PT Tsui 徐炳添
ST Lai 黎錫滔
WS Leung 梁偉宣
NS Mok 莫毅成
CW Wu 胡志和
ST Lau 劉雪婷
YC Choi 蔡炫材

Prolonged jaundice following percutaneous coronary intervention and ticlopidine therapy

在經皮冠狀干涉和ticlopidine治療後的延長黃疸

Ticlopidine, an adenosine diphosphate receptor blocker, is widely used to prevent subacute stent thrombosis after percutaneous coronary intervention. Along with neutropenia and thrombotic thrombocytopenic purpura, cholestatic hepatitis is one of the most serious potential side-effects of ticlopidine therapy. Four patients with prolonged jaundice after ticlopidine therapy, including one fatal case, are presented. Alternative antithrombotic therapy for subsequent percutaneous coronary intervention is also described. Clopidogrel therapy was found to be safe and effective in two patients with a history of ticlopidine-related cholestatic hepatitis.

作為一種腺甘二磷酸受體塊的ticlopidine，已被廣泛用於經皮冠狀的干涉後預防亞急性管架血栓症。同嗜中性白血球減少症和血栓形成的血小板減少紫癜一樣，膽汁鬱積肝炎是 ticlopidine 治療最嚴重的潛在副作用之一。本文介紹四名在 ticlopidine 治療後有延長黃疸患者，包括一致命病例。還描述了經皮冠狀的干涉之後可選擇的抗血栓形成的治療方案。對兩名有 ticlopidine 相關的膽汁鬱積肝炎病史患者施行 clopidogrel 治療，被證明是安全有效的。

Key words:
Angioplasty;
Cholestasis;
Jaundice;
Liver/pathology;
Ticlopidine/adverse effects

關鍵詞：
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Department of Medicine and Geriatrics, Princess Margaret Hospital, 2-10 Princess Margaret Hospital Road, Laichikok, Hong Kong
PT Tsui, MRCP, FHKAM (Medicine)
ST Lai, FRCP (Glasg), FHKAM (Medicine)
WS Leung, FRCP (Glasg), FHKAM (Medicine)
NS Mok, MRCP, FHKAM (Medicine)
CW Wu, MRCP, FHKAM (Medicine)
ST Lau, FRCP (Edin), FHKAM (Medicine)
YC Choi, FRCP (Glasg), FHKAM (Medicine)

Correspondence to: Dr PT Tsui

Introduction

The number of patients receiving percutaneous coronary intervention (PCI) is growing as a result of the increasing prevalence of coronary heart disease and accessibility to catheterization laboratory facilities. Both catheter-based interventional modalities and adjunctive pharmacological therapies are increasing in number. An effective and commonly used antiplatelet agent, ticlopidine can be problematic due to hepatic side-effects. We report four cases of prolonged jaundice from ticlopidine-related cholestatic hepatitis following PCI and describe subsequent use of clopidogrel as an alternative.

Ticlopidine is an antiplatelet agent that selectively and irreversibly inhibits binding of adenosine diphosphate (ADP) to its receptor on the platelet surface. It thus prevents ADP-dependent activation of the platelet glycoprotein IIb/IIIa receptor, the final common pathway of platelet aggregation. Randomised controlled trials have shown that combination treatment with ticlopidine and aspirin is superior to aspirin alone or aspirin plus an oral anticoagulant, in preventing subacute stent thrombosis or other adverse cardiac events after coronary stenting.[1-4] Furthermore, ticlopidine has been found to be effective in preventing cardiovascular ischaemic events in high-risk subjects. In the Canadian American Ticlopidine Study (CATS),[5] ticlopidine reduced the incidence of stroke, myocardial infarction (MI), and vascular death by 30.2% (95% confidence interval [CI], 7.5-48.3%) compared with placebo in patients with recent stroke. Ticlopidine has also been shown to reduce the incidence of death or non-fatal stroke by 12% (95%CI, -2–26%) compared with aspirin.[6]

Although the clinical application of ticlopidine therapy is expanding, its use is limited by potential side-effects. Neutropenia has been reported to occur in 1% of patients receiving ticlopidine therapy, while thrombotic thrombocytopenic purpura is an uncommon but potentially fatal complication.[7] Abnormal liver

function tests (LFT) were reported in 4.4% of patients treated with ticlopidine in the CATS trial.[5] Elevation of alkaline phosphatase (ALP) levels was the most common finding, with jaundice rare.

Case reports

Case 1

A 68-year-old man with a history of hypertension presented with a non-Q wave MI. An echocardiogram showed hypokinetic myocardium in the anteroseptal region. Cardiac catheterization was undertaken and revealed severe triple vessel disease. Staged PCI to the right coronary artery (RCA) and the left circumflex artery (LCX) was successful. The patient was given ticlopidine as per protocol (250 mg twice daily for 2 days prior to PCI, followed by 250 mg daily for 1 month) to prevent subacute stent thrombosis. The patient subsequently developed 'tea-coloured' urine 2 weeks after PCI. Liver function tests were consistent with obstructive jaundice. Serology results for hepatitis (A,B,C) and anti-mitochondrial antibodies (AMA) were negative. Ultrasonography (USG) of the upper abdomen did not reveal any space-occupying lesion or extrahepatic biliary tract obstruction. The course of ticlopidine was discontinued. Serum bilirubin levels subsequently peaked at 276 μmol/L (normal range, 5-21 μmol/L) in the fourth week, while jaundice persisted for 3 to 4 months. The prothrombin time was normal throughout this period.

