Original Paper

Impact of Intravenous P2Y₁₂-Receptor Inhibition with Cangrelor in Patients Presenting with Acute Coronary Syndrome and Cardiogenic Shock – a Case Series

Michal Droppa^a Oliver Borst^a Dominik Rath^a Karin Müller^a Meinrad Gawaz^a
Deepak L. Bhatt^b Tobias Geisler^a

^aDepartment of Cardiology and Cardiovascular Medicine, University Hospital of Tuebingen, Tuebingen, Germany, ^bBrigham and Women's Hospital Heart & Vascular Center and Harvard Medical School, Boston, MA, USA

Key Words

Cardiogenic shock • Cangrelor • P2Y₁₂-receptor inhibitor • Platelet aggregation • Percutaneous coronary intervention • Myocardial infarction

Abstract

Background/Aims: Patients with acute coronary syndromes (ACS) presenting with cardiogenic shock (CS) are at particular risk for death and adverse cardiac events. Impaired effects and absorption of oral P2Y₁₂-receptor inhibitors due to decreased organ hypoperfusion or hypothermia and challenges regarding oral administration contribute to this risk. We report a single center experience regarding the use of intravenous P2Y₁₂-receptor inhibitor cangrelor in patients with CS treated with percutaneous coronary intervention (PCI). **Methods:** Twelve patients with ACS and CS undergoing PCI, not pretreated with oral P2Y₁₂-receptor inhibitors, were treated with cangrelor. Platelet inhibition was assessed by multiple electrode aggregometry (MEA) before and after PCI, immediately and 2 hours after stopping the cangrelor infusion. **Results:** Nine patients recovered from their cardiogenic shock, 3 patients died. Platelet reactivity decreased from 65.9 (SD 41.0) U before PCI to 15.8 (SD 10.8) U after PCI, 13.4 (SD 7.7) U at the end of infusion and 33.8 (SD 19.9) 2 hours after stopping the cangrelor infusion. There was no non-responder under cangrelor infusion (MEA < 46 U). **Conclusions:** Due to its favorable PK/PD profile, cangrelor overcomes problems with reduced absorption and effects of oral P2Y₁₂-receptor inhibitors and should be considered for periprocedural treatment of patients with CS.

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Introduction

Patients with acute coronary syndromes (ACS) presenting with cardiogenic shock (CS) are at particular risk for death and cardiac adverse events. Impaired effects and absorption of oral P2Y₁₂-receptor inhibitors due to decreased organ perfusion or hypothermia and

Tobias Geisler

Department of Cardiology and Cardiovascular Medicine, University Hospital of
Tuebingen, Otfried-Mueller-Strasse 10, 72076 Tuebingen, (Germany)
Tel. +49 7071 29-83688, E-Mail tobias.geisler@med.uni-tuebingen.de

challenges regarding oral administration contribute to the risk and represent an unresolved clinical problem. This could impact the outcome, particularly ischemic events such as reinfarction or stent thrombosis after percutaneous coronary intervention (PCI). Recently, the new P2Y₁₂-receptor inhibitor cangrelor has become available and could overcome some of those problems due to its intravenous route of delivery. However, limited experience exists regarding its use in patients presenting with CS. We present a single center experience of antiplatelet treatment with cangrelor in patients with CS.

Materials and Methods

We reviewed all cases of patients with cardiogenic shock treated with PCI and the intravenous P2Y₁₂-receptor inhibitor cangrelor. Cangrelor was administrated peri-interventionally and up to 2 hours after the procedure. Patients were loaded with ticagrelor at the time of the procedure, or prasugrel 30 minutes before the end of the cangrelor infusion, or clopidogrel at the end of the cangrelor infusion. We reviewed patients' history, periprocedural characteristics, therapy of CS and antiplatelet medication used. In-hospital mortality was assessed. In the majority of patients, platelet function was measured by ADP-stimulated multiple electrode aggregometry (MEA) [Multiplate® Roche, Germany] as reported previously [1]. To illustrate possible advantages of cangrelor therapy in specific patients with cardiogenic shock, 3 cases are presented.

