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Ranitidine-Induced Anaphylaxis: Clinical Features, Cross-Reactivity, and Skin Testing

Running title: Ranitidine-Induced Anaphylaxis

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Abstract

Background: Histamine H₂ receptor antagonists are commonly prescribed medications and are known to be well tolerated. However, 99 cases of ranitidine-induced anaphylaxis occurred in Korea from 2007–2014.

Objective: The purpose of this study was to determine the incidence, clinical features, and diagnostic methods for ranitidine-induced anaphylaxis.

Methods: Ranitidine-related pharmacovigilance data from 2007 to 2014 were reviewed.

Adverse drug reactions with causal relationships were selected and clinical manifestations, outcomes, and drug-related information were assessed. For further investigation, 8 years of pharmacovigilance data were collected at a single center. Twenty-three patients participated in *in vivo* and *in vitro* studies. Skin tests, oral provocation tests, and laboratory tests were performed, including tests using other kinds of histamine H₂ receptor antagonists.

Results: Over 7 years, 584 patients suffered adverse reactions to ranitidine. The most common manifestation was cutaneous symptoms. Among them, 99 patients (17.0%) experienced anaphylaxis. In a single-center study, skin prick tests were positive in 91.7% of ranitidine-induced anaphylaxis patients (11/12); the optimal concentration was 20 mg/mL. Detection of ranitidine-specific immunoglobulin E failed. Cimetidine and proton pump inhibitors showed no cross-reactivity with ranitidine based on the skin prick test, oral provocation test, or clinical determination. Surprisingly, 82.6% of patients re-introduced ranitidine and re-experienced the same adverse reactions because ranitidine was not considered the culprit drug.

Conclusions & Clinical Relevance: Although ranitidine is known as a safe drug, it can also cause diverse adverse reactions, including anaphylaxis. This study demonstrates the need to pay attention to adverse reactions to ranitidine and consider ranitidine as a cause of anaphylaxis.

Key words

Adverse drug reaction, Anaphylaxis, Histamine H₂ receptor antagonists, Ranitidine

Introduction

Ranitidine is a widely used H₂ receptor antagonist (H₂RA) and is generally considered to be safe [1]. It is prescribed worldwide for gastroduodenal ulcer, gastroesophageal reflux disease, ulcer bleeding/prophylaxis [2], and chronic urticaria [3]. In addition, it can even be used in anaphylaxis management [4]. Despite the fact that it is commonly used, few studies exist on

the adverse drug reactions (ADRs) of ranitidine. According to a study of 209 million patients worldwide who used ranitidine [1], common ADRs were abnormal liver enzyme levels (5.9 events/million treatments), nausea and/or vomiting, and skin rash. Hypersensitivity reactions were rare. Among worldwide spontaneous adverse reactions, the anaphylaxis rate was 0.86 events/million treatments. Contrary to these safety profiles, we report 99 cases of ranitidine anaphylaxis in Korea, including 23 patients at a single tertiary care center. The objectives of this study were to analyze the clinical manifestations of ranitidine ADRs, cross-reactivity against other H₂RAs, and to clarify the immunoglobulin E (IgE)-mediated immunologic reaction to ranitidine.

Materials and Methods

Subjects

Ranitidine pharmacovigilance data were collected from the Korea Institute of Drug Safety-Korea Adverse Event Reporting System (KIDS-KAERS) database of the Korea Institute of Drug Safety and Risk Management (Ministry of Food and Drug Safety). This system consists of 27 pharmacovigilance centers in Korea, including Severance Hospital (Seoul, Korea).

