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Mini-review

Antiplatelet therapy in patients with glucose-6-phosphate dehydrogenases deficiency after percutaneous coronary intervention: A reappraisal for clinical and interventional cardiologists ☆

Marco Zuin [a,b], Gianluca Rigatelli [c], Mauro Carraro [b], Maria Paola Galasso [b], Fabio Dell'Avvocata [c], Rossella Paolini [d], Giovanni Zuliani [a], Loris Roncon [b,*]

[a] Section of Internal and Cardiopulmonary Medicine, Department of Medical Science, University of Ferrara, Ferrara, Italy
[b] Department of Cardiology, Rovigo General Hospital, Rovigo, Italy
[c] Cardiovascular Diagnosis and Endoluminal Interventions, Rovigo General Hospital, Rovigo, Italy
[d] Department of Oncoematology, Rovigo General Hospital, Rovigo, Italy

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ABSTRACT

Glucose-6-phosphate dehydrogenase (G6PD) deficiency represents one of the most common erythrocyte enzymopathy. In the era of drug-eluting stents (DESs), the use of prolonged dual antiplatelet therapy (DAPT) with aspirin (ASA) and thienopyridine (clopidogrel or ticlopidine) has become mandatory in the treatment of patients with acute coronary syndromes (ACS) and/or after percutaneous coronary intervention (PCI). However, the use of ASA, and more in general of antiplatelet drugs in patients with G6PD deficiency remains controversial, also for the absence of specific guidelines and scientific evidences. In the present manuscript, we reviewed the few cases available in medical literature, regarding patients with G6PD deficiency treated with percutaneous coronary artery intervention (PCI) and DAPT, with the aim to discuss and clarify the optimal treatment in these patients.

1. Introduction

In the era of drug-eluting stents (DESs), the use of prolonged dual antiplatelet therapy (DAPT) with aspirin (ASA) and thienopyridine (clopidogrel or ticlopidine) has become mandatory in the treatment of patients with acute coronary syndromes (ACS) and/or after percutaneous coronary intervention (PCI). As known, during the last years, DESs have rapidly replaced bare-metal stents (BMSs) for treatment of coronary artery disease (CAD). The rationale of DAPT is to avoid potentially catastrophic stent thrombosis (ST), secondary to delayed endothelization. However, the use and safety of DAPT in patients with gluocose-6-phospate dehydrogenases (G6PD) deficiency remain uncertain [1]. Indeed, ASA is considered a mild hemolytic agent in patients with G6PD deficiency. Currently, only few case reports have analyzed the long-term efficacy and safety of DAPT in patients with GPD6 deficiency treated with PCI [2]. Moreover, no recommendations are available in the current guidelines on the management of acute coronary syndrome. As result, medical treatment in these patients is particularly challenging, especially in the acute setting. In the present manuscript, we review the available literature on DAPT after PCI in patients with G6PD deficiency.

2. Glucose-6-phosphate dehydrogenases deficiency definition

As known, G6PD is an enzyme involved in the oxidation of glucose and production of nicotine-amide dinucleotide phosphate (NADPH). Through this reaction G6PD protects erythrocytes from oxidative stress and hemolysis [2,3]. From an epidemiological point of view, G6PD deficiency represents one of the most common erythrocyte enzymopathy with a higher prevalence in some geographical areas as Mediterranean area, Middle East and Asia where it shows a similar distribution as thalassemia [3,4]. Indeed, the similarity between the regions where G6PD deficiency is widely diffuse and *Plasmodium falciparum* is endemic, suggests circumstantial evidences that G6PD deficiency confers resistant against malaria [3,4]. As known, G6PD deficiency is an X-linked, hereditary genetic defect characterized by a widely heterogeneous group of mutations which can lead to a different reduction of enzyme activity in red blood cells. The enzymatic deficiency is associated with a wide range of clinical and biochemical phenotypes [1]. Generally, most G6PD-deficient subjects remain asymptomatic during their life and often unaware of their genetic status. Conversely, in other subjects, the primary clinical manifestation is represented by an acute hemolysis,

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* Corresponding author at: Department of Cardiology, Santa Maria della Misericordia Hospital, Viale Tre Martiri 140, 45100 Rovigo, Italy. Tel.: +39 0425393286; fax: +39 0425393597.
E-mail address: roncon.loris@azisanrovigo.it (L. Roncon).

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triggered by drugs, infections or fava bean ingestion [3]. However, also acute myocardial infarction (AMI) could precipitate hemolysis in these subjects [5]. Over the years, several drugs have been related to acute hemolysis in G6PD-deficient subjects. Nowadays, aspirin (ASA) is considered as a mild hemolytic agent in these patients. In most of cases, a severe hemolytic process occurred after the assumption of small therapeutic doses, generally not exceeding 2 g/day [1]. However, whether a specific drug directly provokes hemolytic crisis in G6PD-deficient patients remains matter of speculation.

3. Material and methods

A mini-review was conducted using the PubMed database. The relevant studies were identified through search engine using a combined text words and MeSH (Medical Subject Headings) search strategy. The following combination of keywords was used: "G6PD deficiency and dual antiplatelet therapy", "G6PD deficiency and percutaneous coronary artery intervention", "G6PD and acute coronary syndrome" and "G6PD acute myocardial infarction". Moreover, we searched the bibliographies of target studies for additional references. From the final review, we excluded both reports and studies which were not related with ischemic heart disease (IHD).

