Caso clínico

Hypersensitivity reaction to Calcium Levofolinate – a clinical case

Reação de Hipersensibilidade ao Levofolinato de Cálcio – a propósito de um caso clínico

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Abstract

The frequency of allergic reactions to calcium levofolinate is unknown and anaphylactic reactions are described as very rare.

The authors present the case of a 43-year-old male allergic to levofolinate with a positive oral provocation test.

Clinicians should be aware of hypersensitivity reaction with calcium-levofolinate, especially when is administered concomitantly with oxaliplatin, despite its lower risk to cause hypersensitivity reactions. Furthermore, the similar signs and symptoms associated to the hypersensitivity reactions of each agent highlight the importance of having a specialized allergist team to make a prompt diagnosis of the causative agent in order to prevent patient harm and proceed properly without unnecessary delays in the scheduled chemotherapy treatments.

Keywords: *Calcium levofolinate; Hypersensitivity; Reactions; Chemotherapy.*

Resumo

A frequência de reações alérgicas ao levofolinato de cálcio é desconhecida e as reações anafiláticas são descritas como muito raras.

Os autores apresentam o caso de um homem de 43 anos alérgico ao levofolinato de cálcio com teste de provocação oral positivo.

Os profissionais de saúde devem estar alerta para as reações de hipersensibilidade com levofolinato de cálcio, especialmente quando administrado concomitantemente com oxaliplatina, apesar da sua menor frequência relativamente às platinas. Além disso, os sinais e sintomas semelhantes associados às reações de hipersensibilidade de cada fármaco destacam a importância de existir uma equipa de imunoalergologistas especializada para fazer um diagnóstico correto do agente implicado na reação e proceder adequadamente, sem atrasos desnecessários nos tratamentos quimioterápicos programados.

Palavras-chave: Levofolinato de cálcio; Hipersensibilidade; Reação; Quimioterapia.

Introduction

The association of calcium-levofolinate with 5-fluorouracil (5-FU) represents a gold standard in the treatment of many cancers, because enhances the cytotoxic effects of chemotherapy.[1]

In this case, calcium-levofolinate is not used for the purpose of "rescue"; furthermore, it amplifies the effect of 5-FU by inhibiting thymidylate synthase. [2]

Any drug can potentially trigger a hypersensitivity reaction (HSR). Reactions to cancer drugs, particularly chemotherapy agents and monoclonal antibodies, are common.[3,4,5]

Of all the chemotherapy agents that more frequently cause HSR, approximately 12-19% of the reactions are associated with platins (carboplatin, oxaliplatin and, less often, cisplatin) and 5-45% with taxanes, namely paclitaxel and docetaxel.[5,6] In oncology calcium-levofolinate has been rarely involved in adverse allergic reactions.[7]

The frequency of allergic reactions to calcium levofolinate is unknown and anaphylactic reactions are described as very rare. [7]

Clinical Case

The authors present the case of a 43-year-old male, without significant past medical history, which had a recent diagnosis of gastric adenocarcinoma Stage IIIC, pT3 N3b M0. He had been submitted to subtotal gastrectomy with Roux-en-Y reconstruction after a gastric antrum stenosis and gastrointestinal stasis syndrome. Due to lymph nodes involvement, the patient was selected to adjuvant chemotherapy with calcium-levofolinate 200mg/m^2, intravenous (IV) Infusion with 250ml Glucose 5% over 2 hours concurrent with oxaliplatin, oxaliplatin 85 mg/m^2, 5-fluorouracil 2600 mg/m^2 via infusor device with 0.9% sodium chloride over 24 hours IV Infusion and docetaxel 50mg/m^2 IV Infusion with 250ml Sodium Chloride 0.9% over 1 hour (FLOT).

In the first cycle of chemotherapy, it was administered a perfusion of both calcium-levofolinate and oxaliplatin. One hour after starting the treatment (about half the dose) he developed generalized cutaneous erythema (face, upper body and hands), non-pruriginous, without any other signs or symptoms.

