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# Clopidogrel-induced hepatotoxicity after percutaneous coronary stenting

## 施行經皮冠狀動脈內支架術後氯吡格雷引發的肝毒

Clopidogrel, an adenosine diphosphate receptor blocker, is widely used as an adjunctive antiplatelet therapy in acute coronary syndrome and percutaneous coronary stenting. The occurrence of hepatotoxicity is rare. We describe the occurrence of symptomatic liver disease in a 74-year-old man 5 weeks following commencement of therapy with clopidogrel. The reported cases of clopidogrel-induced hepatotoxicity are reviewed and the clinical significance of this event are discussed.

氯吡格雷（又作克羅匹多）是一種腺苷二磷酸受體阻斷劑，在醫治急性冠狀動脈綜合症和經皮冠狀動脈內支架術中作為輔助性血小板治療而得到廣泛應用。因使用氯吡格雷而出現肝毒的情況十分罕有。本報告描述一位74歲的男性病者，在接受氯吡格雷治療後5星期出現肝病的症狀，並檢視已知的氯吡格雷引發肝毒的病例，及討論這類病例的臨床重要性。

### Introduction

The use of percutaneous coronary intervention as an alternative to coronary artery bypass graft surgery has expanded dramatically in the past two decades. Periprocedural death, myocardial infarction, and vessel occlusion are the major complications following balloon angioplasty. They are due to arterial thrombus formation at the site of mechanical plaque disruption and distal embolisation of platelet thrombi into the coronary circulation. Antiplatelet therapy is an important adjunctive treatment that reduces ischaemic complications in patients undergoing percutaneous coronary intervention.

The thienopyridine derivatives, ticlopidine and clopidogrel, produce an irreversible inhibition of the platelet adenosine diphosphate receptor, and thereby attenuate platelet aggregation in response to adenosine diphosphate released from activated platelets. The PCI-CURE study<sup>1</sup> showed that clopidogrel, in addition to aspirin, before and continued beyond the standard course of 4 weeks after percutaneous coronary intervention was superior to placebo in preventing major ischaemic events. In randomised trials, clopidogrel and ticlopidine had similar efficacy, but ticlopidine was associated with more side-effects.<sup>2</sup> The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy thus recommended the use of clopidogrel rather than ticlopidine following stent placement.<sup>3</sup> Both thienopyridine derivatives are rapidly hydrolysed in the liver to produce active and inactive metabolites. Abnormal liver biochemical tests were reported in 4.4% of patients treated with ticlopidine in the Canadian American Ticlopidine Study.<sup>4</sup> Prolonged cholestasis has also been reported.<sup>5</sup> Clopidogrel has not demonstrated hepatic enzyme induction in healthy volunteers<sup>6</sup> and hepatotoxicity has

#### Key words:

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#### 關鍵詞：

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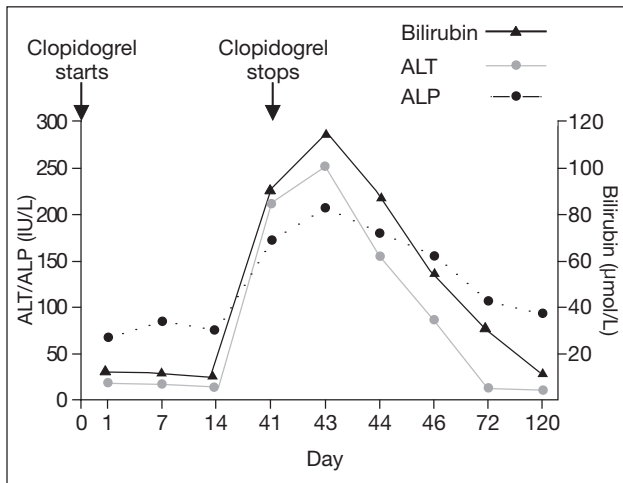
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**Fig. Serial liver biochemical tests after introduction and discontinuation of clopidogrel**

ALT denotes alanine transaminase, and ALP alkaline phosphatase

rarely been reported.<sup>7-10</sup> We report a case of hepatotoxicity associated with the use of clopidogrel in a patient undergoing coronary artery stenting.

