Case Report

Dual Antiplatelet Therapy in Patients with Glucose-6-Phosphate Dehydrogenase Deficiency undergoing PCI with Drug-Eluting Stents
A Case Series and Review of the Evidence

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Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common human enzyme defect, affecting more than 400 million people worldwide. In patients with G6PD deficiency, the use of aspirin is controversial, since past studies have reported a potential risk of haemolysis related to its administration, even at low doses. More recent publications have shown that low-dose aspirin administration is safe in these patients. At the same time, no authors have previously reported more than single cases regarding low-dose aspirin treatment in patients with G6PD deficiency undergoing percutaneous coronary intervention (PCI), and most physicians are still sceptical about aspirin administration in these patients. In this paper, we report a case series of five patients with G6PD deficiency receiving PCI with drug-eluting stents (DES) and treatment with dual antiplatelet therapy (DAPT) containing low-dose aspirin, without clinical complications. Moreover, we discuss our internal protocol for managing these patients and provide an overview of the available data.


Key words: G6PDH deficiency, Aspirin and PCI, Dual antiplatelet therapy, Drug-eluting stent

Introduction

Glucose-6-phosphate dehydrogenase (G6PD) is an enzyme present in red blood cells and is involved in the oxidation of glucose and production of nicotinamide adenine dinucleotide phosphate (NADPH), the coenzyme that protects red blood cells from oxidative stress. G6PD deficiency, an x-linked, hereditary genetic defect caused by mutations in the G6PD gene, is the most common human enzyme defect, affecting more than 400 million people worldwide. The clinical presentation of G6PD deficiency is acute haemolytic anaemia triggered by drugs, infection or fava bean ingestion. The association between drugs (such as aspirin) and haemolytic anaemia in these patients is classified as definite, possible or doubtful1). It follows that the use of aspirin in patients with G6PD deficiency is controversial. Past studies, dating back to 1960, report a potential aspirin-induced haemolysis risk2-3). More recent publications, however, have shown that low-dose aspirin administration is safe in 44 patients4). Moreover, aspirin causes haemolysis at doses far exceeding the usual antiplatelet dose (1,200-1,800 mg/daily versus 100 mg/daily)2, 5). Clarifying this controversy is clinically relevant, as low-dose aspirin is a milestone treatment in patients with ischaemic heart disease, although clopidogrel may be an alternative to lifelong aspirin6). The issue as to whether G6PD-deficient patients can be safely treated with aspirin becomes even more clinically relevant in the setting of acute coronary syndromes (ACS) and/or percutaneous coronary intervention (PCI), where dual antiplatelet therapy (DAPT, low-dose aspirin + P2Y12 inhibitor) is mandatory.
artery (LAD). After unfractionated heparin administration through the right radial artery (RA), which had not undergone an enzyme activity test or molecular analysis. Coronary artery angiography (CAA) was performed (Export XT catheter 6F Medtronic CardioVascular, Santa Rosa, CA, USA). We obtained a good angiographic result. During the procedure, a tirofiban (37 ml) bolus was administered because of the high thrombus burden. The patient also received antiplatelet monotherapy with clopidogrel (loading dose 600 mg, maintenance dose 75 mg), as the physician, considering the presence of G6PD deficiency, preferred not to administer aspirin. At the time of this case (2010), ticagrelor and prasugrel were not available in the market. Three days later, stent thrombosis (ST) occurred. A second CAA procedure was performed through the right femoral artery (FA), and the patient was treated with both manual (Export XT catheter 6F Medtronic CardioVascular, Santa Rosa, CA) and mechanical thrombectomy (AngioJet Rheolytic Thrombectomy system, Medrad Interventional/Possis, Minneapolis, MN, USA). He received i.v. unfractionated heparin (8,000 UI) and a tirofiban bolus (37 ml). Unfortunately, the final angiographic result was suboptimal due to the presence of a residual thrombus within the stent. For this reason, the tirofiban infusion (13 ml/hour) was continued for 24 hours. After the ST event, we

To the best of our knowledge, there are only three single case reports describing the clinical management of such patients undergoing PCI for ischaemic heart disease (IHD) (Table 1).7-9. In the current work, we report the history and management of five patients with G6PD deficiency and IHD, discuss our internal protocol for managing these patients and provide an overview of the available data, with particular regard to DAPT management.

