JEURMEDS

J Eur Med Sci 2024;5;(3):68-71

Case Report

DOI: 10.4274/jeurmed.galenos.2025.43531

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Glucose-6-Phosphate Dehydrogenase Deficiency: Case Report

Glukoz-6-Fosfat Dehidrogenaz Eksikliği: Olgu Sunumu

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ABSTRACT

A Glucose-6-phosphate dehydrogenase (G6PD)-deficient patient, therefore, lacks the ability to protect red blood cells against oxidative stresses from certain drugs, metabolic conditions, infections, and ingestion of fava beans. Numerous drugs, infections, and metabolic conditions have been shown to cause acute hemolysis of red blood cells in the G6PD-deficient patient, with the rare need for blood transfusion. The most effective management strategy is to prevent hemolysis by avoiding oxidative stressors. This report presents a case of general anesthesia management in a patient with G6PD deficiency. A 28-year-old male with G6PD deficiency was scheduled for plastic surgery operation under general anesthesia with total intravenous anesthesia (TIVA) including propofol and remifentanyl. The intraoperative and postoperative course was uneventful with respect to hemolytic problems, malignant hyperthermia or methemoglobinemia. We think that general anesthesia with TIVA can be performed successfully with special attention in patients with G6PD deficiency.

Keywords: Glucose-6-phosphate dehydrogenase deficiency, TIVA, general anesthesia

ÖZ

Glukoz-6-fosfat dehidrojen (G6PD) eksikliği olan hastalarda belirli ilaçların, metabolik durumların, enfeksiyonların ve bakla bitkisinin sindiriminin yol açtığı oksidatif strese karşı eritrositleri koruma yeteneği eksiktir. G6PD eksikliği olan hastalarda pek çok ilacın, enfeksiyonların ve metabolik durumların kırmızı kan hücrelerinde, nadiren kan transfüzyonu gerektiren, akut hemolize yol açtığı bilinmektedir. Hemolizi önlemede en etkin yönetim stratejisi oksidatif stresörlerden kaçınmaktır. Bu yazıda, G6PD enzim eksikliği olan bir hastadaki genel anestezi uygulaması sunuldu. Yirmi sekiz yaşındaki erkek hastaya plastik cerrahi operasyonu için propofol ve remifentanil içeren total intravenöz anestezi (TİVA) ile genel anestezi uygulandı. Ameliyat ve ameliyat sonrası dönem sorunsuz seyretti. Hemolitik sorunlar, malign hipertermi veya methemoglobinemi görülmedi. G6PD enzim eksikliği olan olgularda, özel dikkat ile TİVA'nın güvenle uygulanabileceğini düşünmekteyiz.

Anahtar Kelimeler: Glukoz-6-fosfat dehidrogenaz eksikliği, TİVA, genel anestezi

INTRODUCTION

The case was a 28-year-old male patient, weighing 83 kilograms, with a soft tissue mass in the left pectoral region and was planned to be operated by the plastic surgery clinic for breast and adipose tissue excision. From his medical history, it was learned that glucose-6-phosphate dehydrogenase (G6PD) deficiency was diagnosed at the age of 10 years following the development of abdominal pain and icterus following the ingestion of fava beans.

CASE REPORT

Physical examination revealed normal findings

In the preoperative laboratory examination, G6PD enzyme level was measured quantitatively as 2.4 IU/g hemoglobin (Hb) (4.6-13.5 IU/g Hb). Hb was 15.4 g/dL, hematocrit 45.6%, total bilirubin 1.4 mg/dL, direct bilirubin 0.1 mg/dL, lactate dehydrogenase (LDH) 10^3 U/L, uric acid 5.2 mg/dL, erythrocyte 5.150/mm³, platelet 165.000/mm³, international normalized ratio 1.26 mm³. No erythrocytes, Hb, bilirubin and urobilinogen were detected in the urine. Electrolyte and renal function test values were within normal limits.

