

# Tazobactam and piperacillin-induced thrombocytopenia: A case report

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**Abstract.** The present study reports a case of tazobactam and piperacillin (TZP)-induced thrombocytopenia in an elderly patient, from which complete clinical data and peripheral blood samples were collected. Platelet numbers were decreased 1 day following TZP treatment initiation; however, they were revealed to have increased 1-2 days following withdrawal of TZP, and had reached normal levels 3-5 days later. There was no evidence of bone marrow suppression, antibodies against peripheral plasma platelets were absent and levels of complement C3 were decreased. These results suggested that TZP was able to cause rapid and reversible thrombocytopenia, which was not associated with bone marrow suppression but may have involved activation of complement C3. The results of the present study therefore suggest that doctors should be aware of the risk of thrombocytopenia in patients treated with TZP.

## Introduction

In normal human blood, every mm<sup>3</sup> contains 10-30x10<sup>4</sup> platelets, the average lifespan of which is 8-10 days (1). If the platelet count decreases to <10x10<sup>4</sup> mm<sup>3</sup>, the patient is diagnosed with thrombocytopenia (2). Thrombocytopenia, if severe, may cause symptoms, such as mucosal bleeding from the nose, mouth and gastrointestinal tract (3). Tazobactam and piperacillin (TZP) are antibiotics that are used to treat the majority of infections caused by  $\beta$ -lactamase-producing

bacteria (4,5). Common adverse reactions associated with TZP treatment include neutropenia, leukopenia and thrombocytopenia, urticaria, allergic shock, exfoliative dermatitis, and adverse reactions of the nervous system (6-8). These adverse reactions typically occur simultaneously and thrombocytopenia rarely manifests independently of other symptoms (9). The patients with thrombocytopenia associated with TZP may report severe bleeding at a number of locations, including gastrointestinal tract bleeding, a cerebral hemorrhage or subcutaneous bleeding (10). The mechanism by which TZP causes thrombocytopenia is unclear, however, drug-induced thrombocytopenia is typically hypothesized to have three possible underlying mechanisms; these are immune-mediated, direct platelet number decreases and bone marrow suppression (11). The present study investigated the occurrence of thrombocytopenia in a single patient treated with TZP, as well as its clinical features, in order to investigate potential underlying mechanisms.

## Case report

A 76-year-old male patient with a 20-year history of hypertension was admitted to the intensive care unit (ICU) of Ningbo First Hospital (Ningbo, China) in February 2013 complaining of dizziness, vomiting and slurred speech. Informed consent was obtained from the patient, after which blood samples were taken and a clinical evaluation was conducted. A computed tomography scan of the brain and lungs suggested that the patient was suffering from a cerebral infarction and pneumonia. The patient was treated with aspirin, in order to reduce the levels of platelets, with nifedipine, in order to control blood pressure and improve cerebral circulation, and with TZP (dose, 4.5 g; administered every 8 h intravenously), starting from the 3rd day following admission. However, the platelet levels of the patient rapidly dropped to 13x10<sup>9</sup> platelets/l, but the size of the liver and spleen were deemed normal, determined using B-scan ultrasound examination. In order to ameliorate the platelet deficit, aspirin treatment was terminated, and the patient was administered 10 units infused platelets, 40 mg methylprednisolone and 5 g gamma globulin once daily, for 2 weeks. However, the platelet levels remained low and, on the 16th day following admission, TZP treatment was substituted with meropenem

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**Abbreviations:** ESR, erythrocyte sedimentation rate; TZP, tazobactam and piperacillin

**Key words:** piperacillin-tazobactam, thrombocytopenia

Table I. WBC and PLT levels altered over time during TZP and meropenem treatment.

Day	WBC (10 <sup>9</sup> /l)	PLT (10 <sup>9</sup> /l)
1	7.6	223
3	16.8	13
4	8.4	22
5	6.1	45
6	8.7	36
7	3.1	20
8	13.4	56
9	13.1	69
10	13.5	72
11	10	49
12	10.9	38
13	12.9	12
14	8	20
15	9	18
16	9.3	19
17	7.9	42
18	10.3	197
19	7.7	145
20	8.4	16.2
21	11.9	75
22	8.4	35
23	7	19.6
24	4.6	32.6
25	9.7	105
26	4.1	57
27	5.1	61
28	7	92
29	7.4	107

TZP treatment was initiated on days 3 and 20, and was withdrawn and replaced by meropenem treatment on days 16 and 23. WBC, white blood cells; PLT, platelets; TZP, tazobactam and piperacillin.

treatment (dose, 1.0 g; administered every 8 h intravenously) in order to restore platelets to normal levels (Table I and Fig. 1A). Over the next 2 days, the platelet count of the patient increased from  $19 \times 10^9$  to  $19.7 \times 10^{10}$  platelets/l. On the 20th day following admission, the TZP treatment regimen was restored, inducing the platelet count of the patient to decrease to  $16.2 \times 10^9$  platelets/l; substitution of TZP with meropenem on the 23rd day following admission again caused the platelet count to return to normal ( $10.5 \times 10^{10}$  platelets/l) over a period of 2 days. The preliminary diagnosis of the patient was idiopathic thrombocytopenic purpura.

