

RESEARCH ARTICLE

Hypersensitivity reaction to ranitidine: Description of a case and review of the literature

Caterina Foti¹, Nicoletta Cassano¹, Rosanna Panebianco¹, Gian Franco Calogiuri², and Gino A. Vena¹

¹Department of Internal Medicine, Immunology and Infectious Diseases, Unit of Dermatology, University of Bari, Bari, Italy, and ²4th Pneumologic Division, Hospital for Pulmonary Diseases A. Galateo, San Cesario di Lecce, Italy

Abstract

Ranitidine is an H₂-receptor antagonist which is usually well tolerated. Hypersensitivity reactions to ranitidine, as well as other H₂ antihistamines, have been rarely described. We report the case of a 47-year-old woman who developed an anaphylactic reaction to ranitidine used as intravenous premedication before anesthesia induction. The patient's history revealed that previous use of oral ranitidine for a peptic ulcer disease did not cause any adverse reaction. Intradermal test with ranitidine at a dilution of 1:100 gave an intense positive reaction. The protective role of H₂-receptor antagonists as premedication is still unclear and should be carefully reconsidered on the basis of the available controversial evidence and the possible risk of hypersensitivity reactions.

Keywords: Anaphylaxis; Hypersensitivity; Ranitidine; Premedication; Anesthesia

Introduction

Histamine H₂-receptor antagonists are widely used for the treatment of peptic ulcers, acute stress ulcers, gastro-esophageal reflux, and disorders related to acid hypersecretion. These drugs are frequently given before surgery because they reduce the incidence of postoperative nausea and vomiting, as well as the risk of acid reflux and pulmonary aspiration.^(1,2) Moreover, H₂ blocking agents are sometimes used in combination with H₁ antihistamines and/or corticosteroids to prevent allergic or pseudoallergic reactions prior to the administration of anesthetics or contrast media.^(3,4) Here we describe the case of a patient who developed a hypersensitivity reaction to ranitidine used as premedication before general anaesthesia.

Description of the clinical case

A 47-year-old non-atopic woman was referred to our outpatient unit because of a hypersensitivity reaction

which had occurred one month earlier in concomitance with an intravenous premedication before the induction of general anaesthesia for an elective cervical microdiscectomy. Such a precautionary prophylaxis, consisting of 2,000mg methylprednisolone (Solu-medrol) and subsequent 50mg ranitidine (Zantac), was recommended by the anesthesiologist as the patient reported to be intolerant to acetylsalicylic acid (ASA).

A few minutes after the intravenous administration of ranitidine, the patient experienced generalized itch, throat constriction, and hypotension, accompanied by a marked erythema at the site of infusion and along the course of the vein proximal to this site. Symptoms were promptly controlled by intramuscular administration of epinephrine.

The patient's history disclosed no other relevant findings with the exception of a peptic ulcer disease healed after treatment with H₂-blocking agents, including ranitidine, and proton pump inhibitors. The patient denied any type of adverse reaction to these or other drugs. Apart from ASA skin prick tests with ranitidine

Address for Correspondence: Caterina Foti, M.D., Unit of Dermatology – Department of Internal Medicine, Immunology and Infectious Diseases, University of Bari, Policlinico, Piazza Giulio Cesare, 11, I-70124 Bari, Italy. E-mail: c.foti@dermatologia.uniba.it

(Received 30 April 2008; revised 14 May 2008; accepted 15 May 2008)

ISSN 0892-3973 print/ISSN 1532-2513 online © 2009 Informa UK Ltd
DOI: 10.1080/08923970902739078

<http://www.informahealthcare.com/ipi>

and metilprednisolone were performed and proven negative, as well as the intradermal test with metilprednisolone at dilutions of 1:100 and 1:10. An intense reaction was instead observed after intradermal testing with ranitidine 1:100. Intradermal tests with ranitidine at both 1:100 and 1:10 dilutions gave negative results in 10 healthy volunteers.

Discussion

Ranitidine hydrochloride is a widely used H2-receptor antagonist which is usually well tolerated.⁽⁵⁾ The use of this drug has been rarely associated with cutaneous adverse reactions, such as lichenoid eruption,⁽⁶⁾ photosensitivity,^(7,8) occupational or non-occupational allergic contact dermatitis,⁽⁹⁻¹²⁾ toxic epidermal necrolysis,^(13,14) and acute generalized exanthematous pustulosis.⁽¹⁵⁾ Few reports exist on immediate type hypersensitivity reactions to ranitidine, consisting in asthma and rhinitis,⁽¹⁶⁾ urticaria, and anaphylaxis.⁽¹⁷⁻²⁷⁾ These reactions were observed in patients treated with either oral or intravenous ranitidine, including patients who underwent a premedication protocol containing ranitidine prior to chemotherapy or anaesthesia. Interestingly, many ranitidine-induced anaphylactic/anaphylactoid reactions occurred in obstetric patients.^(18,19,21,23) Some reports documented the positivity of skin test results to ranitidine,^(20-22,24-27) as in our case, thus suggesting that the drug can evoke hypersensitivity reactions through an IgE-mediated mechanism. Another indirect evidence of immediate hypersensitivity was proven by the leukocyte histamine release test,⁽²²⁾ while serum specific IgE reacting to ranitidine were detected in a patient using enzyme-linked immunosorbent assay.⁽²⁴⁾ As concerns the cross-reactivity between ranitidine and other H2 antihistamines, the available findings indicate the possible cross-reaction with nizatidine in the absence of cross-reactivity with cimetidine or famotidine.^(20,22,24)

