CASE REPORT

Aspirin safety in glucose-6-phosphate dehydrogenase deficiency patients with acute coronary syndrome undergoing percutaneous coronary intervention

Julien Feghaly,[1,2] Abdul Rahman Al Hout,[1,2] Mattew Mercieca Balbi[2]

[1]St George's, University of London, London, UK
[2]Department of Cardiology, Mater Dei Hospital, Msida, Malta

Correspondence to
Dr Julien Feghaly,
feghaly.julien@gmail.com

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SUMMARY

The use of aspirin, as part of a dual antiplatelet therapy regimen, is an established standard following coronary stenting in patients suffering from acute coronary syndrome (ACS). However, in glucose-6-phosphate dehydrogenase (G6PD) deficient patients, precaution is always taken with aspirin use, due to the risk of haemolysis. We reviewed all previous cases of G6PD deficient patients with ACS, in addition to a review of the available literature, to better understand the safety of aspirin use in this population. To date, there are no reported cases of haemolysis following aspirin use in this patient group and no guideline is established to date.

BACKGROUND

Deficiency of glucose-6-phosphate dehydrogenase (G6PD) is the most common human enzyme deficiency. It affects 400 million people worldwide.[1] G6PD deficiency exhibits an X-linked mode of inheritance. Mutations of the G6PD gene result in different phenotypical variants with different levels of enzyme activity. The most common clinical manifestations of the disease are acute haemolytic anaemia and neonatal jaundice. Acute haemolysis is caused by oxidative stress; this could be in the form of an oxidative drug, infection, or fava beans. Avoidance of these stressors is the treatment of acute haemolysis which is generally self limiting. Yet, in some cases, acute haemolysis might be severe, warranting blood transfusion.[2]

The pentose phosphate pathway (PPP) is a series of chemical reactions that yields the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) and therefore protects cells against oxidative stress. Red blood cells (RBCs) lack mitochondria, making the PPP their only source of NADPH. Any enzyme deficiency or malfunction in the PPP will render RBCs vulnerable to oxidative stress. G6PD is the first enzyme of the PPP, and hence RBCs are dependent on G6PD as much as they are dependent on the PPP.[3] Many drugs have been reported to cause haemolysis in G6PD deficient patients. Aspirin has long been believed to be one of those drugs.

The European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines currently recommend aspirin in addition to a P2Y12 inhibitor (such as ticagrelor, prasugrel or clopidogrel) for a 12 month period to reduce the risk of recurrent atherothrombotic events and stent thrombosis in patients following coronary stent implantation.[4] The initiation of aspirin following coronary stent insertion in G6PD deficient patients has been very controversial, and many clinicians have approached this matter with caution or hesitance. Aspirin treatment in G6PD deficient patients has been previously contraindicated in the past.[5 6] Yet despite several reports showing no evidence of haemolysis following initiation of aspirin in this patient subgroup,[7–10] no guideline has been published.

CASE PRESENTATION

Fifteen years ago, a 56-year-old Maltese women presented with recurrent intermittent retrosternal chest discomfort on exertion that was non-responsive to sublingual nitrate. She had an established medical history of G6PD deficiency. She was and still is a non-diabetic, non-hypertensive non-smoker. However, she has longstanding familial hyperlipidaemia, and a family history of ischaemic heart disease and cerebrovascular disease.

On admission, ECG showed flattening of the T wave in the aVL lead and a creatine phosphokinase level of 86 (normal range 10–190 u/L). A coronary angiogram was preformed showing mild left anterior descending (LAD) coronary artery disease with significant lesion in the left circumflex (LCx) coronary artery (50–69% occlusion). Percutaneous transluminal coronary balloon angioplasty without stenting was preformed and she was administered aspirin 75 mg once daily for 2 days as secondary prevention for atherothrombotic disease, that was then switched to ticlopidine 250 mg twice daily due to fear of haemolysis. She had no signs of haemolysis or a decrease in haemoglobin during the period following aspirin administration. No measurements were taken for haptoglobin, a protein used as a marker that decreases in the setting of haemolysis. Eight months later ticlopidine was stopped in view of deranged liver function tests and she was switched to lifelong clopidogrel 75 mg once daily. The following year, while on clopidogrel, she underwent a laparoscopic cholecystectomy in view of multiple episodes of right upper abdominal quadrant pain, the presence of gallstones on ultrasound and deranged liver function tests.

