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# Methemoglobinemia - A review and recommendation for management - Acute methemoglobinemia with hemolytic anemia following suicidal use of aniline based substance

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### ABSTRACT

Methemoglobinemia is a rare disease classification related with congenital or acquired (usually iatrogenic) hemoglobin oxygenation disorder. Despite the fact that number of potentially methemoglobin forming agents is very long, methemoglobinemia is still a case-report of patients admitting to the Emergency Departments. The patient was brought after consuming resin hardener for suicidal purposes from the Center of lower reference to the hospital Emergency Department with suspected burns of the gastrointestinal tract. The patient presented cyanosis, dyspnoea and brown-colored urine on admission.

**Keywords:** Methemoglobinemia; management

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## Introduction

Methemoglobinemia is a disease in which erythrocytes contain methemoglobin (in an amount of more than 1% of the total hemoglobin). Methemoglobin is a type of hemoglobin in which hem is in an oxidized form (Fe<sup>3+</sup>), different then in hemoglobin Fe<sup>2+</sup>. The oxidized form of hem loses the ability to transport oxygen, leading to tissue hypoxia independent from MetHb levels so-called: functional anemia<sup>[1]</sup>. Methemoglobin is being produced constantly, physiologically however, thanks to a special enzymatic system reducing its value does not exceed 1%. Two mechanisms are responsible for maintaining an adequate level of methemoglobin. The first is the pentose phosphate pathway present in erythrocytes, where takes place the reduction to Fe<sup>2+</sup> with the participation of glutathione. The second and also the main pathway is enzymatic transformation in the presence of cytochrome b5 reductase or / and NADPH reductase<sup>[2]</sup>.

Methemoglobinemia can occur in hereditary and acquired forms. Domain form is associated with altered forms of hemoglobin e.g. M or with cytochrome b5 reductase deficiency leading to a different clinical picture depending on the form (I-IV). Acquired forms are caused by iatrogenic effects by the administration of methaemoglobinogenic drugs or by accidental ingestion of oxidizing substances (biocides, nitrogen compounds including preservatives and poppers, aniline). Methaemoglobinogenic effects have local anesthetics (ligno- and benzocaine also in the form of ointments)<sup>[3,4]</sup>, analgesics and antipyretics, nitroglycerin, dapsone, silver nitrate dressings<sup>[5]</sup>, metoclopramide<sup>[6]</sup>, sodium nitroprusside and contaminated drugs e.g. cocaine<sup>[7]</sup>.

Oxygenation to the Fe<sup>3+</sup> form is much easier for fetal hemoglobin and when the level of cytochrome b5 reductase is much lower, hence the greater risk of methemoglobinemia in children. Symptoms of cyanosis appear at MetHb> 15%, but in healthy people, apart from cyanosis, there are no other symptoms at 20-30%<sup>[8]</sup>. It is worth emphasizing that the relationship between the clinical condition and the methemoglobin level is not linear and depends largely on

coexisting diseases. The symptoms appearing during the increase of methemoglobin level include: headache, dyspnea, lightheadedness, confusion, bradyarrhythmia, seizures, profound acidosis, coma. People with congenital methemoglobinemia usually do not have any symptoms except for the blue color of the skin. >70% is considered to be a death level but the literature shows a case of a 2-year-old boy who survived the level of methemoglobin on 94%<sup>[9]</sup> and 26 years old who in suicidal purposes consumed the methemoglobin forming agents with the level of MetHb on 91%. Both people survived intoxication without any neurological defects.

