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Glucose-6-phosphate dehydrogenase deficiency and cardiac surgery

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Abstract

Cardiac surgery involving cardiopulmonary bypass (CPB) in its conventional form involves many processes leading to free radical production, such as perioperative ischemia, reperfusion, circulation of whole body blood through the CPB circuit, hypothermia and acidosis. The red blood cells of a glucose-6-phosphate dehydrogenase (G6PD)-deficient person are unable to scavenge these free radicals, resulting in haemolysis. Here, we describe the successful anaesthetic management of two G6PD-deficient children who underwent cardiac surgery, on and off CPB, without any obvious haemolytic reaction, followed by a discussion of the disorder, with specific consideration of perioperative management of such cases.

Keywords

G6PD deficiency; cardiac surgery; cardiopulmonary bypass; anaesthesia; haemolysis

Introduction

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the commonest enzymatic disorder of red blood cells (RBC) in humans, affecting about 400 million people all over the world[1]. The G6PD enzyme catalyzes the first step in the pentose phosphate pathway, leading to production of antioxidants.[2] A G6PD-deficient patient lacks the ability to protect RBC against oxidative stresses from certain drugs, metabolic conditions, infections, and ingestion of fava beans.[3] Perioperative ischemia, reperfusion, circulation of whole body blood through the cardiopulmonary bypass (CPB) circuit, hypothermia, acidosis, hypoperfusion and hyperperfusion are all events that commonly occur during cardiac operations[4,5], leading to increased production of free radicals[6-8]. The RBC of G6PD-deficient people are unable to scavenge these free radicals, resulting in haemolysis. Preoperative administration of free radical scavengers reduces postoperative haemolysis and inflammatory response after open heart procedures[9-11]. Here, we describe the anaesthetic management of two G6PD-deficient children who underwent cardiac surgery at our institute, followed by a discussion of the disorder, with specific consideration of possible consequences following CPB.

Case history 1: A six-year-old male child presented with a history of repeated cough and fever, off and on since childhood. He was diagnosed with G6PD deficiency (enzyme activity 35-40%) at the age of one year, after an episode of fever, and was referred for evaluation of continuous precordial murmur to the Cardiology Department. Preoperative echocardiography revealed an 11-mm perimembranous ventricular septal defect (VSD) with peak gradient of 48 mmHg and a 2-mm patent ductus arteriosus (PDA) with left to right shunt. Drugs known to cause haemolysis in G6PD-deficient patients, such as preoperative vitamin K, sevoflurane for induction, and isoflurane for initiation and maintenance of anaesthesia were avoided (Table 1). Morphine and propofol infusions were used for induction and maintenance of anaesthesia. Vecuronium was used for muscle relaxation. Epsilon amino caproic acid (EACA) was given to minimize blood loss. CPB was instituted by standard cannulation and the patient was cooled to 32° Celsius. Antegrade intermittent hypothermic blood cardioplegia was used for myocardial protection. PDA clipping and VSD closure

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were done and the patient was weaned from CPB. Postoperatively, in addition to standard post cardiac surgery evaluation, laboratory parameters such as fall in haemoglobin, rise in reticulocyte count, rise in lactate dehydrogenase (LDH) levels, total and conjugated bilirubin and urine examination for free haemoglobin were studied. No signs of active haemolysis, such as hypotension, tachycardia, haemoglobinuria and scleral icterus, were detected in the intensive care unit (ICU), subsequently, and no blood products were administered. The patient was discharged on the ninth postoperative day.

Case history 2: A three-and-a-half-year-old male child presented with a complaint of high coloured urine for five days. He was diagnosed with G6PD deficiency (enzyme activity 35-40%) at the age of two years. The patient had a PDA for which coil occlusion was performed. Post procedure, the patient had evidence of intravascular haemolysis. Post device closure, preoperative echocardiography and cardiac catheterization revealed residual flow across the PDA. Investigations revealed evidence of active haemolysis and anaemia (haemoglobin of 6.6 mg/dL) which was corrected by blood transfusion to 10 mg/dL.

Drugs known to cause haemolysis in G6PD-deficient patients were avoided. Induction and maintenance of anaesthesia was performed with halothane and fentanyl. Vecuronium was given to facilitate tracheal intubation. EACA was given to minimize blood loss.

Following left thoracotomy, the PDA (~ 4-5 mm diameter) was snugged. Aortic cross-clamping, followed by descending thoracic aortotomy at the origin of PDA and coil retrieval, were performed off bypass under normothermic conditions. No signs of active haemolysis, as mentioned above, were detected in ICU, subsequently, and no blood products were administered. The patient was discharged on the ninth postoperative day.