Case Series

From 2010 to July 2014, 3,382 patients received PCI for IHD in our Cath Lab (Cardiology Unit, Azienda Ospedaliera-Universitaria S.Anna di Ferrara). Five (0.15%) of the subjects reported a documented history of G6PD deficiency (Table 1).

Case #1

A 41-year-old man was admitted for anterior ST-segment elevation myocardial infarction (STEMI). The patient referred to a previous history of acute haemolytic anaemia after fava bean ingestion, although he had not undergone an enzyme activity test or molecular analysis. Coronary artery angiography (CAA) was performed through the right radial artery (RA), which showed plaque rupture, with evidence of a thrombus in the mid portion of the left anterior descending artery (LAD). After unfractionated heparin administration (8,000 UI i.v.), manual thrombectomy was performed (Export XT catheter 6F Medtronic CardioVascular, Santa Rosa, CA) and a drug-eluting stent (DES) (Endeavor Sprint 3.5×18 mm, Medtronic, Santa Rosa, CA, USA) was implanted. Following post-dilation with a non-compliant balloon (NC Trek 4.0×15 mm, Abbott Vascular, Santa Clara, California, USA), we obtained a good angiographic result. During the procedure, a tirofiban (37 ml) bolus was administered because of the high thrombus burden. The patient also received antiplatelet monotherapy with clopidogrel (loading dose 600 mg, maintenance dose 75 mg), as the physician, considering the presence of G6PD deficiency, preferred not to administer aspirin. At the time of this case (2010), ticagrelor and prasugrel were not available in the market. Three days later, stent thrombosis (ST) occurred. A second CAA procedure was performed through the right femoral artery (FA), and the patient was treated with both manual (Export XT catheter 6F Medtronic CardioVascular, Santa Rosa, CA) and mechanical thrombectomy (AngioJet Rheolytic Thrombectomy system, Medrad Interventional/Possis, Minneapolis, MN, USA). He received i.v. unfractionated heparin (8,000 UI) and a tirofiban bolus (37 ml). Unfortunately, the final angiographic result was suboptimal due to the presence of a residual thrombus within the stent. For this reason, the tirofiban infusion (13 ml/hour) was continued for 24 hours. After the ST event, we
Case #2

A 64-year-old man was admitted to our institution because of worsening effort angina. The patient had no previous history of acute haemolytic anaemia and presented with a Class III Seattle 844C variant G6PD variant according to the WHO classification (20% enzyme residual activity). The day before CAA, low-dose aspirin (75 mg) and a clopidogrel loading dose (600 mg) were administered. The CAA procedure showed critical stenosis of the mid portion of the circumflex (LCX) artery and a long critical disease of the LAD. The LCX was treated with direct stenting (Cre8 3.0 × 18 mm, CID, Saluggia, Italy). After multiple attempts at predilation (Tazuna 2 × 15 mm, Terumo Corporation, Tokyo, Japan; NC Trek 2.5 × 15 mm and 3 × 15 mm Abbott Vascular, Santa Clara, California, USA), we implanted two overlapping DES in the LAD (Cre8 3 × 28 mm and 3.5 × 28 mm, CID, Saluggia, Italy). The patient was treated with DAPT for six months; aspirin therapy was well tolerated and not harmful. Hemolytic parameters were monitored and remained stable during hospitalization (admission: haemoglobin 14.8 g/dl; discharge: haemoglobin 14.8 g/dl; red blood cell count 5,040,000/μl). Haemolytic parameters were monitored and remained stable during hospitalization (admission: haemoglobin 15.3 g/dl; red blood cell count 5,040,000/μl). Double antiplatelet therapy was then continued indefinitely. So far (after three years), the patient has not experienced any clinical problems.

Case #3

A 67-year-old woman was admitted to our Intensive Care Unit for the treatment of no ST-segment
were withdrawn, along with the simultaneous initiation of clopidogrel treatment (loading dose 600 mg, maintenance dose 75 mg), which was recommended to be continued lifelong.

