CASE REPORT

Individualised dual antiplatelet therapy in a patient with short bowel syndrome after acute myocardial infarction with coronary artery stenting

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Accepted 16 June 2015

SUMMARY

Short bowel syndrome after extensive surgical resection of the intestine is characterised by inadequate digestion and absorption of nutrients. Additional clinical problems include impaired absorption and metabolism of diverse drugs requiring individualised medical therapy or alternative treatments. We report a case of individualised dual antiplatelet therapy in a patient who underwent an extensive intestinal resection complicated by acute myocardial infarction requiring percutaneous coronary intervention and stent implantation. Genetic testing of CYP2C19 gene polymorphisms and platelet aggregation testing were used to assess responses to aspirin, clopidogrel, prasugrel and ticagrelor. Given its unique pharmacokinetics with good absorption and without need of metabolism to an active substance, ticagrelor appears to be the best for patients with short bowel syndrome who require dual antiplatelet therapy after coronary stent implantation.

BACKGROUND

Short bowel syndrome is a rare condition characterised by intestinal failure due to inadequate length of intestine following surgical resection. Depending on the length of resected intestine and degree of adaptation in the remaining intestine, complications such as malnutrition, cachexia, electrolyte disturbances and diarrhoea occur. Additional problems include impaired absorption and metabolism of diverse drugs requiring individualised medical therapy or alternative treatments.

Patients with ST-elevation myocardial infarction are typically managed by emergency percutaneous coronary intervention (PCI) with stent implantation to open an occluded coronary artery. To prevent stent thrombosis, dual antiplatelet therapy (DAPT) with aspirin and a P2Y₁₂-receptor inhibitor is indicated for at least 12 months in these patients. The three available P2Y₁₂-receptor inhibitors—clopidogrel, ticagrelor and prasugrel—have significant pharmacokinetic differences. Clopidogrel and prasugrel are prodrugs that must be converted to an active drug through different metabolic pathways, while ticagrelor reversibly binds to the P2Y₁₂ receptor on platelets. Absorption of all three drugs takes place in the stomach and intestine. However, there are no data available on absorption and effectiveness of these drugs after oral administration in patients with short bowel syndrome. Monitoring the efficacy of DAPT is crucial to prevent

potentially fatal complications after PCI in this group of patients.

In our case report, we present an individualised DAPT in a patient who underwent an extensive intestinal resection, complicated by a myocardial infarction requiring PCI.

CASE PRESENTATION

A 50-year-old man presented with severe diffuse abdominal pain lasting for 2 h. His medical history was significant for chronic obstructive pulmonary disease, nicotine abuse, deep venous thrombosis and pulmonary embolism. There was no family history of thrombophilia, premature myocardial infarction or sudden cardiac death. Physical examination was notable for diffuse abdominal tenderness and guarding. The patient's symptoms and physical examination were concerning for acute peritonitis warranting emergent laparotomy. Owing to perforation of the jejunum 50 cm above the suspensory ligament of duodenum, partial jejunum resection was performed.

The postoperative course was complicated by anterior ST-segment elevation myocardial infarction 6 h after the surgery. Emergent coronary angiography demonstrated one-vessel coronary artery disease with a severe stenosis of proximal and thrombotic occlusion of middle left anterior descending coronary artery warranting ad hoc thrombus aspiration and balloon angioplasty followed by stenting with three bare metal stents. DAPT with aspirin (loading dose 500 mg) and clopidogrel (loading dose 600 mg) was started immediately.

On postoperative day 1, the patient developed recurrent abdominal discomfort with signs of severe sepsis including fever, leucocytosis, elevated C reactive protein and lactic acidosis, warranting surgical exploration. Extended small intestinal ischaemia due to thrombotic occlusion of the superior mesenteric artery was discovered, and resection of necrotised jejunum and ileum was performed. Only the duodenum and 30 cm of the proximal jejunum remained vital and were preserved after the second operation. Consequently, the patient developed short bowel syndrome.