Proceeding in case of methemoglobinemia as a consequence of intoxication mainly involves stopping exposure by discontinuation of a drug suspected for causing symptoms, gastric lavage, and decontamination in the case of volatile matter intoxication. Treatment consists of 15 l/min oxygen therapy through a mask with a reservoir and in the case of unconscious people or people with respiratory failure symptoms - of securing airway patency and mechanical ventilation. For people with a concentration of MetHb> 30%, the treatment of choice is methylene blue at a dose of 1mg/kg of body mass only for 5 minutes and depending on the patient's condition and MetHb concentration (decrease after approx. 30-60 minutes) re-administration to a maximum dose of 7mg/kg/day<sup>[10,11]</sup>. Daily dose is not recommended due to the potential for paradoxical methemoglobinemia. Methylene blue is more effective the higher the MetHb concentration is. Is not applicable in the form of congenital methemoglobinemia with glucose-6-phosphate dehydrogenase deficiency. Side effects of methylene blue include are:

blue skin color impeding the assessment of cyanosis, in case of intoxication e.g. with aniline, it may increase the formation of Heinz bodies in erythrocytes and hemolytic anemia dizziness, paraesthesia, chest pain, dysgeusia, nausea, sweating, arrhythmias, hypotension, necrosis in case of extravasation<sup>[12]</sup>.

The manufacturer does not give absolute contra-

indications to use of the drug, attention should be paid to possibility of malignant serotonin syndrome when used in parallel with SSRIs, SNRIs and MAO inhibitors.

If methylene blue is ineffective, oxygen therapy in a hyperbaric chamber <sup>[13]</sup> or/and exchange transfusion is recommended. There are reports in the literature about use of ascorbic acid however, its administration should be limited to the innate form, because its action in acute intoxication is too slow and data on hemodialysis is insufficient <sup>[14]</sup>.

### Case report

A 35-year-old patient was referred to the Clinical Department of Emergency Medicine from the district hospital after oral ingestion of resin hardener at work. Few hours earlier the patient took an unknown amount of substance for suicidal purposes based on aniline (as it turned out later). The exact time from consumption of the methemoglobin forming agent to time of admission to hospital could not be determined. The patient did not provoke vomiting, no gastric lavage was performed. After initial supply, the patient was transferred to local unit for gastroscopy with suspected burns of gastrointestinal tract. The patient with a soporific effect, dyspnoea, GCS 14, oxygen saturation in a flow of 15 l/m - mask with reservoir - 80%, livid skin, livid mucous membranes of the oral cavity, no burns signs, RR 24/min, HR 80/min, jugular veins not enlarged, BP 135/80 mmHg, auscultatory symmetrical vesicular sound above lungs, soft and painless stomach, peritoneal symptoms (-), edema (-). During history taking without chronic diseases and permanent drugs. The patient has consumed large amounts of alcohol in recent days. Despite extremely low saturation and livid skin tone, the patient consciously refused any treatment. During the stay developed green urine (photo. 2). Methemoglobin forming agent intoxication was suspected and Toxicology Center in Poznan was contacted due to the absence of methylene blue in the remaining facility, hospital ambulances were sent to the neighboring facilities for available amount of drug. After about 45 minutes, the patient's family appeared

in the ward and convinced the patient to undertake diagnostics and implement treatment. Chocolate color blood not lightening after contact with air (as in the case of deoxyhemoglobin) was taken for arterial gasometry, obtaining MetHb 43.8 %, pCO<sub>2</sub> 33.7, pO<sub>2</sub> 193, Hg 17.1 g/dl, Bil 4.7, Lac 32 mg/dl. At request of duty physician of Toxicology Department, the patient was given Metiblo 150 mg at hourly intervals, a gradual improvement was obtained, followed by a re-decrease in saturation down to 75%, control examination MetHg 25.2. During the stay developed green urine (photo. 1). The patient underwent gastroscopy, where blue tinted content and features of edema and congestion of antrum mucosa and of initial duodenum part were visualized. Gastrointestinal tract burn symptoms were excluded. Part of visible digestive tract was aspirated. The patient was given a total of 700mg of methylene blue and 500mg of Vitaminum C, torasemide infusion, metoclopramide and a proton pump inhibitor at a dose of 80mg intravenously. The patient family's report shows that, the patient trusted a colleague who turned out to be a fraud and lost all his savings. Similar incident of suicidal attempt by taking aniline derivatives took place in the same workplace about a year earlier - the patient could not be saved due to the loss of all assets, the patient attempted suicide by consuming a "checked" product.