The patient was consequently given a low molecular weight heparin (LMWH) in place of a platelet ADP-receptor blocker for the second-stage PCI to the bifurcation lesions in the left anterior descending artery (LAD). The procedure was uneventful. Despite receiving LMWH therapy, however, the patient experienced subacute stent thrombosis, which resulted in an acute anteroseptal MI, 1 week after PCI. Thrombolytic therapy was successful in restoring patency of the LAD, and subsequent catheterization showed widely patent stents in the mid-LAD and diagonal branch. A new stenosis in the distal RCA was also noted. This patient subsequently underwent PCI to the distal RCA with adjunctive clopidogrel therapy. No untoward hepatic side-effects were noted.

Case 2

A 49-year-old man with a history of hypertension, hyperlipidaemia, and chronic smoking presented with unstable angina, electrocardiographic (ECG) findings of deep T-wave inversions in leads V2 to V6, and normal serum cardiac enzymes. Cardiac catheterization revealed significant stenosis in the mid-LAD and the distal LCX. Percutaneous coronary intervention was performed, and two stents were deployed in the LAD. Ticlopidine therapy was initiated as per protocol to prevent subacute stent thrombosis. The procedure was successful, and the patient was discharged. The patient presented with fever and skin rash 1 week after PCI and subsequently developed cholestatic jaundice. Ticlopidine therapy was discontinued. Ultrasonography and magnetic resonance cholangiopancreatography showed that the biliary tract was not dilated. Serology results for hepatitis (A,B,C) and AMA were negative. Liver biopsy showed mild portal inflammation compatible with drug-induced cholestasis. Serum bilirubin levels peaked at 330 μmol/L in the fifth week, and jaundice persisted for 3 to 4 months. The prothrombin time was consistently normal. One year later, the patient developed diffuse proliferative in-stent restenosis, which resulted in total LAD occlusion. A second PCI with stenting was performed. On this occasion the patient was given clopidogrel rather than ticlopidine, and there was no evidence of drug-related hepatitis.

Case 3

A 64-year-old man with a history of chronic renal impairment, hypertension, hyperlipidaemia, and gout was seen following MI (non-Q wave). An echocardiogram revealed mild apical and inferior wall hypokinesia. Cardiac catheterization revealed severe triple vessel disease. Percutaneous coronary intervention with stenting to the LCX and RCA was performed, and ticlopidine therapy was given as per protocol. The patient developed cholestatic jaundice in the second week after the PCI procedure. Ticlopidine therapy was then discontinued. Serology results for hepatitis (A,B,C) and AMA were negative. Ultrasonography of the upper abdomen showed a bulky pancreatic tail and the absence of extrahepatic biliary obstruction. The patient then developed acute pancreatitis and acute on chronic renal failure. Subsequent endoscopic retrograde cholangiopancreatography (ERCP) confirmed the USG findings. Supportive medical treatment failed, and the patient subsequently died from these complications.

Case 4

A 68-year-old man with a history of hypertension and smoking, presented with unstable angina and ECG findings of ST segment depression in leads V5,V6, I, and aVL. Cardiac catheterization revealed significant proximal LAD stenosis. The patient underwent PCI with stenting. Ticlopidine therapy was started as per protocol, and the procedure was uneventful. Two weeks later, the patient presented with epigastric pain and jaundice. Liver function tests indicated a diagnosis of cholestatic hepatitis. Ticlopidine therapy was discontinued, and a 5-day course of LMWH was given to prevent subacute stent thrombosis. Ultrasonography, a computed tomography scan of the abdomen, and ERCP did not reveal any space-occupying lesion or extrahepatic biliary obstruction. The pancreas was noted to be bulky, and serum amylase levels were normal. The patient refused liver biopsy. Serum bilirubin levels peaked at 427 μmol/L during the second month, and jaundice persisted for more than 6 months. The prothrombin time was normal throughout the clinical course.

Discussion

Isolated case reports of cholestatic hepatitis following ticlopidine therapy have been reported in the literature.[8] The

Table. Clinical features of four patients with cholestatic hepatitis following percutaneous coronary intervention and ticlopidine therapy