The frequency of anaphylactic reactions to H2-receptor antagonists and proton pump inhibitors together has been estimated to be up to 0.7%, with only 2 cases of anaphylaxis to ranitidine revealed among 8,304 first-referral patients over a 13-year period.⁽²⁵⁾ Although ranitidine appears to induce rarely immediate hypersensitivity reactions, it seems to be the most frequent culprit of anaphylaxis among all H2 antihistamines, with cimetidine and nizatidine being involved only exceptionally in such reactions.⁽²⁸⁻³⁰⁾

It cannot be ruled out that anaphylactic or anaphylactoid reactions due to ranitidine may be underestimated and more frequent than expected. For instance, a hypersensitivity reaction to ranitidine during premedication is likely to be erroneously attributed to other drugs either contained in the same premedication protocol or given

after the premedication (e.g., anesthetic or chemotherapeutic drugs). Moreover, the concomitant administration of corticosteroids and/or H1 antihistamines which are commonly used on such occasions could attenuate or even partially prevent symptoms of immediate hypersensitivity, thus creating difficulties in the correct identification of these adverse reactions.

The role of H2-receptor antagonists as premedication is however controversial. The prophylactic use of H2 antihistamines in combination with anti-H1 agents is thought to give better protection against anaphylactic or anaphylactoid reactions than the administration of single drugs, although other evidences do not support this hypothesis.^(4,31) Moreover, some findings seem to suggest that the presumptive protective effect of ranitidine can be nullified, and its use may become even dangerous in patients who develop anaphylaxis because of the increased risk of heart block or bronchial hyperreactivity.^(32,33)

Conclusion

On the basis of our case report and literature data, the use of ranitidine as prophylactic treatment against anaphylaxis should be revised and carefully evaluated in clinical practice.

Acknowledgments

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Doenicke, A.W., Hoernecke, R., Celik, I. Premedication with H1 and H2 blocking agents reduces the incidence of postoperative nausea and vomiting. *Inflamm. Res.* 2004, 53 (Suppl 2), S154-S158.
2. Gouda, B.B., Lydon, A.M., Badhe, A., Shorten, G.D. A comparison of the effects of ranitidine and omeprazole on volume and pH of gastric contents in elective surgical patients. *Eur. J. Anaesthesiol.* 2004, 21 (4), 260-264.
3. Kimura, K., Adachi, M., Kubo, K. H1- and H2-receptor antagonists prevent histamine release in allergic patients after the administration of midazolam-ketamine. A randomized controlled study. *Inflamm. Res.* 1999, 48 (3), 128-132.
4. Liccardi, G., Lobefalo, G., Di Florio, E., Di Iorio, C., Occhiochiuso, L., Romano, L., Savoia, G., Massa, R.M., D'Amato, G., Cardarelli Hospital Radiocontrast Media and Anesthetic-Induced Anaphylaxis Prevention Working Group. Strategies for the prevention of asthmatic, anaphylactic and anaphylactoid reactions during the administration of anesthetics and/or contrast media. *J. Invest. Allergol. Clin. Immunol.* 2008, 18 (1), 1-11.
5. Mills, J.G., Koch, K.M., Webster, C., Sirgo, M.A., Fitzgerald, K., Wood, J.R. The safety of ranitidine in over a decade of use. *Aliment. Pharmacol. Ther.* 1997, 11 (1), 129-137.

