



*Jackson Lake and the Grand Tetons*

## PIC QUESTION OF THE WEEK: 2/28/11

Q: Describe the association of clopidogrel with thrombotic thrombocytopenic purpura?

A: Clopidogrel (Plavix) was first approved by the FDA in November of 1997 and labeled for the reduction of atherosclerotic events in patients with recent MI or stroke or established peripheral arterial disease. This antiplatelet agent is now one of the most commonly prescribed medications in the United States. Although generally well-tolerated, the drug has been associated with the development of thrombotic thrombocytopenic purpura (TTP). TTP is a complex disorder characterized by thrombocytopenia, microangiopathic hemolytic anemia, neurologic complications such as stroke, mildly elevated serum levels of lactate dehydrogenase, and, on occasion, renal insufficiency. Most cases of idiopathic TTP arise as a result of deficiency in a metalloproteinase enzyme known as ADAMTS-13. This enzyme is responsible for cleaving ultra-large von Willebrand factor (vWF) multimers into smaller units. vWFs are normally released from endothelial cells and contribute to platelet aggregation. Accumulation of ultra-large multimers enhances platelet aggregation and can result in TTP. The disorder has been associated with a number of autoimmune disorders and malignancy. In addition, several medications such as gemcitabine, cyclosporine, and tacrolimus have been associated with TTP. The FDA safety database has identified the thienopyridine compounds ticlopidine and clopidogrel as two of the most common drugs implicated in TTP. Ticlopidine generally produces TTP within 2-12 weeks of initiating treatment and results from production of antibody to ADAMTS-13. TTP secondary to clopidogrel typically develops within 2 weeks after initiating treatment. Unlike idiopathic and ticlopidine-associated TTP, clopidogrel does not induce antibodies or decrease ADAMTS-13 levels. In susceptible patients, clopidogrel appears to produce direct microvascular endothelial cell damage resulting in an inflammatory response and cell injury. These endothelial cells then release greater quantities of ultra-large vWFs and increase platelet aggregation. TTP is usually treated with therapeutic plasma exchange (TPE). Approximately 90% of patients with ticlopidine-induced TTP generally respond to TPE within several days of treatment. TPE does not produce this degree of response in clopidogrel-induced TTP and recovery may only be observed after several weeks of treatment. It should be noted that nearly 70% of patients with clopidogrel-induced TTP experience recovery without TPE. TTP is relatively rare; however, it must always be considered in patients who are prescribed clopidogrel and develop thrombocytopenia shortly after beginning treatment with the drug.

### References:

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- Bennett CL, Kim B, Zakarija A, et.al. Two mechanistic pathways for thienopyridine-associated thrombotic thrombocytopenic purpura: a report from the SERF-TTP Research Group and the RADAR Project. *J Am Coll Cardiol* 2007;50:1148-53.

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**The PIC Question of the Week is a publication of the Pharmaceutical Information Center, Mylan School of Pharmacy, Duquesne University, Pittsburgh, PA 15282 (412.396.4600).**