	Case 1	Case 2	Case 3	Case 4
Sex	Male	Male	Male	Male
Age (years)	68	49	64	68
Presenting symptom	Jaundice	Skin rash jaundice	Jaundice	Epigastric pain
Liver function test results at presentation:				
Bilirubin (μmol/L)	189	213	316	43
Alkaline phosphatase (U/L)	254	680	486	241
Aspartate aminotransferase (U/L)	366	190	108	331
Peak bilirubin (μmol/L)	276	330	443	427
Duration of jaundice (months)	3-4	3-4	-	>6

onset has varied among patients from 1 week to 3 months after initiation of ticlopidine therapy. Liver function tests have shown moderate elevation of serum bilirubin and ALP levels, together with mild elevation of serum transaminase levels. In all reported cases LFT normalised, but over a variable period of 10 days to more than 1 year following discontinuation of ticlopidine therapy. Progression to chronic disease was not seen and no deaths were reported. Liver biopsies showed either pure cholestasis or hepatocellular injury mixed with cholestasis. An epitheloid granuloma affecting all areas of a hepatic lobule has also been reported to occur.[9] Both drug hypersensitivity reaction and direct hepatotoxic effects have been postulated as mechanisms by which ticlopidine induces cholestatic hepatitis. In the four cases reported here, skin rash was found only in the second patient, and none of the patients had eosinophilia, a marker of hypersensitivity reaction.

The four current cases presented with cholestatic hepatitis (Table) within the first month of ticlopidine therapy. Extrahepatic biliary obstruction and other potential causes of cholestasis were eliminated. The jaundice persisted for several months and subsided after discontinuation of ticlopidine therapy in three patients (Fig). Despite aspirin plus parenteral anticoagulation therapy, the first patient developed a subacute stent thrombosis. This outcome supports the view that platelet aggregation plays a more important role than coagulation in the pathogenesis of subacute stent thrombosis. Clopidogrel was used in the first and second patients for subsequent PCI, and in neither case was there evidence of a cross-hypersensitivity reaction. The third patient had underlying renal failure and developed fulminant pancreatitis concurrent with ticlopidine-induced cholestatic hepatitis, while the fourth patient had the longest duration of jaundice and LFT abnormalities. Alkaline phosphatase and bilirubin levels remain elevated in this patient at the time of writing this article. The last two patients showed evidence of increased pancreatic bulk, which could represent an adverse pancreatic reaction to ticlopidine therapy.

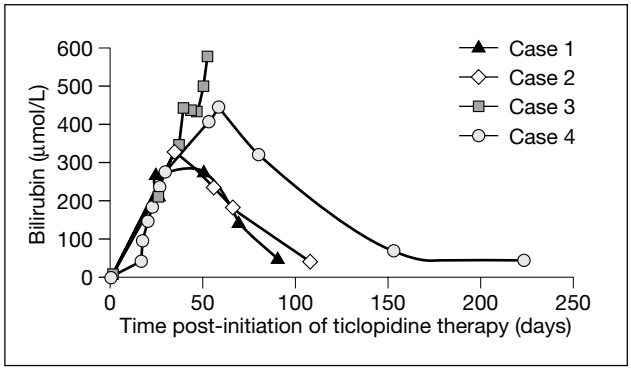

Fig. Bilirubin profiles from four patients with cholestatic hepatitis secondary to ticlopidine therapy

Although ticlopidine-related cholestatic hepatitis is not common, it does cause significant and prolonged jaundice. In addition to monitoring of the complete blood count for neutropenia, monitoring of LFT for potential cholestatic hepatitis should be undertaken, especially during the first month of ticlopidine therapy. Ticlopidine therapy should be promptly discontinued once abnormal LFT results are noted. Clopidogrel can be utilised as an alternative antiplatelet agent for patients with a history of ticlopidine-related cholestatic hepatitis. The haematological and hepatic side-effects of ticlopidine reported in this paper have led to a change in the protocol followed at Princess Margaret Hospital, with clopidogrel replacing ticlopidine as the antiplatelet agent used for coronary stenting procedures.

References

1. Leon MB, Baim DS, Gordon P, et al. Clinical and angiographic results from the stent anticoagulation regimen study (STARS). Circulation 1996;94(Suppl 1):4002AS.
2. Schomig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med 1996;334:1084-9.
3. Bertrand M, Legrand V, Boland J, et al. Full anticoagulation versus ticlopidine plus aspirin after stent implantation: a randomized multicenter European study: the FANTASTIC trial. Circulation 1996; 94(Suppl 1):4003AS.
4. Urban P, Macaya C, Rupprecht HJ, et al. Randomized evaluation of anticoagulation versus antiplatelet therapy after coronary stent implantation in high-risk patients: the multicenter aspirin and ticlopidine trial after intracoronary stenting (MATTIS). Circulation 1998;98:2126-32.
5. Gent M, Blakely JA, Easton JD, et al. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. Lancet 1989;1:1215-20.
6. Hass WK, Easton JD, Adams HP Jr, et al. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. Ticlopidine Aspirin Stroke Study Group. N Engl J Med 1989;321:501-7.
7. Quinn MJ, Fitzgerald DJ. Ticlopidine and clopidogrel. Circulation 1999;100:1667-72.
8. Iqbal M, Goenka P, Young MF, Thomas E, Borthwick TR. Ticlopidine-induced cholestatic hepatitis: report of three cases and review of the literature. Dig Dis Sci 1998;43:2223-6.
9. Ruiz-Valverde P, Zafon C, Segarra A, Ribera R, Piera L. Ticlopidine-induced granulomatous hepatitis. Ann Pharmacother 1995;29:633-4.