Primary physicians from local clinics, pharmacists from regional pharmacies, and patients can report adverse events to the 27 centers. These centers are placed throughout the country, including in all metropolitan cities, provinces in Korea. ADR reports from 2007 to 2014 were investigated. Clinical manifestations were reported according to World Health Organization-Adverse Reaction Terminology (WHO-ART) and included assessment results from World Health Organization-Uppsala Monitoring Center (WHO-UMC) causality criteria [5]. In this study, the demographics, reporter, generic name of the drug, administration dose/route, clinical manifestations/severity, re-challenge, and causality information from the ADRs were

analyzed. ADRs that were assessed as certain and as probable/likely were selected. Patients using ranitidine as a concomitant drug were excluded from the analysis. For a more precise diagnosis of anaphylaxis, all reports were reviewed and newly assessed as anaphylaxis according to World Allergy Organization (WAO) diagnostic criteria [4]. The study algorithm is shown in Figure 1.

To obtain more detailed clinical information and identify the anaphylaxis mechanism, ranitidine ADR reports were collected from Severance Hospital Regional Pharmacovigilance Center, which is part of Yonsei University in Seoul, Korea. This tertiary teaching hospital operates a well-established pharmacovigilance center with the assistance of the government; it began in 1990, and there were 7,331 ADR reports in the year 2013. The reports were collected spontaneously from doctors, nurses, pharmacists, paramedical persons, and patients and then analyzed by specialists consisting of doctors and pharmacists. The authors analyzed all ranitidine-related ADR reports over 9 years (January 1, 2007 to May 31, 2015) and selected anaphylaxis cases. Only if the patients provided their written informed consent, we collected sera and performed skin prick tests (SPTs) and/or intradermal tests (IDTs) using ranitidine and other H₂RAs. Negative control participants were also enrolled for skin and serologic testing; they demonstrated clinical tolerance to ranitidine. This study was approved by the Institutional Review Board of the Yonsei University Health System (No. 1-2014-0566).

Skin prick test

SPTs were performed with ranitidine (Curan[®] 10 mg/mL, 20 mg/mL, and 25 mg/mL; Il-Dong Pharmaceuticals, Seoul, Korea), cimetidine (Tagamet[®] 25 mg/mL, 50 mg/mL, and 100 mg/mL, Yuhan, Seoul, Korea), and famotidine (Gaster[®] 5 mg/mL, 10 mg/mL, and 20 mg/mL; Dong-A ST, Seoul, Korea) to determine cross-reactivity between H₂RAs. The negative control was normal saline with 0.3% phenol and 50% glycerol, and 0.1% histamine (Allergy Therapeutics, Worthing, UK) was used as a positive control. All participants were able to discontinue medications that might influence the SPT. SPT results were interpreted after 15 minutes, and wheal sizes greater than 3 mm were considered positive reactions.

Intradermal test

IDTs were performed using the 3 H₂RAs mentioned above. Ranitidine was used at concentrations of 0.2 mg/mL, 0.5 mg/mL, 1.0 mg/mL, 5.0 mg/mL, and 25.0 mg/mL. Five concentrations of cimetidine ranging from 0.8 mg/mL to 100 mg/mL were administered, as were 5 concentrations of famotidine ranging from 0.16 mg/mL to 20.0 mg/mL. The negative control was the same as for the SPT, and 0.017% histamine was used as the positive control (Allergopharma, Reinbek, Germany). IDTs were performed by a well-trained specialized nurse under allergist supervision. We carefully monitored symptoms and signs of possible anaphylactic reactions. Test results were interpreted after 15 minutes and wheal sizes greater than 3 mm were considered positive reactions. For ranitidine, if the wheal size was greater than that of the positive control or systemic symptoms appeared, the IDT was immediately discontinued.

Oral provocation test and tryptase

To determine anaphylaxis culprits and possible cross-reactive H₂RAs, an oral provocation test (OPT) was performed after obtaining informed consent. Patients were challenged under hospitalization status. The starting dose of ranitidine in the OPT was 37.5 mg or 75 mg according to previous anaphylactic reactions. Tryptase (Phadia, Uppsala, Sweden) was also checked after the anaphylaxis event.

