Desensitization to Filgrastim in a 2-Year-Old Girl With a Vaginal Endodermal Sinus Tumor

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Recombinant human granulocyte-stimulating factors (G-CSF) are administered to cancer patients to minimize the intensity and duration of neutropenia associated with chemotherapy and radiotherapy. The commercially available members of this family in Spain are filgrastim (Neupogen, Amgen SA), lenograstim (Granocyte, Italfarmaco SA), and pegfilgrastim (Neulasta, Amgen SA).

The drugs are usually administered subcutaneously. Recombinant human G-CSF are generally considered to be safe, and anaphylactic episodes and hypersensitivity reactions caused by these drugs are rare [1,2]. Desensitization protocols have been reported for adults, but not for children [3].

A 2-year-old girl with no known allergies was diagnosed with a vaginal endodermal sinus tumor at the age of 18 months and initially treated at Badajoz Hospital, Badajoz, Spain. She experienced generalized urticaria, facial angioedema, and oculonasal itching during her third cycle of filgrastim (5 µg/kg/d × 14 d) 4 hours after administration. She required treatment with dexchlorpheniramine and prednisolone, and after administration of premedication and without adverse effects.

In the case we report, skin prick tests with the drug were not sensitive enough. The mechanism of these reactions is unknown. Severe adverse effects of recombinant human G-CSF are rare. Anaphylactic episodes are extremely rare, although hypersensitivity reactions have been reported [1].

The patient continued with this subcutaneous regimen for a further 3 days. Tolerance was excellent.

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In the case we report, skin prick tests with the drug were negative, possibly because of the implication of a non–IgE-mediated underlying immunological mechanism or because the skin prick tests were not sensitive enough.

Table. Desensitization Protocol in 12 Steps With Neupogen

<table>
<thead>
<tr>
<th>Step</th>
<th>Solution</th>
<th>µ/L</th>
<th>Flow, mL/h</th>
<th>Time, min</th>
<th>Dose Administered, µg</th>
<th>Cumulative Dose, µg</th>
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<td>0.01</td>
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<tr>
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<td>15</td>
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<td>0.04</td>
</tr>
<tr>
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<td>A</td>
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<td>8</td>
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<tr>
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<td>0.22</td>
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<tr>
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<tr>
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<td>30</td>
<td>45.00</td>
<td>69.60</td>
</tr>
</tbody>
</table>

Solution A (1/100): 5 mL of solution B + 45 mL of physiological saline solution.
Solution B (1/10): 5 mL of solution C + 45 mL of physiological saline solution.
Solution C: 1 mL of 0.3 mg/mL + 99 mL of 5 mL physiological saline solution.

*Step 12 is presented twice, corresponding to the 2 occasions in which the protocol was applied, reaching 120 µg and 69.60 µg on the first and the second occasion, respectively.
Nowadays, desensitization is indicated in cases of hypersensitivity reactions to a first-line drug for which no equivalents are available. It is achieved by progressively increasing the dose of the drug until the necessary dose is reached and a state of tolerance that protects against anaphylaxis is induced [4].

Although anaphylaxis to G-CSF and granulocyte-monocyte colony-stimulating factor has been reported, desensitization protocols have rarely been described [5].

In the present case, it is interesting that the patient tolerated the new filgrastim regimen despite having been 48 hours without receiving the drug. This can be explained by the pharmacokinetics of the drug, since the median serum elimination half-life of filgrastim after a single subcutaneous dose ranged from 2.7 hours to 5.7 hours. The half-life can increase after 7 days of administration to 8.5-14 hours. Because the complete elimination of a drug is approximately 5 half-lives, the drug was probably still present in the patient’s body because she had been receiving it for several days [6].

One valid explanation could be that reducing the infusion rate was sufficient to ensure tolerance.

According to the clinical history, the parents believed that this step was carried out in Badajoz Hospital, although there was no record of it; therefore, it was not chosen as the first option, and we proceeded directly to desensitization as a safer procedure.

Intradermal testing was not performed because the patient required urgent treatment and the result was not going to rule out desensitization. Furthermore, the patient’s status precluded oral drug challenge.

The most commonly used intravenous desensitization protocols are standardized 12- to 16-step approaches modeled after in vitro protocols. These can be personalized for all drugs, with adjustment of the target dose, time intervals between doses, and starting dose, as was the case in this report [7].

Our experience suggests that desensitization protocols could be useful and safe for the administration of recombinant human G-CSF drugs in children.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Previous Presentation

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References