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مقاله نویسی علوم انسانی

اصول تنظیم قراردادها

آموزش مهارت های کاربردی در تدوین و چاپ مقاله
**Case Report**

Thrombotic Thrombocytopenic Purpura associated with Clopidogrel: a case report and review of the literature

**Taleb Azarm**\(^a\), **Ayatollah Sohrabi**\(^b\), **Hamid Mohajer**\(^c\), **Arezou Azarm**\(^d\)

**Abstract**

Thrombotic Thrombocytopenic Purpura (TTP) is a life-threatening, multisystem disease characterized by thrombocytopenia, microangiopathic hemolytic anemia, neurological changes, renal failure, and fever. These signs and symptoms are thought to be caused by microthrombi, composed of agglutinated platelets and fibrin, which deposit in the arterioles and capillaries without mediation by an inflammatory process. TTP can occur in the first two weeks of initiation of Clopidogrel therapy. Early signs of TTP may be a skin reaction, which may precede the onset of TTP or it may be other type of purpura or neurological changes. We report the clinical and laboratory findings in a 67 years old female patient in whom TTP developed soon after treatment with 40 mg/day oral Clopidogrel after 8 days. She developed thrombocytopenia (platelets count 12000/mm\(^3\)). Her clinical signs and symptoms were fever (39.6°C), bleeding from the nose and gum, large skin bruises (purpura and ecchymoses), neurological changes including hallucinations, bizarre behavior, altered mental status (fluctuating), headache, and renal dysfunction. Physicians should be aware of the possibility early onset of this syndrome when initiate Clopidogrel treatment.

**KEYWORDS:** Thrombotic Thrombocytopenic Purpura (TTP), Clopidogrel, plasma exchange.

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Acquired TTP is due to breast, gastrointestinal tract, and prostate cancer.\(^6\) Pregnancy can also trigger congenital and acquired TTP, especially in second trimester and postpartum after delivery.\(^7,8,14\) Some disease such as HIV, autoimmune diseases like systemic lupus erythematosus (SLE) may cause TTP by an acute immune-mediated response or dose-related toxicity.\(^9\) Heparin is the most common medication associated with thrombocytopenia (3-7% of patients with IV heparin use).

Other drugs which may be associated with TTP are Ticlopidine, Quinine, immune-mediated ingredient, cancer chemotherapeutic agents (Mitomycin C, Gemcitabine, Cisplatin, Tamoxifen, Bleomycin, Cytosine arabinoside, and Daunomycin), Cyclosporine A (CyA), oral contraceptives, Penicillin, Rifampin and anti-platelet drugs like ticlopidine.\(^10\) Other factors...
that can be associated with TTP are toxins (e.g. bee venoms), infectious process and sepsis, splenic sequestration, transplant-associated TTP, Vasculitis, vascular surgery (after 5-9 days), infections like Streptococcus pneumonia and cytomegalovirus.\textsuperscript{10-15}

The antiplatelet drug Clopidogrel is a new thienopyridine derivative whose mechanism of action and chemical structure are similar to those of ticlopidine.\textsuperscript{16} The estimated incidence of ticlopidine-associated TTP is 1 per 1600 to 5000 treated patients, whereas no Clopidogrel-associated cases have been observed among 20,000 closely monitored patients treated in third phase of clinical trials and cohort studies.\textsuperscript{17} Because of the association between the usage of ticlopidine and TTP and other adverse effects, Clopidogrel has achieved widespread clinical acceptance because it has a more favorable safety profile in comparison with ticlopidine.\textsuperscript{28} The two drugs are derivatives of thienopyridine, differing only in one carboxymethyl group.\textsuperscript{20} They have short half-life in the circulation and different metabolites. These drugs act by blocking an adenosine diphosphate–binding site on platelets, which inhibits the expression of glycoprotein IIb/IIIa receptor in the high-affinity configuration that binds fibrinogen and large multimers of von Willebrand factor.\textsuperscript{20}

**Case Report**

We report the clinical and laboratory findings of a patient that developed TTP eight days after treatment with Clopidogrel. The patient was a 67 year old female who suffered from hypertension and Hyperlipidemia for seven years. She had chest pain and acute cardiac ischemia due to coronary artery disease 15 days before using Clopidogrel. She had received coronary artery stents (because the patient did not consent to surgery) and medicated with Clopidogrel 75 mg/day, Metoprolol 50 mg bd/day, Amlodipin 5 mg/day and Lovastatin 20 mg/day. The last three drugs had been administered for seven years.