Detection of specific IgE (sIgE) against ranitidine

For the detection of ranitidine-sIgE, ranitidine was conjugated with human serum albumin (HSA) by 2 methods. First, a cross-linker was used to conjugate ranitidine to HSA as previously reported [6, 7]. Second, an amine-to-sulfhydryl substituted ranitidine analog (TRC Canada, North York, ON, Canada) was directly conjugated with HSA [8]. Conjugation methods are shown in the supporting information. The 2 compounds are shown in Figures 2B and 2C. An enzyme-linked immunosorbent assay (ELISA) and 2-site ELISA were performed on these 2 compounds. Each conjugated compound was coated onto a 96-well ELISA plate at 2 µg/mL, 5 µg/mL, and 10 µg/mL concentrations and kept at 4°C overnight. After blocking with 3% skim milk, the anaphylaxis patients' and negative control patients' sera were incubated from 1 hour to overnight. Biotinylated anti-human IgE (Vector, Burlingame, CA, USA) and streptavidin-peroxidase (Sigma-Aldrich, Sydney, Australia) were each incubated for 1 hour. Color development was achieved with a 3,3',5,5'-tetramethylbenzidine substrate solution (Kirkegaard Perry Laboratories, Gaithersburg, MD, USA) and absorbance was read at A₄₅₀ using a ELISA plate reader (Versamax ELISA microplate reader; Molecular Devices, Sunnyvale, CA, USA).

A 2-site ELISA was performed using anti-HSA as a capture antibody. Anti-HSA 5 µg/mL (Sino Biological, Beijing, China) was coated onto a 96-well ELISA plate overnight and blocked with skim milk for 1 hour. Two ranitidine conjugates and HSA were used as antigens and incubated for another hour. Then, anaphylaxis and control sera were incubated for 1 hour. Finally, biotinylated anti-IgE, streptavidin-peroxidase, and substrate solution were added using the same technique as described above.

Results

Characteristics of ranitidine-induced adverse drug reactions

There were 5,299 ADR reports (3,496 persons) related to ranitidine. A total of 694 reports (584 persons) considered to have causal relationships were chosen for analysis. The mean age was 50.3 years, and 37.5% of the patients were male. Serious adverse reactions occurred in 87 cases (14.9%). Neither mortality nor congenital deformities occurred. Serious cases were mostly related to hospitalization and significant medical issues. Information about the reporter was limited (n = 463); 52.3% of the cases were reported by nurses, 19.7% by doctors, and 13.8% by pharmacists. Regarding administration route, cases involving intravenous ranitidine were 9 times more frequent than those involving oral ranitidine. There were 281 reports with re-challenge data, and 48 cases re-experienced adverse reactions after repeated administration. The baseline characteristics and clinical manifestations are shown in Table 1 and Table 2, respectively. The most common ADR was cutaneous symptoms such as urticaria, angioedema, skin rash, and injection site irritation, representing 39.6% of the cases. Gastrointestinal symptoms and signs were second most frequent. The third most common manifestation was anaphylaxis (14.3%, 99 patients). There were also mental status changes, hypotension, and respiratory compromise cases that did not fulfill the WHO anaphylaxis

criteria. Dizziness and headache were not uncommon ADRs. Fever, chest discomfort, hepatitis, cough, eosinophilia, gynecomastia, and lactation were also reported.

Characteristics of the ranitidine-induced anaphylaxis patients (N = 99)

The mean onset age among the ranitidine-induced anaphylaxis patients was 50.6 years. Males represented 45.5% of the patients. Age ($P = 0.861$) and sex ($P = 0.135$) were not significantly different from the non-anaphylaxis ADR patients. In contrast with Table 1, reporters were more commonly doctors. There was no casualty from anaphylaxis. The characteristics, symptoms, and signs of the anaphylaxis ADR reports are described in Table 3. Among 99 anaphylaxis patients, 58 (58.6%) were originally reported as anaphylaxis and 41 were newly re-assessed as anaphylaxis. The next most common manifestation was cutaneous symptoms (44.4%). Respiratory compromise (dyspnea, wheezing) was observed in one-third of the patients. Gastrointestinal symptoms and hypotension were reported in 20.2% and 16.2% of the cases, respectively. The number of patients intravenously administered ranitidine was 3.6 times greater than the number of patients orally administered ranitidine; however, there was no statistically significant difference ($P = 0.350$).