A laboratory examination demonstrated that the erythrocyte sedimentation rate (ESR; 37 mm/h) and the levels of immunoglobulin (Ig) G (2,260 mg/dl) were increased; however, IgA, IgM, complement C3, complement C4, streptolysin and rheumatoid factors, anti-cardiolipin (ACA), antinuclear, anti-Smith, anti-U1-nuclear ribonucleoprotein, anti-Ro/Sjögren's-syndrome-related antigen A, anti-Ro-52,

Table II. Laboratory examination of the patient.

Variable	Result	Change	Normal range	Unit
ESR	37	+	<15	mm/h
IgG	2,260	+	726-1,685	mg/dl
IgA	158	n	69-382	mg/dl
IgM	67	n	63-277	mg/dl
C3	70.4	-	85-193	mg/dl
C4	12.1	n	12-36	mg/dl
ASO	70.9	n	0-200	IU/ml
RF	<20	n	0-30	IU/ml
ACA	N	n	N	N/A
ANCA	N	n	N	N/A
ANA	N	n	N	N/A
Sm-Ab	N	n	N	N/A
U1-Nrnp-Ab	N	n	N	N/A
Anti-SSA	N	n	N	N/A
Ro-52-Ab	N	n	N	N/A
Anti-SSB	N	n	N	N/A
Scl-70-Ab	N	n	N	N/A
Jo-1-Ab	N	n	N	N/A
dsDNA-Ab	N	n	N	N/A
AnuA-Ab	N	n	N	N/A
PCNA-Ab	N	n	N	N/A
AMA-M2	N	n	N	N/A
AHA-Ab	N	n	N	N/A
PM-Scl-Ab	N	n	N	N/A
r-Prot-Ab	N	n	N	N/A
AKA	N	n	N	N/A
anti-PLT	N	n	N	N/A

ESR, erythrocyte sedimentation rate; Ig, immunoglobulin; C, complement; ASO, anti-streptolysin O; RF, rheumatoid factors; ACA, anti-cardiolipin; ANCA, anti-neutrophil; ANA, antinuclear; Sm, anti-Smith; U1-Nrnp, anti-U1-nuclear ribonucleoprotein; Ab, antibody; Anti-SSA, anti-Ro/Sjögren's-syndrome-related antigen A; Anti-SSB, anti-La/Sjögren's-syndrome-related antigen B; AnuA, anti-nucleosome; PCNA, anti-proliferating cell nuclear antigen; AMA-M2, anti-mitochondrial-M2; AHA, anti-histone; r-Prot, anti-ribosomal P-protein; AKA, anti-keratin; anti-PLT, anti-platelet; N, negative; n, normal; +, positive change; -, negative change.

anti-La/Sjögren's-syndrome-related antigen B, anti-Scl-70, anti-Jo-1, anti-dsDNA, anti-nucleosome, anti-proliferating cell nuclear antigen, anti-mitochondrial-M2, anti-histone, anti-PM-Scl, anti-ribosomal P-protein, anti-keratin and anti-neutrophil cytoplasmic antibodies were normal (Table II), determined using immunoturbidimetry, in accordance with a previous study (12). IgG levels were detected by immunoturbidimetry with an IMMAGE 800 system (Beckman Coulter, Inc., Brea, CA, USA). A bone marrow smear examination detected no obvious abnormalities. Additional assays were conducted as follows: ACA and anti-neutrophil antibodies were detected using western blotting (data not shown); anti-hepatitis C and anti human immunodeficiency virus using an enzyme-linked immunosorbent assay (ELISA;

