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Case Report on Metaclopromide Induced Methemoglobinemia in a CKD Patient.

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ABSTRACT

Methemoglobin is an oxidized metabolite of hemoglobin, and its normal physiologic level is (< 1%). Abnormality occurs as methemoglobin levels increase. Methemoglobinemia occurs when red blood cells (RBCs) contain methemoglobin at levels higher than 1%. This may be from congenital causes, increased synthesis, or decreased clearance, and acquired causes. Increased levels may also result from exposure to toxins that acutely affect redox reactions, increasing methemoglobin levels. A 49 year old male a known chronic kidney disease patient, whose blood sample sent for biochemical analysis showed dark brown (chocolate brown) serum. On analysis the patient found to have methemoglobinemia. His arterial methemoglobin level of 22%. Going into detailed history he was found to be using Inj.metaclopromide for gastroesophageal reflux, though it is rarely reported to cause methemoglobinemia in adults compared to infants. He was treated with dialysis, cautious use of methylene blue and his clinical symptoms improved and the methemoglobin level returned to normal within 24 hours. By analysing this case we discuss the clinical features, diagnosis, cause and treatment of acquired methemoglobinemia induced by metoclopramide.

Keywords: Metochlopromide, methemoglobinemia, chronic kidney disease.

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INTRODUCTION

Methemoglobinemia is a condition due to elevated levels of methemoglobin in the blood are caused when the mechanisms that defend against oxidative stress within the red blood cell are overwhelmed and the oxygen carrying ferrous ion (Fe^{2+}) of the heme group of the hemoglobin molecule is oxidized to the ferric state (Fe^{3+}). This leads to convertion of hemoglobin to methemoglobin, resulting in a reduced ability to release oxygen to tissues and thereby hypoxia. This gives the blood a bluish or chocolate-brown color. Spontaneously formed methemoglobin is normally reduced (regenerating normal hemoglobin) by protective enzyme systems, e.g., NADH methemoglobin reductase (cytochrome-b5 reductase) (major pathway), NADPH methemoglobin reductase (minor pathway) and to a lesser extent the ascorbic acid and glutathione enzyme systems. Disruptions with these enzyme systems lead to methemoglobinemia. Metoclopramide is a centrally active anti-emetic drug commonly used both in pediatric and adult age groups. It is frequently used in patients complaining of nausea and vomiting. Several cases of Metoclopramide-induced methemoglobinemia are more common in infants than adults [1-5].

Case Report

A 49 year old male a known case chronic kidney disease developed increased heart rate, dizziness, headache, abdominal pain and mild cyanotic change in skin. His blood sample was taken and sent for biochemical analysis .The blood sample appeared chocolate brown in colour . Serum colour remained brown even after centrifuge for 20 min. He was admitted in ICU. Apart from dialysis he was on oral drugs for Chronic kidney disease and also h/o frequent usage of Inj.metaclopromide for gastro esophageal reflux noted.

Serum Sample of the Patient

Lab Investigations

Arterial methemoglobin level -22%, Hemoglobin – 10.2gm%,pH- 7.56,pCO2- 3.4kpa, pO2- 36.4 kpa, Bicarbonate – 22.6mmol/L, oxygen saturation 79%, Blood glucose- 109mg/dl, Blood urea- 184mg/dl, Serum creatinine – 9.4mg/dl, Liver Function test- Total bilirubin -2.95mg/dl, Direct bilirubin- 2.15mg/dl, Indirect bilirubin- 0.80mg/dl, SGOT -45U/L, SGPT – 64U/L, ALP – 186 U/L, IGT – 96U/L, Total protein – 6.6g/L, Albumin- 3.2 , Globulin – 4.1.

DISCUSSION

Methemoglobinemia due to metaclopromide is a rare complication in adults. The increased frequency of metoclopramide use in recent years makes health care providers to be aware of this potential adverse

effect. In this case, the patient already a known case of chronic kidney disease has used metaclopromide frequently. Methemoglobin is formed when the hemoglobin molecule is oxidized from the normal ferrous (Fe) to the ferric (Fe) state. In normal individuals, the level of methemoglobin is maintained at less than 0.6% by cytochrome b reductase (NADH-dependent methemoglobin reductase). If low levels of this enzyme are present,or if the red blood cells are under excessive oxidative stress, methemoglobin levels may rise.

Normally the methemoglobin level will not exceed 2-3% of the total hemoglobin. In acute cases increases up to 20-30% in methemoglobin levels are tolerated well in patients without anemia, but, an increase to 70% or more is typically fatal. Classical finding of methemoglobinemia is blue-gray cyanosis not responding to oxygen therapy . Acquired methemoglobinemia is mainly due to the excessive production of methemoglobin following exposure to oxidant drugs, chemicals, or toxins such as nitrites, nitrates, chlorates, kinins, aminobenzens, nitrobenzens, nitrotoluenes, phenacetine, chloroquine, dapsone, phenytoin, sulphanomides and local anesthesics.

Metaclopramide or its metabolites have been proved to have a direct oxidizing effect on erythrocytes. Metoclopramide, a derivative of orthoprocainamide, is primarily metabolized (at the first pass through the gut wall or liver) tometoclopramide N-4-sulfate, but as much as 25–40% of the parent compound may undergo renal clearance. Due to chronic kidney disease of the patient the renal clearance of the drug metaclopromide was affected. In addition, CYP2D6 may also be involved in the metabolism of metoclopramide.

Pharmacokinetic of metaclopramide in adults

Data Parameter	**Value**
Vd (L/kg)	~ 3.5
Plasma Protein Binding	~ 30%
t1/2 (hr)	5-6
Oral Bioavailability	80%±15.5%

Renal impairment affects the clearance of metoclopramide.

Treatment

The first step to treat (acquired) metoclopramide induced methemoglobinemia is to stop using the causative agent. Methylene blue may be used, particularly if the methemoglobin levels are markedly elevated or if there are signs of hypoxia. The dose is 1–2 mg/kg of a 1% solution, delivered by slow intravenous infusion, and maybe repeated if needed. Methylene blue is an effective electron acceptor from NADPH-dependent methemoglobin reductase and is converted to leucomethylene blue, which then reduces methemoglobin to hemoglobin. Vitamin C can reduce cyanosis associated with chronic methemoglobinemia but not effective in treatment of acute acquired methemoglobinemia. The serum concentration of methylene blue and leucomethylene blue increases in renal impaired patients [6-10].

In this case patient was started with dialysis, metoclopramide use is discontinued, methylene blue used with caution.

CONCLUSION

Metaclopramide induced methemoglobinemia is very rare in adults, but usage of this drug in renal impairment patients increases the incidence. Patients with kidney disease should use other drugs for gastroesophageal reflux or reduced the dose of the drug.

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