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How often we diagnose allergy to ranitidine?

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Abstract. – H2 receptors' antagonists (H2RA) are widely used drugs and they are generally well-tolerated. Ranitidine hypersensitivity reactions (HR) are rarely reported. The article emphasizes the importance of recognizing ranitidine as a cause of anaphylaxis and the advantages and limits of allergological evaluation to establish a positive diagnose. We reviewed a series of published cases of ranitidine-induced hypersensitivity reactions, starting from a clinical case presentation. Moreover, we analyzed the ranitidine related adverse events in the Eudravigilance European database of adverse reactions. Most of the allergic reactions induced by ranitidine are type I HR with immediate onset after exposure, with variable clinical presentation. But in a few cases, there were also described delayed reactions, some after occupational exposure. The article underlines the importance of allergy evaluation to avoid future contact with the drug to reduce the risk of more severe reactions. The suspected reactions should be reported, allowing pharmacovigilance systems to analyse them and to establish further recommendations for clinicians.

Key Words:
Hypersensitivity reaction, Ranitidine, Pharmacovigilance.

Introduction

Drug induced hypersensitivity reactions have variable clinical manifestations, from common urticaria to anaphylaxis. Hypersensitivity reactions (HR) could occur after administration of any drug to any patient[1].

Ranitidine gained an unpleasant fame after a temporary suspension of all ranitidine medicines across EU in April 2020 due to the presence of low levels of N-nitrodimethylamine. Before that, ranitidine was a popular antisecretory drug used and available in many UE countries without prescription. Ranitidine is a competitive antagonist of H_2 receptors, recommended for the treatment of peptic ulcer, gastroesophageal-reflux disease or to prevent upper gastric bleeding from stress induced ulcers. It is a well-tolerated drug; gastrointestinal side effects are the most frequently observed, along to headache and somnolence[2]. The frequency of HR to ranitidine is very low, but the reactions could be extremely variable. Mild moderate skin and mucosa reactions are the dominant ones. The severe reactions like bronchospasm, anaphylactic reactions and toxic epidermal necrolysis are very rare[3,4]. But it is possible that severe reactions are neglected in some patients, and thus, it could become life-threatening. For patient safety, it is essential to recognize rapidly the severe reactions to initiate the specific treatment immediately and to differentiate them from mild-moderate reactions.

The aim of this review is to analyze the published cases of ranitidine-induced HR, starting from a clinical case, to underline the importance of allergy evaluation and the role of pharmacovigilance in analysing the reported cases. It also provides a practical guidance for the clinician in front of a suspected HR.

Case Vignette from Our Practice

A 35 yo male patient, from urban area came to the allergy specialist to evaluate his persistent allergic rhinitis to pollen. The disease onset was 6 years previous the presentation.

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In this interval of time, during an episode of exacerbation of rhinitis, the patient also accused diffuse epigastric pain. The gastroenterologist recommended ranitidine 300 mg/day for 2 weeks. The patient had previous exposure to ranitidine for acute gastritis, he tolerated the treatment without side effects. On the second day after he started ranitidine therapy, 2 hours after administration, he presented angioedema of the face and generalized urticaria. The gastroenterologist recommended to stop ranitidine and to continue with omeprazole 20 mg/day, treatment that was well tolerated. No allergy evaluation was performed at this point. Eight months after the described episode, the patient presented similar intense epigastric pain and decided to self-administer ranitidine 150 mg/day. Within first hour after administration he presented angioedema of lips, eyes, and face and generalized urticaria. The patient decided to self-administer a H_1 antihistaminic drug and to stop ranitidine administration. As the symptoms subsided within 12 hours, the patient no longer presented to the doctor. In the next year, at the beginning of grass pollen season, the patient presented specific symptoms for allergic rhinitis that were not reduced by desloratadine 5 mg/day as in the previous seasons. The rhinitis symptoms occurred daily, and they affected patient's quality of life and his sleep. The patient could no longer perform his activity outdoors during the last 5 days before presentation. He decided to ask help from an allergist.

