CLOPIDOGREL AND THROMBOTIC THROMBOCYTOPENIC PURPURA

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Summury:

Clopidogrel has replaced ticlopidine (in the united states but not worldwide). Clopidogrel can either be used independently or in combination with other antiplatelet agents. Clopidogrel has a lower frequency of associated thrombotic thrombocytopenic purpura than ticlopidine, a lower rate of neutropenia, and better gastrointestinal tolerance. We describe a case of thrombotic thrombocytopenic purpura in a patient 20 days after the start of clopidogrel treatment. All symptoms are reversed with cessation of clopidogrel. Clinicians should be alert to this adverse effect of clopidogrel and monitor platelet counts in patients receiving it.
Key-words: Clopidogrel - thrombotic thrombocytopenic purpura.

Introduction:

Thrombotic thrombocytopenic purpura is a rare thrombotic microangiopathy. It is a life threatening multisystem disease characterized by intravascular platelet aggregation which leads to profond thrombocytopenia (usually < 2000/ul), mechanical heamolytic anaemia, fever, and tissue ischaemia, commonly affecting the brain and kidneys (thrombosis of the small vessels) (1). Il is often fatal in the absence of treatment (mainly based on plasmapheresis). The cause is generally unknown. A drug-related cause is very rarely sought, and a causal link with a drug is difficult to establish. Ticlopidine is the drug most often involved. Recent reports involve clopidogrel. Other drugs, such as cytotoxic and immunosuppressive compounds have also been mentioned (2).
Ticlopidine and clopidogrel are specific and potent inhibitors of platelet aggregation. The two drugs are structurally related derivatives of thienopyridine, differing only by one carboxymethym group. Ticlopidine has been associated with the development of thrombotic thrombocytopenic purpura, with an estimated incidence of 1 case per 1600 to 5000 patients treated (3, 4).
Clopidogrel is a new antiplatelet drug that has achieved widespread clinicla acceptance because it has a more favorable safety profile than ticlopidine (5).

We describe a case of TTP occured in a patient 20 days after the start of clopidogrel treatment.

Case Report:

Our patient is a 71 year – old woman who had an anterior myocardial infarction in April 2004. After percutaneous transluminal angioplasty and stent placement, she was given PLAVIX* (clopidogrel), MONICOR* (5- isosorbid mononitrate), TENORMIN* (Atenolol), ASPEGIC*(Acetyl salicylic acid) and TAGAMET* (cimetidin). Six days after the start of medication, she has developped a stomach pain. A few days, later, she has presented an epistaxisis, purpura with renal insufficiency and anemia. Platelet counts were 38000/mm3, hemoglobin value was 10,8g/ml. Serum creatinine level was 328uml/l. The patient has also developped an acute liver injury, with marked elevation of serum aminotransferase levels and ASAT/ALAT= 1000/950 µI/l free bilirubin (38 umol/l). The prothrombin level (TP) was very low (19%). The abdominal echography has showed a steatosis. So, the patient underwent a plasma transfusion with drawal of all the therapy. The evolution was marked by resolution of symptoms and laboratory abormalities five days after stopping the drugs. The rechallenge of the therapy with the excption of clopidogrel has not led to recurrence of symptoms.

Discussion:

An inquiry of pharmacovigilance has been realized according to frensh imputation method. It has allowed to suspect strongly the responsibility of clopidogrel. The score of imputability has been evaluated at (C2 S2) I2 B3 “plausible”.

Since clopidogrel was approved by the FDA in early 1998, more than 3 million people have received the drug, and eleven cases of thrombotic thrombocytopenic purpura that occurred after clopidogrel use have been reported until 2000 (6). Naraw and al in 2001 (7) describe a case of TTP associated with the use of clopidogrel. Discontinuation of the drug and transfusion of 17 units of cryodepleted plasma resulted in resolution of the hematoglogical abnormalities. The eleven reports of TTP were analyzed using the bayesian Adverse Reaction Diagnostic Instrument to calculate the posterior probability that clopidogrel caused the TTP based on epidemiological and clinical trials data (expressed as prior adds) and the clinicla characteristics of each case (expessed as likelihood ratios). The result show that clopidogrel was implicated as the causative factor of the TTP(PsP > 0,75) in only five of the 11 cases (8).

It has been demonstrated that TTP plasmas contain heterogeneous platelet aggregating factors and that TTP plasmas induce the opoptosis of microvascular endothelial cell. Fibrinolysis has been shown decreased. Von Willebrand factor (VWF) under high shear stress is unfolded and becomes adhesive to platelets to induce platelet aggregation. Recently it is found that VWF protease is deficient in hereditary TTP, intermittent relapsing TTP, idiopathic acute TTP, and ticlopidine-induced TTP (9,10,11).

Thrombotic thrombocytopenic purpura can occur after the initiation of clopidogrel therapy, often within the first two weeks of treatment. So there is sufficient evidence to alert clinicians to this possibility and to the need to inform patients of this potential risk.

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