

CONTACT POINTS

CONTACT DERMATITIS 2010: 63: 107–115

JOHN WILEY & SONS A/S 2010

ALL RIGHTS RESERVED

CONTRIBUTIONS TO THIS SECTION WILL NOT UNDERGO PEER REVIEW, BUT WILL BE REVIEWED BY THE EDITOR

Delayed hypersensitivity to heparin in a patient with cancer: fondaparinux may be safe but needs to be tested

Contact Dermatitis 2010: 63: 107–108

Amira Colagiovanni, Angela Rizzi, Alessandro Buonomo, Tiziana De Pasquale, Valentina Pecora, Vito Sabato, Arianna Aruanno, Lucilla Pascolini, Eleonora Nucera and Domenico Schiavino

Allergy Department, Catholic University – Policlinico “A. Gemelli”, Largo F. Vito, 1–00168 Rome, Italy

Key words: cancer; fondaparinux; heparin hypersensitivity; thrombosis.

Venous thromboembolism, which includes both deep vein thrombosis and pulmonary embolism, is the second leading cause of death in patients with cancer (1). Anticoagulant therapy, such as heparin, is used for prophylaxis and treatment for thrombosis in patients with cancer. Heparin may cause all types of allergic reactions, particularly cell-mediated type IV and antibody-mediated type II reactions (2). Risk factors for cell-mediated hypersensitivity to heparins include female sex, obesity, and long treatment duration.

Case Report

A 61-year-old woman was referred to our Allergy Department following a generalized, pruritic, maculo-papular erythema occurring after injection of sodium enoxaparin. She had a history of breast cancer 15 years earlier. Five years before review, she underwent pulmonary bi-lobectomy and adjuvant chemotherapy (via central venous access) for adenocarcinoma of the lung. She then developed deep vein thrombosis of the superior vena cava and was treated with calcium nadroparin.

Subcutaneous sodium enoxaparin was used at the end of chemotherapy treatment to remove the central venous access port. Two hours after the injection of enoxaparin, she developed generalized maculo-papular erythema that receded after treatment with parenteral corticosteroids and antihistamines within 7 days. Allergological evaluation was performed 5 weeks later. Prick, intradermal, and patch tests were performed with a panel of heparins: sodium enoxaparin, sodium heparin, calcium nadroparin, sodium reviparin, sodium dalteparin, and fondaparinux, a synthetic heparinoid. Undiluted solutions of the commercial drugs were used for prick test and, if negative, they were tested intradermally, starting at 1:1000 dilution until a maximum of 1:10 dilution was achieved, according to protocols in the literature (2). Histamine (10 mg/ml) was used as the positive control and saline as the negative control.

Immediate reactions with a diameter of at least 3 mm more than the control (prick tests) and 5 mm more than the control (intradermal tests) were considered positive. In case of a delayed reaction, immediate-type skin tests were read after 20 min and also after 48 hr. An infiltrated erythema with a diameter of more than 5 mm was considered a delayed positive reaction.

Patch tests were performed with undiluted solutions of the drugs that were applied in the interscapular region and evaluated at 48 and 72 hr. Positivity was assessed according to the recommendations of the European Network for Drug Allergy (3).

Intradermal tests and patch tests were positive after 48 hr for sodium enoxaparin, calcium nadroparin, and sodium dalteparin. The intradermal test for sodium heparin was positive at 48 hr, but the patch test was negative. Diagnosis of delayed hypersensitivity to sodium enoxaparin, sodium heparin, calcium nadroparin, and sodium dalteparin was made.

We then performed a subcutaneous challenge with fondaparinux 2.5 mg/0.5 ml. A first dose of 0.25 ml was injected subcutaneously, and after

30 min, a second dose of 0.25 ml was administered. No reactions were observed after 6 hr and in the following 7 days. The patient underwent treatment at home with this agent without any problems.

Discussion

Patients with cancer are predisposed to the development of venous thromboembolism because of patient-related risk factors, as well as risk factors related specifically to the cancer disease and treatment (4). Adequate prophylaxis and treatment of these patients is needed. Adverse reactions to anticoagulant therapy could be a serious limitation for the treatment of patients with cancer and venous thromboembolism. Allergological evaluation in a patient with suspected hypersensitivity is mandatory.

Our patient showed a broad spectrum of cross-reactivity between different heparins. According to published data, patch tests are less sensitive than intradermal tests. In our report, patch testing of heparin sodium was negative, unlike the intradermal tests (5). Fondaparinux can be considered an alternative in patients with delayed hypersensitivity to heparins (6). The choice of a different heparin is strictly related to the results of the allergy work up, because cross-reactions may occur between all heparin classes, even with the ultra-low-molecular-weight heparin fondaparinux (7).

References

1. Khorana A A, Francis C W, Culakova E et al. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost* 2007; 5: 632–634.
2. Bircher A J, Harr T, Hohenstein L, Tsakiris D A. Hypersensitivity reactions to anticoagulant drugs: diagnosis and management options. *Allergy* 2006; 61(12): 1432–1440.
3. Brockow K, Romano A, Blanca M, Ring J, Pichler W J, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy* 2002; 57: 45–51.

4. Falanga A, Zacharski L. Deep vein thrombosis in cancer: the scale of the problem and approaches to management. *Ann Oncol* 2005; 16(5): 696–701.
5. Koch P. Delayed-type hypersensitivity skin reactions due to heparins and heparinoids. Tolerance of recombinant hirudins and of the new synthetic anticoagulant fondaparinux. *Contact Dermatitis* 2003; 49: 276–280.
6. Harr T, Scherer K, Tsakiris D A, Bircher A J. Immediate type hypersensitivity to low molecular weight heparins and tolerance of unfractionated heparin and fondaparinux. *Allergy* 2006; 61(6): 787–788.
7. Hohenstein E, Tsakiris D, Bircher A J. Delayed-type hypersensitivity to the ultra-low-molecular-weight heparin fondaparinux. *Contact Dermatitis* 2004; 51(3): 149–151.

Address:

Dr Amira Colagiovanni
Allergy Department
Catholic University–Policlinico
“A. Gemelli”
Largo F. Vito
1–00168 Rome, Italy
Tel: +39 0630 1558 96
Fax: +39 0630 1569 99
e-mail: allergologia@hotmail.com