3.1. Review of the current evidences from the literature

The treatment of patients with IHD, which also had contraindications to the use of antiplatelet drugs, represents a nightmare for cardiologists, especially in the acute phase of CAD. In current medical literature, data about the use of antiplatelet therapy in patients with CAD and G6PD deficiency are scant. Indeed, the issue has been analyzed and discussed only in form of case reports or small case series. These manuscripts often suggested different therapeutic protocols, which they have not subsequently validated in larger cohort [2,6–8]. Moreover, the absence of a consensus opinion, complicates the treatment of these patients. The DAPT regimen with P2Y12 inhibitor and aspirin is a cornerstone in the treatment of IHD. The rationale of DAPT is to minimize possible thrombotic complications in both the short- and long-term period after stent implantation [1,9]. Furthermore, DAPT management has progressively increased its importance after the widespread diffusion of second and third-generation drug-eluting stent (DES). As known, ASA induces a dose-independent inhibition of thromboxane-A2 mediated platelet function. Due to the increased use of PCI and DES implantation in the treatment of ACS, the prevalence of patients on DAPT and with G6PD-deficiency is set to increase in the future.

Although some authors suggested that the genetic condition of G6PD deficiency could be associated with a lower cardiovascular (CV) risk, the real prevalence of this genetic disorder is far to be established in CAD patients [10,11]. Until now, only Biscaglia et al. analyzed the problem, reporting only 5 patients (0.15%) with G6PD-deficiency, after reviewing 3382 subjects treated with PCI over 4 years [2]. The absence of larger studies, often induces cardiologists to avoid the use of ASA in these patients. A mini-review of the literature, performed in Pubmed, on the management of patients treated with PCI for IHD and G6PD deficiency, revealed only ten cases. As shown in Table 1, patients were 63.7 ± 11.8 years old, more frequently female (60%) and admitted for STEMI, NSTEMI and stable coronary artery disease in 60%, 30% and 10% of cases, respectively. The most frequent comorbidities were arterial hypertension (50%), diabetes (50%) and smoking habits (60%). PCI was performed in 9 patients and CAD was more frequently treated with DESs versus BMSs (90% vs 10%). Pharmacological treatment included the use of ASA, clopidogrel and ticagrelor in 80%, 40% and 50% of cases, respectively. Adverse events associated with the G6PD deficiency were observed in only two cases (20%); in the first one, the complication was due to a hemorrhagic complication at the site of femoral sheath insertion while in the second it was due to an ST before ASA administration. In these studies, alternative time-based pharmacological and interventional approaches were adopted to minimize possible adverse events due to the G6PD deficiency. Porto et al. described a case of STEMI treated using manual thrombectomy and intracoronary administration of abciximab without any stent implantation [8]. Conversely, Rigattieri et al. successfully treated a STEMI in a 64-year-old man with a DES and without the administration of ASA during the acute phase [6]. Recently, an intriguing algorithm has been proposed by Biscaglia et al. [2]. According to their suggestions, STEMI patients with previous documented history of G6PD deficiency must be initially treated with P2Y12 inhibitors. Subsequently, UHF or bivalirudin should be administered during PCI and DES implantation. Moreover, during this phase, GP IIb/IIIa inhibitors must be reserved for those patients without higher risk of bleeding. After the interventional procedure, ASA could be safely administered at the lowest cardiovascular dose (75 mg). On the contrary, patients with stable CAD or N-STEMI should be initially treated with a single ASA administration (75 mg), followed by a P2Y12 inhibitor and finally with administration of UFH or bivalirudin, at operator's discretion, during the DES implantation. For both STEMI and N-STEMI patients, the administration of 100 mg of ASA should start two days after the interventional procedure and with a tide monitoring of hemoglobin (HB) values. To limit potential hemolysis, ASA administration has been recommended for six months while, after the DAPT period, clopidogrel was suggested as lifelong antiplatelet treatment. (See Table 2.)

3.2. Searching for a good-sense management and future directions

Due to the few number of cases reported in medical literature it is difficult to establish the safety and efficacy of DAPT in G6PD deficient patients. The increasing use of DAPT in clinical practice puts a great number of G6PD deficient patients at risk for hemolytic crisis. The residual enzyme deficiency, which is a necessary but not a sufficient condition for triggering hemolysis, is associated with the individual variations in drugs catabolism, making the prediction of the event a challenging, if not impossible task [1–3]. Sudden and premature discontinuation of DAPT is an independent predictor of early ST, especially in patients with previous ACS [9]. According the recent guidelines and randomized trials on myocardial reperfusion, DESs have been preferred over BMSs [9]. Although the implantation of BMSs could represent an alternative treatment, DES should be preferred to avoid ST. On the other side, the choice of a single antithrombotic or antiplatelet therapy after the implantation of a second or third generation DES, is not able to prevent restenosis, especially in severe, long and diffuse disease. Concerning the type of stent, we believe that the use of a second- or third-generation stent should be recommended, instead of BMS, as reported in most presented cases. Moreover, the new available DES requiring a short DAPT must be considered in these patients. However, the optimal duration of DAPT after PCI and DES implantation must be assessed in G6PD deficient patients. Probably, routine use of manual

Table 1
Demographical and clinical characteristics of patients with G6PD deficiency treated with PCI.

Reference	CV event	Age	Gender	Comorbidities
Porto et al. [8]	STEMI	82	♀	HT
Biscaglia et al. [2]	STEMI	54	♂	HT; Smok
"	STEMI	59	♂	Dysl; Smok
"	N-STEMI	67	♂	HT; Dysl; Smok
"	SCAD	64	♂	HT; Dysl
"	STEMI	41	♂	Smok
Rigattieri et al. [6]	STEMI	64	♂	Smok
Pappas et al. [7]	STEMI	70	♂	HT; Dysl; Smok
Kafkas et al. [8]	N-STEMI	58	♂	–
"	N-STEMI	78	♂	HT

STEMI: ST-segment elevation myocardial infarction; N-STEMI: No ST-segment elevation myocardial infarction; HT: Arterial Hypertension; Smok: Smoking habits; Dysl: Dyslipidemia.

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