Eight days after receiving Clopidogrel she achieved thrombocytopenia (platelets count 12000 /mm3). Her clinical signs and symptoms were fever (39.6°C), bleeding from the nose and gum, large skin bruises (purpura and ecchymoses), neurological changes including hallucinations, bizarre behavior, altered mental status (fluctuating), and headache.

Other findings such as laboratory tests were as the following: Renal dysfunction (serum Creatinine level 2.5 mg/dl); microangiopathic hemolytic anemia (schistocyte on peripheral blood film examination); hemoglobin 6.3 g/100; hematocrit values were less than 21 percent; reticulocyte count 18%; lactate dehydrogenase (LDH) 980 u/l; serum SGOT(AST) 118 u/l; SGPT(ALT) 39 u/l; Total Bilirubin 17.8 mg/100 and direct bilirubin 0.6 mg/100.

Clopidogrel treatment was discontinued and patient underwent plasma exchange for 40 cc/kg body weight every day. Her plasma was replaced with fresh frozen plasma (FFP). Daily plasmapheresis was started and the patient received an average exchange of 3000 ml of FFP each day. Eleven days after her admission and plasma exchange, signs, symptoms and laboratory abnormalities disappeared and the platelet count normalized. Plasmapheresis was stopped three days later. The patient was visited every two days for three weeks and then every week for four weeks in an outpatient clinic. Afterwards we followed her monthly for 6 month, meanwhile everything was alright, and all tests was within normal range.

**Discussion**

It seems that the characteristics of TTP in our case was different from other TTP cases who used Ticlopidine. In our case, TTP occurred 8 days after the initiation of treatment. Other studies suggest that Clopidogrel-associated TTP is 15 times more likely to occur within the first 2 weeks of drug use.\textsuperscript{17,18}

TTP is a fulminant disease characterized by platelet aggregation, thrombocytopenia, renal insufficiency, neurologic changes, and mechanical injury to erythrocytes. Most idiopathic cases of TTP are characterized by ADAMTS13 (a disintegrin and metalloprotease, with thrombospondin-1-like domains) and metallo-
protease activity deficiency. The use of anti-platelet agents such as the thienopyridine deri- 
vatives like Clopidogrel and ticlopidine, is known to be associated with drug induced 
TTP.17-19

TTP is a rare complication of thienopyridine treatment. Thienopyridine toxicity appears to 
occur by two different pathways, primarily characterized by the time of onset. If TTP oc-
curs after 2 weeks of Ticlopidine or Clopidogrel therapy, therapeutic plasma exchange 
must be promptly performed to enhance like-
lihood of survival.20

The mechanism by which Clopidogrel can 
cause TTP is not known.21 Patients with idi-
opathic and Ticlopidine-associated TTP have 
an immune-mediated deficiency of von Wille-
brand factor–cleaving protease activity in 
plasma.21,22 Since 1999, identification of Clopi-
dogrel-associated TTP was started through in-
dependent active surveillance.29 Subsequent 
cases have been identified by pharmaceutical 
 suppliers of Clopidogrel and the Food and 
Drug Administration (FDA). The evaluation 
of quality and appropriateness of data for Clopi-
dogrel-associated TTP was reported during 
1998 to 2002. Regarding Clopidogrel, it was 
through 3 reporting systems [independent ac-
tive surveillance (n=13), pharmaceutical sup-
pliers (n=24), and the FDA (n=13)] and identi-
fied prognostic factors associated with mortal-
ity.17