The perfusion was interrupted and the patient was treated with hydrocortisone (200 mg, IV) and clemastine (2 mg, IV), showing complete remission of the erythema after an hour and being able to complete de cycle of chemotherapy without further problems.

Before the second cycle, considering the allergic reaction described previously, pre-medication with intravenous clemastine was administered and the patient was able to complete the cycle of chemotherapy without developing erythema or other signs of allergy.

The same procedure was applied before the third cycle. However, minutes after starting the perfusion of levofolinate and oxaliplatin, the patient developed generalized cutaneous erythema, without any other signs or symptoms associated. After stopping the perfusion and immediate bolus of hydrocortisone (200 mg, IV) and clemastine (2 mg, IV), complete remission was achieved in a few minutes. Then, an attempt was taken to complete the cycle, administering only calcium-levofolinate, which triggered again a cutaneous reaction with generalized cutaneous erythema as previously described.

Following this episode, the patient was referred to outpatient allergy consultation. To determine what caused the allergic reaction, skin prick tests with calcium-levofolinate 10 mg/ml were performed with negative results, as were intradermic tests with progressive dosage increase, starting with 1/100, then 1/10 and finally 1/1 (**Table 1.**).

Table 1. Results of skin prick tests and intradermal tests

	Prick tests (mm)	Intradermic tests (mm)		
Dilution	1/1	1/100	1/10	1/1
Saline	0	0	-	-
Histamine	6	-	-	-
Calcium levofolinate (10 mg/ml)	0	0	0	0

Considering that the selected chemotherapy is the first line treatment for this patient, finding the potential allergen was of extreme importance, which was the reason why it was decided to proceed to the provocation test with the suspected drugs.

First, it was administered oxaliplatin, which he completed uneventfully, initially with the infusion rate reduced to half of the recommended (70 ml/h) and then increased to double (140 ml/h). Then, perfusion with calcium levofolinate was started and after 20 min (Cumulative Dose ~ 30mg) the patient developed itchy rash on the face, neck and hands, and reported dizziness and nausea, without showing any other signs or symptoms. Following this episode, he was put on perfusion of clemastine and methylprednisolone with complete resolution of the clinical picture.

Tryptase was dosed two hours after the reaction with the result of 8.23 ng/mL (normal value <11,4 ng/mL).

It was considered a positive provocation test for calcium levofolinate, so the patient started a new therapeutic regimen with oxaliplatin and capecitabine, with no record of complications to date.

Discussion/Conclusion

After reviewing the literature, there are only a few previously described cases of an immediate hypersensitivity reaction to calcium levofolinate. These reactions most often occur with platinum and taxanes. [9]

The concentrations used in the skin tests are not standardized so the authors chose to do the prick test with the pure stratum 10 mg/ml and intradermal test with increasing dilutions in order to assess the possible local irritability, using the following concentrations: 1/100, 1/10 and then 1/1.

Evidence of drug provocation, considered the gold standard in the diagnosis of hypersensitivity[9,10] allowed to clarify the diagnosis and to establish alternative therapy in a short time, so that the main objective was not delayed – finishing the adjuvant treatment with chemotherapy.

Clinicians should be aware of hypersensitivity reaction with calcium-levofolinate, especially when is administered concomitantly with oxaliplatin, despite its lower risk to cause hypersensitivity reactions. [10] Furthermore, the similar signs and symptoms associated to hypersensitivity reactions to each agent, highlight the importance of having a specialised allergist team to make a prompt diagnosis of the causative agent in order to prevent patient harm and proceed properly without unnecessary delays in the scheduled chemotherapy treatments. [10]

Contributorship Statement / Declaração de Contribuição

IF: acquisition, analysis and interpretation of data, writing the manuscript, critical review and final approval.

LC: critical review and final approval.

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