Metoclopramide-induced methemoglobinemia in a patient with co-existing deficiency of glucose-6-phosphate dehydrogenase and NADH-cytochrome b5 reductase: failure of methylene blue treatment

A patient with impaired renal function who was treated with metoclopramide for nausea developed severe cyanosis. The patient was subsequently treated with methylene blue. The expected response was not obtained, and indeed a hemolytic episode occurred. The cause of cyanosis was found to be metoclopramide-induced methemoglobinemia due to NADH cytochrome b5 reductase (b5R) deficiency. The patient was also found to have glucose-6-phosphate dehydrogenase (G6PD) deficiency and was therefore unable to utilize methylene blue in the NADPH- dependent reduction of methemoglobin.

Two types of methemoglobinemia are known: the most common is acquired due to increased oxidative stress of erythrocytes after exposure to drugs and chemicals, the other is hereditary, a rare condition caused by a deficiency of NADH cytochrome b5 reductase (b5R) or abnormal HbM.[1,2] In this communication, we describe a case of methemoglobinemia in an adult Jordanian male (his parents are first cousins) with chronic renal failure given metoclopramide for vomiting and in whom methylene blue treatment failed. Laboratory investigation revealed anemia, 6.6 gr Hb/dL, urea 180 mg%, creatinine 9.4 mg% and normal blood gas analysis (ABG).

Metoclopramide 10 mg was administered intravenously on admission and another dose after 24 hours. The patient developed cyanosis and dyspnea 28 hours after the first administration of metoclopramide. The ABG analysis did not reveal any change. Methemoglobin level was 43% (normal <1.8%). The patient was prescribed ascorbic acid 150 mg/8 hours and methylene blue 60 mg by slow intravenous infusion. The patients' consciousness deteriorated. Administration of methylene blue, 40 mg, was repeated two hours later but his condition deteriorated rapidly and he died twelve hours after the onset of cyanosis.

A blood sample taken a few hours before death was found visually to be considerably hemolysed after centrifugation. Enzymatic measurements were, therefore, performed on whole blood hemolysate instead of washed erythrocytes.

The sample of whole blood was frozen and thawed to lyse the erythrocytes. G6PD and b5R were assayed quantitatively as described by Beutler.[3] The result of the assay showed that the level of b5R was about 8 U/g of Hb at 30°C (mean for control samples prepared similarly from whole blood was 17 U/g of Hb). The whole blood sample was found to be severely deficient in G6PD activity with a residual activity 5-10% of normal. Based on the level of b5R activity, we suggest the patient was heterozygous for b5R deficiency.

Metoclopramide is known to cause methemoglobinemia in newborn and premature babies.[1,2,4] A renally excreted metabolite of metoclopramide is believed to be the agent causing methemoglobinemia.[5] Infants and premature babies are more susceptible to metoclopramide toxicity because of their immature renal function and lower b5R activity.[1,2,5] Methemoglobenmia has been reported as a side-effect of metoclopramide administration in adults in only two cases.[6,7] Our patient had reduced b5R activity and impaired renal function which together contributed to the development of severe methemoglobinemia upon administration of metoclopramide. The decreased reductive capacity of the erythrocytes due to the decreased activity of b5R together with the increased oxidative stress of metoclopramide due to reduced renal clearance, induced methemoglobinemia in our patient.

Administration of ascorbic acid cannot be expected to improve methemoglobinemia because it acts slowly and is, therefore, not generally recommended for treatment of acquired severe methemoglobinemia. On the other hand, a single dose of methylene blue 1 mg/kg intravenously, is expected to reduce the methemoglobin concentration within 30-60 minutes to a normal level provided the patient has a level of G6PD activity adequate to provide sufficient amounts of the NADPH required for the methylene-blue stimulated NADPH-methemoglobin reductase system. Our patient had severe G6PD deficiency and therefore did not benefit from methylene blue administration: instead, he probably suffered from a hemolytic episode as judged from the state of the blood sample collected a few hours after methylene blue administration. Methylene blue has been associated with hemolysis in G6PD-deficient subjects[8] though the dosage causing hemolysis was about 3.5 times higher than that which our patient received. Our case represents the second reported patient in literature with a combined deficiency of G6PD and b5R[9] and the third case of co-existence of G6PD deficiency and inherited[9] or drug-induced[8] methemoglobinemia.

In conclusion, metoclopramide should be used with caution in patients with impaired renal function. Patients with severe methemoglobinemia, whether acquired or inherited, should be checked for G6PD deficiency, especially if they belong to any race known for its relatively high incidence of G6PD deficiency, before the administration of methylene blue. The adminstration of methylene blue in such circumstances cannot be expected to be of any benefit, but rather, can be expected to initiate a hemolytic episode.

Naif S. Karadsheh, Qandil Shaker,° Basem Ratroat °*

**Department of Biochemistry and Physiology,*
°Department of Internal Medicine, Faculty of Medicine,
University of Jordan, Amman, Jordan

Key words: methemoglobinemia, metoclopramide, G6PD , NADH-cytochrome b5 reductase.

Correspondence: Naif S. Karadsheh, Ph.D., Professor and Chairman, Department of Biochemistry & Physiology, Faculty of Medicine, University of Jordan, Amman, Jordan. Fax: international +962-6-5355511 – E-mail: nsohk@yahoo.com

References

1. Hultquist DE. Cytochrome b5 reductase deficiency and enzymatic hereditary methemoglobinemia. In: Scriver CR, Beaudet Al, Sly Ws, Valle D, editors. The Metabolic and Molecular Basis of Inherited Disease. New York: McGraw-Hill; 1995. p. 3399.
2. Griffin JP. Methaemoglobinaemia. Adv Drug React Toxicol Rev 1997; 16:45-63.
3. Beutler E. Red Cell Metabolism: a manual of biochemical methods. 3rd ed. New York: Grune & Stratton; 1984.
4. Kearns GL, Fiser DH. Metoclopramide-induced methemoglobinemia. Pediatrics 1988; 82:364-6.
5. Zanesco L, Caril M. A metoclopramide metabolite with a methemoglobinizing action. Act Pediatr Lat 1970; 23:34-9.
6. Mary AM, Bhupalam L. Metoclopramide-induced methemoglobinemia in an adult. J Ky Med Assoc 2000; 98:245-7.

7. Grant SC, Close JR, Bray CL. Methaemoglobinaemia produced by metoclopramide in an adult. Eur J Clin Pharmacol 1994; 47:89.
8. Rosen PJ, Johnson C, McGehee WG, Beutler E. Failure of methylene blue treatment in toxic methemoglobinemia. Association with glucose-6-phoshate dehydrogenase deficiency. Ann Intern Med 1971; 75:83-6.
9. Neimann N, Dreyfus JC, Pierson M, Ducas J, Stoessel JM. La methemoglobinemie congenitale et recessive. Son association avec le deficiet en glucose 6 phosphate deshdrogenase et la thalassemie minure. Rev Fr Etud Clin Biol 1963; 8:757-64.