**Case #4**

A 59-year-old man had a previous history of acute haemolytic anaemia after fava bean ingestion at 6 years of age. Five years later, he was hospitalized for jaundice, which was caused by another acute episode of haemolysis during a fever. Afterwards, he underwent a molecular analysis which showed a Class IV Mediterranean 563T variant with low enzyme residual activity (6%). The patient was admitted to our Cath Lab because of anterior STEMI. CAA showed acute occlusion of the proximal LAD and critical stenosis of the right coronary artery (RCA) and first obtuse marginal branch (OM). After therapy with i.v. unfractionated heparin (6,000 UI), a tirofiban bolus (65 ml) and ticagrelor loading dose (180 mg), we performed LAD predilation (Falcon Bravo 2.0 × 10 mm, Medtronic Cardiovascular, Santa Rosa, California, USA) and implantation of two overlapping DES (Biomatrix Flex 3 × 18 mm and 3.5 × 24 mm, Biosensors International, Singapore). Post-dilation was performed with a non-compliant balloon (NC Trek 3.5 × 8 mm and 4.0 × 8 mm), with a good final angiographic result. After stent implantation, optical coherence tomography (OCT, Intravascular Imaging System and Dragonfly, St. Jude Medical, St. Paul, MN, USA) was used to evaluate the residual thrombus burden. The total thrombus score (number of involved quadrants in each frame along the stent) was 23 and the thrombus length was 3.9 mm. As previously established (Fig. 1), we administered 75 mg of aspirin at the end of the procedure, which was well tolerated. The next morning, we started therapy with a standard aspirin dose (100 mg/day). After five days of DAPT and clinical stabilization, a staged procedure was performed on the LCX and RCA. Following predilation (Quantum Maverick 2.5 × 15 mm, Boston Scientific, Natick, Massachusetts, USA), a DES (Biomatrix Flex 3 × 18 mm, Biosensors International, Singapore) was implanted in the mid portion of the RCA. The direct DES stenting technique was utilized in the OM branch (Biomatrix Flex 2.5 × 24 mm, Biosensors International, Singapore), and the angiographic result for the LAD was satisfactory. We repeated the OCT scan, which showed complete thrombus resolution. During the patient’s subsequent hospitalization, no clinical or laboratory signs of haemolysis were noted (admission: haemoglobin 11.8 g/dl, red blood cell count 3,820,000/μl; discharge: haemoglobin 12.7 g/dl; red blood cell count 4,080,000/μl). DAPT was administered for six months. Thereafter, clopidogrel was started with a 600 mg loading dose and continued lifelong (75 mg/day).

**Case #5**

A 54-year-old man with a Class II Mediterranean 563T variant associated with 5% enzyme residual activity had a previous history of acute haemolytic anaemia during sulfamethoxazole treatment for acute bronchitis. The patient was directly referred to our Cath Lab for emergency PCI to treat anterior STEMI. CAA performed through the right RA showed a sub-occlusive thrombotic lesion of the predivisional LM proximal LAD with thrombotic occlusion of the mid LAD. The patient was already on chronic treatment with aspirin for significant atherosclerotic carotid disease. He received i.v. unfractionated heparin (8,000 UI), a tirofiban bolus (37 ml) and a ticagrelor loading dose (180 mg). Due to the onset of cardiac shock, an intra-aortic balloon pump (IABP) was placed through the right femoral artery (FA) before PCI. After achieving first diagonal branch and LCX protection, we performed several LM-LAD predilation procedures (Quantum Maverick 2.0 × 15 mm, 2.5 × 15 mm and 3.0 × 15, Boston Scientific, Natick, Massachusetts, USA). Afterwards, we implanted three overlapping DES on the LM-LAD axis (Xience Pro 2.5 × 28 mm, Xience Pro 3.0 × 28 mm, and Xience Pro 4.0 × 28...
and performed multiple post-dilation procedures using a kissing balloon with NC-balloons (NC Trek 2.0×15 mm and 3.0×8 mm and 4.0×15 mm, Abbott Vascular, Santa Clara, California, USA). The final angiographic result was acceptable. Adequate apposition of the stents was controlled with intravascular ultrasound (IVUS) imaging (Atlantis Pro catheter, Boston Scientific, Natick, Massachusetts, USA). No complications occurred during the patient’s hospital stay and his haemolytic parameters remained stable (admission: haemoglobin 14.4 g/dl; red blood cell count 4,560,000/μl; discharge: haemoglobin 14.3 g/dl; red blood cell count 4,620,000/μl). He was discharged on day 7 and is currently on DAPT without complications.

