

Piperacillin-Tazobactam Toxicity Questions the Need for Pediatric Adverse Event Profiling

Sabrina A Gmuca*, Nicole Pouppirt and Gabrielle Gold-von Simson

New York University Langone Medical Center, New York, USA

Abstract

A 14-year-old, 86 kg, female treated with piperacillin-tazobactam [cumulative dose of 114.75 g (1.3 g/kg)] for a bone-related infection developed neutropenia and bone marrow suppression/cell line destruction after 10 days of treatment. Reported cases of piperacillin-induced myelosuppression in adults typically occur after 15 days of therapy, and this adolescent received a much shorter duration of therapy. As we are beginning to understand how the frequent use of antibiotics in the pediatric population affects their unique microbiome, which may have long-term implications on their health, we also need to consider if adverse event profiles are distinct or different in children. While this case will not answer these important questions, it underscores the need for further investigation. One could postulate that pediatric pharmacovigilance is better served by restricting data mining analysis to a smaller pediatric subset, as adverse/possible events in children cannot be solely compared to or tabulated with adult data. Further studies are needed to determine pediatric-specific drug safety profiles for piperacillin-tazobactam and other drugs used in the pediatric population.

Keywords: Myelosuppression; Piperacillin-Tazobactam; Toxicity; Pharmacovigilance

Abbreviations: ANC: Absolute Neutrophil Count; FDA: Food and Drug Administration; MCV: Mean Corpuscular Volume; RBC: Red Blood Cell; WBC: White Blood Cell

Introduction

The inhibition of granulopoiesis by penicillin agents has been known for some time with case reports dating back to 1946 [1,2]. Piperacillin is a parenteral, semi-synthetic, extended spectrum penicillin, approved for use by the FDA in 1993, that is known to cause bone marrow toxicity by inducing proliferation arrest of myeloid cells [3] and thus reversible neutropenia [4]. Therefore healthcare professionals frequently discontinue the use of such therapy in patients with decreasing white blood cell counts. Some sources report rarity of neutropenia secondary to piperacillin before 10 days of therapy whereas others report a minimum of 15 days of therapy before the adverse effects of myelosuppression are clinically apparent [2,3]. Some investigators propose that piperacillin-tazobactam toxicity is greater in children [5]. In fact, in the 3 cases of piperacillin-tazobactam-induced neutropenia reported in children, toxicity developed after 11-15 days of treatment, a shorter interval than reported for adults [6]. Thus despite the common use of piperacillin there is a lack of clear guidelines regarding safe duration of administration and specific adverse events in the pediatric population. Furthermore, if these events were mined in a smaller pediatric database, perhaps we could ascertain a more comprehensive pediatric pharmacovigilance profile.

Case Report

AP is a 14-year-old, 86 kg female with no significant past medical or surgical history who sustained a right tibia and fibula fracture after jumping out her first floor bedroom window at night. She had external traction performed on the day of the injury and an open reduction; internal fixation performed 12 days later. Post-operatively, she developed fever and drainage from the wound site. She was subsequently started on piperacillin-tazobactam and continued on this therapy for a total of 11 days. On day 9 of therapy, she developed a high-grade fever and the piperacillin-tazobactam was discontinued on day 11. Her initial dose was 2.25 g q8h for the first 5 days, started an outside hospital, and then she was increased to 3.375 g q6h for the

remainder of her course. The patient also had wound debridement and skin flap placement during this same time course. Her only other medications included acetaminophen alone and in conjunction with hydrocodone as needed for pain management.

Within 10 days, the patient significantly dropped her hemoglobin, her WBC, and ANC; and she developed thrombocytopenia on day 11 of therapy and the medication was subsequently discontinued (Table 1). In summary, during the patient's piperacillin-tazobactam course, her hemoglobin decreased 43% (from 9.2 to 5.2 g/dL) on day 8 with a corresponding RBC mass decrease of 42% (from 3.32 to 1.9 M/uL). Her WBC decreased 53% (from 7.5 to 3.5 K/uL) and the ANC decreased 57% (from 4950 to 2100 cells/ml) on day 10 of therapy. The patient's platelets decreased 74% overall (from 522 to 134 K/uL). Shortly after the piperacillin-tazobactam was discontinued, the patient defervesced and all hematologic indices normalized.

Discussion

Review of existing literature reveals a general consensus of a minimum duration of piperacillin administration of 15 days in order to induce acute myelosuppression [7]. In addition, large cumulative doses are needed to result in neutropenia, however, what constitutes a large cumulative dose is poorly defined in the literature and is not pediatric specific or selective. A few case reports, including our patient case, support a shorter duration of therapy and a smaller cumulative dose necessary for inducing bone marrow suppression in pediatric patients.