An article published in Prescriber Update in 
February 1997, advised that some studies have 
shown that in addition to some fatalities, Tic-
lopidine may cause life threatening hematolo-
gical reactions that are usually reversible. Re-
cent evidence indicates that its related mortal-
ity and adverse reactions may occur more fre-
quently than what was expected previously.22

The survival rate for patients suffering from 
Clopidogrel-associated TTP was 71.2%. Receipt 
of therapeutic plasma exchange within 3 days 
of onset of TTP significantly increased the like-
lihood of survival (100% versus 27.3%). Clopi-
dogrel-associated TTP often occurs within two 
weeks from drug initiation. If plasma exchange 
doesn’t start soon, the rate of relapses and 
highly mortality will increase.22 TTP requires 
up to 30 plasma exchanges before clinical im-
provement occurred.

Our findings have important clinical impli-
cations. Clopidogrel has largely replaced Tic-
lopidine in clinical practice.25 One of the rea-
sons for this change was the association of TTP 
with the usage of Ticlopidine. Other reasons 
were the lower rates of skin, hematologic, and 
gastrointestinal adverse effects associated with 
Clopidogrel and its more convenient dosing 
schedule.23,24,26 The development of cardiac or 
neurologic changes after the initiation of Clo-
pidogrel therapy may be mistakenly attributed 
to the underlying condition for which it was 
prescribed.18,19,24

However, patients who take Clopidogrel 
should be warned about the risk of TTP and its 
symptoms. The likelihood of the death of pa-
tients on these medications can be reduced by 
up to 60% if cases with a high index of suspi-
cion are referred to a hematologist for early 
intervention including plasmapheresis.19,23,27

Conclusions
TTP can occur in the first two weeks of initia-
tion of Clopidogrel therapy. Early signs of TTP 
may be a skin reaction, which may precede the 
onset of TTP or it may be an indication of pur-
pura, and neurological changes. Complete 
blood count and creatinine level determination 
assist in the diagnosis. Physicians should be 
aware of the possible early onset of this syn-
drome when initiate Clopidogrel treatment.

Conflict of Interests
Authors have no conflict of interests.
Authors’ Contributions
TA coordinated the study and prepared the manuscript. AS provided assistance in manuscript preparation. HM visited the patient and gathered the data. AA provided assistance in manuscript preparation. All authors have read and approved the content of the manuscript.