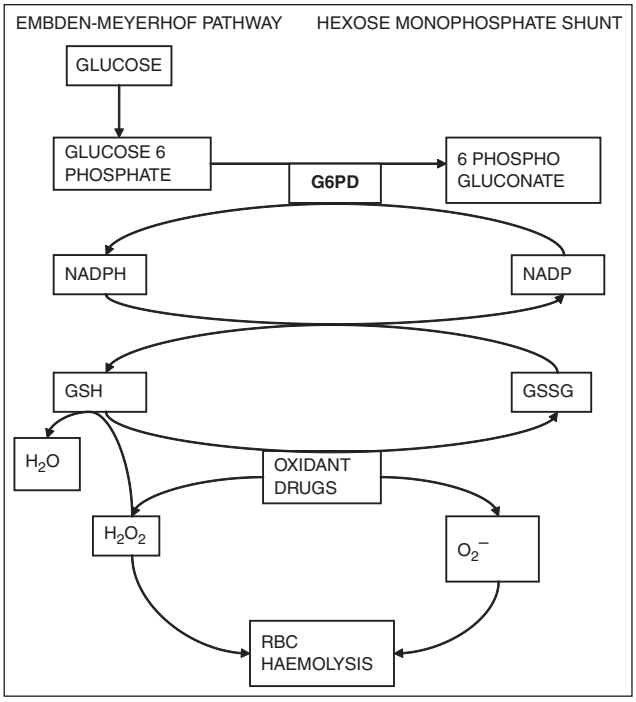

Figure 1. Schematic illustration of oxidant protection in red blood cells involving the regeneration of NADPH and glutathione via the Embden-Meyerhof pathway and the hexose monophosphate shunt.

Discussion

G6PD deficiency is inherited in a sex-linked fashion. The most common of the G6PD deficiency variants is the A-form seen in subjects of African descent. The other common variants of G6PD deficiency are the Mediterranean and Oriental forms which behave in a similar manner[12]. G6PD is an enzyme that catalyzes the first step in the pentose phosphate pathway(PPP) (Figure 1). The PPP includes the creation of nicotineamide adenine dinucleotide phosphate (NADPH) which maintains the reduced glutathione within the cell which serves as an antioxidant. Unlike other cells, RBC do not have the other NADPH-producing metabolic pathways, making them especially susceptible to oxidative stress, resulting in haemolytic anaemia.

The World Health Organization has classified the different G6PD variants as follows[3,13]:

Class I: severe enzyme deficiency (≤10% of normal); chronic haemolytic anaemia;
Class II: severe enzyme deficiency, intermittent haemolysis;
Class III: moderate enzyme deficiency (10 to 60% of normal); intermittent haemolysis;
Class IV: mild enzyme deficiency or haemolysis;
Class V: increased enzyme activity.

Both of our patients belonged to category III, with enzyme activity between 35-40%.

The severity of haemolysis in G6PD-deficient patients depends on the amount of the offending agent and the enzymatic activity of the patient. A number of drugs, as listed in Table 1[3,14-16], can precipitate haemolysis in G6PD-deficient subjects by producing free oxygen radicals. These oxidants accumulate within enzyme-deficient cells, leading to loss of function and cell death[3,14-17]. Altikat et al. studied the effects of certain anaesthetic agents on the enzymatic activity of G6PD (Table 1). They found that, although isoflurane, sevoflurane, diazepam and midazolam had an inhibitory effect on G6PD activity in vitro, halothane, ketamine, and prilocaine had none. No documentation shows that codeine, benzodiazepines, propofol, fentanyl, or ketamine can cause haemolytic crisis in the G6PD-deficient patient in vivo. Nevertheless, haemolytic crises induced by inhalational general anaesthetic agents

are still being studied, especially because some authors have related G6PD deficiency to malignant hyperthermia[18]. Vitamin K, administered routinely before cardiac surgery, should be avoided[3,14,15].

Institution of CPB activates the inflammatory responses with the production of oxygen derived free radicals, leading to endothelial injury[4.5]. Apparently, the lungs are the main organ affected by this damage[19]. Consequently, these patients lose pulmonary oxygenation reserve compared with normal individuals. A study by Gerrah et al. indicates that CPB is a causative factor for hypoxia in G6PD-deficient patients, leading to increased haemolysis[19].

