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A novel ganciclovir desensitization protocol for a pediatric patient: A case report

Un nouveau protocole de désensibilisation au ganciclovir pour un patient pédiatrique : un rapport de cas

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ARTICLE INFO

Article history:

Received 14 January 2021

Accepted 22 March 2021

Available online xxx

Keywords:

Anaphylaxis
Desensitization
Drug allergy
Ganciclovir
Child

Mots clés :

Anaphylaxie
Désensibilisation
Allergie médicamenteuse
Ganciclovir
Enfant

ABSTRACT

A nine year-old girl, having high temperature and stomach ache symptoms, was diagnosed with primary haematophagocytic lymphohistiocytosis. During the treatment, she had neutropenic fever, dyspnea and bronchospasm. Laboratory tests revealed a 7,189,566 cytomegalovirus (CMV)-DNA copies/mL. Ganciclovir therapy was started for CMV pneumonia. At the second infusion of ganciclovir, she had dyspnea, bronchospasm, tachycardia and urticaria. Adrenaline, antihistamines and corticosteroids were administered for anaphylaxis. Treatment was replaced with valganciclovir but there was no clinical or laboratory regression. Because valganciclovir was ineffective and foscarnet could not be provided, we decided to apply desensitization with ganciclovir without performing skin tests because the reaction was anaphylactic. Total dose was 350 mg, for the patient's weight of 35 kg, according to 10 mg/kg daily dose. A (1/1000 dilution), B (1/100 dilution), C (1/10 dilution) and D (no dilution) solutions were prepared. Desensitization began with a 1/10,000^e of the therapeutic dose, followed by 14 administrations of increasing doses every 30 minutes and lasted 6.5 hours. There was no reaction during desensitization. Patient was subsequently treated with ganciclovir every day without any problem for 21 days. After the treatment, clinical symptoms resolved and CMV-DNA copies were found < 31 IU/mL. In conclusion, we present a rare case of ganciclovir hypersensitivity (allergic or non-allergic?) and a novel protocol of ganciclovir desensitization.

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R É S U M É

Une fillette de neuf ans, ayant une fièvre élevée et des maux d'estomac, a été diagnostiquée comme ayant une lymphohistiocytose hémaphagocytaire primaire. Pendant le traitement, elle a présenté une fièvre neutropénique, une dyspnée et un bronchospasme. Les tests de laboratoire ont révélé 7 189 566 copies/mL d'ADN du cytomégalo virus (CMV). Un traitement au ganciclovir a été instauré pour une pneumonie à CMV. Lors de la deuxième perfusion de ganciclovir, elle a présenté une dyspnée, un bronchospasme, une tachycardie et une urticaire. Cette réaction anaphylactique a été traitée par de l'adrénaline, des antihistaminiques et des corticoïdes. Le traitement a été remplacé par le valganciclovir, mais sans régression clinique ou biologique. Le valganciclovir étant inefficace et le foscarnet n'ayant pas pu être administré, nous avons décidé d'appliquer une désensibilisation au ganciclovir sans effectuer de tests cutanés, car la réaction était anaphylactique. La dose

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<https://doi.org/10.1016/j.reval.2021.03.195>

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totale a été de 350 mg, pour un poids de 35 kg, selon une dose quotidienne de 10 mg/kg. Des solutions A (dilution 1/1000), B (dilution 1/100), C (dilution 1/10) et D (sans dilution) ont été préparées. La désensibilisation a commencé avec une dose de 1/10 000^e de la dose thérapeutique, suivie de 14 administrations de doses croissantes toutes les 30 minutes, et a duré 6,5 heures. Aucune réaction n'est survenue pendant la désensibilisation. La patiente a ensuite été traitée avec du ganciclovir tous les jours sans problème pendant 21 jours. Après le traitement, les symptômes cliniques se sont résolus et des copies d'ADN-CMV ont été trouvées < 31 IU/mL. En conclusion, nous présentons un cas rare d'hypersensibilité au ganciclovir et un nouveau protocole de désensibilisation à ce médicament.