References
1. Sadler JE, Moake JL, Miyata T, George JN. Recent advances in thrombotic thrombocytopenic purpura. Hematology Am Soc Hematol Educ Program. 2004;407-23.
2. Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of new black box warnings and withdrawals for prescription medications. JAMA 2002; 287(17): 2215-20.
3. Levy GG, Nichols WC, Lian EC, Foroud T, McClintick JN, McGee BM, et al. Mutations in a member of the ADAMTS gene family cause thrombotic thrombocytopenic purpura. Nature 2001; 413(6855): 488-94.
4. Tsai H-M, Rice L, Savode R, Chow TW, Moake JL. Antibody inhibitors to von Willebrand factor metalloproteinase and increased von Willebrand factor-platelet binding in ticlopidine-associated thrombotic thrombocytopenic purpura. Ann Intern Med 2000; 132(10): 794-9.
5. Furlan M, Robles R, Solenthaler M, Wassmer M, Sandoz P, Lämmlle B. Deficient activity of von Willebrand-factor cleaving protease in chronic relapsing thrombotic thrombocytopenic purpura. Blood 1997; 89(9): 3097-103.
6. Fujikawa K, Suzuki H, McMullen B, Chung D. Purification of human von Willebrand factor-cleaving protease and its identification as a new member of the metalloproteinase family. Blood 2001; 98(6): 1662-6.
7. George JN. The association of pregnancy with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Curr Opin Hematol 2003; 10(5): 339-44.
8. George JN. Clinical practice. Thrombotic thrombocytopenic purpura. N Engl J Med 2002; 347(8): 589-600.
9. Chang JC, Shipstone A, Llenado-Lee MA. Postoperative thrombotic thrombocytopenic purpura following cardio-vascular surgeries. Am J Hematol 1996; 53(2): 133-4.
10. Au, WY, Lie, AK, Kwong, YL. Rituximab in thrombotic microangiopathy: response to Castagna et al. Br J Haematol. 2007; 139(1): 166.
11. Kincaid-Smith P, Fairley KF, Kloss M. Lupus anticoagulant associated with renal thrombotic microangiopathy and pregnancy-related renal failure. Q J Med 1998; 68(258): 795-815.
12. Willye BF, Garg AX, Macnab J, Rock GA, Clark WF; Members of the Canadian Apheresis Group. Thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome: a new index predicting response to plasma exchange. Br J Haematol 2006; 132(2): 204-9.
13. Bennett CL, Connors JM, Carwile JM, Moake JL, Bell WR, Tarantolo SR, et al. Thrombotic thrombocytopenic purpura associated with clopidogrel treatment: evidence of a nonimmunological etiology. Transplantation 2002; 74(6): 885-7.
14. Rock GA. Management of thrombotic thrombocytopenic purpura. Br J Haematol 2002; 109(3): 496-507.
15. Palmisano J, Agraharkar M, Kaplan AA. Successful treatment of cisplatin-induced hemolytic uremic syndrome with therapeutic plasma exchange. Am J Kidney Dis 1998; 32(2): 314-7.
16. Majhail NS, Lichtin AE. Clopidogrel and thrombotic thrombocytopenic purpura: no clear case for causality. Cleveland Clin J Med 2003; 70(5): 466-70.
17. Bennett CL, Connors JM, Carwile JM, Moake JL, Bell WR, Tarantolo SR, et al. Thrombotic thrombocytopenic purpura associated with clopidogrel. N Engl J Med 2000; 342(24): 1773-7.
18. Rock GA. Management of thrombotic thrombocytopenic purpura. Br J Haematol 2000; 109(3): 496-507.
19. Palmisano J, Agraharkar M, Kaplan AA. Successful treatment of cisplatin-induced hemolytic uremic syndrome with therapeutic plasma exchange. Am J Kidney Dis 1998; 32(2): 314-7.
20. Patel TN, Kreindel M, Lincoff AM. Clopidogrel and Ticlopidine Mediation of TTP: A Case Report. J Invasive Cardiol 2006; 18(7): E211-3.
21. Bennett CL, Connors JM, Carwile JM, Moake JL, Bell WR, Tarantolo SR, et al. Thrombotic thrombocytopenic purpura associated with clopidogrel. N Engl J Med 2000; 342(24): 1773-7.
22. Rock GA. Management of thrombotic thrombocytopenic purpura. Br J Haematol 2000; 109(3): 496-507.
23. Palmisano J, Agraharkar M, Kaplan AA. Successful treatment of cisplatin-induced hemolytic uremic syndrome with therapeutic plasma exchange. Am J Kidney Dis 1998; 32(2): 314-7.
24. Majhail NS, Lichtin AE. Clopidogrel and thrombotic thrombocytopenic purpura: no clear case for causality. Cleveland Clin J Med 2003; 70(5): 466-70.
25. Wood AJ. Thrombotic thrombocytopenic purpura and clopidogrel: a need for new approaches to drug safety. N Engl J Med 2000; 342(24): 1824-6.
26. McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet 2004; 364(9444): 1519-21.
27. Ong AT, McFadden EP, Regar E, de Jaegere PP, van Domburg RT, Serruys PW. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. J Am Coll Cardiol 2005; 45(12): 2088-92.
28. Mangalpally KK, Kleiman NS. The safety of clopidogrel. Expert Opin Drug Saf 2011; 10(1): 85-95.
29. Yoshii F. Clopidogrel-associated thrombotic thrombocytopenic purpura. Rinsho Shinkeigaku 2009; 49(6): 374-5.
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