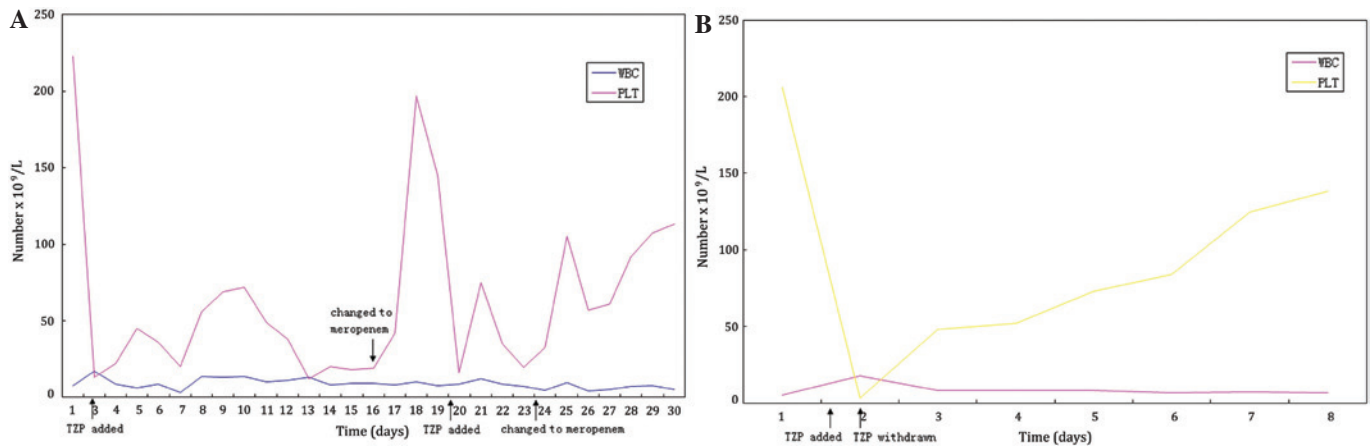


Figure 1. Alterations in the levels of WBC and PLT following TZP treatment at (A) first and (B) the second admission. Arrows indicate times of the indicated treatments. WBC, white blood cells; PLT, platelets; TZP, tazobactam and piperacillin.

Table III. WBC and PLT levels altered over time following the second TZP treatment.

Day	WBC (x10 <sup>9</sup> /l)	PLT (x10 <sup>9</sup> /l)
1	5.4	206
4	17.6	3
5	8.2	48
6	8	52
7	8	73
8	6.7	84
9	7.1	125
10	6.5	138

TZP treatment was initiated and withdrawn on day 4 following admission of the patient. WBC, white blood cells; PLT, platelets; TZP, tazobactam and piperacillin.

Zhuhai Livzon Diagnostics, Inc., Zhuhai, China); and platelet antibodies using a solid-phase antiglobulin test using an immunity micro column incubator (Changchun Boyan Technology Instrument Co., Ltd., Changchun, China). Assays for ACA, anti-neutrophil, anti-hepatitis C virus, anti-human immunodeficiency virus and plasma platelet antibodies were negative (13). Furthermore, the thyroid function of the patient was normal, and the liver and spleen sizes were demonstrated to be normal via an abdominal B ultrasound. The patient was discharged from the hospital after 41 days of treatment.

In December 2013, the same patient was re-hospitalized complaining of an inability to swallow, pulmonary aspiration and a high temperature. The patient was diagnosed with aspiration pneumonia and was treated with 4.5 g TZP every 8 h, in order to eliminate the infection; however, on the same day, the levels of platelets were markedly reduced to 3x10<sup>9</sup> platelets/l, as determined via manual counting. Conversely, substitution of TZP treatment with cefoperazone (dose, 2.0 g; administered every 8 h intravenously) resulted in the platelet levels returning to normal after 5 days, suggesting that there was an association between TZP and the occurrence

of thrombocytopenia. Therefore, the initial diagnosis of idiopathic thrombocytopenic purpura was revised to drug-induced thrombocytopenia (Table III and Fig. 1B).

## Discussion

TZP treatment is commonly used in the ICU; however, TZP-induced thrombocytopenia is not commonly reported. In the present study, an elderly patient admitted to the ICU presented with thrombocytopenia, which was associated with TZP treatment. Clinical laboratory results demonstrated that the TZP-induced thrombocytopenia was abrupt (12 h later it had markedly decreased) and reversible, as platelet numbers were normal within 3-5 days following withdrawal of TZP. Although the platelet count decreased following treatment with methylprednisolone and gamma globulin, the platelet number remained particularly low for 1 month. However, subsequent to withdrawal of TZP treatment, the platelet level increased, confirming the hypothesis that thrombocytopenia was induced by TZP.

The main reason that doctors may ignore the association between TZP treatment and platelet reduction is that it has only rarely been reported in the literature (10,14,15). The present study suggested that doctors should be aware of the risks of TZP-induced thrombocytopenia, and that TZP treatment should be discontinued following detection of drug-induced thrombocytopenia.

The mechanism underlying TZP-induced thrombocytopenia is currently unclear. Previous studies have suggested that drug-induced thrombocytopenia may occur due to drug-induced suppression of the bone marrow (16,17). Conversely, other studies have suggested that TZP, which is a 500-1,000 Da drug, may associate with the platelet membrane antigen, stimulating the body to produce antibodies against the TZP-platelet complex; this, in turn, may activate the complement system in order to promote platelet destruction (18-20). In the present study, the adverse effects of TZP were predominantly associated with immune-mediated thrombocytopenia; however, the molecular pathogenesis underlying TZP-induced thrombocytopenia has yet to be elucidated and requires additional study.

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