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1. Introduction

A drug allergy is an adverse reaction appearing as a result of immunologic mechanisms to a specific medication. In children adverse allergic-like drug reactions are a problem of differential diagnosis because most of these reactions are not allergic [1]. But the prevalence of allergic drug reactions isn't actually known. According to the World Allergy Organization recommendations, drug allergies can be divided into two groups, based on the timing of the reaction, as: immediate (onset within 1 h of administration) or non-immediate [2]. Immediate reactions are often IgE-mediated (type 1 hypersensitivity), although they can also result from non-allergic hypersensitivity. The symptoms include skin symptoms (urticaria, angioedema, pruritus, flushing), respiratory symptoms (dyspnea, wheezing, cough, etc.), gastrointestinal symptoms (nausea and/or vomiting, abdominal pain), or anaphylaxis. Whereas skin symptoms are the most common symptoms, anaphylaxis is the most serious one. Reactions may occur after multiple doses of the drug as well as at the first dose [3]. The most common drug allergies in children are due to beta-lactam antibiotics [4]. Skin prick and intradermal tests (when feasible), and drug provocation tests can be used for diagnosis of a drug allergy [5–7].

Desensitization is based on the administration of progressively increasing doses of a drug every 15–30 minutes until a full therapeutic dose is clinically tolerated [8]. It is usually used for IgE-mediated reactions, but may also be used for some delayed drug reactions such as mild maculopapular exanthemas and fixed drug eruptions [9]. However, the induced tolerance is temporary [10–12], and disappears after the two times half-life period of the drug. Desensitization can be considered in patients who have proven or strongly suspected IgE-mediated drug allergy and severe immediate non-allergic reactions when there are no acceptable alternative drugs [13,14].

We present a ganciclovir desensitization protocol applied to a 9-year-old girl who had developed anaphylaxis to ganciclovir. Informed consent was obtained from her parents.

2. Case report

A nine year-old girl, born to unrelated parents at 38th gestational age, consulted our emergency department with a high temperature (41.5 °C) and stomach ache. She had been treated with cefixime for a urinary tract infection for two days. She was diagnosed with intussusceptions and pneumatic reduction was performed. During the following days, she was evaluated for persistent fever, with no finding at physical examination except bilateral cervical lymphadenopathy (max. 1 cm) and minimal splenomegaly. White blood cell count was 10,600/mm³ with 75% neutrophils, haemoglobin: 10 gr/dL, hematocrit 31.8%, platelet count: 282,000/mm³. C reactive protein was 17 mg/dL and erythrocyte sedimentation rate was 70 mm/h. Thoracoabdominal computerized tomography showed mesenteric lymphadenopathy. Ferritin was 31,300 µg/L, fibrinogen 80 mg/dL

and triglyceride 330 mg/dL. Bone marrow aspiration and biopsy revealed haematophagocytic lymphohistiocytosis (HLH). Further evaluation (genetic analysis, infectious serologic markers and cultures, immunologic parameters) did not reveal any etiology for secondary HLH. One month later, during the treatment for HLH, she developed neutropenic fever, dyspnea and bronchospasm. Chest radiography showed bilateral infiltration. Antibiotherapy (meropenem, vancomycin) was started according to neutropenic fever protocol. Because of worsening symptoms, she was admitted to intensive care unit for respiratory distress and septicemia. Laboratory tests revealed a 7,189,566 cytomegalovirus (CMV)-DNA copies/ml, not found in previous examinations. Ganciclovir therapy was started for CMV pneumonia. During the second infusion of ganciclovir, she developed a severe anaphylactic reaction (dyspnea, bronchospasm, and tachycardia with urticaria). The drug infusion was stopped immediately, and adrenaline, antihistamines and corticosteroids were administered.

Treatment was replaced with valganciclovir, but no clinical or laboratory regression occurred after a week of therapy. She did not have any allergy history in her past life or a family history of allergy.

Because valganciclovir was ineffective and foscarnet could not be provided and because it was necessary to use an appropriate medication for the CMV infection, we decided to apply desensitization with ganciclovir without performing skin tests because the reaction was anaphylactic. Total dose was 350 mg, based on the patient's weight of 35 kg, according to a 10 mg/kg daily dose. A (1/1000 dilution), B (1/100 dilution), C (1/10 dilution) and D (without dilution) solutions were prepared. The first dose was 1/10,000^e of the therapeutic dose, followed by 14 injections of progressively increasing doses ($\times 2$ /the previous dose) every 30 minutes and lasted 6.5 hours (Table 1). We did not apply premedication before desensitization. Patient was monitored and her temperature, pulse rate, respiratory rate, blood pressure was noted every half an hour. There were no reactions during desensitization. The patient was subsequently treated with ganciclovir every day, with two divided doses, without any problem for 21 days. After the treatment, clinical symptoms resolved and CMV-DNA copies were found < 31 IU/mL.

