

Case report

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Piperacillin induced bone marrow suppression: a case report

Ashish Kumar, Gourdas Choudhuri and Rakesh Aggarwal*

Address: Department of Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Raebareli Road, Lucknow 226014, India

Email: Ashish Kumar - ashishk@sgpgi.ac.in; Gourdas Choudhuri - gourdas@satyam.net.in; Rakesh Aggarwal* - rakesh@sgpgi.ac.in

* Corresponding author

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Abstract

Background: Piperacillin (and piperacillin/tazobactam) is a commonly prescribed antibiotic and is generally considered safe. We report a case of piperacillin induced bone marrow suppression.

Case presentation: A 19-year-old boy was being treated with piperacillin followed by piperacillin/tazobactam for infected pancreatic pseudocyst. After 21 days of treatment, he developed neutropenia and thrombocytopenia. These reversed promptly after stopping piperacillin/tazobactam. The time course of events suggested that piperacillin was the cause of bone marrow suppression in this patient.

Conclusion: Bone marrow suppression is a serious adverse effect of piperacillin, which should be kept in mind while treating patients with this drug.

Background

Piperacillin is a commonly prescribed antibiotic and is generally considered safe. We report a case of bone marrow suppression induced by piperacillin (and piperacillin/tazobactam).

Case Report

A 19-year-old boy had an attack of idiopathic acute pancreatitis following which he developed a large pseudocyst occupying the body and tail of the pancreas. Endoscopic cystogastrostomy was done four months after the onset of pancreatitis. Two weeks later, the patient presented with high fever. Investigations revealed: hemoglobin 10.6 g/dL; total leukocyte count (TLC) $9.3 \times 10^9/L$ (neutrophils 58%, lymphocytes 38% and eosinophils 4%). Blockage of the cystogastrostomy stent and infection in the cyst cavity were suspected. The stent was removed and a nasocystic drainage tube was placed for drainage of pus and irrigation of cyst cavity. Pus was sent for culture and sensitivity, and piperacillin and amikacin were started empirically. Culture of pus obtained at the time of placement of naso-

cystic tube grew *Pseudomonas aeruginosa* (sensitive to piperacillin, amikacin, piperacillin/tazobactam and ciprofloxacin) and enterococcus species (sensitive to all common antibiotics). His fever responded within three days. However, 13 days later, he again developed high fever in spite of antibiotics. Suspecting resistant organisms, fresh cultures were sent and piperacillin was replaced by piperacillin/tazobactam; amikacin was continued. Four days later, results of second pus culture revealed growth of bacteroides species sensitive to metronidazole, which was added. On fifth day following start of piperacillin/tazobactam (i.e. 21 days after start of piperacillin), the patient developed neutropenia and thrombocytopenia (TLC $0.9 \times 10^9/L$ [neutrophils 58%, lymphocytes 40% and eosinophils 2%], absolute neutrophil count $0.52 \times 10^9/L$; platelets $72 \times 10^9/L$). His hemoglobin remained normal. Suspecting bone marrow suppression due to piperacillin or piperacillin/tazobactam, the latter combination was discontinued immediately. Metronidazole and amikacin were continued. His absolute neutrophil count on the next day was $0.58 \times 10^9/L$.

L. Four days after stopping the drug, it improved to $1.00 \times 10^9/L$, and, on the sixth day, it became normal ($8.4 \times 10^9/L$). Platelet count followed a similar course ($122 \times 10^9/L$ on day 6). The patient became afebrile within two days.

Discussion

Piperacillin is an aminobenzyl-penicillin derivative used for treatment of infection with organisms like *Pseudomonas aeruginosa*, *Enterobacteraceae*, *Escherichia coli*, *Proteus mirabilis*, *Klebsiella*, *Enterobacter serratia*, *Citrobacter*, *Salmonella* and *Shigella* spp [1]. In mild infections, a dose of 4–12 g/day is used; however, serious infections require a dose as high as 12–24 g/day [2,3]. Its known adverse effects include hypersensitivity reactions, neurotoxicity, hepatotoxicity, electrolyte and acid-base disturbances, bleeding disorders, neutropenia and thrombocytopenia, and rarely hemolytic anemia [1]. Piperacillin is susceptible to beta-lactamases; hence, tazobactam, a beta-lactamase inhibitor, is often combined with piperacillin. This combination (piperacillin 4 g, tazobactam 0.5 g) has an extended spectrum of action against beta-lactamase producing organisms. It is also one of the favorite drugs used in "febrile neutropenia". Its adverse effects are similar to those of piperacillin alone, except diarrhea, which was reported more often with the combination [1].

Leucopenia is an uncommon but serious adverse effect of piperacillin and other beta-lactam antibiotics. There have been several previous reports of leucopenia and bone marrow suppression following the use of piperacillin [4–7], and piperacillin/tazobactam [8–10]. This bone marrow suppression is usually reversible, recovers with discontinuation of the drug and is possibly related to direct toxicity to myeloid precursors [11]. Large cumulative doses are needed and neutropenia rarely develops before 10 days of therapy [11,12]. Leucopenia is usually associated with mild thrombocytopenia. When anemia occurs, it is most commonly immune-hemolytic type [13]. Also, isolated thrombocytopenia, which is usually immune-mediated, has been reported with piperacillin [14–17] and piperacillin/tazobactam [18].

Our patient developed neutropenia 21 days after the start of piperacillin treatment (and 5 days after change over to piperacillin/tazobactam). In previous reports, neutropenia has been reported 11 to 17 days after the therapy was begun [8,9]. Our patient had received piperacillin in a dose of 8 g/day and piperacillin/tazobactam in a dose of 13.5 g/day, with a cumulative piperacillin dose of 3547 mg/Kg body weight. In a previous report, bone marrow suppression occurred in patients who had received a cumulative piperacillin/tazobactam dose of 4919 ± 1975 mg/Kg, [8] i.e. 4372 ± 1755 mg/Kg body weight of piperacillin. The dose received by our patient falls within this range.

Our patient was also receiving amikacin and metronidazole when bone marrow suppression was noticed. However, metronidazole had been administered beginning only 12 hours prior to leucopenia and was thus unlikely to be the cause. Amikacin, a widely used drug, has never been implicated as a cause of bone marrow suppression. Also, leucopenia and thrombocytopenia promptly reversed with discontinuation of piperacillin/tazobactam, while amikacin and metronidazole were continued.

Conclusion

Bone marrow suppression is a serious adverse effect of piperacillin, which should be kept in mind while treating patients with this drug. Since the frequency of this adverse effect is not known, it may be difficult at present to recommend routine monitoring for this complication. However, a vigil must be kept in patients who have received a high cumulative dose.

Authors' contributions

AK was the treating senior resident and GC and RA were the consultants in-charge of the case. All authors read and approved the final manuscript.

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Written consent was obtained from the patient for publication of study.

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