Fifteen months after the initial presentation, she presented with sudden onset compressive central

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chest pain, lasting 3 min and resolving spontaneously. ECG showed ST sagging in V4–V6 chest leads and creatine phosphokinase was 62 (normal range 10–190 u/L). She was started on intravenous heparin, a percutaneous coronary intervention (PCI) to LCx coronary artery was performed with a sirolimus drug eluting stent (DES) implanted. Following PCI, clopidogrel 75 mg once daily lifelong was continued.

One year later following PCI she presented with recurrent chest pain radiating to the neck; repeat coronary angiogram showed normal coronaries and no thrombosis of the previous stent. Ten years after the initial presentation she had a permanent dual chamber pacemaker implanted due to dizzy spells and bradycardia induced by carotid sinus massage.

Fourteen years after the initial presentation she presented yet again due to severe central compressive chest pain, radiating from the epigastrium to the left arm and neck, that began on exertion, was intermittent in nature and which resolved spontaneously. Clinically, the physical examination was unremarkable, other than tenderness in the epigastrium and suprasternal region. Initial and repeat ECG showed no ischaemic changes; however, she had an increase in troponin from 155 to 212 (normal range 3–14 ng/L) and was treated as a non-ST elevation myocardial infarction (NSTEMI). She again was not prescribed aspirin but was given enoxaparin 60 mg (1 mg/kg) twice daily subcutaneously alongside her established regular clopidogrel 75 mg.

A coronary angiogram was preformed showing two sequential lesions in the mid LAD coronary artery, moderate in severity (50–74% occlusion), mild ostial lesion in the LCx and a tight significant lesion in the distal portion of the pre-existing LCx stent (95–99% occlusion). The significant lesion was likely secondary to stent thrombosis over time. No new stent was inserted and there was the worry of starting aspirin. Her case was discussed with haematology who advised to use clopidogrel only or clopidogrel and dipyridamole. Additionally, her case was discussed with cardiothoracic surgeons who did not recommend artery grafting due to the obstacle of starting aspirin.

She then had a PCI the following day with one everolimus DES placed in the mid LCx. She had no complications or signs of haemolysis in the post-procedure phase. Her clopidogrel was later switched to prasugrel 10 mg daily once it was available and she was discharged to follow-up.

OUTCOME AND FOLLOW-UP

Four months post re-stenting an echocardiogram showed normal size and function of the left ventricle, left atrium, right ventricle and right atrium. Only noted was impaired left ventricle relaxation based on the transmitral spectral Doppler flow pattern. Left ventricular systolic function and wall motion were normal. The mitral, tricuspid and pulmonary valves were normal, with the aortic valve showing mild aortic valve stenosis. Ejection fraction was measured at 59.7%.

She is alive and well 15 years after the initial presentation. On follow-up 7 months after the last PCI, she showed no signs or symptoms of haemolysis, such as jaundice, pallor, dark coloured urine, abdominal pain or back pain. Her repeat haemoglobin of 12.7 (normal range 12.0–15.5 g/dL) and bilirubin of 13.1 (normal range 0–21 µmol/L) were within normal limits. Additionally, urine analysis was negative for both erythrocytes and bilirubin.

DISCUSSION

To our knowledge, there have only been 10 reported cases to date of G6PD deficient patients requiring some form of intervention for acute coronary syndrome; 9 of the 10 cases received aspirin therapy with none showing signs of haemolysis in the acute phase and on follow-up tables 1 and 2. Rigattieri *et al* were the first to describe a case of a myocardial infarction in a patient with G6PD deficiency. They did not give aspirin in the initial phase and the patient was successfully treated with balloon angioplasty. The patient went on to receive aspirin 100 mg under strict monitoring. Four days following initial presentation, the patient had a PCI preformed with insertion of two DES. The patient had a transient decrease in haemoglobin that was attributed to groin swelling at the femoral sheath insertion site. The patient was alive, well and free from haemolytic complications 3 months following the procedure.[7]

Porto *et al* were the second to describe a case of myocardial infarction in a patient with G6PD deficiency. However, this case was managed with a thrombectomy and intracoronary with abciximab (IIb/IIIa glycoprotein inhibitor) with no stent implanted. A repeat angiography showed an intermediate proximal LAD lesion, with Thrombolysis in Myocardial Infarction grade 3 flow, which was not stented and aspirin was not administered due to the history of G6PD deficiency. The patient was alive, well and free from complications 2 years following the procedure.[11]