Sheetz and colleagues reported a systematic review of piperacillin-induced neutropenia. In their review of case reports, all cases of neutropenia secondary to piperacillin occurred 15 days or greater after initiation of beta-lactam treatment. Laboratory values normalized in

*Corresponding author: Sabrina Gmuca, MD, 316 East 34St Apt 2B NY, NY 10016, USA, Tel: 718-614-5251; Fax: 212-263-8172; E-mail: sabrina.gmuca@nyumc.org

Received May 09, 2013; Accepted May 25, 2013; Published May 30, 2013

Citation: Gmuca SA, Pouppirt N, Gold-von Simson G (2013) Piperacillin-Tazobactam Toxicity Questions the Need for Pediatric Adverse Event Profiling. *Pediat Therapeut* 3: 144. doi:10.4172/2161-0665.1000144

Copyright: © 2013 Gmuca SA, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Lab Value			WBC	RBC	Hgb	HCT	PLT	MCV	RDW	Retic	ANC
Normal Range			(4.0-10.5 K/uL)	(4.10-5.30 M/uL)	(12-15g/dL)	(35.0-47.0%)	(150-400 K/uL)	(78-95 FL)	(11.5-14.5%)	(0.5-2.2%)	(>1,500 cells/uL)
Dose of Piperacillin-Tazobactam	Date (day of therapy)	Time									
2.25 g q8h	START 4/15 (1)	14:20	7.5	3.32	9.2	26.6	522	79.9	12		4,950
2.25 g q8h	4/18 (4)	14:22	6.6	3.24	8.8	25.9	451	79.9	12.1		3,960
2.25 g q8h	4/20 (6)	23:45	8.9	2.92	8.1	22.9	362	78.4	12.5		
3.375 g q6h	4/21 (7)	7:15	5.7	3.09	8.1	24.7	375	79.8	12.5		
3.375 g q6h	4/22 (8)	5:45	6.4	1.9	5.2*	15.2	274	79.9	12.5		
3.375 g q6h	4/22 (8)	8:51	6.2	2.71	7.2	21.5	319	79.4	12.5		
3.375 g q6h	4/23 (9)	13:41	3.6	2.84	7.9	21.7	209	76.6	12.6		2,412
3.375 g q6h	4/24 (10)	19:25	3.5	2.45	6.7	18.8	280	76.8	12.7		2,100
3.375 g q6h	STOP 4/25 (11)	14:05	4.2	2.91	7.4	22.2	134	76.3	13	1.3	
	4/30	6:30	6.6	3.3	8.5	26	497	78.7	14.3		4,290
	5/3	12:19	4.5	2.67	6.9	21	434	78.5	14.7		2,565
	5/4	7:39	4	3.11	8	24.2	364	78	14.7		2,240
	5/5	4:45	4.3	3.12	8.1	24.5	385	78.6	14.8		2,322
	5/7	2:45	4.9	3.1	7.8	24.1	359	77.7	14.7		2,499

Table 1: Complete blood counts and indices.

all cases after discontinuation of therapy and length to normalization averaged 3.8+/-1.5 days (2-5 days). However, the researchers did identify 62 cases from the AERS (Adverse Event Reporting System) database where piperacillin had been administered for less than 15 days. The authors state that they were not able to gather sufficient data to conclude that piperacillin can induce neutropenia prior to 15 days of therapy. However, they do state that the number of cases that developed despite brief exposure to piperacillin suggests that practitioners should consider its role in neutropenia during this time period.

Kumar and colleagues report a case of piperacillin induced bone marrow suppression in a 19-year-old male who was treated with piperacillin followed by piperacillin-tazobactam for an infected pancreatic pseudocyst. The patient was first placed on a regimen of piperacillin and amikacin empirically while pus was sent for culture. Thirteen days after initiating therapy, he began to have high fevers and piperacillin was replaced with piperacillin-tazobactam. On day 21 of antibiotic therapy, he developed neutropenia and thrombocytopenia and the drug was stopped. Four days later, his ANC returned to normal and platelets normalized by day 6. The patient became afebrile 2 days after stopping therapy. Therefore in this case, the patient did not experience any clinical findings of bone marrow suppression until day 21 of therapy. Additionally, the authors state that large cumulative doses are needed and neutropenia rarely develops before 10 days of therapy [8,9]. They state that in previous reports, neutropenia has been reported only after 11 to 17 days of therapy [5,10]. They also note that large cumulative doses need to be given to induce bone marrow suppression, typically 4,919+/-1,975 mg/kg. Our patient, AP, received a cumulative dose of 114.75 g, for a cumulative dose of 1,334.3 mg/kg. This is a much smaller dose than what has been reported to induce bone marrow suppression [11].

In another study, Peralta and colleagues reported neutropenia in patients treated with piperacillin-tazobactam for bone-related infections. This retrospective study reviewed patients treated for at least 10 days. Thirty-four percent of these patients developed neutropenia, which was apparent after a mean duration 26.8 days of therapy (range 18-51 days) and a mean cumulative dose of 330.3 g of piperacillin (range, 204-612 g). In fact, a significant inverse relationship was found between the cumulative dose of piperacillin administered and the neutrophil count obtained at the end of treatment. Therefore, this article suggests that prolonged use of piperacillin-tazobactam at the suggested dose for the treatment of bone-related infections should be administered cautiously, particularly for younger patients.