During the allergy history the patient mentioned the above described episodes of angioedema and urticaria after ranitidine administration. The specialist decided to treat rhinitis symptoms with levocetirizine 5 mg/day and fluticasone furoate 37.5 mcg, 2puffs/day immediately until the end of grass pollen season and to re-evaluate the atopic status and a possible HR induced by ranitidine. The skin prick test (SP) was postponed until the end of summer. It was also recommended to avoid the administration of ranitidine and other H_2RA until the final diagnosis was established. The immediate and during pollen season evolution was good, with rhinitis symptoms controlled in few days of treatment and no episodes of urticaria and angioedema when he had no exposure to ranitidine. He returned at the end of treatment to perform the skin prick test. SP test indicated the presence of atopy, with moderate sensitization to grass pollen, olive pollen and cat dander. SP test for ranitidine was performed using a solution 25 mg ranitidine/ml and was positive after 15 minutes, with a size of wheal of 6 mm. The intradermal test was done using a 1/10 dilution from the standard solution. The test was positive after 15 minutes (diameter of wheal was 8 mm).

The patient received the recommendation to avoid H_2RA and to use proton pump inhibitors (PPIs) if he needed an antisecretory therapy. He started sublingual allergen specific immunotherapy with grass pollen during autumn and he continued for 2 years with a positive response.

How to Diagnose of Drug Allergy

Hypersensitivity reactions (HR) are immune mediated, with different mechanisms, divided in 4 types of HR: type I, IgE mediated; type II, cytotoxic reactions; type III, immune complexes mediated and type IV, lymphocytes T (lyT) mediated reactions. In clinical practice that classification is not always very practical[1]. A simplified classification takes into account the temporal criteria, the interval of time from drug exposure to occurrence of clinical manifestations, respectively. The HR could occur[1,5,6]:

- Immediately, in less than 1 hour after drug exposure: rhinitis, conjunctivitis, bronchospasm, localized or generalized urticaria, anaphylaxis. The mechanisms are type I HR, IgE mediated[1];
- Tardive, from 1 hour to a few days after exposure. These reactions have a high clinical variability according to their mechanism of production[6];
- Tardive, without systemic manifestations, in 6-10 days after the first exposure and in maximum 3 days after the 2nd exposure. These reactions include delayed onset urticaria, maculopapular rash, and fixed drug eruptions.

Tardive with systemic manifestations:

- In 2-6 weeks after the first exposure and in 3 days after the 2nd one: DRESS syndrome (generalized maculopapular eruption, fever, lymphadenopathy, increased AST and ALT and eosinophilia);
- In 7-14 days after the first exposure and within 3 days after the 2nd one: toxic epidermal necrolysis or Steven Johnson syndrome (painful skin eruption, fever, erosions, skin and mucosa ulceration, vesicles and blisters;
- In 3-5 days after the first exposure: acute generalized exanthematous pustulosis (generalized pustules with negative bacterial culture, fever and neutrophilia)[6].

The positive diagnose for drug allergy is based on patient history and the clinical manifestations described by the patient or present in the moment of evaluation[6,7]. The confirmation is made by lab test and specific allergy tests, including drug provocation test.

Clinical Evaluation

The first step in the evaluation of a patient with drug allergy is a complete anamnesis to establish the association between adverse event and culprit drug. If a HR is suspected it is essential to define the symptoms and their chronology (previous exposure, delayed response, if symptoms persist in case of treatment discontinuation), if other drugs were concomitantly administered together with the culprit one, if the patient has a personal history of atopy or other drug allergies. All these above-mentioned criteria were detailed in a standardized questionnaire by European Network of Drug Allergy (ENDA), aiming to harmonize the procedures needed to diagnose correctly a drug induced allergic reaction (https://www.eaaci.org/attachments/668_Questionnaire_DrugIG.pdf)[7].

The absence of case reports in the literature does not exclude a possible HR induced by a drug. The probability is low if the clinical manifestations can be attributed to other diseases, or if they occur in the absence of drug exposure or only gastrointestinal manifestations are present.