Clinical characteristics, *in vivo*, and *in vitro* tests of ranitidine-induced anaphylaxis patients from a single center (N = 23)

There were 23 anaphylaxis patients from a single center among the 153 ADR cases. The demographics, clinical manifestations, and SPT, IDT, and OPT results are shown in Table 4. The mean onset age was 51.7 years, and females represented 69.6% of the patients; they were all Korean. Among the 23 patients, 7 were administered ranitidine at our center, and the other

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15 were referred from other hospitals to determine the cause of anaphylaxis. Anaphylaxis manifestations were mainly cutaneous or involved the respiratory system. Hypotension occurred in 47.8% of patients. Although there was no casualty, 1 patient required 1 hour of cardiopulmonary resuscitation and survived with hypoxic brain damage. Four patients collapsed and recovered without sequelae. One patient visited the emergency room 3 times because of ranitidine-induced anaphylaxis. The mean number of unintended re-challenges was 2.6, and a patient self-reported up to 6 episodes of ranitidine-induced anaphylaxis. Re-administration occurred in 82.6% of patients because ranitidine was overlooked as the cause of anaphylaxis. The mean interval between the reaction and the allergological examination was 24.3 months.

The skin prick test and intradermal test

SPTs using ranitidine, cimetidine, and famotidine were performed on 12 anaphylaxis patients. The mean size of a positive reaction was a 5.9 ± 2.5 mm wheal and a 23.8 ± 12.5 mm flare. The sensitivity rate is shown in Table 4. The ranitidine SPT had 91.7% sensitivity and 100% specificity (11 negative controls). The optimal concentration was 20 mg/mL. Ranitidine-induced anaphylaxis patients showed no reaction to cimetidine or famotidine at the highest concentrations. The IDT showed 63.6% sensitivity and 100% specificity at a 0.2 mg/mL concentration of ranitidine. Cimetidine (0.8 mg/mL) and famotidine (0.8 mg/mL) tests were both negative in the 12 patients who participated. If the concentration of the H₂RA was increased, the false-positive rate was increased.

The oral provocation test and tryptase

Six out of twenty-three patients agreed to undergo an OPT. All patients experienced an acute onset of IgE-mediated responses (urticaria, angioedema, skin rash, and hypotension). One patient was able to undergo testing with ranitidine, cimetidine, and famotidine (patient No. 15), but there was no cross-reactive response to ranitidine or other H₂RAs. After the ranitidine provocation test, the patient experienced generalized urticaria and dyspnea; their tryptase level was checked, and it was elevated at 14.80 µg/L (reference range: 0–13.5 µg/L). One patient (patient No. 20) experienced both ranitidine-induced and nizatidine-induced anaphylaxis. Because ranitidine-induced anaphylaxis occurred twice, the provocation test was performed using nizatidine, and generalized urticaria appeared immediately. Patient No. 10 visited the emergency room to be treated for ranitidine-induced anaphylaxis; his tryptase level was found to be elevated (19.10 µg/L).

Detection of ranitidine-sIgE

To detect ranitidine-sIgE, ELISA and 2-site ELISA were performed using 2 kinds of ranitidine-HSA conjugation compounds. Both compounds were well conjugated with HSA (Figure S1). While neither ELISA method detected ranitidine-sIgE, 2-site ELISA detected ranitidine-HSA-sIgE in 2 anaphylaxis patients. However, they were false-positive reactions, as the 2 patients' sera also reacted to HSA alone. The results of the 2-site ELISA are shown in Figure 2D. One patient (No. 7) showed an IgE response to both indirectly conjugated ranitidine-HSA (iRNT-HSA) and the directly conjugated compound (dRNT-HSA). The other positive patient's (No. 13) serum was not sufficient for both tests; thus, we only tested against dRNT-HSA; her serum reacted to both dRNT-HSA and HSA.