Pappas *et al* were the third to describe such a case but in this case a bare metal stent was implanted instead of a DES. Following the procedure, the patient was treated with aspirin for an unspecified duration.[8] No haemolysis was ever reported. Further cases were reported by Kafkas *et al*; two patients underwent a single DES implantation each in one diseased coronary

Table 1 Patient background data

Case No	Reference	Event	Age (years)	Sex	Comorbidities	No of diseased vessels	No of stents	Stent type
1	Rigattieri[7]	STEMI	64	M	Sm	2	2	DES
2	Pappas[8]	STEMI	70	M	HTN; Dysl; Sm	1	1	BMS
3	Kafkas[9]	NSTEMI	78	M	None	1	1	DES
4	Kafkas[9]	NSTEMI	58	M	HTN	1	1	DES
5	Biscaglia[10]	STEMI	41	M	Sm	1	1	DES
6	Biscaglia[10]	SCAD	64	M	HTN; Dysl	2	2	DES
7	Biscaglia[10]	NSTEMI	67	F	HTN; Dysl; Sm	1	2	DES
8	Biscaglia[10]	STEMI	59	M	Dysl; Sm	3	4	DES
9	Biscaglia[10]	STEMI	54	M	HTN; Sm	1	3	DES
10	Porto[11]	STEMI	82	F	Dysl	1	0	Thrombectomy

BMS, bare metal stent; DES, drug eluting stent; Dysl, dyslipidaemia; HTN, hypertension; NSTEMI, non-ST segment elevation myocardial infarction; SCAD, stable coronary artery disease; Sm, smoker; STEMI, ST segment elevation myocardial infarction.

Table 2 Intervention, medical treatment and outcome data

Case No	Reference	UFH	GpI	ASA	Dur	Ticag	Dur	Clop	Dur	AE	Outcome
1	Rigattieri[7]	Y	Y	Y	NR	N		Y	NR	Y*	No haemolysis, AW after 3 m
2	Pappas[8]	N	N	Y	NR	N		N		N	No haemolysis, time unspecified
3	Kafkas[9]	N	N	Y	12 m	Y	12 m	N		N	No haemolysis, AW after 1 year
4	Kafkas[9]	N	N	Y	12 m	Y	12 m	N		N	No haemolysis, AW after 1 year
5	Biscaglia[10]	Y	Y	Y	12 m	N		Y	LL	Y†	No haemolysis, time unspecified
6	Biscaglia[10]	Y	N	Y	6 m	N		Y	LL	N	No haemolysis, AW after 3 years
7	Biscaglia[10]	Y	N	Y	12 m	Y	12 m	Y	Started at 12 m until LL	N	No haemolysis, time unspecified
8	Biscaglia[10]	Y	Y	Y	6 m	Y	6 m	Y	Started at 6 m until LL	N	No haemolysis, time unspecified
9	Biscaglia[10]	Y	Y	Y	NR	Y	NR	N	To start after DAPT	N	No haemolysis, time unspecified
10	Porto[11]	N	Y	N		N		Y	LL	N	No haemolysis, AW after 2 years

*In stent thrombosis.

†Haemoglobin decrease due to groin swelling at the femoral sheath insertion site.

AE, adverse events; ASA, aspirin; AW, alive and well; Clop, clopidogrel; DAPT, dual antiplatelet therapy; Dur, treatment duration; GpI, glycoprotein IIB/IIIA inhibitor; LL, lifelong; m, month; N, no; NR, not reported; Ticag, ticagrelor; UFH, unfractionated heparin; Y, yes.

artery. Afterwards both received a dual antiplatelet course of aspirin and ticagrelor for a 12 month period, showing no signs of haemolysis after a 12 month follow-up.[9]

Biscaglia *et al* were the first to present multiple cases and create a protocol as to how to approach G6PD deficient patients needing a stent and subsequent aspirin treatment. They helped to confirm both the safety and feasibility of aspirin use in this subgroup of patients. The approach that was used included a dual antiplatelet regimen, composed of aspirin and a P2Y12 inhibitor that reduced the risk of stent thrombosis following stent insertion. However, strict monitoring following the initial aspirin administration was performed. Patients were started with a single dose of aspirin 75 mg, and then in the absence of side effects the dose was increased to 100 mg.[10] Prior to discharge, the patients and their general practitioners received detailed information regarding signs and symptoms of haemolysis.