3. Conclusion

Desensitization is a procedure defined as induction of a state of unresponsiveness to a drug responsible for hypersensitivity, and is usually performed in patients with IgE-mediated reactions when there is no alternative medication. We present the case of a 9-year-old girl with ganciclovir-induced anaphylaxis and who was successfully treated with this drug based on a rapid desensitization protocol.

This girl was diagnosed as having HLH and, during the treatment, she developed neutropenic fever and CMV pneumonia. She was treated with ganciclovir, but developed anaphylaxis during the second infusion of this drug. Ganciclovir desensitization was planned because the valganciclovir treatment was unsuccessful and there was no alternative medication for CMV infection.

Table 1
Desensitization protocol performed to our patient for 350 mg ganciclovir.

Time of administration	Solution type	Solution dose mL (mg)	Cumulative dose (mg)
0. minute	A (1/1000)	0.7 mL (0.035 mg)	0.035 mg
After 30 minutes	A (1/1000)	1.4 mL (0.07 mg)	0.1 mg
After 30 minutes	A (1/1000)	2.8 mL (0.14 mg)	0.24 mg
After 30 minutes	A (1/1000)	5.6 mL (0.28 mg)	0.52 mg
After 30 minutes	B (1/100)	1.1 mL (0.56 mg)	1.08 mg
After 30 minutes	B (1/100)	2.2 mL (1.08 mg)	2.16 mg
After 30 minutes	B (1/100)	4.4 mL (2.16 mg)	4.32 mg
After 30 minutes	B (1/100)	8.8 mL (4.32 mg)	8.64 mg
After 30 minutes	C (1/10)	1.7 mL (8.64 mg)	17.28 mg
After 30 minutes	C (1/10)	3.4 mL (17.2 mg)	34.4 mg
After 30 minutes	C (1/10)	6.8 mL (34.4 mg)	68.8 mg
After 30 minutes	C (1/10)	13.6 mL (68.8 mg)	137.6 mg
After 30 minutes	Without dilution	1.5 mL (75 mg)	212.6 mg
After 30 minutes	Without dilution	2.7 mL (137.4 mg)	350 mg

Successful desensitization protocols for antibiotics, antiepileptics, and chemotherapeutics have been reported in children [15–19]. A successful oral 12 step valganciclovir desensitization, performed in a 64-year-old patient, with an 0.1 mg initial dose followed by doubled doses has been reported [20]. There are also three reports of successful oral aciclovir desensitization in adults [21–23]. To our knowledge, we report the first successful protocol of ganciclovir desensitization in children. When IgE-mediated hypersensitivity is suspected, rapid desensitization is used, whereas a graded desensitization protocol is indicated in patients with cell-mediated hypersensitivity [22]. In our patient who developed anaphylaxis during drug infusion, we suspected an IgE-mediated hypersensitivity and planned a rapid desensitization. In the literature, the recommended initial dose of desensitization for a drug causing anaphylaxis is 1/1,000,000 to 1/10,000 of the therapeutic dose, followed by doubled doses administered every 15–30 minutes [15]. We started with a 1/10,000 initial dose with a 1/1000 dilution solution and doubled doses every 30 minutes. Desensitization ended at the 14th step with a non-diluted solution. Desensitization was completed without any adverse reactions, and the patient was treated with ganciclovir during further 21 days without any reaction.

In conclusion, cases of ganciclovir (IgE-mediated or non-allergic) hypersensitivity are rare and, to the best of our knowledge, we report the first case of successful ganciclovir desensitization in children.

Disclosure of interest

The authors declare that they have no competing interest.