In Vivo Tests

If a HR induced by a drug is suspected, the diagnostic algorithm imposes to perform *in vivo* test: skin prick (SP) and intradermal (ID) tests. The allergy tests should be performed only by a trained specialist, according to international guidelines[8]. EAACI Drug Allergy Interest Group published in 2013 a position paper[8], establishing the validated concentrations for SP test and ID test for some of the drugs that frequently determine HR. This paper underlines that a nonirritative concentration for allergological test can not be established in all the cases. Because H_2RA are rarely suspected to induce allergic reaction, there is no standard concentration for SP and ID tests.

Double blind placebo oral provocation test (OPT) represents the gold standard in diagnosing drug induced HR. Because it has some risks, this method is recommended only if the positive diagnosis cannot be established based on the tests mentioned above[1,5,6]. The OPT is contraindicated if the patient had a severe anaphylactic reaction as previous manifestation of his/her drug allergy.

In Vitro Laboratory Tests

They include determination of serum tryptase to confirm the diagnostic of anaphylaxis, but it is a nonspecific test and cannot permit to identify the culprit drug. Measurement of specific IgE to H_2RA through radioallergosorbent test (RAST) technique is useful to detect a type I HR, but they are not available in all the laboratories worldwide. Lymphoblastic transformation test is useful to diagnose a type IV HR, but it is expensive and rarely used[6].

Methods

A search on ranitidine hypersensitivity of was performed using Eudravigilance database of suspected adverse drug reaction reports recorded before 1st of June 2020, evaluating total individual cases of suspected reactions (ICSR) related to ranitidine in European European Area (EEA). A second search of case-reports of ranitidine allergy in the last 10 years (2010-2020) was performed in Embase and PubMed.

Results

From 6917 reported adverse reactions (3117 cases were reported from EEA), 860 individual cases (12.43%) were immune-allergic reactions. Seventeen cases were fatal anaphylactic reactions[9]. Five cases of anaphylactic reactions were reported in children, including the category under 2 years old. So, these cases are not rare, as we would be tempted to believe.

Total published cases or total ICSR are a small fraction of total cases that occurs in current practice. It is estimated that in UK 90% of adverse reactions are not reported, while in USA up to 98-99% of severe adverse reactions are not reported in a centralized network[10]. A different geographical distribution of cases across EEA is reported to ranitidine, but it is proportional with total spontaneous reports. By comparing registered data, only 20 cases of all ranitidine adverse events from Eudravigilance counted as Romania reports, France reported 583 cases of ranitidine induced adverse events, UK 536 cases, while Netherlands, with a similar population as Romania, reported 272 cases[10]. This difference is due to the low spontaneous reporting in some countries, not to a difference in prevalence.

The analysis of 8-years pharmacovigilance data from Korea showed that from all ranitidine-induced reactions, 17% (99 patients) were anaphylaxis reactions. However, in more than 80% of cases ranitidine was re-administered, motivated by the fact that the reaction was not initially associated with this drug and that they were not investigated through allergic tests[3]. This attitude could be life-threatening in some cases.

Published case-reports are a valuable source, not so much because of their number, which is quite small compared to ICSR in pharmacovigilance databases, but because it gives us a clearer picture of real patients and caregiver attitude toward a specific drug. Thirteen cases published in medical journals indexed in PubMed and Embase were analysed. The characteristics of the cases are presented in Table I.