Results

We treated 12 patients with CS. Patients' characteristics are summarized in Table 1. Nine patients recovered from their cardiogenic shock and could be discharged, while 3 patients died. Five patients were treated with mechanical circulatory support (Impella or extracorporeal life support - ECLS). Nine patients underwent cardiopulmonary resuscitation: 4 in-hospital and 5 out-of-hospital. Platelet function analysis was performed in 8 patients. It showed rapid and effective platelet inhibition. Platelet reactivity decreased from 65.9 (SD

Table 1. Characteristics of patients with cardiogenic shock treated with cangrelor. ECLS – extracorporeal life support, GFR – glomerular filtration rate, LAD – left anterior descending, LCX – left circumflex, LM – left main coronary artery, LV-EF – left ventricular ejection fraction, NSTEMI – non-ST-elevation myocardial infarction, RCA – right coronary artery, SD – standard deviation, STEMI – ST-elevation myocardial infarction

Characteristics	N (%)
Sex female/male	2 (16.7%)/10(83.3%)
Age in years, mean±SD	65.2±3.1
Diagnosis	
NSTEMI	3 (25%)
STEMI	9 (75%)
3-vessel disease	11 (91.7%)
Infarct related artery	
LM	2 (16.7%)
LAD	8 (66.7%)
LCX	1 (8.3%)
RCA	1 (8.3%)
LV-EF %, mean±SD	30.8±2.9
Cardiopulmonary resuscitation	9 (75%)
Assist device	
ECLS	3 (25%)
Impella	1 (8.3%)
ECLS+Impella	1 (8.3%)
Diabetes	5 (41.7%)
GFR ml/min, mean±SD	81.5±12.2
Morphine use	1 (8.3%)
P2Y ₁₂ -receptor blocker after cangrelor infusion	
Ticagrelor	7 (58.3%)
Prasugrel	4 (33.3%)
Clopidogrel	1 (8.3%)
In-hospital mortality	3 (25%)

Fig. 1. Platelet aggregation by multiple electrode aggregometry during cangrelor therapy. Platelet aggregation measured by ADP stimulated multiple electrode aggregometry. ADP – adenosine diphosphate, CI – confidence interval, MEA – multiple electrode aggregometry, PCI – percutaneous coronary intervention.

41.0) U before PCI to 15.8 (SD 10.8) U after PCI, 13.4 (SD 7.7) U at the end of cangrelor infusion and 33.8 (SD 19.9) U 2 hours after stopping the cangrelor infusion (Fig. 1). There was no non-responder with cangrelor (MEA < 46 U).

Case presentation

Patient 1. A 64 year-old woman called emergency services due to chest pain and dyspnea. In the presence of the emergency physician, the patient lost consciousness and had to be resuscitated due to ventricular fibrillation. Spontaneous circulation could be established after 5 minutes of resuscitation and defibrillation. ECG showed ST-depressions in V2-V6 leads, laboratory examination revealed elevation of troponin, consistent with the diagnosis of NSTEMI. Coronary angiography showed 3-vessel coronary artery disease with chronic total occlusion of RCA, mid-grade stenosis of LAD, and thrombotic occlusion of LCX. Patient was in CS due to severely impaired left ventricular function. During antiplatelet treatment with aspirin and cangrelor (bolus of 30 µg/kg, continuous infusion of 4 µg/kg/min for 2 hours) we performed PCI with PTCA and coronary stent implantation (DES) in LCX. Due to cardiogenic shock, Impella CP assist device was implanted transfemorally. The patient was loaded with ticagrelor after that and antiplatelet treatment with aspirin and ticagrelor was continued. Groin hematoma at the insertion site of the Impella was treated conservatively. The patient was stabilized and cardiac support with catecholamines and Impella was weaned successfully. The patient was extubated and recovered well without any significant neurological deficit.

Patient 2. A 46 year-old man fell from a scaffold during construction work due to a cardiac arrest. Resuscitation and repeated defibrillation were necessary. Diagnosis of ST-elevation myocardial infarction (STEMI) was established based on the electrocardiogram (ECG). The patient was on vasopressors due to CS. Due to anisocoria, an initial CT scan of the brain was performed. It showed intracerebral contusion-bleeding and a small subdural hematoma (Fig. 2). Coronary angiography revealed severe 3-vessel disease with a high grade stenosis of the proximal LAD and RCA. Due to CS, we performed PCI with implantation of 6 DES in the LAD and RCA. Peri-interventional anticoagulation was performed using bivalirudin. Antiplatelet treatment with aspirin was given, and cangrelor was started peri-interventionally (bolus of 30 µg/kg, continuous infusion of 4 µg/kg/min for 2.5 hours). Intracranial bleeding was

Fig. 2. Head CT scans of the patient on day 1, 3, 7, and 18 after the procedure. It shows traumatic intracerebral contusion-bleeding and small subdural hematoma without progression during the antiplatelet therapy and good resorption within 18 days

managed conservatively, head-CT during cangrelor therapy showed no progression of the intracranial hemorrhage, allowing a switch from cangrelor to ticagrelor. Subsequent CT scans showed good resorption of the bleeding without complication (Fig. 2). The patient recovered well without any severe neurological deficit and was transferred to a rehabilitation facility after 26 days.

