General Anesthesia in a Glucose-6-Phosphate Dehydrogenase Deficiency Child: A Case Report

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We performed general anesthesia on a 3-year-old boy with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Patients with G6PD deficiency exhibit jaundice and anemia due to hemolysis caused by a lack of the G6PD enzyme. To maintain anesthesia, we used propofol and remifentanyl, which may prevent hemolytic attacks by exerting an antioxidant effect. In addition, because the patient was in a high-risk group for the development of methemoglobinemia, we used mepivacaine as a local anesthetic. We liaised with the patient's attending physician to make sufficient arrangements, such as securing an emergency transfer on the day of anesthesia. The patient did not develop hemolytic attacks during or after the procedure, and he progressed well without problems.

Key Words: G6PD deficiency; Glucose-6-phosphate dehydrogenase; Methemoglobinemia; Superoxide dismutase.

Glucose-6-phosphate dehydrogenase (G6PD) is an enzyme that plays an important role in maintaining the concentrations of antioxidants in the body. When this enzyme is deficient, excessive oxidative stress can cause acute hemolytic attacks. Oxidative stress can be precipitated by diverse factors, including oxidative drugs and invasive surgeries.¹ Therefore, caution should be exercised when selecting drugs for patients with G6PD deficiency for general and local anesthetic management. Here, we report the case of a 3-year-old patient with G6PD deficiency who underwent outpatient general anesthesia for dental treatment. Informed consent to report the case was obtained from the patient's legal guardian.

CASE PRESENTATION

A 3-year, 7-month-old male child, with weight 22 kg and height 108 cm, presented to us for treatment of caries. The patient had been diagnosed with G6PD deficiency at birth. He had no history of acute hemolytic attacks,

any other illnesses, or allergies and was not under any medication treatment. As the patient was uncooperative during examination, we scheduled him for caries treatment under general anesthesia.

Preoperative blood tests revealed normal indirect bilirubin, potassium, and lactic acid dehydrogenase values. In addition, his hemoglobin count was normal, 11.9 g/dL. We observed no physical signs indicating hemolysis, including jaundice. Electrocardiogram and chest X-ray were unremarkable.

We did not administer any medication prior to anesthesia. Intraoperative monitoring included oxygen saturation, electrocardiogram, noninvasive blood pressure, capnography, and body temperature. Anesthesia was gradually induced with 5% sevoflurane and oxygen at 6 L/min. Following anesthesia induction, intravenous access was secured, and 14 mg of rocuronium bromide was administered to facilitate intubation, which was performed without difficulty. Anesthesia was maintained with oxygen 1 L/min, air 2 L/min, propofol 8–10 mg/kg/h (133–166 µg/kg/min), and remifentanyl 0.2–0.3 µg/kg/min. The patient received pressure-controlled ventilation with a peak inspiratory pressure of 17 cm H₂O, respiratory rate was 16 breaths per minute, and inspiration to expiration ratio was 1:2. During the operation, the end-tidal CO₂ was maintained at 33–35 mm Hg. Dental treatment involved 8 dental restorative procedures including pulpectomy with a total of 3.6 mL of mepivacaine used. Bispectral index levels fluctuated between 45 and 65, without the detection of any

Received August 3, 2017; accepted for publication August 14, 2018.

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Anesth Prog 66:94–96 2019 | DOI 10.2344/anpr-66-01-05

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abnormalities, and the patient was extubated under deep anesthesia to minimize stress and avoid delirium. After adequate recovery, the patient was transferred to the ward of our dental hospital. The time under anesthesia was 2 hours 43 minutes, and the dental treatment lasted for 1 hour 52 minutes. We observed no increase in potassium, lactic acid dehydrogenase, or indirect bilirubin in the blood tests performed following the dental treatment. In addition, no signs of anemia were noted. Accordingly, the patient was discharged on the same day. We followed up with the patient's family daily for 3 days postoperatively via the telephone, with no issues reported.