The main difference in management within the protocol was the timing of administration of aspirin. In the management of ST segment elevation myocardial infarction (STEMI), aspirin was initiated following PCI, with only a P2Y12 inhibitor administered in the initial phase. However, in NSTEMI or stable coronary artery disease, aspirin was administered alongside a P2Y12 inhibitor prior to PCI.

DES were used in all cases due to their reduced risk of stent thrombosis following insertion compared with BMS.[12]Dual antiplatelet therapy (DAPT) duration after DES insertion varied between 6 and 12 months before switching to lifelong clopidogrel only. DAPT duration of 6 months has been shown not to be inferior to a duration of 12 months.[13] DAPT duration of <6 months has been associated with higher rates of total myocardial infarction, lower rates of major bleeding and similar rates of stent thrombosis, cardiovascular mortality and all cause mortality, compared with DAPT duration of 12 months in second generation DES.[14] Moreover, recent data have shown the possibly of a 1 month duration of DAPT in patients at high risk of bleeding receiving polymer free umirolimus coated versus bare metal stents.[15] However, the data did not compare the established DAPT duration of 12 months with that of 1 month.

Zuin *et al* conducted a review of the available research in an attempt to create a chart as to how to optimise pharmacological treatment of G6PD deficient patients requiring cardiac revascularisation. They concluded that the optimal way to approach these patients began with differentiating STEMI from NSTEMI/unstable angina patients. This is followed by administering a full loading dose of a P2Y12 inhibitor to all patients prior to PCI and stent implantation.[16] Like Biscaglia,[10] they recommended initiating aspirin following PCI in STEMI patients, the use of DES with the shortest course of DAPT to reduce the possibility of haemolysis and cautious observation for haemolysis following the procedure. If a decrease in haemoglobin was detected, clinicians were to evaluate reticulocyte count, liver function, creatinine, lactate dehydrogenase, haemoglobinuria, ECG changes and examine the patient clinically. Signs suggesting haemolysis included: shortness of breath, fatigue, abdominal pain, back pain, chest pain, cold extremities and jaundice. Zuin *et al* did not however comment on the significance of haptoglobin measurements, which could have been used as a marker for haemolysis, especially in the initial days of aspirin administration.

Beyond the choice of what antiplatelet drug to use, the dosage should be taken into consideration. Aspirin doses of up to 3.6 g were not shown to show any signs of haemolysis in G6PD deficient patients,[17] with any haemolysis being attributed to concurrent infections and fever, not aspirin itself when aspirin was administered at a dose of 50 mg/kg body weight/day for 4 days.[18] Nonetheless, it is recommended that aspirin is administered at a low dose of 75 mg/day in G6PD deficient myocardial infarction patients before increasing to 100 mg/day, 2 days following the interventional procedure.[16]

Despite clopidogrel being regarded as a suitable substitute for patients who have contraindications to aspirin, we need to consider that many patients have clopidogrel non-responsiveness or resistance; the prevalence of clopidogrel non-responsiveness is approximately 21% (95% CI 17% to 25%) in patients undergoing PCI.[19] Additionally, care needs to be taken with prescription of P2Y12 inhibitors due to their risk of major bleeding. In a comparison of prasugrel with clopidogrel, as part of DAPT alongside aspirin, prasugrel showed a major bleed HR of 1.32 (95% CI 1.03 to 1.68).[20] When ticagrelor was compared with clopidogrel, as part of DAPT alongside aspirin, ticagrelor showed a major bleed HR of 1.25 (95% CI, 1.03 to 1.53).[21]

Following a literature review, we realised that, in our case, aspirin could have been used. However, as with previous reports and despite some suggested protocols, the data remain limited. To our knowledge, there has yet to be a case reported of haemolysis following aspirin administration in a G6PD deficient patient requiring coronary stenting. We are further limited by the number of diagnosed G6PD deficiency cases. It is probable that there are multiple G6PD deficient patients that receive aspirin following coronary stenting that are undiagnosed. We agree with previous studies that G6PD deficiency should not be an absolute

contraindication to low dose aspirin in G6PD deficient patients with acute coronary syndrome undergoing coronary stenting.

