Green-Blue Discolouration of Brain at Autopsy: A Case Report

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Abstract

Methylene blue is a solid; its water solution is deep blue. It has been described as "the first fully synthetic drug used in medicine." Methylene blue was first prepared in 1876 by German chemist Heinrich Caro. It is on the World Health Organization's List of Essential Medicines. It has been increasingly used in the management of refractory distributive shock. A 16 years old boy following liver transplantation developed septicemia. During autopsy when dissecting brain, grey matter showed colour change from grey to green-blue in a few seconds. Green-blue discolouration of brain was an incidental finding in this case and when back referred it was found that young male developed acute liver failure and had undergone liver transplantation. Following transplant rejection he developed refractory hypotension, septic shock and multiple organ dysfunction syndrome. So in that critical condition methylene blue was given which is an effective drug for refractory shock.

Key words: Acute liver failure, liver transplantation, refractory hypotension and sepsis, methylene blue, green-blue discolouration of brain.

Introduction

Methylene blue is a reduction agent traditionally used in the treatment of methemoglobinaemia, however, it has been increasingly used in the management of refractory distributive shock. Its mechanism of action is based on the inhibition of the nitric oxide-cyclic guanosine monophosphate pathway leading to the increased vasomotor tone in the arterioles[1,2]. It is an organic chloride salt and a formal derivative of phenothiazine. It contains 3,7-bis (dimethylamino) phenothiazine -5-ium. It is a commonly used dye, but also exhibits antimicrobial, antioxidant, antimalarial, cardioprotective and neuroprotective actions. Synonyms are basic blue, swissblue, uroleneblue, solventblue, methylthioninium chloride[3,4]. "Pistachio" or "avatar" green-blue discolouration of brain is a phenomenon associated with methylene blue[5].

Case report

A 16 years old boy who was apparently normal without any co-morbidities developed symptoms including vomiting and tiredness in the evening after returning home from school. There were two episodes of vomiting. The vomitus was black in color. He was treated on outpatient basis in a local hospital

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with intravenous fluids and supportives. His initial investigations including LFT (Liver Function Test) were normal apart from Leucopenia in complete blood count. As he became symptomatically better; got discharged and went home. But the symptoms persisted and he had multiple episodes of vomiting for two days and got admitted in hospital and this time his repeat LFT was deranged (LFT: AST/ALT/ALP=5031/2575/557). Next day he developed altered sensorium and diagnosed with acute fulminant hepatic failure and referred to a higher centre. As he had hypotension, sinus tachycardia, SPO_2 96%, grade 3 hepatic encephalopathy and severe acidosis; elective intubation was done at casualty of higher centre. Because of acute fulminant hepatic failure and hepatic encephalopathy; liver transplantation with cadaveric liver was done on the very next day after several investigations and evaluations.

After a week of transplantation he developed refractory hypotension and subsequently septic shock and hypovolemic shock. In spite of all resuscitative measures he succumbed to death 2weeks after development of initial symptoms. Since it was a case of post liver transplantation death of a young male with acute hepatic failure of unknown etiology (? drug/toxin induced); body was kept for medico-legal autopsy.

Postmortem examination was conducted on next day in the mortuary wing of Department of Forensic Medicine, Government Medical College, Thiruvananthapuram. External examination revealed yellowish discolouration of sclerae, violaceous discolouration with swelling on inner four toes of right foot and inner two toes of left foot. Both lower limbs were oedematous. Surgical wounds of transplantation procedure were present over abdomen. Internal examination findings were suggestive of multiple organ dysfunction and septicemia. The transplanted cadaveric liver was enlarged and yellowish. On dissection the brain appeared normal initially, but on exposure to air the colour changed to green-blue especially on cortical and sub-cortical grey matter areas [Fig.1, 2&3].

Blood and brain samples were collected and sent for culture to Microbiology Laboratory and the report revealed vancomycin resistant enterococci in blood and scanty growth of Klebsiella in brain tissue. Histopathological examination showed extensive necrosis of transplanted cadaveric liver with portal and lobular mild inflammation composed of lymphocytes and neutrophils. Other findings were suggestive of multiple organ dysfunction syndrome. Perusal of records revealed administration of methylene blue intravenously to treat refractory shock was the reason for green-blue discolouration of brain at autopsy.

Fig. 1: Green-blue discolouration of brain surface.

Fig. 2 & 3: Green –blue discolouration of dissected brain on exposure to air.

Discussion

Methylene blue (Methylthioninium chloride) is an organic chloride salt having 3,7-bis (dimethylamino) phenothiazin-5-ium as the counterion[1]. It has a role as monoamine oxidase inhibitor, acid-base indicator, a fluorochrome, an antidepressant, a cardioprotective agent, cholinesterase inhibitor, a histological dye, guanylate cyclase inhibitor, an antioxidant, an

antimicrobial agent, a neuroprotective agent, a physical tracer and an antimalarial. The intravenous form of methylene blue is approved by the FDA for the treatment of paediatric and adult patients with acquired methemoglobinemia. Other clinical applications of methylene blue include improvement of hypotension associated with various clinical states, an antiseptic in urinary tract infections, treatment of hypoxia and hyperdynamic circulation in cirrhosis of liver and severe hepatopulmonary syndrome, and treatment of ifosfamide induced neurotoxicity[3]. It has been described as "the first fully synthetic drug used in medicine." Methylene blue was first prepared in 1876 by German chemist Heinrich Caro. It is on the World Health Organization's List of Essential Medicines. Its use in the treatment of malaria was pioneered by Paul Guttmann and Paul Ehrlich in 1891. It was discovered to be an antidote to carbon monoxide poisoning and cyanide poisoning in 1933 by Matilda Brooks[4].