Discussion

Pharmacological treatment after coronary stent implantation in patients with G6PD deficiency is controversial. Despite increasing evidence of the feasibility and safety of aspirin in these patients, most physicians are still sceptical and prefer not to use this drug. The literature is scanty, since no authors have previously reported more than single cases in patients with G6PD deficiency undergoing PCI. Our case series confirms the feasibility and safety of aspirin administration in patients with G6PD deficiency and suggests a favourable risk/benefit ratio for aspirin use in such patients. The DAPT regimen with aspirin and a P2Y12 inhibitor is mandatory for minimizing the risk of thrombotic complications after stent implantation. Our first case is a paradigmatic example confirming this observation. The acute setting of MI and absence of the DAPT regimen negatively interacted in this case, causing ST and reinfarction, prompting us to reconsider the risk/benefit ratio of aspirin use. Obviously, in patients with G6PD deficiency, the first dose of aspirin should be administered under strict monitoring. After case #1, we decided to elaborate and share an institutional protocol to manage the timing and dose of antiplatelet agent administration in patients with G6PD (Fig. 1). Of course, this protocol is arbitrary and should be considered only as a hypothesis-generating protocol. Nevertheless, in our daily clinical practice, this method demonstrated safety and efficacy. We started with a single administration of the lowest aspirin dose with a cardioprotective effect (75 mg). In the absence of side effects, we recommend a standard daily dose of 100 mg. Before hospital discharge, the patients and general practitioners received detailed information about all risk factors (antimicrobial and/or non-steroidal anti-inflammatory drug administration, fever, foods) favouring haemolysis. Aspirin administration was limited to the lowest possible number of months, according to the clinical presentation, stent type and coronary artery disease (generally six months). Obviously, this management was slightly different in patients presenting with STEMI. Current guidelines suggest the use of aspirin administration (150-300 mg) as soon as possible. This is not applicable in patients with a documented history of G6PD deficiency. Accordingly, we decided to postpone aspirin administration after PCI conclusion. In order to minimize the risk of ischaemic complications, we utilized GP IIb/IIIa inhibitors in the absence of a high bleeding risk. After the PCI procedure, aspirin was administered without a loading dose, starting from the lowest cardiovascular approved dose (75 mg). Finally, we chose to implant second-generation DES because of their optimal safety profile, with a low occurrence of stent thrombosis. Current guidelines recommend second-generation DES over BMS, and no data support different advice in patients with G6PD deficiency. Several studies have suggested that DAPT therapy may be limited to 3-6 months after second-generation DES implantation. Accordingly, in our protocol and our patients with G6PD deficiency, we decided to limit aspirin administration to six months in order to minimize the risk of haemolysis. As for lifelong antiplatelet treatment, we suggested clopidogrel (lifelong administration after the DAPT period). The efficacy of lifelong treatment with clopidogrel is supported by the results of a randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). At the moment, there are no available data related to lifelong treatment with newer P2Y12 inhibitors (ticagrelor or prasugrel).

In conclusion, our cases suggest that aspirin can be safely administered in patients with G6PD deficiency undergoing PCI and stent implantation. Although the number of cases is limited, no adverse events were reported and all patients were compliant with the DAPT regimen. Obviously, our protocol is arbitrary, as it reflects a single centre experience, and must not be considered as a guideline for the treatment of G6PD-deficient patients undergoing PCI. We acknowledge that the frequency of G6PD deficiency in our case series is lower than expected based on the previous literature. The main reason for this finding may be related to the underdiagnosis of patients with G6PD deficiency and no previous history of haemolysis. At the same time, this observation confirms and enforces the safety of aspirin in this sub-
set of patients. It is highly probable that patients with G6PD deficiency received PCI, DES implantation and thus aspirin treatment. Nevertheless, during the 1-year clinical follow-up available in all patients receiving PCI in our Cath lab, there was no evidence of acute haemolytic anaemia. Nevertheless, our findings strongly suggest that G6PD deficiency should not be considered an absolute contraindication to low-dose aspirin prescription and that DAPT therapy should not be denied to patients with G6PD deficiency receiving PCI.

Conflicts of Interest

The authors declare no relationships that could be construed as a conflict of interest.

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