The patient in improved condition was transported to Toxicology Center, 140 km away, where stayed for a total of 13 days. In the first two days, an additional 600mg (400mg + 200mg) of methylene blue was given. Sinusoidal fluctuations in MetHb level were observed with the highest result on the first day 66.3%, physiological level was obtained on 11th day from moment of intoxication. The fluctuations in methemoglobin levels in table may have been due to the failure to wash the stomach in the first hour, the affinity of the aniline derivative to adipose tissue and later gradual release from tissue deposits, as well as to pharmacokinetics of aniline itself. However, aniline and its derivatives do not work directly through their metabolites. Good fat solubility is caused by high toxicity towards own. No

lethal dose of aniline has been established yet. The consequence of aniline derivative intoxication and high doses of methylene blue was massive hemolysis with maximal bilirubin levels on 6th day after intoxication, which required a transfusion of a total of 14 pRBC units and 2 FFP units. Purpose of monitoring the aniline removal

used for determination of Paracetamol level in urine which declined down to 1.8 ug/ml in fifth day of hospitalization. The patient was consulted psychiatrically. Due to high inflammation parameters was switched on Augmentin, Biotrakson (Ceftriaxonum) and later on based on examined cultures with Linezolid with Imipenem.

	I	II	III	IV	V	VII	IX	XI
WBC ( thous / ul)	17.8	27.76	36.91	49.54	51.65	30.98	10.39	4.97
Hb (g / dl)	14.4	13.5	12.7	11.9	10.8	9.2, 8.5	7.3	8.1
PLT ( thous / ul)	234	135, 66	52	50, 38	35	80, 52	102.134	506
CRP (mg / L)	-	165	-	231	-	334.87	-	11.58
Procalcitonin ( ng / ml)	-	1.33	0.66	0.89	-	2.13	1.76	-
Bilirubine mg / dl	1.75	1.56	3.1	3.4, 4.1	4.8, 5.1	3.7	2.18	-
AST (U / L)	25	67	81	156	-	331	-	20
LDH (U / L)	436	1768	4082	5530, 8445	11099, 13753	12858, 10453	-	1323
Paracetamol ( ug / ml)	-	80.8, 35.3	35.1, 16.9	17	-	-	-	-
Troponin T ( ng / ml)	-	0.112	-	-	-	-	-	-
MethHb (%)	25.3, 60.2, 56	62.2, 65.4, 66.3	46.2, 58.6	48.3, 45.4, 35.3	32.2, 23.2, 20.0	7.1	-	2.4

The patient reported to Clinical Department of Emergency Medicine after 3 months with the symptoms of weakness, headache, and markers of hemolytic anemia in performed laboratory tests. Two months after discharge a hemoglobin level amounted 15.61 g / dl, followed by a decrease of hemoglobin to 9.38 g / dl within a month, with an increase of bilirubin to 2.26 mg / dl (with norm <1.2). The patient was started on to iron preparation and had a check-up in 14 days. An increase of hemoglobin to 10.5 g / dl, a decrease of bilirubin to 0.24mg / dl was obtained. The patient remains under constant hematological control and is awaiting diagnostics for hemolytic anemia / myelodysplastic syndrome.

## Discussion

In this case report we are dealing with intoxication of aniline derivatives for suicidal purposes. Emergency department physicians and ambulance personnel should be familiar with the symptoms of methemoglobin intoxication. Originally in this case due to the lack of willingness to cooperate on the patient side, a burn of the gastrointestinal tract was diagnosed. In our center,

on the basis of clinical symptoms, methemoglobin intoxication was suspected, but despite accurate diagnosis, the patient did not agree to treatment. The patient was encouraged to undertake diagnostics and treatment by a supportive family. Attention is drawn to the lack of available methylene blue in our center (> 500 beds), which was later explained by the fact that last case of intoxication occurred several years earlier. During hospitalization, fluctuations in the MethHb level were observed, with a maximum value of 66.3% on the second day after taking the substance. The patient developed hemolytic anemia 3 months after leaving the hospital, probably as a distant consequence of aniline derivative intoxication or high doses of methylene blue given. The patient is waiting for further hematological diagnostics.

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