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# Ticlopidine Induced Cholestatic Jaundice

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## ABSTRACT

**Ticlopidine hydrochloride (Ticlid) has been increasingly used as an antiplatelet agent. Some studies showed that it has higher efficacy in reducing stroke recurrence when compared to conventional aspirin. Side effects like gastrointestinal disturbances and blood dyscrasias are common but ticlopidine induced cholestatic jaundice has been reported only rarely. We present a case report on a patient who has ticlopidine induced cholestatic jaundice.**


**Keywords: cholestatic jaundice, ticlopidine, adverse side effects**

## INTRODUCTION

Like aspirin, ticlopidine hydrochloride is widely used to treat many different vascular conditions because of its antiplatelet activity. Reversible abnormal liver function tests were reported in only 1% of patients receiving ticlopidine hydrochloride in 2 large clinical trials[1,2]. However, with its increasing widespread use, more cases of clinically severe cholestasis have been reported. To date there have been only 11 published case reports of ticlopidine-induced cholestasis, of which only three are in the English medical literature.

We report a Chinese patient with intrahepatic cholestasis associated with use of ticlopidine.

## CASE REPORT

A 65-year-old Chinese female was hospitalised for painless jaundice with tea-coloured urine of ten days duration. There was no history of blood transfusion, jaundice, significant alcohol ingestion, hepatitis or gallstone disease. She had a previous history of anteroseptal myocardial infarction 6 months ago and later became bed-bound after a brainstem stroke two months before the present admission. She was cared for at home and was treated with sublingual glyceryl nitrate and ticlopidine for the past two months. Ticlopidine 250 mg bd was started to treat her brainstem ischaemia. On clinical examination, she was deeply jaundiced, febrile and aphasic. Her blood pressure and pulse rate were 110/80 mmHg and 90 beats per minute respectively. No other stigmata of chronic liver disease was present. Her abdomen was soft, not tender and both the liver and spleen were non palpable. Her urine was markedly tea-coloured.

### Investigations

Haemoglobin level 10.2g/dL, total white cell count 21.2 x $10^9$/L, differential count - polymorphs 79%, lymphocytes 7%, monocytes 4%, eosinophils 9% and basophils 1%, platelet count of 375 x $10^9$/L, total protein 52 g/L(62-82), albumin 27 g/L(37-51), total bilirubin 118 μ/mol/L(3-24), alkaline phosphatase 1,158 U/L (32-103), ALT 251 U/L(7-36), AST 173 U/L(15-33), GGT 1,699 U/L(7-32). Urine showed presence of bile but no urobilin, urobilinogen or bile salts were detected; prothrombin time 11s (control 11s), activated partial thrombin time 23.5s (control 28s); serological tests for hepatitis A, B and C were negative, antimitochondrial and anti-smooth muscle antibodies were negative and leptospiral serology was also negative. Abdominal ultrasound and CT scan revealed a normal sized liver without any focal lesions. The intra and extra-hepatic biliary ducts were not dilated and no gallstones were detected. Her urine microscopy also showed pyuria of 70 to 80 white blood cells. Blood and urine cultures did not grow any micro-organisms.

She was treated for her urinary tract infection with intravenous ceftriaxone and gentamicin for a week and the ticlopidine was discontinued. A percutaneous liver biopsy was not carried out because she was unable to understand instructions and was not likely to cooperate during the procedure. Her liver function test repeated 8 weeks later showed total bilirubin of 10 μmol/L, alkaline phosphatase 797 U/L, ALT 77 U/L and AST 48 U/L. Unfortunately, she developed another stroke and died 12 weeks after her initial admission.

## DISCUSSION

Ticlopidine hydrochloride is widely used in a spectrum of vascular diseases as an antiplatelet agent and with increased usage, more reports of its possible side effects are available. In the Canadian American Ticlopidine Study, 4.4% of the 525 patients given ticlopidine developed abnormal liver function and two out of 23 patients were considered to have severe abnormal liver function[1]. However, in the Swedish Ticlopidine Multicentre Study, 6 out of 346 patients (1.8%) receiving ticlopidine developed hepatic symptoms as did an equal number of subjects in the placebo arm[3]. Presently, there have been 12 case reports of ticlopidine-induced cholestasis of which only 3 reports are in the English language.

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From the available literature, the following information on ticlopidine induced cholestatic jaundice is obtained:

1. Age of patients ranged from 45 to 92 years.
2. Onset of jaundice from day of commencement of ticlopidine ranged from 1 to 12 weeks[4,5].
3. Time taken for liver function to normalise after discontinuation of ticlopidine ranged from 5 days to 8 months[6,7].
4. Alkaline phosphatase and transaminase levels were elevated and varied widely.
5. None of the reported cases with ticlopidine induced cholestatic jaundice died from the condition.

The risk factors that predispose patients to ticlopidine induced cholestatic jaundice is still unknown as there is no clinical study to investigate the causal relationship between ticlopidine and cholestatic jaundice. From the available case reports, a common characteristic is that the majority of the patients except one, were elderly patients.

Our patient presented with cholestatic jaundice and extensive investigations ruled out other common causes such as viral hepatitis, leptospirosis, primary biliary cirrhosis, chronic active hepatitis, hepatobiliary sepsis, sclerosing cholangitis and gallstone disease. The repeat liver function test showed an improvement after her ticlopidine was discontinued. We believe that ticlopidine was the likely cause of our patient's cholestatic jaundice although, without re-challenge, it is impossible to prove the causation.

Cholestatic jaundice due to ticlopidine is a rare idiosyncratic side effect and clinicians who prescribe the drug must be aware of this potentially reversible condition. Thus, with this knowledge, when one encounters a patient with cholestatic jaundice and who is also currently on ticlopidine, a simple and effective way of managing the patient is to stop the drug without having to embark on extensive investigations.


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