Safely used H₂RAs and proton pump inhibitors (PPIs) in anaphylaxis patients

Because this study was retrospective in design, we could not confirm the cross-reactivity of H₂RAs by provocation testing. Instead, we analyzed the medical records of anaphylaxis patients. Twelve patients used another H₂RA or PPI after ranitidine-induced anaphylaxis. Cimetidine and a PPI were safely used in 6 patients (50%, 1 patient was confirmed by an OPT) and 9 patients (75%), respectively. The data are shown in Figure 3.

Discussion

In this study, the medical records of ranitidine-induced anaphylaxis patients were systematically reviewed using 7–8 years of national and single-center pharmacovigilance data. This study demonstrates comprehensive data regarding ranitidine-induced anaphylaxis including clinical features, SPT results, cross-reactivity, and provocation test results. Several case studies on ranitidine-induced anaphylaxis have been reported in Italy [9-12], India [13, 14], Germany [15], Spain [16], France [17], the UK [18], Japan [19], Turkey [20], Tunisia [21], as well as in Korea [6, 7, 22, 23]. The number of published reports on anaphylaxis patients was highest among the Korean population.

To our knowledge, this is the first integrated large-scale study on ranitidine-induced anaphylaxis. The findings of this study show that ranitidine-induced anaphylaxis can be diagnosed by an SPT. The sensitivity of the SPT (91.7%) was higher than that of the IDT (63.6%). No patient experienced anaphylaxis during the SPT, and the optimal concentration of ranitidine was 20 mg/mL. Regarding the IDT, when the concentration of ranitidine was

increased, false positivity was also increased. At a concentration of 1 mg/mL, the false-positive rate was 60%. The recommended IDT concentration of ranitidine is 0.2 mg/mL.

The number of re-administrations was unacceptably high at 2.6 times in this study, as ranitidine was not initially suspected as the cause of anaphylaxis. If an H₂RA is not suspected as the culprit, clinical outcomes could deteriorate, as ranitidine is also used for anaphylaxis management [23]. In addition to ranitidine, cimetidine [24] and famotidine [25] can cause anaphylaxis. Regarding cutaneous hypersensitivity, an H₂RA can be both an aggravating factor in urticaria and used in the treatment of urticaria [26].

The findings of this study documented cross-reactivity between ranitidine and nizatidine during OPTs. Cimetidine and PPIs demonstrated no cross-reactivity with ranitidine. These results correspond well with those of previous studies [12, 27]. Cross-reactivity with famotidine is controversial [20, 23]. Cimetidine was used safely in 50% of the patients, and PPIs were used safely in 75% of the patients. The chemical structures of the H₂RAs are shown in Figure 4. The structural similarities between ranitidine and nizatidine help to explain their cross-reactivity. Cimetidine, pantoprazole, and lansoprazole have different functional groups than ranitidine.

There are limitations to this study. First, it is based on self-reported ADRs and is retrospective in design. A limited number of patients agreed to participate in the SPT, IDT, and serum sampling. Because of personal information protection laws, it was impossible to determine if the 23 single-center patients were included in the KIDS-KAERS database. Second, ranitidine has been available as an over-the-counter drug not requiring a prescription

in Korea, and it is difficult to estimate the total number of persons who used ranitidine over 7 years. For this reason, the incidence of ranitidine-induced anaphylaxis could not be calculated exactly. However, at this single pharmacovigilance center, the incidence of ranitidine-induced anaphylaxis was 0.003% (7/224,718). In Korea, ranitidine has been available as an over-the-counter medication since March 2013; we collected nationwide prescription information from 2010 to 2012. The incidence of ranitidine-induced anaphylaxis during those 3 years was 0.0003% (46/14,909,912 persons). Of the 23 ranitidine-induced anaphylaxis patients at this single center, 7 were administered the drug at this hospital; the other 18 were excluded from the incidence estimation because they visited this center for an evaluation of ranitidine-related anaphylaxis after having the drug prescribed at another hospital. The incidence of ranitidine-induced anaphylaxis was 36 times higher than the incidence reported in a previous study [1]. There is a possibility that the incidence has increased over time, similar to cefaclor anaphylaxis [28]. The study was based on a self-reported database that may have underestimated the true incidence in Korea. It is difficult to apply this incidence directly to populations worldwide, but this study suggests genetic susceptibility to ranitidine-induced anaphylaxis in Korea.

