

Clopidogrel-induced hepatotoxicity

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Following elective percutaneous coronary intervention (PCI), a 56-year-old man received clopidogrel 75 mg OD along with his long-term medication (> five years treatment with aspirin 75 mg OD and simvastatin 40 mg OD). Pre-PCI, his liver biochemistry (LFT's) was normal. Two months post PCI the patient complained of general malaise and was found to have deranged LFT's - [Figure 1]. There was no history of alcohol abuse.

Drug-induced liver disease was suspected and the patient was advised to discontinue clopidogrel. Serology for acute viral hepatitis, anti-mitochondrial antibody and anti-smooth muscle antibody all proved negative. Abdominal ultrasound revealed no abnormalities. At four weeks there was a marked improvement in his LFTs [Figure 1]. Clopidogrel was reintroduced but the patient again developed non specific symptoms and deranged LFTs [Figure 1]. Clopidogrel was discontinued indefinitely.

Clopidogrel-induced hepatotoxicity is an extremely rare side-effect (six cases in the published literature) and has not been reported in healthy volunteers.^[1]

Clopidogrel is converted by the hepatic cytochrome P450 (CYP3A4) to an active thiol metabolite. This metabolite binds specifically and irreversibly to the P2Y12 receptor, resulting in effective inhibition of ADP-induced platelet aggregation. Simvastatin is a lipophilic statin which is also metabolized by the CYP3A4 system to an inactive substrate. However, there is no pharmacodynamic evidence to suggest that the hepatotoxic effect of clopidogrel is attenuated by statin therapy or vice versa. Conversely, hepatic cytochrome P450 inhibitors (e.g. calcium channel blockers, macrolide antibiotics) are recognized to increase the risk of statin-induced hepatotoxicity.

The Maria and Victorino scale confirmed our diagnosis of drug-induced hepatitis.^[2] The scale has five components: the temporal relationship between drug administration and the onset of the clinical picture, exclusion of alternative causes,

extrahepatic manifestations, re-exposure and previous reports in the medical literature.

Current PCI guidelines recommend the obligatory use of dual antiplatelet therapy (clopidogrel and aspirin) in patients undergoing PCI.^[3] The previously used thienopyridine ticlopidine is associated with a wider side-effect profile,^[4] namely neutropenia in 2% and deranged LFTs in 4.3% of patients and has no current UK license.^[5] It is not known if there is cross-sensitivity to both agents. We therefore did not substitute clopidogrel for ticlopidine. The patient was treated with an increased dose of aspirin (150 mg OD) and remains well with normal LFTs six months post PCI.

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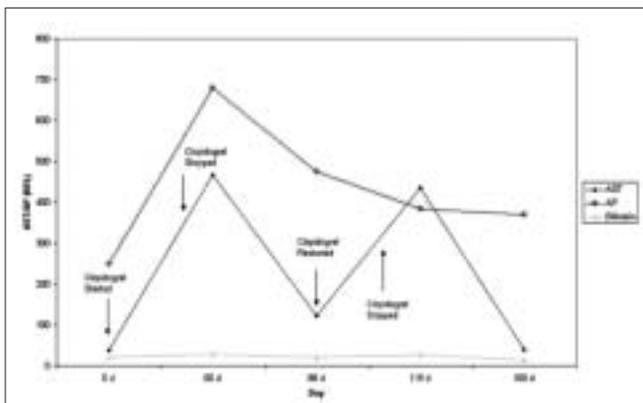


Figure 1: LFT

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