Tazobactam and piperacillin-induced thrombocytopenia: A case report

HONG CHEN1,2*, ZHEN FAN1,2*, FEI GUO3*, YUMIN YANG1,2, JIE LI1,2, JIE ZHANG1,2, YUDAN WANG1,2, JIANWEI LE1,2, ZHIYU WANG1,2 and JIANHUA ZHU1,2

1Intensive Care Unit, Ningbo First Hospital; 2Intensive Care Unit, Ningbo Hospital of Zhejiang University; 3Clinical Laboratory, Ningbo First Hospital, Ningbo, Zhejiang 315000, P.R. China

Received March 9, 2015; Accepted October 29, 2015

DOI: 10.3892/etm.2016.3062

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 mm³ contains 10-30x10⁴ platelets, the average lifespan of which is 8-10 days (1). If the platelet count decreases to <10x10⁴ mm³, 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 β-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 13x10⁹ 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.
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 19x10^9 to 19.7x10^9 platelets/l. On the 20th day following admission, the TZP treatment regimen was restored, inducing the platelet count of the patient to decrease to 16.2x10^9 platelets/l; substitution of TZP with meropenem on the 23rd day following admission again caused the platelet count to return to normal (10.5x10^10 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, anti-La/Sjögren's-syndrome-related antigen B, anti-Scl-70, anti-Jo-1, anti-dsDNA, anti-nucleosome, anti-proliferating cell nuclear antigen, anti-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.

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

| Day | WBC (10^9/l) | PLT (10^9/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.

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/A          |
| ANCA                | N      | n      | N/A          |
| ANA                 | N      | n      | N/A          |
| Sm-Ab               | N      | n      | N/A          |
| U1-Nmp-Ab           | N      | n      | N/A          |
| Anti-SSA            | N      | n      | N/A          |
| Ro-52-Ab            | N      | n      | N/A          |
| Anti-SSB            | N      | n      | N/A          |
| Scl-70-Ab           | N      | n      | N/A          |
| Jo-1-Ab             | N      | n      | N/A          |
| dsDNA-Ab            | N      | n      | N/A          |
| AnuA-Ab             | N      | n      | N/A          |
| PCNA-Ab             | N      | n      | N/A          |
| AMA-M2              | N      | n      | N/A          |
| AHA-Ab              | N      | n      | N/A          |
| PM-Scl-Ab           | N      | n      | N/A          |
| r-Prot-Ab           | N      | n      | N/A          |
| AKA                 | N      | n      | N/A          |
| anti-PLT            | 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-Nmp, 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.
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 3x10^9 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.

| Day | WBC (x10^9/l) | PLT (x10^9/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.

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

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.
Acknowledgements

The present study was supported by grants from the Ningbo Natural Science Foundation of China (grant no. 2013A610234), the Zhejiang Natural Science Foundation of China (grant no. LQ15H150001) and the Chinese Medicine Research Program of Zhejiang Province, China (grant no. 2015ZA185). The authors of the present study would like to thank Dr Xiang Hou (Ningbo University, Ningbo, China) for assistance in platelet quantification.

References

1. Bautista AP, Buckler PW, Towler HM, Dawson AA and Bennett B: Measurement of platelet life-span in normal subjects and patients with myeloproliferative disease with indium oxine labeled platelets. Br J Haematol 58: 679-687, 1985.

2. Smock KJ and Perkins SL: Thrombocytopenia: An update. Int J Lab Hematol 36: 269-278, 2014.

3. Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussel JB, Chong BH, Cines DB, Gernsheimer TB, Godeau B, et al: International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 115: 168-186, 2010.

4. Gonçalves-Pereira J and Póvoa P: Antibiotics in critically ill patients: A systematic review of the pharmacokinetics of β-lactams. Crit Care 14: 208-225, 2010.

5. Bourget P, Lesne-Hulin A, Le Reveillé R, Le Bever H and Carsin H: Clinical pharmacokinetics of piperacillin-tazobactam combination in patients with major burns and signs of infection. Antimicrob Agents Chemother 40: 139-145, 1996.

6. Finsterer J and Kotzailias N: Thrombocytopenia under ciprofloxacin and tazobactam/piperacillin. Platelets 14: 329-331, 2003.

7. Reichardt P, Handrick W, Linke A, Schille R and Kiess W: Leukocytopenia, thrombocytopenia and fever related to piperacillin/tazobactam treatment - a retrospective analysis in 38 children with cystic fibrosis. Infection 27: 355-356, 1999.

8. Anand A and Chauhan HK: Piperacillin and vancomycin induced severe thrombocytopenia in a hospitalized patient. Platelets 22: 304-309, 2011.

9. Macwilliam JL, Mistry R, Floyd MS Jr and Baird AD: Piperacillin/tazobactam induced thrombocytopenia - a delayed response. BMJ Case Rep 2012: bcr0320125981, 2012.

10. Uzun G, Onem Y, Hatipoglu M, Turhan V, Mutluoglu M and Ay H: Piperacillin/tazobactam-induced neutropenia, thrombocytopenia, and fever during treatment of a diabetic foot infection. Scand J Infect Dis 45: 73-76, 2013.

11. Ramot Y and Nyska A: Drug-Induced Thrombosis - Experimental, clinical, and mechanistic considerations. Toxicol Pathol 35: 208-225, 2007.

12. Cines DB, Bussel JB, Liebman HA and Luning Prak ET: The ITP syndrome: Pathogenic and clinical diversity. Blood 113: 651-652, 2009.

13. Zhang L, Li H, Zhao H, Ji L and Yang R: Hepatitis C virus-related adult chronic idiopathic thrombocytopenic purpura: Experience from a single Chinese centre. Eur J Haematol 70: 196-197, 2003.

14. Macwilliam JL, Mistry R, Floyd MS Jr and Baird AD: Piperacillin/tazobactam-induced thrombocytopenia - a delayed response. BMJ Case Rep, 2012.

15. Shaik S, Kazi HA and Ender PT. Rapid-onset piperacillin-tazobactam induced thrombocytopenia. J Pharm Pract 28: 204-206, 2015.

16. Ruiz-Irastorza G, Barreiro G and Aguirre C: Reversible bone marrow depression by high-dose piperacillin/tazobactam. Br J Haematol 95: 611-612, 1996.

17. Kumar A, Choudhuri G and Aggarwal R: Piperacillin induced bone marrow suppression: A case report. BMC Clin Pharmacol 3: 2, 2003.

18. Kelton JG, Meltzer D, Moore J, Giles AR, Wilson WE, Barr R, Hirsh J, Neame PB, Powers PJ, Walker I, et al: Drug-induced thrombocytopenia is associated with increased binding of IgG to platelets both in vivo and in vitro. Blood 58: 524-529, 1981.

19. Pérez-Váquez A, Pastor JM and Riancho JA: Immune thrombocytopenia caused by piperacillin/tazobactam. Clin Infect Dis 27: 650-651, 1998.

20. Grégoire C, Brumpt C, Loirat D, Lau N, Bruel C, Philippart F, Couzigou C, Garrouste-Orgeas M and Misset B: A case of daptomycin-induced immune thrombocytopenia. Antimicrob Agents Chemother 56: 6430-6431, 2012.