure and sensorium improved; and he was gradually extubated. Hence, our clinical experience suggests that methylene blue is a safe treatment option for refractory anaphylactic shock.

KEYWORDS: methylene blue, refractory vasoplegia, anaphylactic shock

ARTICLE DETAILS

Published On:
16 October 2023

Available on:
https://ijmscr.org/

INTRODUCTION

Anaphylaxis is a fatal or potentially life-threatening multisystem allergic or hypersensitivity reaction. It is rapid in onset and is characterized by serious airway, breathing and/or circulatory problems. Anaphylactic shock is an end manifestation of anaphylaxis which occurs when there is inadequate tissue perfusion causing end organ damage. Refractory anaphylaxis is defined as anaphylaxis which, after the treatment with at least 2 doses of minimum 300 microgram epinephrine, does not achieve normalization of symptoms.[1]

Epinephrine is the mainstay of treatment for anaphylaxis. Epinephrine acts by stimulation of alfa and beta adrenoceptors. Stimulation of alfa adrenoreceptors increases peripheral vascular resistance leading to improved blood pressure and coronary perfusion. Stimulation of beta adrenoceptors has positive inotropic and chronotropic cardiac effects, bronchodilation as well as reduced release of inflammatory mediators.

Histamine is the mediator that plays a significant role in the cardiovascular manifestations of anaphylaxis. These effects are mainly mediated through histamine1 - and H2-receptors.[2] Histamine also acts on the vasculature through nitric oxide. Nitric oxide leads to vasodilation indirectly by increasing the activation of guanylyl cyclase, which further increases the levels of smooth muscle cyclic guanosine monophosphate (cGMP) that finally causes relaxation of vascular smooth muscles.[3,4] These vasodilatory actions of nitric oxide are inhibited by methylene blue, which is a competitive inhibitor of guanylate cyclase. Here we present a case of refractory anaphylactic shock reversed with methylene blue.

CASE

A 21-year-old male was found unresponsive at home. He was brought to the emergency room by his parents at 11 pm. There was a history of ingestion of red meat at 8 pm. He had a known history of allergy to red meat. Clinical examination revealed decreased consciousness, Spo2 78%, heart rate 50/min, respiratory rate 26/min and BP 60/40 mmHg. He had angioedema and facial urticaria.

With the probable diagnosis of anaphylactic shock, first dose of epinephrine 0.5mg intramuscular was given. Intravenous line was secured and 1 litre bolus of crystalloid fluids were administered. Patient was started on oxygen therapy at 10 litre/min via simple face mask. On re-assessment, SpO2 was 92% with 10 litre/min face mask, heart rate 58/min and BP remained low at 70/40mmHg. He was administered second dose of epinephrine 0.5 mg intramuscular. Hydrocortisone 200mg IV and Pheniramine maleate 22.75 mg IV were also given. Due to low Glasgow Coma Score and persistent hypotension, his airway was secured with a 6.5 Fr endotracheal tube anticipating difficult airway. In view of persistent unresponsiveness, a third dose of intramuscular

epinephrine was repeated, followed by an intravenous infusion of epinephrine at 0.15mcg/kg/min.

The patient failed to improve even after 30 minutes of resuscitation. In view of refractory vasoplegia, the use of IV methylene blue was considered. Intravenous infusion of methylene blue 1.5 mg/kg in 50 ml 5% Dextrose (100 mg) over 20 minutes was begun. Within few minutes of starting the infusion, his BP improved to 110 /70 mmHg and heart rate also normalized.

Epinephrine infusion was gradually tapered and stopped. Subsequently, the patient's sensorium improved and his vitals remained stable. He was gradually extubated.

DISCUSSION

Anaphylaxis is a clinical syndrome that can affect multiple target organs, including skin, respiratory, gastrointestinal, and cardiovascular system. It occurs mainly by a classic IgE mediated reaction from a previously sensitised mast cells or basophils.

Anaphylactic shock is a type of distributive shock believed to be caused due to activation of multiple pathways involving massive release of mediators such as histamine, platelet activating factor, leukotrienes, and TNF -α. Histamine may also affect the vasculature through nitric oxide (NO).

NO is synthesized from L arginine by NO- Synthase. NO has been shown to be important for the control of the vascular tone. Nitric oxide increases cyclic guanosine monophosphate (cyclic GMP) through activation of guanylate cyclase. This leads to smooth muscle relaxation and vasodilation.

Dysregulation of NO synthesis and vascular smooth cell guanylate cyclase activation may have a role in refractory vasoplegia. Refractory vasoplegia is generally defined as a mean arterial pressure (MAP) 2.5 L·min−1·m−2, right atrial pressure 0.5 μg·kg−1·min−1), left atrial pressure 0.5 μg·kg−1·min−1) and low SVR (0.5 μg·kg−1·min−1) in the absence of obvious infection and despite high doses of IV norepinephrine infusion (>0.5 μg·kg−1·min−1).

Methylene blue is a competitive inhibitor of NO synthase and guanylate cyclase. Thus, blocking the effects on cGMP mediated smooth muscle relaxation and vasodilation and mast cell mediator release. Thus, methylene blue has been implicated as a treatment option for refractory vasoplegia. Methylene blue has been used in various clinical states including cardiac surgery, septic shock, hepatopulmonary syndrome, anti-malarial and methemoglobinemia.

A study to evaluate the effectiveness and outcome of methylene blue therapy in vasoplegia after cardiac surgery was conducted. The study concluded that the use of methylene blue for vasoplegia post cardiac surgery was associated with rapid recovery of haemodynamics and shorter need for vasopressors.[5]

A case of methylene blue (MB) administration in a patient with refractory distributive shock secondary to Streptococcal Toxic Shock Syndrome (TSS) was reported with subsequent sustained decreased vasopressor and inotropic requirements.[6]

The evidence for the use of methylene blue in the management of anaphylactic shock is scarce in the literature.

CONCLUSION

Our clinical experience strongly suggests that methylene blue is a lifesaving treatment option for anaphylactic shock refractory to the standard line of management. The literature does not provide us with robust data to proves its effectiveness in this clinical scenario. Further research is needed to evaluate the role of methylene blue in refractory anaphylactic shock.

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VII. taylor and stephanie nonas doi: http://dx.doi.org/10.1016/j.chest.2020.08.838

Figure 1 Methylene blue induced green urine

Figure 2 Methylene blue 100 mg ampoule