DISCUSSION

G6PD deficiency is an X-linked recessive genetic disease that exhibits symptoms including acute hemolytic attacks, jaundice, and anemia due to the oxidation of hemoglobin following impaired defense of red blood cells against oxidative stress caused by the lack of G6PD.¹ The main function of G6PD is to reduce nicotinamide adenine dinucleotide phosphate (NADP) to NADPH (reduced form of NADP), which is essential for maintaining the concentrations of reduced glutathione, the main erythrocyte antioxidant. Since red blood cells lack mitochondria, the supply of NADPH depends on the pentose phosphate pathway. Therefore, if the production of NADPH is impaired due to abnormalities in G6PD, which is the rate-limiting enzyme of the pathway, the concentration of reduced glutathione decreases, thus causing hemolysis under oxidative stress conditions. Thus, patients with G6PD deficiency cannot use antioxidant antimalarial drugs or naphthalenes and should avoid ingesting broad beans. G6PD deficiency is classified into Class I to V based on red blood cell G6PD activity. The prevalence of G6PD deficiency differs with the geographical location. Rates of 10–20% are reported in Africa, Southern Europe, and the Middle East. Approximately 400 million people worldwide are known to carry the genetic abnormality. In this case report, the patient's mother was Cambodian, and his father was Nepalese. In Cambodia, the country of birth of the patient, the prevalence of G6PD deficiency is high; therefore, screening tests are conducted at birth, and the patient was diagnosed with the deficiency at birth.

The most important aspect of anesthetic management in patients with G6PD deficiency is to reduce oxidative stress to avoid hemolysis. We induced anesthesia gradually with sevoflurane, while maintaining it with propofol and remifentanyl. Since sevoflurane has been shown to inhibit G6PD activity *in vitro*,² propofol was selected for maintaining anesthesia as it has a phenol

ring and exhibits potent antioxidant activity, comparable to vitamin E,^{3,4} with no documented cases of hemolytic attacks with use in patients with G6PD deficiency *in vivo*. Remifentanyl directly increases the levels of superoxide dismutase, which is an oxidative stress inhibitor that suppresses cytotoxicity by inhibiting the production of active ("radical") oxygen species, independent of the sympathetic nervous system.⁵ Based on its antioxidant property, we believed that remifentanyl would be appropriate for patients with G6PD deficiency. Hence, sevoflurane was used only for the brief induction of anesthesia, while propofol and remifentanyl were used for its maintenance.

Methemoglobinemia is also a concern in patients with G6PD deficiency. Methemoglobin is reduced by reduced glutathione in the presence of NADPH. Therefore, patients with G6PD deficiency, with resultant deficient NADPH supply, have a greater tendency to develop methemoglobinemia.^{6,7} It is known that methylene blue, which is used for the treatment of methemoglobinemia, does not show a complete response in patients with G6PD deficiency. The reason is that NADPH is necessary for the activity of methylene blue as a reducing agent. In addition, since methylene blue is an oxidant, it cannot be used in patients with G6PD deficiency, with the inability to form reductants. Furthermore, it has been reported that prilocaine and lidocaine can occasionally cause methemoglobinemia.⁸ Prilocaine and lidocaine have similar structural formulas with an additional methyl group in lidocaine at the *o*-position of the amino group of the benzene nucleus. Since the ability to form methemoglobin is related to the number of methyl groups, lidocaine can be more stable against hydrolysis while minimally forming methemoglobin. Prilocaine has a much greater tendency than does lidocaine to cause methemoglobinemia as its primary metabolite, *O*-toluidine, oxidizes hemoglobin. Clinical symptoms may not manifest unless high doses are used because of the effects of primary reducers of methemoglobin, NADH and NADPH methemoglobin reductase. Therefore, the use of local anesthetics that can induce methemoglobinemia, such as prilocaine and, to a lesser degree, lidocaine, from among the dental local anesthetics used in Japan (lidocaine, prilocaine, mepivacaine) should be avoided in patients with G6PD deficiency.^{2,9} As pulpectomy treatment was required, we used mepivacaine for local anesthesia. We observed no methemoglobinemia throughout the perioperative period in our case, suggesting that mepivacaine was used safely in this patient with G6PD deficiency. In addition, benzocaine and nitroglycerin are also known to cause methemoglobinemia and should be avoided in patients with G6PD deficiency.

The most common cause of hemolysis in patients with G6PD deficiency is infections. Quereshy et al⁸ reported cases of patients with G6PD deficiency who developed hemolytic anemia secondary to maxillofacial infection caused by severely decayed teeth. Although the present case merely involved restorative dental treatment, when treating dental or orofacial infections, examination of the general condition of the patient, including jaundice, should be taken into consideration as the patient may already be in a hemolytic state.

