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RESEARCH ARTICLE

MANAGEMENT OF METHEMOGLOBINEMIA FOLLOWING DRUG INTOXICATION WITH DAPSONE IN THE ABSENCE OF METHYLENE

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Abstract

Methemoglobinemia is an altered state of hemoglobin by auto-oxidation resulting in impaired oxygen delivery to tissues. Methemoglobinemia can be congenital, but the acquired form is the most common, often caused by various drugs and toxins. Methylene blue is the most effective antidote for acquired methemoglobinemia. When methylene blue is not available, alternative treatments such as ascorbic acid, cimetidine, and hyperbaric oxygen may be helpful. In this article, we report a case of methemoglobinemia due to intoxication following voluntary ingestion of 50 tablets of dapsone for the purpose of suicide in a young child of 10 years.

Introduction:-

Methemoglobin is formed when ferrous ions (Fe2 +) in heme are oxidized to ferric ions (Fe3 +), which are unable to bind to oxygen molecules. In addition, their presence enhances the O2 binding affinity of the ferrous hemes remaining in the hemoglobin tetramer, which impairs their ability to transport oxygen to tissues.

Methemoglobin forms less than 1% of hemoglobin in normal individuals. Cyanosis occurs when 10-25% of total hemoglobin converts to methemoglobin [1].

Methemoglobinemia can be congenital, but the acquired form is more often caused by various drugs and toxins, including dapsone, nitrates, prilocaine, antimalarials and sulfonamides, have been found to be responsible for acquired methemoglobinemia [2].

The diagnosis of acquired methemoglobinemia depends on clinical suspicion, the patient's drug history and the methemoglobin level measured by co-oximetry [3].

The purpose of the presentation of this case is to emphasize the importance of considering other treatments for methemoglobinemia given the unavailability of methylene blue in our context.

Clinical case :

A 9-year-old child, with no particular pathological history, is brought to the emergency room of a regional hospital by the family 2 hours after his suicide attempt by voluntary ingestion of 50 dapsone tablets.

On clinical examination, the patient is conscious with a SG: 15/15, on the respiratory level we note a patient with marked cyanosis on the face where it is particularly intense at the level of the lips (slate gray appearance), polypneic

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to 35c / min, SpO2 at 70% in ambient air and 85% under 6l of O2 by high concentration mask. Hemodynamically, a stable patient is noted with normal cardiopulmonary auscultation.

Faced with the worsening respiratory plan, he was transferred to pediatric intensive care for further treatment.

The biological results are as follows: gas analysis on an arterial sample (chocolate-colored blood (figure1)) under 6 l / min of oxygen, Ph: 7.337, PaO2: 363 mmHg, PC02: 30.8 mmHg, BEecf: -9, HCO3 : 16.5, tCo2: 17mmol / L, Spo2: 100%, lactate: 1.18, hemoglobin level 11.7 g / dL, GB: 8500mm³, platelets: 332,000mm³, PT: 74%, Liver function tests and renal function are normal . The ECG and chest x-rays show no abnormalities.

The methaemoglobinemia assay by co-oximetry not done, given the unavailability in our context.

The intensive care unit consisted of oxygen therapy by mask at high concentration: 12 l / min, vitamin C tablet 2g / 8h (injectable form not available) and cimetidine tablet 10mg / kg / 8h. One day after his admission to intensive care unit, the evolution was marked by the regression of cyanosis, a eupneic patient put on O2 glasses with a saturation of 88%.

The child was reported discharged after 4 days of admission, conscious, hemodynamically and respiratory stable with complete regression of cyanosis, pink lips, 97% Spo2, and eupneic at 22 c / min.

Figure 1:- Chocolate color of the patient's arterial blood.

Discussion:-

The majority of cases of acquired methemoglobinemia described in the literature have resulted from exposure to exogenous oxidizing agents such as nitrites used as preservatives in food or as a deliberate poison [4,5], amyl nitrate used as a recreational agent, abuse of paint thinner by drug addicts, intake of vegetables containing nitrate, use of EMLA cream, and intake of Dapsone [6,7].

In a retrospective review of methemoglobinemia acquired in a teaching hospital, dapsone was the most frequently identified cause of methemoglobinemia [7].

Peak plasma concentrations of Dapsone are reached within 2 to 8 hours of ingestion. The mean elimination half-life varies from 10 to 80 hours in case of overdose. Methemoglobinemia occurs indirectly via a metabolite formed by the oxidative metabolism of dapsone in the cytochrome P450 system. This metabolite of dapsone hydroxylamine is responsible for the actual oxidation of hemoglobin to methemoglobin [8-9]. The long half-life of this metabolite explains the prolonged duration of methemoglobinemia as well as the frequent need for repeated doses of methylene

blue after exposure to dapsone. Cimetidine's inhibition of the P450 isoenzymes responsible for dapsone metabolism (CYP3A4) explains its efficacy in the treatment of dapsone-induced methemoglobin [10].