References

- [1] Smyth RM, Gargon E, Kirkham J, Cresswell L, Golder S, Smyth R, et al. Adverse drug reactions in children – a systematic review. *PLoS One* 2012;7:e24061.
- [2] Johansson SGO, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: report of the nomenclature review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004;113:832–6.
- [3] Muraro A, Lemanske Jr RF, Castells M, Torres MJ, Khan D, Simon HU, et al. Precision medicine in allergic disease – Food allergy, drug allergy, and anaphylaxis-PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. *Allergy* 2017;72:1006–21.
- [4] Fazlollahi MR, Bidad K, Shokouhi R, Dashti R, Nabavi M, Movahedi M, et al. Frequency and risk factors of penicillin and amoxicillin allergy in suspected patients with drug allergy. *Arch Iran Med* 2017;20:34–7.
- [5] Esposito S, Castellazzi L, Tagliabue C, Principi N. Allergy to antibiotics in children: an overestimated problem. *Int J Antimicrob Agents* 2016;48:361–6.
- [6] Brockow K, Romano A, Blanca M, et al. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy* 2002;57:45–51.
- [7] Chiriac AM, Rerkpattanapipat T, Bousquet PJ, Molinari N, Demoly P. Optimal step doses for drug provocation tests to prove beta-lactam hypersensitivity. *Allergy* 2016;29:552–61.
- [8] Celik GE, Pichler WJ, Adkinson NF. Drug Allergy. In: Adkinson NF, Bochner BS, Wesley Burks A, Busse WW, Holgate ST, et al., editors. *Middleton's allergy principles and practice*. 8th ed Philadelphia, USA: Elsevier Saunders; 2014. p. 1274–95.
- [9] Scherer K, Brockow K, Aberer W, Gooi JH, Demoly P, Romano A, et al., ENDA, the European Network on Drug Allergy and the EAACI Drug Allergy Interest Group. Desensitization in delayed drug hypersensitivity reactions – an EAACI position paper of the Drug Allergy Interest Group. *Allergy* 2013;68:844–52.
- [10] Castells M. Rapid desensitization for hypersensitivity reactions to medications. *Immunol Allergy Clin North Am* 2009;29:585–606.
- [11] Schnyder B. Approach to the patient with drug allergy. *Med Clin North Am* 2010;94:665–79.
- [12] Joint Task Force on Practice Parameters: American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol* 2010;105:259–73.
- [13] Brockow K, Aberer W, Atanaskovic-Markovic M, et al. Drug allergy passport and other documentation for patients with drug hypersensitivity – An ENDA/EAACI drug allergy interest group position paper. *Allergy* 2016;71:1533–9.
- [14] Cernadas JR, Brockow K, Romano A, Aberer W, Torres MJ, Bircher A, et al., European Network of Drug Allergy and the EAACI interest group on drug hypersensitivity. General considerations on rapid desensitization for drug hypersensitivity – a consensus statement. *Allergy* 2010;65:1357–66.
- [15] Cernadas JR. Desensitization to antibiotics in children. *Pediatr Allergy Immunol* 2013;24:3–9.
- [16] Sims-McCallum RP. Outpatient carboplatin desensitization in a pediatric patient with bilateral optic glioma. *Ann Pharmacother* 2000;34:477–8.
- [17] Itomi S, Okumura A, Ikuta T, Negoro T, Watanabe K. Phenytoin desensitization in a child with symptomatic localization-related epilepsy. *Brain Dev* 2007;29:121–3.
- [18] Toker O, Tal Y, Horev L, Shmoeli D, Gilboa T. Valproic acid hypersensitivity and desensitization. *Dev Med Child Neurol* 2015;57:1076–8.
- [19] Demir E, Cigerci Günaydin N, Karadaş N, Gülen F, Tanac R, Yılmaz D. A successful desensitization protocol for horse-derived antithymocyte globulin in severe aplastic anemia. *Pediatr Allergy Immunol* 2015;26:168–72.
- [20] Gonzalez-Estrada A, Fernandez J. Novel valganciclovir desensitization protocol. *Transplantation* 2014;1598:e50–1.
- [21] Snape SE, Finch RG, Venkatesan P. Aciclovir desensitisation and rechallenge. *BMJ Case Rep* 2011;1–3 [bcr.10.2010.3392].
- [22] Kawsar M, Parkin JM, Forster G. Graded challenge in an acyclovir allergic patient. *Sex Transm Infect* 2001;77:204–5.
- [23] Henry RE, Wegmann JA, Hartle JE, et al. Successful oral acyclovir desensitization. *Ann Allergy* 1993;70:386–8.