Mechanism of action: It inhibits the enzymes nitric oxide synthase and guanylate cyclase. By inhibiting the nictric oxide guanosine monophosphate pathway, it increases the vasomotor tone of arterioles; also it increases mean arterial blood pressure through an increase in cardiac index and systemic vascular resistance. So it is used in hypotension and refractory shock. Also it increases the partial pressure of oxygen. So it is used in cases like hepato-pulmonary syndrome, anaphylaxis etc. Since it is a cation it binds to negatively charged particles like nucleus. Since the grey matter has mainly neuronal cell bodies bluish discoloration is seen in grey matter. The pistachio or avatar discoloration occurs when the colourless metabolite leucomethylene blue is oxidized to methylene blue upon the exposure to atmospheric oxygen[1,4].

Uses[4]

1. Methemoglobinemia: It is an effective antidote because of its own oxidizing property. Oxidizes NADPH forming a reduced product leucomethylene blue which reduces heme group from methemoglobin to hemoglobin.
2. Cyanide poisoning: Since its reduction potential is similar to that of oxygen and can be reduced by components of Electron Transport Chain (ETC), large doses are used as an antidote.
3. Ifosfamide toxicity: Methylene blue was first reported for the treatment and prophylaxis of ifosfamide toxicity. Here the toxic metabolite Chloroacetaldehyde (CAA) disrupts mitochondrial respiratory chain leading to accumulation of NADH. Methylene blue acts as an alternative electron acceptor and reverses NADH inhibition of hepatic gluconeogenesis and also inhibit the formation of CAA.
4. Dye or Stain:
    - Chromoendoscopy - to identify dysplasia
    - Urinary tracts - to identify any leak
    - Sentinel lymph node dissection - to visualize the lymphatic drainage
    - Fistulas, pilonidal sinus - to identify the tracts
5. To treat septic shock and anaphylaxis
6. To increases blood pressure in people with vasoplegic syndrome (redistributive shock), but has not been shown to improve delivery of oxygen to tissues or to decrease mortality
7. Has been used in calcium channel blocker toxicity as a rescue therapy for distributive shock unresponsive to first line agents.

Side effects[4]

- Cardio vascular system: Hypertension, precordial pain
- Central nervous system: Dizziness, mental confusion,headache,fever
- Dermatologic: Staining of skin, injection site necrosis
- Gastro intestinal tract: Faecal discolouration, nausea, vomiting, abdominal pain
- Genito-urinary tract: Discolouration of urine, bladder irritation
- Haematological: Anaemia.

Differential diagnosis[7]

- Hydrogensulphide poisoning: Affects all internal organs

- Hyperbilirubinemia: Yellowish or greenish in colour and no relation with exposure to air.
- Putrefaction of the body: Along with greenish discolouration of organs there will be other evidences of putrefaction also.

Green-blue discolouration of brain was an incidental finding in this case and when back referred it was found that young male developed acute liver failure and had undergone liver transplantation. Following transplant rejection he developed refractory hypotension, septic shock and multiple organ dysfunction syndrome. So in that critical condition methylene blue was given which is an effective drug for refractory shock. Similar findings were observed in various previously published case reports. In an article published by Linda and Kyle (2016), the authors have described green-blue discolouration of serosal surfaces in autopsy of a 68years old man, admitted for abdominal pain and distention; who undergone surgery 3days prior, during his short hospital stay, developed sepsis which was treated with methylene blue[5]. Another case was reported by Afzal A etal (2020) in which the authors described a 58years old male who died of septic shock due to Pseudomonas aeroginosa bacteraemia secondary to acute folliculitis and epididymo-orchitis. He was given methylene blue for reversal of septic shock but he did not respond and expired. Autopsy findings were significant for bluish-green discoloration of organs, especially the heart, lungs, and brain during prosection secondary to methylene blue. This accumulation was in a dose related fashion and the discolouration increased from green to turquoise blue as the organs were set on the table for dissection[6]. In yet another case report by Carlos Durao etal (2020) greenish-blue discoloration of the brain and heart was observed during the autopsy of a 63years old woman who had been treated with methylene blue for septic shock following a traffic accident[7]. Dumbarton etal (2012) reported a case of tissue ischaemia in a patient with refractory shock, led to distal digital necrosis due to methylene blue extravasations which might be the reason for violaceous discolouration and swelling of toes found in the present case[8].

Conclusion

Even though methylene blue associated discolouration of brain is a rare entity; timely identification of such a possibility and differentiating them from other changes may help to avoid unnecessary investigations and dilemma during postmortem examination of such cases.

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