Piperacillin-tazobactam (Zosyn[®]) was FDA approved in 1993 [12]. Both components are minimally metabolized prior to renal excretion. This 86-kg girl is expected to have the renal capacity of an adult based on her age and size, and her pharmacokinetic parameters should be consistent with defined adult properties; she was dosed according to adult dosing and administration guidelines. Thus, our case is noteworthy not only as a unique pediatric adverse event but also as a previously unreported effect in an adult.

The etiology of A.P.'s bone marrow suppression is multifactorial. It is difficult to explain how marrow suppression alone could have decreased red cell mass 42% within 8 days based on cited mechanisms of maturation arrest. Although this patient's peripheral smear was unremarkable and her MCV and reticulocyte count did not suggest ongoing hemolysis (Table 1), we acknowledge that in this case there may have been additional destruction of blood elements either in the bone marrow or periphery and this process may have been in progress at least partially when drug therapy commenced. Nonetheless, these confounding conditions are often present in those that require

treatment with piperacillin-tazobactam and need to be taken into consideration when using this agent in special populations as our case delineates.

Childrens' microbiomes differ from that of adults [13]. In developing countries, children receive about 10-20 courses of antibiotics prior to age 18 [1]. Antibiotics are intended to achieve predetermined serum concentrations in order to target pathogenic bacteria but they also inadvertently affect host microbiota [1]. It could be argued that perhaps children's unique microbiomes make them more or less susceptible to various adverse effects of antibiotics or may explain, in part, why they respond differently. Moreover, antibiotics cause shifts in microbial composition that can induce long-term physiological changes. Therefore the interplay between the patient's microflora and piperacillin-tazobactam may theoretically play a role in an adverse event profile, specific to the pediatric population.

In summary, our case describes the myelosuppressive effects of piperacillin-tazobactam in an adolescent after 10 days of antibiotic treatment. All blood cells lines were affected and normalized soon after drug discontinuation. The understanding from this particular case will improve clinical practice by increasing physician awareness regarding the toxic side effects of piperacillin-tazobactam and how they may be more frequent at lower dosages and after shorter treatment duration than previously suspected. In addition, the role of antibiotics in general (use and overuse) and the alteration of the microbiome may play an important role in the inflammatory response and adverse effects of antibiotics, an interesting point for hypothesis testing. These findings suggest the need for more investigation in pediatric pharmacovigilance to better elucidate a pediatric-specific drug safety profile for piperacillin-tazobactam, as well as many other drugs, to enhance our preventative health measures to enable provision of optimal patient care.

References

1. Blaser, Martin. Stop the killing of beneficial bacteria: concerns about antibiotics focus on bacterial resistance-but permanent changes to our protective flora could have more serious. *Nature*, 2011 Aug 25: 393.
2. Scheetz MH, McKoy JM, Parada JP, Djulbegovic B, Raisch DW, et al. (2007) Systematic review of piperacillin-induced neutropenia. *Drug Saf* 30: 295-306.
3. Lee KW, Chow KM, Chan NP, Lo AO, Szeto CC (2009) Piperacillin/tazobactam Induced Myelosuppression. *J Clin Med Res* 1: 53-55.
4. Gerber L, Wing EJ (1995) Life-threatening neutropenia secondary to piperacillin/tazobactam therapy. *Clin Infect Dis* 21: 1047-1048.
5. Reichardt P, Handrick W, Linke A, Schille R, Kiess W (1999) Leukocytopenia, thrombocytopenia and fever related to piperacillin/tazobactam treatment—a retrospective analysis in 38 children with cystic fibrosis. *Infection* 27: 355-356.
6. Peralta FG, Sánchez MB, Roíz MP, Pena MA, Tejero MA, et al. (2003) Incidence of neutropenia during treatment of bone-related infections with piperacillin-tazobactam. *Clin Infect Dis* 37: 1568-1572.
7. Kumar A, Choudhuri G, Aggarwal R (2003) Piperacillin induced bone marrow suppression: a case report. *BMC Clin Pharmacol* 3: 2.
8. Neffel KA, Hauser SP, Müller MR (1985) Inhibition of granulopoiesis in vivo and in vitro by beta-lactam antibiotics. *J Infect Dis* 152: 90-98.
9. Singh N, Yu VL, Miele LA, Wagener MM (1993) Beta-Lactam antibiotic-induced leukopenia in severe hepatic dysfunction: risk factors and implications for dosing in patients with liver disease. *Am J Med* 94: 251-256.
10. Ruiz-Irastorza G, Barreiro G, Aguirre C (1996) Reversible bone marrow depression by high-dose piperacillin/tazobactam. *Br J Haematol* 95: 611-612.
11. Lang R, Lishner M, Ravid M (1991) Adverse reactions to prolonged treatment with high doses of carbenicillin and ureidopenicillins. *Rev Infect Dis* 13: 68-72.
12. Desai NR, Shah SM, Cohen J, McLaughlin M, Dalal HR (2008) Zosyn (piperacillin/tazobactam) reformulation: Expanded compatibility and coadministration with lactated Ringer's solutions and selected aminoglycosides. *Ther Clin Risk Manag* 4: 303-314.
13. Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, et al. (2012) Human gut microbiome viewed across age and geography. *Nature* 486: 222-227.