INVESTIGATIONS

Given the multiple unexplained thromboembolic events, complementary examinations were performed: Holter monitoring demonstrated no paroxysmal atrial fibrillation. Transoesophageal echocardiogram demonstrated no intracardiac

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To cite: Droppa M, Karathanos A, Gawaz M, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-205227

mass, thrombus or vegetation. Screening for inherited thrombophilias revealed heterozygosity for factor V Leiden mutation.

Given the need for prolonged DAPT and concern about insufficient drug absorption of aspirin and clopidogrel due to short bowel syndrome, on-treatment platelet aggregation was assessed by multiple electrode aggregometry (MEA) (Multiplate, Roche, Germany).^{1 2} This demonstrated response to aspirin with 13 aggregation units but non-response to clopidogrel with 73 aggregation units (with a MEA value <46 units considered an adequate response).^{3–5} The dose of clopidogrel was increased to 75 mg two times per day. After 5 days of continued treatment, when steady-state drug concentration should have been achieved, repeat MEA demonstrated no significant change in response to clopidogrel with 70 units. Consequently, the patient was switched from clopidogrel to prasugrel with a loading dose of 60 mg followed by a daily dose of 10 mg a day. MEA performed at 5 days after prasugrel maintenance dosing again revealed insufficient response after stimulation with ADP (64 U). Thus therapy with prasugrel was substituted by ticagrelor 90 mg two times per day with loading dose of 180 mg. After 5 days of ticagrelor therapy, MEA with ADP stimulation was again performed. Significant decrease of platelet aggregation to 35 U was observed (figure 1, table 1).

Clopidogrel is converted to its active metabolite by cytochrome P450 enzyme, which is highly polymorphic, in the liver. Testing for the most common CYP2C19 genotypes were performed.^{6 7} Alleles *1, *2, *3, *17 were tested using TaqMan assay. It revealed genotype CYP2C19*1/*2, which correspond to intermediate clopidogrel metaboliser.⁷

TREATMENT

Parenteral nutrition was started. DAPT was continued with aspirin 100 mg once daily and ticagrelor 90 mg two times per day. Owing to recurrent thromboembolic events with heterozygous factor V Leiden mutation, anticoagulation was initiated with enoxaparin and, later, warfarin.

OUTCOME AND FOLLOW-UP

Four months after his initial presentation, the patient was hospitalised for severe sepsis secondary to pneumonia. Despite supportive care and broad-spectrum antibiotics, the patient died after a prolonged course in the intensive care unit. Impressively,

Table 1 Measurement of on-treatment platelet reactivity during treatment with all tested antiplatelet drugs, values ≤46 units are considered sufficient response

Drug (mg/day)	Platelet inhibition (MEA units)
Aspirin 100	13
Clopidogrel 75	73
Clopidogrel 150	70
Prasugrel 10	64
Ticagrelor 180	35

MEA, multiple electrode aggregometry.

the patient had no recurrent thromboembolic events 6 months after PCI.

DISCUSSION

Short bowel syndrome is a rare condition characterised by impaired resorption of nutrients and drugs. According to current guidelines,⁸ patients should be treated with DAPT for 12 month after myocardial infarction, preferably with new potent P2Y₁₂-receptor inhibitor (ticagrelor or prasugrel). Patients with additional indication for oral anticoagulation with vitamin K inhibitor should be prescribed clopidogrel during ‘triple therapy,’ due to its lowest bleeding risk. According to current consensus,⁹ triple therapy after acute coronary syndrome is preferred for 6–12 month in patients with low bleeding risk (as is the case in our patient with HAS-BLED score of 1). However, in our case, clopidogrel and prasugrel were not effective in inhibiting platelets and hence would not have showed the desired therapeutic effect. Ticagrelor was the only drug known to inhibit platelets sufficiently, thus it was used in the therapeutic regimen after PCI, for our patient.