Although there was no statistical significance, intravenous administration showed a higher incidence of anaphylaxis. By contrast, oral administration was more frequent in the single-center study. This can be explained by the re-administration numbers and ADR reporters. In the single-center study, 69.6% of patients visited for an evaluation of repeated drug-related anaphylaxis for a drug not administered at this center. More investigations regarding administration route and the incidence of ADRs are required. Third, ranitidine-sIgE detection failed. However, both direct and indirect ranitidine-HSA conjugation were used for IgE measurement by ELISA, and only 2 patients reacted to HSA instead of the ranitidine conjugate. In a previous study, ranitidine-sIgE was detected in 3 out of 10 patients [7]. It has

been difficult to diagnose ranitidine anaphylaxis by sIgE detection, and further experiments are needed. Ranitidine needs to be conjugated with diverse functional groups because the conjugated portion of ranitidine could include the IgE binding site in this experiment.

In conclusion, ranitidine-induced anaphylaxis was not uncommon in Korea, and the SPT was the optimal diagnostic tool at a ranitidine concentration of 20 mg/mL. Cimetidine and PPIs can be safely used in patients who have experienced ranitidine-induced anaphylaxis.

Disclosures

Pharmacovigilance data were provided by the Korea Institute of Drug Safety & Risk Management (Ministry of Food and Drug Safety). This study was supported by Severance Regional Pharmacovigilance Center (Seoul, Korea).

Conflict of interest statement

All authors declare no conflict of interest.

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Tables

Table 1. Baseline characteristics of self-reported ADRs to ranitidine in Korea (N = 694, 584 patients)

Age (years, mean $\pm$ SD)	50.3 $\pm$ 16.2
M:F	215:358
Reporting personnel (N = 463)	N (%)
Doctors	91 (19.7%)
Nurses	242 (52.3%)
Pharmacists	64 (13.8%)
Patients	5 (1.1%)
Unknown	61 (13.2%)
Route of ranitidine administration (N = 136)	
Oral	26 (12.6%)
Intravenous	181 (87.4%)
WHO-UMC* causality assessment (N = 584)	
Certain, N (%)	85 (14.6%)
Probable/likely, N (%)	499 (85.4%)
Serious adverse reactions (N = 87)	
Significant disability/incapacity	5 (5.7%)
Life-threatening	5 (5.7%)
Congenital deformities, death	0 (0%)
Hospitalization	30 (34.5%)

Important medical event	47 (54.0%)
Re-challenge information available (N = 281)	
Challenge results reproduced	48 (8.2% of the total patients)

SD, standard deviation; M, male; F, female; ADR, adverse drug reaction

* World Health Organization-Uppsala Monitoring Center

Table 2. Clinical manifestations of ADRs to ranitidine (N = 694, 584 patients)