### Case report

A 74-year-old man with a history of hypertension, gastritis, and ischaemic heart disease had been taking isosorbide dinitrate, metoprolol, and aspirin for more than 2 years. He presented with retrosternal chest pain. Electrocardiography revealed ST depression and T inversion over the anterior leads. Serial troponin I levels were normal. Treatment was commenced for presumed acute coronary syndrome with the addition of clopidogrel 75 mg daily and pantoprazole 40 mg daily (day 0). There was no evidence of heart failure or hypotension after hospital admission. Nine days later, cardiac catheterization revealed complete occlusion of the left anterior descending artery and 80% occlusion of the left circumflex artery. Percutaneous coronary stenting was successful for both arteries and clopidogrel was continued to prevent subacute stent thrombosis. Four weeks later (day 37), the patient developed tea-coloured urine and jaundice. Liver biochemical tests 4 days later revealed serum bilirubin level to be 91 µmol/L (reference range, 4-20 µmol/L), alkaline phosphatase (ALP) 172 IU/L (35-115 IU/L), and alanine transaminase (ALT) 212 IU/L (1-40 IU/L). Serum albumin level and coagulation profile were normal. Complete blood picture showed mild thrombocytopenia ( $135 \times 10^9$  /L; reference range,  $150-400 \times 10^9$  /L) and a low white cell count ( $3.8 \times 10^9$  /L; reference range,  $4.0-10.0 \times 10^9$  /L).

Serology for acute viral hepatitis, including anti-hepatitis A virus immunoglobulin M (IgM), anti-hepatitis B core IgM, hepatitis B surface antigen, anti-hepatitis C virus (HCV) antibody, HCV RNA, and anti-hepatitis E virus IgM, was negative. Clopidogrel-induced hepatotoxicity was suspected and the drug was stopped (day 41). Repeated serology 1 week later for acute hepatitis A and B remained negative. Anti-smooth muscle antibody and anti-mitochondrial antibody were also negative. Abdominal ultrasound revealed neither a space-occupying lesion in the liver nor a dilated biliary tract. The ALT level peaked at 253 IU/L 2 days following withdrawal of clopidogrel. Five days after stopping clopidogrel, liver biochemistry improved gradually with bilirubin level dropping to 55 µmol/L, ALP to 155 IU/L, and ALT to 86 IU/L (Fig). Approximately 4 weeks after stopping the drug, liver function and complete blood picture were normal.

### Discussion

The diagnosis of clopidogrel-induced hepatitis was established by the temporal relationship between the introduction of the offending drug and the development of liver impairment together with the exclusion of other causes of liver disease. The clinical improvement following withdrawal of clopidogrel also implicated the drug as the underlying cause. The diagnosis was also confirmed in our patient according to the Maria and Victorino scale<sup>11</sup> for the diagnosis of drug-induced hepatotoxicity. Liver biopsy was not performed in view of the rapid improvement of liver biochemistry following withdrawal of clopidogrel. The presence of transient neutropenia and thrombocytopenia also provided additional evidence of drug involvement in the hepatic lesion. Bone marrow suppression leading to thrombocytopenia, neutropenia, and even fatal aplastic anaemia has been reported in some patients using clopidogrel.<sup>12</sup>

When patients are prescribed multiple drugs, identification of the culprit drug can be difficult. In our patient, two drugs—clopidogrel and pantoprazole—were added to treatment prior to the development of liver injury. All other drugs had been taken for more than 2 years without any adverse effects. To date, only one case of suspected pantoprazole-induced hepatitis has been reported.<sup>13</sup> Nonetheless an alternative cause of the liver injury might have been possible. Liver biochemistry improved dramatically in our patient despite continuation of pantoprazole that was thus vindicated. As both clopidogrel and pantoprazole are metabolised in the liver via CYP 2C19 and CYP 3A4 of the cytochrome

P450 enzyme system,<sup>14</sup> the possibility of any significant clinical interaction between the two drugs that could lead to liver injury requires further investigation.