After routine preparation, the patient was premedicated with 2.5 mg midazolam i.v. after 2 mg/kg propofol induction, the patient was intubated with 0.6 mg/kg rocuronium. Anesthesia maintenance was performed with 60% N_2O + 40% O_2, 10-15 mcg/kg/h remifentanil + 2-3 mg/kg/h propofol dose range with total intravenous anesthesia (TIVA). No additional muscle relaxant was administered to the patient throughout the operation. After 70 minutes of operation, a mixture of 2.5 mg neostigmine + 1 mg atropine sulfate was given to eliminate residual neuromuscular blockade. Morphine 1 mg/kg intravenously was administered intraoperatively for postoperative analgesia. The patient was hemodynamically

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Received: 11.02.2025 **Accepted:** 19.02.2025 **Publication Date:** 17.03.2025

Cite this article as: Laflı Tunay D. Glucose-6-phosphate dehydrogenase deficiency: case report. J Eur Med Sci. 2024;5;(3):68-71

stable in perioperative and postoperative follow-up, no respiratory problems and no adverse reactions to the drugs used were observed. The patient was discharged on the 3rd postoperative day without any problem in the ward follow-up.

DISCUSSION

G6PD deficiency is the most common enzymatic and X-linked disorder of red blood cells in humans. It is estimated that about 400 million people are affected by this deficiency (1). The highest prevalence of G6PD deficiency is reported in Africa, Southern Europe, the Middle East, South East Asia, and the central and Southern Pacific islands; however, because of migration, it is becoming more common all over the word (2). The G6PD enzyme catalyzes the first step in the pentose phosphate pathway, leading to antioxidants that protect cells against oxidative damage (3,4). The enzyme G6PD catalyzes the first step of the pentose phosphate pathway (Figure 1). The pentose phosphate pathway enables the formation of ribose-5-phosphate, a precursor of RNA, DNA, Adenosine Triphosphate, Coenzyme A, Nicotinamide Adenine Dinucleotide and Flavin Adenine Dinucleotide, from glucose and mediates the formation of Nicotinamide Adenine Dinucleotide Phosphate (NADPH). NADPH enables the reduction of glutathione in the cell. Reduced glutathione functions as an antioxidant and protects the cell against oxidative damage (5). In many cells, NADPH is also produced via other metabolic pathways, whereas in red blood cells there are no other metabolic pathways that produce NADPH, so G6PD enzyme deficiency results in a lethal state where any oxidative stress, especially in red blood cells, leads to hemolytic anemia. Some metabolic conditions such as ingestion of fava beans, certain drugs, infections and diabetic ketoacidosis can lead to oxidative stress (6). Acute intravascular hemolysis occurs 2-3 days after exposure to oxidative stressors. Hemolysis can be diagnosed by the presence of symptoms such as fatigue, dyspnea, lumbar or substernal pain. The patient may have tachycardia, cyanosis, pallor, icterus, and dark brown urine color. Laboratory evaluation may reveal anemia due to hemolysis, reticulocytosis, decreased serum haptoglobulin, increased indirect bilirubin level and LDH. Heinz bodies (denatured Hb accumulation in red blood cells) and schizocytosis may be observed in peripheral smear. Urinalysis shows hemosiderin, urobilinogen and brown urine. Since G6PD is not an autoimmune condition, Coombs test is negative. G6PD enzyme level in red blood cells and Heinz body detection are specific tests. "The Beutler enzyme spot test" is the diagnostic test for G6PD deficiency (7,8).

Hemogram and routine biochemical tests including indirect bilirubin, uric acid and LDH were performed once a day for three days to show hemolytic episode in the postoperative period. Since no clinical findings of hemolytic anemia and no abnormal values were found in the laboratory tests for three days, no additional tests were performed. At the outpatient clinic visit on the 7th postoperative day, the patient's complete blood count and biochemical tests were evaluated as normal.

The World Health Organization has classified G6PD enzyme deficiency into five classes according to enzyme activity level and clinical findings;

Class I: Enzyme activity is 10% below normal and chronic hemolytic anemia is observed.