Analysing the clinical manifestations in most of the published cases, the allergic reaction occurs within 1 hour after administration. Only in 2 cases (15.4%) ranitidine was administered orally. Severe immediate reactions after first administration of ranitidine were also described, but the sensitization contact was not determined (22). In 84.6% of the cases, moderate-severe anaphylactic reactions, characterized by hypotension and bronchospasm were reported; most of them occurred after intravenous administration of ranitidine, in perioperative settings[12,18,21,23]. In one case, unknown exposure to ranitidine or other substance that induced cross-sensitivity leads to a severe anaphylactic reaction at a child at first known contact with ranitidine[22]. In one case the reaction was fatal, and in another one the reaction involved only the skin and mucosa, without systemic manifestation. In our case the male patient presented the manifestation immediately after oral administration. He presented only urticaria and angioedema, which are the most frequent clinical manifestation of drug allergy[3]. Symptoms occurred within the first 6 hours after ranitidine administration, at the second exposure. These clinical characteristics suggested an immediate immunologic mechanism, possible IgE mediated. In 2/3 cases the positive diagnose was established by allergy tests, with positivity of SP test. Only in 3 cases, the OPT was done to confirm the positive diagnose. SP and ID tests represent sensitive diagnostic tools, with lower risks than OPT. Only in 3 patients (23%) the level of specific IgE was determined, but in one case this method was essential for the diagnostic confirmation, the previously performed skin tests being negative.

Since cases of H_2RA induced allergy are rarely suspected and encountered in medical practice, a standard concentration for SP and ID tests has not been established. In this case, ranitidine 25 mg/ml solution was used for SP test and 1/10 dilution of standard solution for ID test. In the ENDA/EAACI 2013 consensus, the concentration of 1/100 is mentioned as being non-irritating, the one of 1/10 being able to cause false positive reactions especially to nizatidine[8]. However, the study of Park et al[3], which evaluated 12 patients with ranitidine-induced anaphylaxis, at SP test the mean papule size was 6.4 ± 2.0 mm, while ID test was performed with multiple concentrations of ranitidine, ranging from 0.5 to 25 mg/ml. In the presented case, the ID concentration was 2 mg/ml, a concentration used also in Park's study. Park et al[3] revealed that an increase of test concentration might also increase the false positive results. However, the concentrations used in our case were within the limits described in the literature, so the SP test was considered positive. The ID test concentrations used in the analyzed cases were in the same range as in Park's study[3].

In several studies[14,15], cross-reactions with other H_2RA are common for the patients with positive skin tests for ranitidine. Therefore, it is recommended to avoid all H_2RA in these patients unless a test is performed for each drug to identify alternatives. The analysis of the previously published cases showed that in most situations, an alternative to ranitidine from the group of H_2RA had not been tested. In two of the 13 cases (15.4%) the authors identified cross-reactions with other H_2 antagonists[14,15]. The HR probably due to the furan ring present in the structure of ranitidine[23]. This could also be an explanation for delayed onset HR, but it could not explain the cross-reactions with other H_2RA, knowing that cimetidine contains an imidazole ring like histamine, while famotidine and nizatidine have a thiazole ring[5]. Probably the structure of additional lateral chains may play an important role in cross-reactivity. There are no data regarding possible cross-reactions with PPIs, they have a different chemical structure, so they could be considered a safe alternative from the beginning.

HR after ranitidine occupational exposure have also been reported in workers from pharmaceutical industry[24] and in nurses[25]. A study evaluating the professional risk of contact dermatitis of people with occupational exposure to different drugs or their metabolites. showed a frequency of 13% of reactions associated with drug handling, in all

Table I. Characteristic of cases of type I hypersensitivity reactions induced by Ranitidine.

Case/Reference	Route of administration	Clinical manifestation	Diagnostic test for confirmation	Cross reactivity with H2 other antagonists	Personal history of atopy or other allergies
M 31 yo11	Oral	Urticaria, angioedema of the face, bronchial obstruction, abdominal cramps Hypotension – 6 months previously after a ranitidine dose	Prick-test negative OPT +	–	
M 18 yo[12]	iv	During anesthesia – tachycardia and hypotension	Prick-test + sIgE +	–	Allergic rhinits to pollen
M 36 yo13	iv	Severe dyspnea immediately after administration	Prick-test +	-	Negative
F 64 yo 14	iv	Bradycardia, hypotension, angioedema immediately after administration	Prick-test +	(+) cimetidine (-) famotidine	Negative
F 42 yo15	Oral	Dyspnea, sneezing and angioedema after 30 minutes	OPT +	(+) famotidine	Negative
M 40 yo16	iv	Severe anaphylaxis during anesthesia	Prick-test +	Not done	–
M 75 yo17	iv	Severe anaphylactic reaction, death of patient	–	–	–
F 31 yo18	iv	Severe anaphylactic reaction during anesthesia	Id test +	Not done	Allergic rhinitis
M 60 yo17	iv	Generalized urticaria a few minutes, hypotension, angioedema	Id test negative sIgE positive	Not done	Allergy to amoxicillin
M 66 yo19	iv	Kounis syndrome	Prick-test +	Not done	–
M 57 yo20	iv	Angioedema and acute urticaria (3 episodes)	Prick-test +	Not done	–
F 24 yo21	iv	Hypotension, bronchospasm, tachycardia – during anesthesia	OPT +	Not done	–
M 8 yo22	iv	Angioedema, hypotension, tachycardia, at first administration of Ranitidine	Prick-test + ID test + sIgE +	Not done	–