There have been four other cases of clopidogrel-induced hepatitis worldwide.<sup>7-10</sup> These patients developed liver impairment 4 days to 3 months following commencement of clopidogrel and all of them made a complete recovery when the drug was withdrawn. The liver injury is usually mixed hepatocellular and cholestatic in nature. Reintroduction of clopidogrel in one patient resulted in recurrent liver dysfunction.<sup>7</sup> Structurally, clopidogrel differs from ticlopidine by the addition of a carboxymethyl side group. The existence of cross-sensitivity between ticlopidine and clopidogrel remains uncertain. Clopidogrel has been successfully used in three patients with ticlopidine-induced hepatotoxicity,<sup>5,15</sup> but a similar strategy of using ticlopidine in patients with clopidogrel-induced hepatotoxicity has not been attempted as ticlopidine has been associated with a higher rate of neutropenia and elevated transaminases than clopidogrel.

With increasing use of clopidogrel, especially for a prolonged duration in the era of drug-eluting stent, adverse effects associated with clopidogrel may become more common. Although such reactions are currently rare, physicians should remain vigilant to the possibility of hepatotoxicity and other side-effects associated with clopidogrel. Liver biochemistry and a complete blood picture should be monitored during treatment and the drug discontinued if jaundice or hepatitis develops.

## References

1. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001;358:527-33.
2. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH, Investigators FT. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the clopidogrel aspirin stent international cooperative study (CLASSICS). *Circulation* 2000;102:624-9.
3. Popma JJ, Berger P, Ohman EM, Harrington RA, Grines C, Weitz JI. Antithrombotic therapy during percutaneous coronary intervention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126(3 Suppl):576S-599S.
4. Gent M, Blakely JA, Easton JD, et al. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. *Lancet* 1989;1:1215-20.
5. Tsui PT, Lai ST, Leung WS, et al. Prolonged jaundice following percutaneous coronary intervention and ticlopidine therapy. *Hong Kong Med J* 2002;8:57-9.
6. Pierce CH, Houle JM, Dickinson JP, et al. Clopidogrel and drug metabolism: absence effect on hepatic enzymes in healthy volunteers. *Semin Thromb Hemost* 1999;25(Suppl): 35S-39S.
7. Beltran-Robles M, Marquez Saavedra E, Sanchez-Munoz D, Romero-Gomez M. Hepatotoxicity induced by clopidogrel. *J Hepatol* 2004;40:560-2.
8. Ramos Ramos JC, Sanz Moreno J, Calvo Carrasco L, Garcia Diaz Jde D. Clopidogrel-induced hepatotoxicity [in Spanish]. *Med Clin (Barc)* 2003;120:156-7.
9. Duran Quintana JA, Jimenez Saenz M, Montero AR, Gutierrez MH. Clopidogrel probably induced hepatic toxicity [in Spanish]. *Med Clin* 2002;119:37.
10. Willens HJ. Clopidogrel-induced mixed hepatocellular and cholestatic liver injury. *Am J Ther* 2000;7:317-8.
11. Maria VA, Victorino RM. Development and validation of a clinical scale for the diagnosis of drug-induced hepatitis. *Hepatology* 1997;26:664-9.
12. Trivier JM, Caron J, Mahieu M, Cambier N, Rose C. Fatal aplastic anaemia associated with clopidogrel. *Lancet* 2001; 357:446.
13. Cordes A, Vogt W, Maier KP. Pantoprazole-induced hepatitis [in German]. *Dtsch Med Wochenschr* 2003;128:611-4.
14. Clarke TA, Waskell LA. The metabolism of clopidogrel is catalyzed by human cytochrome P450 3A and is inhibited by atorvastatin. *Drug Metab Dispos* 2003;31:53-9.
15. Zeolla MM, Carson JJ. Successful use of clopidogrel for cerebrovascular accident in a patient with suspected ticlopidine-induced hepatotoxicity. *Ann Pharmacother* 1999; 33:939-41.