Ceftriaxone-related agranulocytosis during outpatient parenteral antibiotic therapy

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Sir,

Agranulocytosis is an extremely rare life-threatening adverse drug reaction associated with more than 100 different non-cancer drugs, including several antimicrobials.1 It has an estimated population incidence of 2.2–15.4 per million per year.1 A case report approximately 20 years ago described granulocytopenia occurring with Clostridium difficile infection, sepsis and drug-induced hepatitis in a patient treated with 2 g of ceftriaxone twice daily for 21 days as an outpatient.2 To our knowledge, there are no other reports of granulocytopenia or agranulocytosis during outpatient therapy with ceftriaxone. Here we report ceftriaxone-associated agranulocytosis at a standard dose during outpatient parenteral antibiotic therapy (OPAT).

A female in her mid-30s with no past history was treated with 2 g of ceftriaxone once daily for western blot-confirmed symptomatic Borrelia burgdorferi infection (Lyme disease), which had not responded to two courses of oral antibiotic therapy 3 months previously. Pre-ceftriaxone full blood count (FBC) was normal, as was an extensive array of baseline investigations including biochemistry, autoantibodies, rheumatoid factor, complement studies and plain radiography. Ceftriaxone therapy was well tolerated with normal haematological indices until day 14, when the neutrophil count declined to 0.96×10⁹/L. This was confirmed on day 16 (see Table 1). There was no concurrent prescribed, recreational or over-the-counter medication exposure. The patient remained entirely well with no clinical symptoms or examination findings, and biochemical and other haematological parameters were normal. Ceftriaxone was immediately stopped and 100 mg of doxycycline twice daily prescribed. Frequency of FBC monitoring was increased.

However, the neutrophil count progressively declined. Doxycycline was stopped after 4 days, on day 20. The neutrophil count continued to fall until all granulocytes became undetectable by both FBC and blood film examination on day 24, despite normal red cell and platelet indices. The patient was hospitalized. On admission, she was clinically well other than having a mild sore throat, which had developed in the hours prior to admission, and examination demonstrated minor pharyngeal erythema with no tonsillar enlargement or regional adenopathy, and a tachycardia of 102 beats per min.

Following an urgent haematology review, she was treated with a single subcutaneous dose of 300 μg of granulocyte-colony stimulating factor (G-CSF). Clarithromycin (500 mg) twice daily was administered to cover possible bacterial pharyngitis, although sore throat is recognized in association with agranulocytosis.1 A bone marrow examination was planned; however, 24 h after the single dose of G-CSF the neutrophil count had recovered to 2.37×10⁹/L. Her clinical symptoms resolved. Inflammatory markers remained normal throughout. Extensive tests for other possible causes of neutropenia, including viral PCR for common respiratory pathogens, blood cultures and throat swabs for bacterial culture, erythrovirus B19, Epstein–Barr virus, cytomegalovirus and HIV serology, were negative. Given these negative findings, the possibility of an undiagnosed infectious cause for agranulocytosis was considered highly unlikely. There was brief exposure to doxycycline following ceftriaxone, but the onset of grade 2 neutropenia preceded doxycycline treatment by more than 48 h and the nadir neutrophil count occurred after discontinuation of doxycycline, making it an improbable cause. Ceftriaxone was considered the probable cause of agranulocytosis and the event was reported to the UK Medicines and Healthcare products Regulatory Agency (MHRA). Over 3 months the patient has remained well

References

Ceftriaxone is a frequent choice for OPAT in common conditions such as skin and soft-tissue infection. Neutropenia is a recognized side effect of ceftriaxone. In a review of adverse events in clinical trials of ceftriaxone, neutropenia was only observed with more than 4 weeks of treatment. The frequency of severe neutropenia or agranulocytosis associated with ceftriaxone is unknown. In a systematic review of 980 case reports of drug-induced agranulocytosis from 1966–2006, ceftriaxone was identified as a probable but not definite cause in five case reports other than that discussed above. None was after 1994, and all were inpatients.

Agranulocytosis caused by non-chemotherapy drugs is idiosyncratic. Despite this, the risk is reported to increase with prolonged treatment. Mortality varies with pre-morbid condition, but is approximately 5% with optimal treatment. Haematopoietic growth factors have been associated with improved survival and neutrophil recovery time in systematic reviews of published case reports and cohort data, but not in a small open-label randomized trial.

This case illustrates an extremely rare but serious potential complication arising from the use of a standard dose and duration of parenteral ceftriaxone in the community. As OPAT services expand throughout Europe, outpatient courses of ceftriaxone will increase, with a possible rise in the risk of serious adverse consequences, highlighting to OPAT practitioners the importance of FBC monitoring in the community setting. This case also underscores the potential risks of treating Lyme disease with longer courses of intravenous ceftriaxone, emphasizing the importance of basing decisions on treatment according to established evidence-based guidelines.

**Table 1. Time course of haematological indices**

<table>
<thead>
<tr>
<th></th>
<th>Three months pre-treatment</th>
<th>Day 0</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 16 (ceftriaxone stopped, doxycycline started)</th>
<th>Day 20 (doxycycline stopped)</th>
<th>Day 24</th>
<th>Day 25 (post-G-CSF)</th>
<th>Final review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils (10⁹/L)</td>
<td>4.77</td>
<td>2.54</td>
<td>2.47</td>
<td>0.96</td>
<td>0.61</td>
<td>0.12</td>
<td>0.00</td>
<td>2.37</td>
<td>2.60</td>
</tr>
<tr>
<td>Leucocytes (10⁹/L)</td>
<td>7.46</td>
<td>4.94</td>
<td>4.08</td>
<td>2.06</td>
<td>1.77</td>
<td>2.17</td>
<td>1.83</td>
<td>5.62</td>
<td>4.75</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>12.6</td>
<td>11.9</td>
<td>12.2</td>
<td>12.1</td>
<td>11.9</td>
<td>11.9</td>
<td>12.4</td>
<td>12.1</td>
<td>11.7</td>
</tr>
<tr>
<td>Platelets (10⁹/L)</td>
<td>300</td>
<td>251</td>
<td>248</td>
<td>185</td>
<td>209</td>
<td>283</td>
<td>236</td>
<td>258</td>
<td>249</td>
</tr>
</tbody>
</table>

with complete resolution of her original presenting symptoms and a normal FBC.

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None to declare.

**References**