In addition, as acetanilide, a historic analgesic and antipyretic agent, can reportedly trigger hemolytic attacks, it is necessary to select analgesics that do not exhibit oxidative activity. There are several reports suggesting that the acetanilide metabolite, acetaminophen, the agent responsible for acetanilide's analgesic/antipyretic action, can be administered safely if recommended doses are not exceeded.^{6,9} A report indicated that high-dose acetaminophen caused methemoglobinemia, and hence, overdose should be avoided. Other reports suggest that short-term administration of nonsteroidal anti-inflammatory drugs and opioids in therapeutic dosages did not increase the risk of hemolysis in children with G6PD deficiency,¹¹ thus making their use appropriate in this patient population as they do not increase oxidative stress or cause methemoglobinemia. In this case, since the need for postoperative pain relief was low and the patient was a child, we selected acetaminophen. In addition, it is known that antimalarials, sulfonamides, and quinolones are drugs with definite risks.

In patients with G6PD disorders, clinical signs and symptoms of hemolysis typically occur between 24 and 72 hours following drug administration and include jaundice, cyanosis, headache, fatigue, tachycardia, dyspnea, and hemoglobinuria.^{12,13} We believe that a same-day outpatient general anesthetic in patients with G6PD deficiency would benefit from a preplanned emergency hospital admit arrangement during a post-discharge 72-hour follow-up period. In the present case, we liaised with the attending physician to arrange for this and followed-up with the patient's family via telephone daily for 3 days following his discharge, to monitor for the development of any hemolytic attacks.

CONCLUSION

We have described the case of a same-day outpatient general anesthetic management in a patient with G6PD

deficiency. For patients with G6PD deficiency, drugs that reduce oxidative stress such as propofol and remifentanyl can be useful. In addition, mepivacaine may be a safer option for local anesthesia than prilocaine, lidocaine, or articaine.

Conflicts of Interest

All authors declare that there are no conflicts of interest relevant to the publication of this article.

REFERENCES

1. Smith CL, Snowdon SL. Anaesthesia and glucose-6-phosphate dehydrogenase deficiency: a case report and review of the literature. *Anaesthesia*. 1987;42:281–288.
2. Altikat S, Ciftçi M, Büyükkuroğlu ME. In vitro effects of some anesthetic drugs on enzymatic activity of human red blood cell glucose 6-phosphate dehydrogenase. *Pol J Pharmacol*. 2002;54:67–71.
3. De Flora A, Benatti U, Guida L, Forteleoni G, Meloni T. Favism: disordered erythrocyte calcium homeostasis. *Blood*. 1985;66:294–297.
4. Lau HK, Li CH, Lee AC. Acute massive haemolysis in children with glucose-6-phosphate dehydrogenase deficiency. *Hong Kong Med J*. 2006;12:149–151.
5. Hartman N, Zhou H, Mao J, et al. Characterization of the methemoglobin forming metabolites of benzocaine and lidocaine. *Xenobiotica*. 2017;47:431–438.
6. Elyassi AR, Rowshan HH. Perioperative management of the glucose-6-phosphate dehydrogenase deficient patient: a review of literature. *Anesth Prog*. 2009;56:86–91.
7. Hegedus F, Herb K. Benzocaine-induced methemoglobinemia. *Anesth Prog*. 2005;52:136–139.
8. Quereshy FA, Gold ES, Powers MP. Hemolytic anemia in a glucose-6-phosphate dehydrogenase-deficient patient triggered by a maxillofacial infection. *J Oral Maxillofac Surg*. 2000;58:805–807.
9. Beutler E. Glucose-6-phosphate dehydrogenase deficiency. *N Engl J Med*. 1991;324:169–174.
10. Kobayashi T. Methemoglobinemia induced by combined use of sodium nitrate and acetaminophen. *Intern Med*. 2000;39:860.
11. Najafi N, Van de Velde A, Poelaert J. Potential risks of hemolysis after short-term administration of analgesics in children with glucose-6-phosphate dehydrogenase deficiency. *J Pediatr*. 2011;159:1023–1028.
12. Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. *Lancet*. 2008;371:64–74.
13. Stoelting RK, Miller RD. *Basics of Anesthesia*. 5th ed. Philadelphia, Pa: Churchill Livingstone; 2007:361.