Class II: Severe enzyme deficiency is present and intermittent hemolytic anemia (secondary to drugs, infection and chemicals) is usually detected.

Class III: Moderate (10-60%) enzyme deficiency and intermittent hemolytic anemia.

Class IV: Enzyme deficiency and hemolysis are not present.

Class V: Enzyme activity is high. Class IV and V have no clinical significance (9).

Since the enzyme level in our patient was 2.4 IU/g Hb (4.6-13.5 IU/g Hb), the patient was considered to have a moderate enzyme deficiency.

Altikat et al. (10) conducted studies to show the effects of many drugs, chemicals and anesthetic agents on G6PD enzyme activity. In the study conducted by Altikat et al. (10), it was suggested that anesthetic agents such as halothane, isoflurane, ketamine, sevoflurane, prilocaine, diazem and midazolam were effective on G6PD enzyme activity and especially sevoflurane, isoflurane, diazem and midazolam had inhibitory effects; however, it was reported that more studies should be conducted on the subject. Another study by Büyükokuroğlu and Süleyman (11) showed that diazepam and midazolam had inhibitory effects on G6PD enzymatic

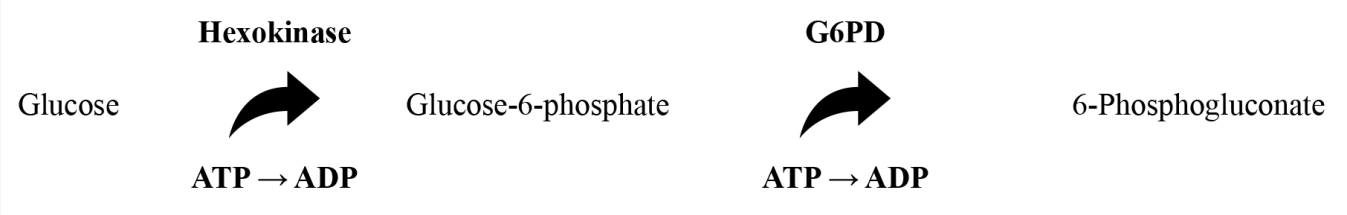

Figure 1. Hexose monophosphate shunt
G6PD: Glucose-6-phosphate dehydrogenase, ATP: Adenosine triphosphate, ADP: Adenosine diphosphate

Table 1. Drugs and chemicals causing hemolysis in G6PD deficiency		
Unsafe for classes I, II and III	**Safe for class II and III**	
Acetanilid	Acetaminophen	Pyrimethamine
Dapsone	Aminopyrine	Quinidine
Methylene blue	Ascorbic acid	Quinine
Nalidixic acid	Aspirin	Sulfamethoxypyridazine
Nitrofurantoin	Chloramphenicol	Streptomycin
Niridazole	Chloroquine	Sulfisoxazole
Primaquine	Colchicine	Trimethoprim
Toluidine blue	Diphenhydramine	Tripelennamine
Vitamin K	Isoniazid	Halothane
Sulfacetamide	L-DOPA	Prilocaine
Sulfamethoxazole	Menadione	Ketamine
Sulfanilamide	Paraminobenzoic acid	Fentanyl
Phenylhydrazine	Phenacetin	Propofol
Furazolidone	Phenytoin	Benzodiazepam (except diazepam)
Trinitrotoluene	Probenecid	
Toluidine blue	Procainamide	
G6PD: Glucose-6-phosphate dehydrogenase		

activity *in vitro* and increased the severity of hemolysis when used together with isofluorane and sevofluorane. Table 1 shows the list of safe and unsafe drugs resulting from these *in vitro* studies (6-12).

However, no cases have been reported showing that benzodiazepine, codeine/codeine derivatives, propofol, fentanyl or ketamine cause hemolytic crisis in vivo in patients with G6PD deficiency (13). However, studies on hemolytic crisis caused by inhalational anesthetic agents are still ongoing, especially some autonomists associate G6PD deficiency with malignant hyperthermia. In fact, there are not enough studies on the effects of inhalational anesthetic agents on patients with G6PD enzyme deficiency (13). These drugs interact with Hb and oxygen, leading to the intracellular formation of hydrogen peroxide and other oxidant radicals. These oxidant radicals accumulate in cells with enzyme deficiency, leading to oxidation of Hb and other proteins, thus leading to loss of function and cell death (6-14).

