Cystic Fibrosis and Piperacillin/Tazobactam: Adverse Reactions

Fibrosis quística y piperacilina tazobactam: reacciones adversas

To the Editor,

Cystic fibrosis (CF) patients commonly have chronic lung infections and frequent exacerbations caused by a range of bacteria, including Pseudomonas aeruginosa (P. aeruginosa) and Achromobacter xylosoxidans, requiring multiple cycles of antibiotics such as piperacillin/tazobactam. This combination has been associated in the literature with increased bone marrow toxicity, and it should be used with caution.1

We report 2 cases of CF patients, presenting with fever and myelotoxicity caused by piperacillin/tazobactam administered for P. aeruginosa infection, who required a switch to another antibiotic.

The first patient was a 20-year-old man with CF genotype F508del/F508, colonized with methicillin-resistant Staphylococcus aureus and P. aeruginosa. He was admitted for a respiratory exacerbation, with increased cough, greenish expectoration, weight loss, and worsening lung function, manifesting as forced vital capacity (FVC) 2950 ml (53%), forced expiratory volume in 1 second (FEV1) 1885 ml (42%), and FEV1/FVC 63.90. Treatment was started with intravenous piperacillin/tazobactam 4/0.5 g every 8 hours, and tobramycin 400 mg/24 h. The patient was discharged after 10 days to complete treatment at home. He was readmitted 7 days later with fever, myalgia, and epigastralgia. Clinical laboratory tests showed anemia (hemoglobin 11.3 g/dl) and leukopenia (2940/mm3), with a normal blood smear. Piperacillin/tazobactam was switched to ceftazidime, while the aminoglycoside was maintained, leading to an improvement in laboratory parameters.

Our second case was a 23-year-old man with CF genotype F508del/unknown mutation with the following lung function status: FVC 2950 ml (60%); FEV1: 1670 ml (42%); and FEV1/FVC (56.56%); along with chronic P. aeruginosa bronchial infection. In view of symptoms of respiratory infection and functional decline, treatment was started with piperacillin/tazobactam 4/0.5 g/8 h and tobramycin 400 mg/24 h. On day 17 of treatment, he developed fever (39.5°C) with no other accompanying signs. Clinical laboratory tests revealed anemia (hemoglobin 12.5 g/dl), thrombocytopenia (96,000/mm3) (Table 1), coagulation changes (prothrombin activity 56% and cephalin time 41.6 s), and hepatic involvement (GOT 170 U/l, GPT 51 U/l, GGT 24 U/l, and LDH 1462 U/l). Piperacillin/tazobactam was switched to levofloxacin. On day 4 after admission, the patient’s platelet count (165,000/mm3), coagulation parameters (prothrombin activity 102% y cephalin time 29.6 s), and liver function (GOT 18 U/l, GPT 27 U/l, GGT 19 U/l, LDH 258 U/l) improved.

Several papers have been published on the adverse effects of piperacillin/tazobactam in CF patients. For reasons that are still unclear, these events seem to be more common in CF than in the general population.2 Risk factors include a high accumulative dose of antibiotics in a short period of time and prolonged treatments (>10 days).1-3 Haptene-induced hemolytic anemia4 has been reported to respond well to intravenous immunoglobulin.2 Leukopenia, thrombocytopenia, fever, and hypersensitivity reactions that range from pruritus and skin rash to anaphylactic shock5

Table 1
Adverse Reactions Associated With Piperacillin/Tazobactam in Cystic Fibrosis.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Number of Patients</th>
<th>Age/Sex</th>
<th>Dose</th>
<th>Onset of Symptoms (day)</th>
<th>Adverse Effects (%)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reichardt P.</td>
<td>1996–1998</td>
<td>32</td>
<td>NR</td>
<td>Accumulated dose over 14 days 4.9 g/kg</td>
<td>11</td>
<td>Fever, general malaise, and headache</td>
<td>Leukopenia and thrombocytopenia</td>
</tr>
<tr>
<td>Bandara M.</td>
<td>2010</td>
<td>1</td>
<td>39/F</td>
<td>4.5 g iv every 6 h</td>
<td>7</td>
<td>Hemolytic anemia</td>
<td>Transfusion, steroids, iv immunoglobulin, PTZ discontinuation</td>
</tr>
<tr>
<td>Zanetti R.C.</td>
<td>2013</td>
<td>1</td>
<td>19/F</td>
<td>NR</td>
<td>13</td>
<td>Hemolytic anemia</td>
<td>Transfusion, immunoglobulina iv, PTZ discontinuation</td>
</tr>
<tr>
<td>Marik P.E.</td>
<td>2013</td>
<td>1</td>
<td>24/M</td>
<td>NR</td>
<td>15</td>
<td>Hemolytic anemia</td>
<td>Transfusion, steroids, immunoglobulina iv, PTZ discontinuation</td>
</tr>
</tbody>
</table>

F: female; iv: intravenous; M: male; NR: not reported; PTZ: piperacillin/tazobactam.

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have also been reported, but no cases of coagulation changes or liver toxicity have been published.

In our experience, CF patients show increased adverse effects to piperacillin/tazobactam, so they should be used with caution in this population. One of our patients, who was a frequent exacerbator (requiring ≥2 intravenous antibiotics/year), received piperacillin/tazobactam in an attempt to improve results obtained with previous antibiotic combinations. We conclude that this drug may be considered for use in second-line treatment, but it is advisable to use it for periods longer than 14 days. High doses should also be avoided, even for short periods of time.

**Conflict of Interests**

The authors state that they have no conflict of interests.

**References**


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