Abbreviations: F, female; M, male, (+), positive; (-), negative; ID, intradermal; iv, intravenous; OPT, oral provocation test; sIgE, specific immunoglobulin E; yo, years old.

Table II. Ranitidine induced delayed hypersensitivity reactions.

Case/Reference	Route of administration	Clinical manifestation	Latency	Diagnostic test for confirmation
M 80 yo26	Oral	Generalized skin eruptions	3 days	LTT +
M 56 yo27	Oral	Acute generalized exanthematous pustulosis	10 days	Patch-test +
F 31 yo28	Oral	Toxic epidermal necrolysis associated with idiopathic thrombocytopenic purpura	7 days	-
M 16 yo29	Oral	DRESS syndrome	3 weeks	Patch-test + ID + after 96 hours

Abbreviations: M, Male; F, female; (+), positive; DRESS, Drug reaction with eosinophilia and systemic symptoms; ID, intradermal; LTT, Lymphoblastic transformation test; yo, years old.

reported dermatitis cases. The most frequently positive patch-tests were noticed for tetrazepam, a drug withdrawn from the market because of severe type IV HR reaction in 2013, ranitidine and zolpidem[25].

Delayed reactions are more difficult to diagnose, and they are even more frequently under-reported compared to immediate type I reactions. Among delayed reactions, type IV HR are rarely induced by H_2RA. Few cases have been reported in the literature until now (Table II). In Eudravigilance database are recorded only 6 cases of ranitidine induced delayed reactions. Given the delayed reaction, sometimes up to 6 weeks in the case of DRESS syndrome, the association between the drug and the adverse reaction is more difficult to do and some of the cases remain undiagnosed.

The authors choose to present the case not to reveal a severe or a particular form of allergy to ranitidine, but to emphasize the importance of the allergic evaluation to confirm a drug allergy, which was carried out in the context of investigating another allergic manifestation. The patient did not receive a recommendation for allergic evaluation after the first episode, which led to the unintentional exposure that caused the second episode to occur. The severity of the manifestations is not always the same; sometimes the re-exposure to the culprit drug can cause an anaphylactic reaction and even the death of the patient. It is essential to perform an allergy evaluation in the first 2 months after a drug suspected adverse event to establish the positive diagnosis, in order to be able to recommend what drugs should be avoided and what alternatives can be used safely in the future. We note that some patients are probably re-exposed because ranitidine is not perceived as one of those classes of drugs that frequently causes allergies, in accidental exposure or professional exposure. Also, these rare reactions should be reported in pharmacovigilance systems to determine more precisely their frequency of occurrence and their severity.

Conclusions

Allergic reactions to ranitidine are not as rare as we would expect. Most of the allergic reactions induced by ranitidine are type I HR with immediate onset after exposure. The clinical presentation of these reactions is extremely variable. The risk of re-exposure, of occupational exposure and the development of HR to the medical personnel handling ranitidine must be considered. We emphasize the importance of the correct diagnosis, the reporting of these adverse reactions, the confirmation of the diagnosis by a specialist through specific skin tests and the absolute contraindication in the use of the whole class due to the risk of cross reactions.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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