Patient 3. A 74 year-old man without history of coronary artery disease (CAD) was admitted with typical angina symptoms. Laboratory evaluation revealed elevated serum troponin, consistent with the diagnosis of non-ST-elevation myocardial infarction (NSTEMI). He underwent coronary angiography which showed 3-vessel coronary artery disease with chronic total occlusion of the RCA and high grade stenosis of the left main and proximal LAD. The patient was treated with provisional stenting of the left main/LAD (2 DES) and subsequent PTCA of the LCX. Antiplatelet therapy with aspirin was given in the emergency department and ticagrelor was given during PCI on the catheterization table. After the PCI during transfer to the ward, cardiopulmonary resuscitation with defibrillation was necessary. We performed repeat coronary angiography which showed acute stent thrombosis of the LAD. The patient was treated with thrombus aspiration using the Export® catheter device (Medtronic) and PTCA. Antiplatelet treatment with cangrelor was started while performing PCI. Platelet function measurement during infusion showed adequate platelet inhibition (MEA ADP of 3 U). Due to hemodynamic instability with repeated cardiopulmonary resuscitation due to cardiogenic shock and severely impaired left ventricular function, transfemoral ECLS was established. Dual antiplatelet therapy with aspirin and ticagrelor was continued. The patient recovered such that ECLS was weaned after 4 days. In the following days he was extubated and mobilized. Unfortunately, 14 days after admission he had to be resuscitated due to sudden pulseless electrical activity. Echocardiography excluded pericardial effusion and showed a left ventricle without contraction. After 30 minutes of cardiopulmonary resuscitation, the patient died. We could not ascertain the cause of the death, as autopsy was refused by the patient's relatives. Possible causes could have been repeat stent thrombosis or systolic dysfunction due to progressive heart failure.

Discussion

Cangrelor is available for use in patients with CAD undergoing PCI. Its efficacy was demonstrated in the CHAMPION trials [2, 3]. Approximately 12,000 patients were treated with cangrelor in a population of patients with ACS as well as stable CAD; however, data about patients with CS are limited [4]. Cangrelor offers several advantages compared with oral P2Y₁₂-receptor inhibitors. First, it is administered intravenously and hence is not subject to variable gastrointestinal absorption. Consequently, it can be easily administered to intubated patients. It has very fast onset and provides effective platelet inhibition [1]. Second, it reversibly binds the platelets and has a very short half-life allowing complete recovery of platelet function within 1 hour after drug cessation, even in patients with renal or hepatic dysfunction. The following clinical and pathophysiological characteristics of patients with cardiogenic shock should be considered with regard to potential advantages of cangrelor.

Delayed onset of platelet inhibition with oral antiplatelet drugs

Patients with CS are often intubated and ventilated which makes oral administration of medications difficult especially in the emergency setting. Drugs can be given by gastric tube after crushing to accelerate absorption and platelet inhibition, however this can cause further delay in therapy. Another problem is impaired absorption of oral antiplatelet drugs. Due to low cardiac output, impaired blood flow to gastrointestinal mucosa may cause slow absorption. Slow metabolism of drugs which need transformation into active metabolites is another potential challenge. These problems can be further exacerbated by therapeutic hypothermia which is often used after cardiac arrest [5]. Delayed onset of platelet inhibition due to the above issues is associated with thrombotic complications after PCI. Patients with CS are at particularly high risk with a high morbidity and mortality of up to 50% reported in the literature [6]. In our patient 3, we found acute stent thrombosis shortly after PCI probably due to insufficient antiplatelet effects after loading with an oral P2Y₁₂-receptor inhibitor. After coronary revascularization and intravenous cangrelor infusion, no documented thrombotic complications occurred in this case series.

Management of bleeding complications

All available oral P2Y₁₂-receptor inhibitors have a delayed offset of action, requiring several days for full recovery of platelet function. This could be a disadvantage in patients with bleeding complications when more targeted antiplatelet therapy is needed. Short acting platelet inhibition with cangrelor allows a “watch and wait strategy” to stop antiplatelet therapy in case of progression of the bleeding. In our experience we could successfully manage intracranial bleeding with therapy with cangrelor in patient 2. Another possible advantage of cangrelor is the possibility to bridge patients in case of urgent surgical revascularization. Cessation of cangrelor lowers perioperative bleeding risk in comparison to oral P2Y₁₂-receptor inhibitors.

In conclusion, we present our first experience with antiplatelet treatment with cangrelor in patients presenting with CS. We successfully treated 12 patients with cardiogenic shock undergoing PCI with a beneficial periprocedural outcome. We did not observe any thrombotic event during or shortly after cangrelor infusion, supporting that adequate antiplatelet effect was obtained.

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