Until now, no data existed on the pharmacological activity of antiplatelet medications in patients with short bowel syndrome. Aspirin is an irreversible inhibitor cyclooxygenase-1 and prevents the thromboxane-dependent activation of platelets. Absorption of aspirin takes place in the stomach and proximal small intestine. Its pharmacological effect begins within 10–20 min as demonstrated by deactivation of thrombocytes in the portal blood.¹⁰ As predicted, our patient had an appropriate response to aspirin given its absorption in the stomach.

Figure 1 Measurement of on-treatment platelet reactivity during treatment with clopidogrel 75 mg, 2×75 mg, prasugrel 10 mg and ticagrelor 2×90 mg. HPR (>46 U; HPR, high on-treatment platelet reactivity; MEA, multiple electrode aggregometry).

Clopidogrel is an irreversible inhibitor of the P2Y₁₂ receptor. It is rapidly absorbed in the intestine. As a prodrug, clopidogrel must be transformed in two steps by cytochrome P450 enzyme to its active metabolite in the liver.¹¹ There is a high interindividual variability of response to clopidogrel. Patients with high platelet reactivity while on clopidogrel have increased cardiovascular risk.¹² Genetic variability in cytochrome P450 enzyme is assumed to be the main mechanism of clopidogrel non-responsiveness. Other possible mechanisms include variability of intestinal absorption and drug-drug interactions. Genotyping in our patient showed heterozygote CYP219 genotype with one loss-of-function allele (*1/*2), characterised as an intermediate clopidogrel metaboliser. Clopidogrel non-responsiveness is associated with major adverse cardiovascular events after PCI.⁷ In our patient, response to clopidogrel did not change significantly despite double the maintenance dose. Thus, low intestinal absorption of clopidogrel was the likely cause of non-responsiveness in our patient.

Prasugrel is also an irreversible inhibitor of the P2Y₁₂ receptor. Similar to clopidogrel, it is a prodrug, but its hepatic activation is much faster. Two steps are necessary. First, hydrolysis to a thiolactone precursor is performed in the intestine. Second, cytochrome P450 enzymes located in the bowel and liver transform thiolactone into the active drug.¹³ Our patient also had inadequate response to prasugrel, likely due to loss of intestinal hydrolysis.

Ticagrelor is a novel reversible P2Y₁₂-receptor inhibitor. In contrast to clopidogrel and prasugrel, ticagrelor does not require conversion from a prodrug.¹⁴ It is rapidly absorbed from the small intestine. In our patient with short bowel syndrome, ticagrelor was the only P2Y₁₂-receptor inhibitor to effectively inhibit platelets.

High on-treatment platelet reactivity increases the risk for early and late stent thrombosis.⁵ Personalised antiplatelet treatment after PCI is debated, and randomised studies failed to show its clinical benefit according to major end points.^{15–17} However, it can be very helpful in cases such as our patient with short bowel syndrome. Our patient had inadequate response to

two of the three available P2Y₁₂-receptor inhibitors, which would increase his risk of stent thrombosis while taking clopidogrel or prasugrel. Given its unique pharmacokinetics, ticagrelor seems to be a better choice for patients with short bowel syndrome.

Contributors MD and AK were involved in acquisition of data. MD was responsible for drafting of the manuscript. AK, MG and TG was responsible for critical revision of the manuscript for important intellectual content. TG were involved in final approval.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Learning points

- ▶ Short bowel syndrome after extensive surgical resection of the intestine is characterised by inadequate digestion and absorption of nutrients and drugs.
- ▶ In patients with short bowel syndrome, standard medical therapy may be less effective, necessitating individualised dosing and monitoring of drugs.
- ▶ Owing to its unique pharmacokinetics with good resorption and without need of metabolism to an active substance, ticagrelor appears to be the best choice for patients with short bowel syndrome undergoing percutaneous coronary intervention.
- ▶ Clopidogrel, due to wide interindividual response, and prasugrel, due to need of metabolism within the intestine, appear to be less effective in patients with short bowel syndrome.

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