In our case, which was planned to be operated under general anesthesia, we preferred TIVA containing propofol and remifentanil as general anesthetic. We used midazolam for premedication, propofol for induction and rocuronium for intubation. We administered morphine as analgesic. We did not observe any side effects to any of the drugs.

In a study conducted by Ozmen et al. (14), the effects of analgesic agents such as remifentanil hydrochloride, fentanyl citrate, alfentanil hydrochloride and pethidine hydrochloride on G6PD activity were investigated. Although remifentanil hydrochloride and fentanyl citrate inhibited G6PD enzyme activity in healthy individuals, it was found that enzyme activity did not change in two of the three individuals with G6PD deficiency included in the study, and alfentanil hydrochloride and pethidine hydrochloride had no effect on enzyme activity in both healthy individuals and those with G6PD deficiency. In 2008, Wada et al. (15) reported that midazolam was safely used in induction in a 5-year-old patient diagnosed with G6PD deficiency who underwent laparoscopic cholecystectomy surgery in Japan. In a retrospective study published in 2013 by John et al. (16), all patients were given propofol, pancuronium or suxamethonium, neostigmine, atropine, and amoxicillin. Halothane was administered to 17 patients, isoflurane to 5 patients, fentanyl to 15 patients, pentazocine to 7 patients, midazolam to 4 patients, and diazepam to 18 patients, and no hemolysis was observed in any of the patients during the one-week follow-up period. In the two cases published by Valiaveedan et al. (8), midazolam was used for induction, rocuronium for intubation, and sevoflurane and fentanyl for maintenance without any problems.

CONCLUSION

The most effective management strategy to prevent hemolysis in patients known to have G6PD deficiency is to avoid oxidative stressors (6). Therefore, drugs used to relieve pain and anxiety should be those known to be safe or those that have not been shown to cause hemolytic crisis, such as benzodiazepines, codeine/codeine derivatives, propofol, fentanyl, and ketamine. Any person with a family history of hemolysis, African, Southern European, Middle Eastern, South East Asian, or central and Southern Pacific islander, and any person suspected of having G6PD deficiency should be screened for G6PD deficiency. A person with G6PD deficiency should avoid oxidative drugs and fava beans. Patients at risk

should be informed about the symptoms and signs of acute hemolytic crisis (cyanosis, headache, dyspnea, fatigue, lumbar/substernal pain, jaundice, scleral icterus, and dark brown urine). It should be kept in mind that laboratory findings of hemolysis may appear within 24-72 hours after exposure to the agent, before clinical findings, and that deepening of anemia may extend up to the 7th day. It is difficult to detect hemolytic crisis in day surgery or short-term hospitalizations (less than 24 hours). Therefore, the physician should inform high-risk patients and their relatives about the symptoms and findings of hemolytic crisis. In fact, a short telephone conversation with the patient after discharge will be beneficial for their health. If an acute hemolytic crisis is noticed in a patient, the patient must be hospitalized and monitored with a complete blood count of at least once a day to determine the need for blood transfusion. General anesthesia may mask early findings of hemolysis, and it is quite difficult to detect hemolytic crisis in an anesthetized patient. The presence of free Hb in plasma and urine is possible evidence of a hemolytic reaction. In treatment, the agent thought to cause hemolysis should be stopped immediately, and urine output should be ensured with crystalloid solutions and diuretics such as mannitol and/or furosemide (17).

Ethics

Informed Consent: The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given her consent for his/her/their images and other clinical information to be reported in the journal. The patient understand that her name and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Acknowledgement

The author would like to extend their sincere thanks to anyone who contributed to this study.

Footnotes

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The author declared that this study has received no financial support.

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