Hypothermia, commonly instituted during cardiac surgery, is also a risk factor for haemolysis in G6PD-deficient patients. Gerrah et al., in their study of 42 patients, described a positive correlation between hypothermia and postoperative haemolysis[19]. The mean temperature during bypass in the study group was 26.7 ± 2.4 degrees Celsius. In our patients, the nasopharyngeal temperature was 32 -34 degrees Celsius during bypass and our patients did not show any signs of haemolysis.

There have been no reports evaluating the safety of antifibrinolytic or antiproteolytic agents on haemolysis and cell injury in G6PD-deficient patients. We used EACA in both our patients and did not observe any signs of haemolysis, but studies with larger sample size are required in this direction to demonstrate conclusively any benefit.

Perioperative acidosis and hyperglycaemia should be treated vigorously [20].

Leukocyte-depleted blood and pyruvate have been shown to decrease the free radical-mediated reperfusion injuries in cardiac surgeries in some studies[21,22]. However, their effect in patients with G6PD deficiency needs to be established.

Drugs, such as lidocaine, prilocaine and silver nitrate, which are known to induce methaemoglobinaemia, should also be avoided[23]. Methylene blue is ineffective for treating methaemoglobinaemia in patients with G6PD deficiency who may require exchange transfusion or hyperbaric therapy, because these patients lack the ability to return haemoglobin to the ferrous form[24]. It may also lead to severe haemolytic anaemia due to its weak oxidizing ability.

General anaesthesia typically masks the immediate signs of haemolysis. Treatment of haemolytic reactions consists of discontinuation of the offending agent and maintenance of urine output by infusion of crystalloid solutions, diuretics and alkalization of urine.[25]

An increasing number of cardiac surgeries are being performed without CPB. Taking into account that CPB is more deleterious to G6PD-deficient patients, off-pump bypass operations can not only reduce oxidative stress and inflammation[26], but also the need for perioperative blood transfusion.

Table 1. Safe and unsafe Drugs, Chemicals and Anaesthetic agents in the G6PD-Deficient population

Unsafe for Class I, II, and III	Safe for Class II and III
Acetanilid	Acetaminophen
Dapsone	Aminopyrine
Furazolidone	Ascorbic acid
Methylene blue	Aspirin
Nalidixic acid	Chloramphenicol
Naphthalene	Chloroquine
Niridazole	Colchicine
Nitrofurantoin	Diphenhydramine
Phenazopyridine	Isoniazid
Phenylhydrazine	L-DOPA
Primaquine	Menadione
Sulfacetamide	Paraaminobenzoic acid
Sulfamethoxazole	Phenacetin
Sulfanilamide	Phenytoin
Sulfapyridine	Probenecid
Thiazosulfone	Procainamide
Toluidine blue	Pyrimethamine
Trinitrotoluene	Quinidine
Vitamin K	Quinine
Anaesthetic Agents*	Sulfamethoxpyridazine
Diazepam	Streptomycin
Isoflurane	Sulfisoxazole
Sevoflurane	Tripelennamine
	Trimethoprim
	Anaesthetic Agents*
	Halothane
	Prilocaine
	Ketamine
	Fentanyl
	Propofol
	Benzodiazepines (except Diazepam)

*As per in vitro studies done by Altikat et al.[17]

Postoperative infection is the most common factor inciting haemolysis in G6PD-deficient subjects[27,.28]. Red blood cells are damaged by phagocytosing macrophages in a mechanism similar to that seen with drug-induced haemolysis[29-31]. Diabetic ketoacidosis can also cause destruction of G6PD-deficient red cells[15,28]. Postoperatively, haemolysis is seen 1 to 3 days after contact with the triggering factors. Acute haemolysis is self-limited, but, in rare instances, it can be severe enough to warrant a blood transfusion[32]. Acetaminophen should not be used for postoperative analgesia in G6PD-deficient patients[3,14,15].

Summary

The most effective management strategy is to prevent haemolysis by avoiding oxidative stressors. Therefore, management for pain and anxiety should include medications that are safe, such as benzodiazepines, codeine/codeine derivatives, propofol, fentanyl, and ketamine.

Lysine analogues, like EACA, appear to be safe in G6PD-deficient patients undergoing cardiac surgeries.

In conclusion, we would like to make four particular suggestions:

1. Exposure to oxidative drugs in the G6PD-deficient patient should be avoided.
2. Ketamine, fentanyl, propofol, midazolam, prilocaine and halothane are safe for perioperative use in the G6PD-deficient patient.
3. Use of isoflurane, sevoflurane and diazepam should be avoided in the G6PD-deficient patient.
4. Perioperative hypothermia, acidosis, hyperglycaemia and postoperative infection can precipitate haemolysis in the G6PD-deficient patient.

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