Learning points

- To date, there is no reported case of haemolysis following aspirin use as part of dual antiplatelet therapy following coronary stent insertion.
- Based on previous reports, clinicians should start to use aspirin in this patient subgroup when applicable but with careful monitoring.
- Aspirin is not an absolute contraindication in G6PD deficient patients.

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REFERENCES

1 Nkhoma ET, Poole C, Vannappagari V, *et al*. The global prevalence of glucose-6-phosphate dehydrogenase deficiency: a systematic review and meta-analysis. *Blood Cells Mol Dis* 2009;42:267–78.
2 Frank JE. Diagnosis and management of G6PD deficiency. *Am Fam Physician* 2005;72:1277–82.
3 Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. *Lancet* 2008;371:64–74.
4 Kolh P, Windecker S, Alfonso F, *et al*. 2014 ESC/EACTS guidelines on myocardial revascularization: the task force on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur J Cardiothorac Surg* 2014;46:517–92.
5 Colonna P. Aspirin and glucose-6-phosphate dehydrogenase deficiency. *Br Med J* 1981;283:1189.
6 Stockman JA, Lubin B, Oski FA. Aspirin-induced hemolysis: the role of concomitant oxidant (H2O2) challenge. *Pediatr Res* 1978;12:927–31.
7 Rigattieri S, Silvestri P, Minucci A, *et al*. Drug-eluting stents in a patient with favism: is the aspirin administration safe? *J Cardiovasc Med* 2008;9:1159–62.
8 Pappas C, Ntai K, Parissis JT, *et al*. Dual anti-platelet therapy in patients with G6PD deficiency after percutaneous coronary intervention. *Int J Cardiol* 2013;165:380–2.
9 Kafkas NV, Liakos CI, Mouzarou AG. Antiplatelet and invasive treatment in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and acute coronary syndrome. The safety of aspirin. *J Clin Pharm Ther* 2015;40:349–52.
10 Biscaglia S, Ferri A, Pavasini R, *et al*. Dual antiplatelet therapy in patients with glucose-6-phosphate dehydrogenase deficiency undergoing PCI with drug-eluting stents. *J Atheroscler Thromb* 2015;22:535–41.
11 Porto I, Leo A, Crea F. Glucose-6-phosphate dehydrogenase (G6PDH) deficiency in a patient with ST-segment elevation acute myocardial infarction successfully treated by simple thrombectomy. *J Atheroscler Thromb* 2011;18:425–30.
12 Philip F, Agarwal S, Bunte MC, *et al*. Stent thrombosis with second-generation drug-eluting stents compared with bare-metal stents. *Circulation: Cardiovascular Interventions* 2014;7:49–61.
13 Colombo A, Chieffo A, Frasheri A, *et al*. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. *J Am Coll Cardiol* 2014;64:2086–97.
14 D'Ascenzo F, Moretti C, Bianco M, *et al*. Meta-Analysis of the duration of dual antiplatelet therapy in patients treated with second-generation drug-eluting stents. *Am J Cardiol* 2016;117:1714–23.
15 Urban P, Meredith IT, Abizaid A, *et al*. Polymer-free drug-coated coronary stents in patients at high bleeding risk. *N Engl J Med* 2015;373:2038–47.
16 Zuin M, Rigatelli G, Carraro M, *et al*. Antiplatelet therapy in patients with glucose-6-phosphate dehydrogenases deficiency after percutaneous coronary intervention: a reappraisal for clinical and interventional cardiologists. *Cardiovasc Revasc Med* 2017;18:226–9.
17 Beutler E. The hemolytic effect of primaquine and related compounds: a review. *Blood* 1959;14:103–39.
18 Glader BE, Schwartz H. A revaluation of aspirin (asa) induced hemolysis associated with erythrocyte glucose:6:phosphate dehydrogenase (g6pd) deficiency. *Pediatr Res* 1974;8:400.
19 Snoep JD, Hovens MM, Eikenboom JC, *et al*. Clopidogrel nonresponsiveness in patients undergoing percutaneous coronary intervention with stenting: a systematic review and meta-analysis. *Am Heart J* 2007;154:221–31.
20 Wiviott SD, Braunwald E, McCabe CH, *et al*. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;357:2001–15.
21 Wallentin L, Becker RC, Budaj A, *et al*. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045–57.