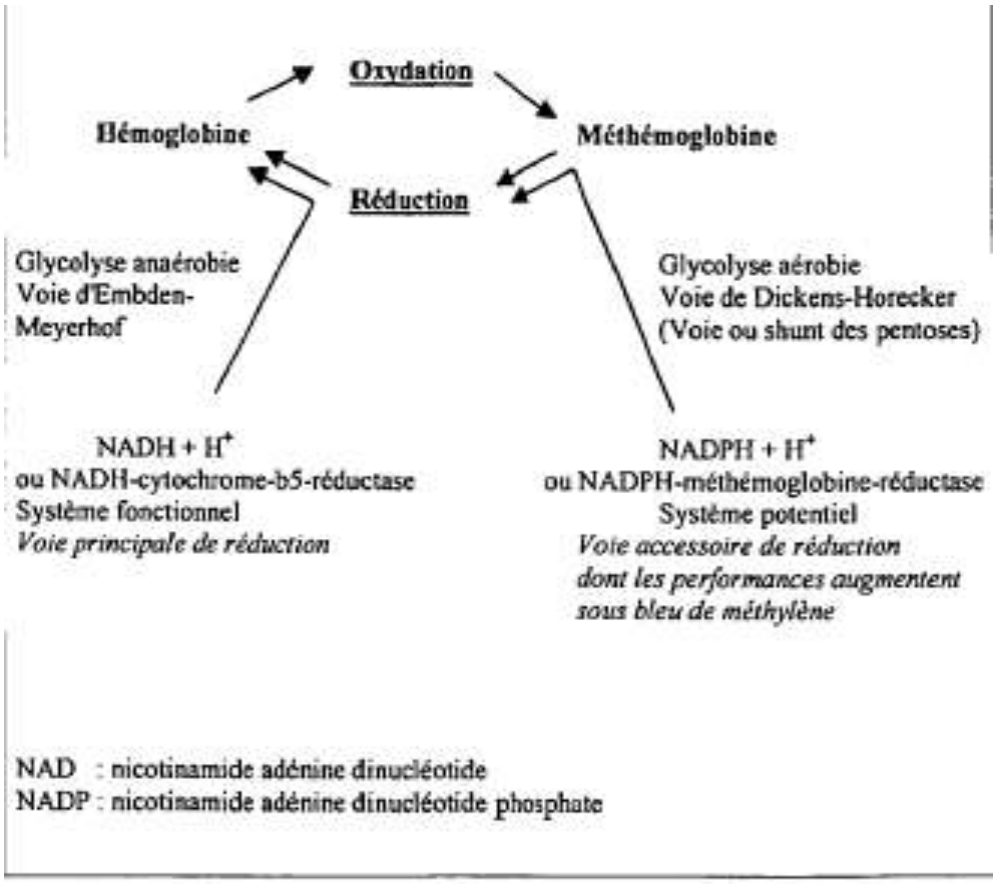

Figure 2:- Reduction of methemoglobin according to DANEL V. and VIALA A. [11,12].

Symptoms of methemoglobinemia usually result from hypoxia, as methemoglobin is unable to fix oxygen, unlike hemoglobin. These symptoms are proportional to the level of methemoglobin. Asymptomatic, if less than 15%; cyanosis at levels above 15%; headache, dyspnea, nausea, tachycardia and weakness at levels above 20%; coma settles above 45% and a high mortality rate is associated with levels above 70% [13].

Treatment of methemoglobinemia should be guided by the severity of the condition and the underlying medical conditions and comorbidities. Methylene blue (1 to 2 mg.kg - 1) administered intravenously has traditionally been considered the main antidote used to treat methemoglobinemia [13,14]. Its use is recommended in all patients with methemoglobin levels greater than 30% or in symptomatic patients at lower levels. Although the maximum recommended total dose is 7 mg / kg. Refractory cases may warrant continuous infusion [15].

Depending on the clinical course, other treatment options may include cimetidine, blood transfusion and hyperbaric oxygen may also be considered in severe life-threatening cases [16].

Dapsone is metabolized via CYP3A4 to form several metabolites, including dapsone hydroxylamine. Cimetidine, an H2 receptor antagonist, inhibits CYP3A4 and should therefore be considered in patients with dapsone-induced methemoglobinemia [17,18].

Ascorbic acid is a powerful reducing agent which participates in many redox reactions. In a recent in vitro study and case reports, ascorbic acid was shown to be beneficial in the treatment of methemoglobinemia. In these studies, ascorbic acid was administered at different doses and times (300 mg / kg IV bolus, 300 mg IV over 24 h and 10 g IV over 6 h) [19,20].

Ex-blood transfusion is usually performed when patients do not improve with the initial administration of methylene blue and in severe poisoning this can be a life-saving measure [21].

This case underlines the importance of a good history, of knowing the drugs likely to cause methaemoglobinemia and the other different treatments involved in the management.

Conclusion:-

In conclusion, acquired methemoglobinemia is a rare blood disease that can be fatal if left untreated. Although methylene blue is a successful treatment for methemoglobinemia, other treatments should be considered when methylene blue is not available.

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