6. Horiuchi, Y., Katagiri, T. Lichenoid eruptions due to the H₂-receptor antagonists roxatidine and ranitidine. *J. Dermatol.* 1996, 23 (7), 510-512.
7. Todd, P., Norris, P., Hawk, J.L., Du Vivier, A.W. Ranitidine-induced photosensitivity. *Clin. Exp. Dermatol.* 1995, 20 (2), 146-148.
8. Kondo, S., Kapeya, M., Yamada, Y., Matsusaka, H., Jimbow, K. UVB photosensitivity due to ranitidine. *Dermatology* 2000, 201 (1), 71-73.
9. Goh, C.L., Ng, S.K. Allergic contact dermatitis to ranitidine. *Contact Dermatitis* 1984, 11 (4), 252.
10. Juste, S., Blanco, J., Garces, M., Rodríguez, G. Allergic dermatitis due to oral ranitidine. *Contact Dermatitis* 1992, 27 (5), 339-340.
11. Gielen, K., Goossens, A. Occupational allergic contact dermatitis from drugs in healthcare workers. *Contact Dermatitis* 2001, 45 (5), 273-279.
12. Ryan, P.J., Rycroft, R.J., Aston, I.R. Allergic contact dermatitis from occupational exposure to ranitidine hydrochloride. *Contact Dermatitis* 2003, 48 (2), 67-68.
13. Miralles, E.S., Núñez, M., del Olmo, N., Ledo, A. Ranitidine-related toxic epidermal necrolysis in a patient with idiopathic thrombocytopenic purpura. *J. Am. Acad. Dermatol.* 1995, 32 (1), 133-134.
14. Vélez, A., Moreno, J.C. Second case of ranitidine-related toxic epidermal necrolysis in a patient with idiopathic thrombocytopenic purpura. *J. Am. Acad. Dermatol.* 2000, 42 (2 Pt 1), 305.
15. Martinez, M.B., Salvador, J.F., Aguilera, G.U., Mas, I.B., Ramírez, J.C. Acute generalized exanthematous pustulosis induced by ranitidine hydrochloride. *Contact Dermatitis* 2003, 49 (1), 4.
16. Martínez, A.J., Callejo Melgosa, A., Fuentes, G.M., Martín García, C. Rhinitis and asthma due to ranitidine. *J. Investig. Allergol. Clin. Immunol.* 2006, 16 (2), 142-143.
17. Picardo, M., Santucci, B. Urticaria from ranitidine. *Contact Dermatitis* 1983, 9 (4), 327.
18. Greer, I.A., Fellows, K. Anaphylactoid reaction to ranitidine in labour. *Br. J. Clin. Pract.* 1990, 44 (2), 78.
19. Barry, J.E.S., Madan, R., Hewitt, P.B. Anaphylactoid reaction to ranitidine in an obstetric patient. *Anaesthesia* 1992, 47 (4), 360-361.
20. Lazaro, M., Compaired, J.A., de la Hoz, B., Igea, J.M., Marcos, C., Dávila, I., Losada, E. Anaphylactic reaction to ranitidine. *Allergy* 1993, 48 (5), 385-387.
21. Powell, J.A., Maycock, E.J. Anaphylactoid reaction to ranitidine in an obstetric patient. *Anaesth. Intensive Care.* 1993, 21 (5), 702-703.
22. Morisset, M., Moneret-Vautrin, D.A., Loppinet, V., Grandidier, S. Cross-allergy to ranitidine and nizatidine. *Allergy* 2000, 55 (7), 682-683.
23. Kaneko, K., Maruta, H. Severe anaphylactoid reaction to ranitidine in a parturient with subsequent fetal distress. *J. Anesth.* 2003, 17 (3), 199-200.
24. Koh, Y.L., Park, H.S., Choi, I.S. Ranitidine-induced anaphylaxis: detection of serum specific IgE antibody. *Allergy* 2006, 61 (2), 269-270.
25. Demirkan, K., Bozkurt, B., Karakaya, G., Kalyoncu, A.F. Anaphylactic reaction to drugs commonly used for gastrointestinal system diseases: 3 case reports and review of the literature. *J. Investig. Allergol. Clin. Immunol.* 2006, 16 (3), 203-209.
26. Thurrot-Guillou, C., Bourrain, J.L., Jacquier, J.P., Beani, J.C. Anaphylactic reaction to ranitidine and dexchlorpheniramine. *Eur. J. Dermatol.* 2007, 17 (2), 170-171.
27. Rethnam, U., Yesupalan, R.S. Anaphylactic reaction associated with ranitidine in a patient with acute pancreatitis: A case report. *J. Med. Case Reports* 2007, 1, 75.
28. Knapp, A.B., Grimshaw, R.S. Jr, Goldfarb, J.P., Farkas, P.S., Rubin, M., Rosenstreich, D.L. Cimetidine-induced anaphylaxis. *Ann. Intern. Med.* 1982, 97 (3), 374-375.
29. Whalen, J.P. Hypersensitivity to cimetidine. *J. Clin. Pharmacol.* 1985, 25 (8), 610.
30. Mira-Perceval, J.L., Ortiz, J.L., Sarrió, F., Miralles, J.C., Hernández, J., Negro-Alvarez, J.M., López-Sánchez, J.D., García-Sellés, F.J., Pagán, J.A.. Nizatidine anaphylaxis. *J. Allergy Clin. Immunol.* 1996, 97 (3), 855-856.
31. Kupczyk, M., Kupryś, I., Bocheńska-Marciniak, M., Górski, P., Kuna, P. Ranitidine (150 mg daily) inhibits wheal, flare, and itching reactions in skin-prick tests. *Allergy Asthma Proc.* 2007, 28 (6), 711-715.
32. Hofman, J., Michalska, I., Rutkowski, R., Chyrek-Borowska, S. The role of H₂-receptors in bronchial reactivity in atopic asthma. *Agents Actions* 1988, 23 (3-4), 370-372.
33. Patterson, L.J., Milne, B. Latex anaphylaxis causing heart block: Role of ranitidine. *Can. J. Anaesth.* 1999, 46 (8), 776-778.