Clinical manifestations	N (%)
Cutaneous (urticaria, angioedema, rash, itching sensation, edema, injection site irritation)	275 (39.6%)
Gastrointestinal (nausea, vomiting, diarrhea, constipation, oral discomfort, pancreatitis, appetite change)	100 (14.4%)
Anaphylaxis	99 (14.3%)
Neurologic (headache, dizziness, vertigo, tremor, mental status change, seizure, syncope, delirium, paralysis, delirium, spasm, burning skin sensation)	96 (13.8%)
General (asthenia, general weakness, fever, rigor, sweating, weight change)	33 (4.8%)
Cardiovascular (chest discomfort, hypotension, palpitations, bradycardia, angina, vascular disorder)	31 (4.5%)
Respiratory (respiratory compromise, dyspnea, cough, rhinitis symptoms)	24 (3.5%)
Hepatic (hepatitis, jaundice)	11 (1.6%)
Hematologic (neutropenia, pancytopenia, thrombocytopenia, thrombocytosis, eosinophilia)	8 (1.2%)
Psychological (anxiety, agitation, insomnia, somnolence, hallucination)	7 (1.0%)
Endocrine (gynecomastia, lactation)	4 (0.6%)
Renal (electrolyte imbalance, kidney function impairment)	2 (0.3%)
Musculoskeletal (arthralgia, dysarthria, myalgia)	2 (0.3%)
Ophthalmic (hyperemia)	2 (0.3%)

ADR, adverse drug reaction

Table 3. Characteristics of self-reported ranitidine-induced anaphylaxis patients in the Korean pharmacovigilance system (N = 99)

Age (years, mean $\pm$ SD)	50.6 $\pm$ 13.6
M:F	45:54
Reporting personnel (N = 77)	N (%)
Doctors	28 (36.4%)
Nurses	19 (24.7%)
Pharmacists	11 (14.3%)
Patients	3 (3.9%)
Unknown	16 (20.8%)
Route of ranitidine administration (N = 23)	
Oral	5 (21.7%)
Intravenous	18 (78.3%)
WHO-UMC* causality assessment (N = 99)	
Certain, N (%)	46 (46.5%)
Probable/likely, N (%)	53 (53.5%)
Serious adverse reactions (N = 57)	
Significant disability/incapacity	2 (3.5%)
Life-threatening	4 (7.0%)
Congenital deformities, death	0 (0%)
Hospitalization	15 (26.3%)
Important medical event	36 (63.2%)
Re-challenge information available (N = 49)	
Re-challenge results reproduced	21 (42.9%)
No information	28 (57.1%)
Reported clinical manifestations (189 reports among 99 patients)	
Anaphylaxis [†]	58 (58.6%)
Cutaneous	44 (44.4%)
Respiratory	33 (33.3%)
Gastrointestinal	20 (20.2%)
Shock	16 (16.2%)
Neurologic	7 (7.1%)
Syncope	5 (5.1%)
Chest pain	4 (4.0%)
Mental status change	2 (2.0%)

SD, standard deviation; M, male; F, female

* World Health Organization-Uppsala Monitoring Center

[†] Among 99 anaphylaxis patients, 58 were originally reported as anaphylactic.

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Table 4. Characteristics of ranitidine-induced anaphylaxis patients at a single pharmacovigilance center (N = 23)

Onset age (years, mean $\pm$ SD)	51.7 $\pm$ 10.3
Sex (M:F)	7:16
Symptoms and signs, N (%)	
Cutaneous	18 (78.3%)
Respiratory	18 (78.3%)
Shock	11 (47.8%)
Gastrointestinal	9 (39.1%)
Dizziness	8 (34.8%)
Mental status change	4 (17.4%)
Re-administration, N (%)	19 (82.6%)
Number of re-administrations	2.58 $\pm$ 1.18
Administration route, including re-administrations, N (%)	
Oral	40 (75.5%)
Intravenous	13 (24.5%)
Underlying reason for ranitidine use	
Gastritis, ulcer, and GERD treatment	13 (56.5%)
Ulcer prophylaxis	9 (39.1%)
Urticaria treatment	1 (4.3%)
<i>In vivo</i> testing	Positivity, N (%)
Skin prick test (N = 12)	11 (91.7%)
Intradermal test (N = 11)	7 (63.6%)
Oral provocation test (N = 6) [†]	6 (100%)

SD, standard deviation; M, male; F, female; GERD, gastroesophageal reflux disease

[†] A nizatidine oral provocation test was also positive in 1 patient.

Figure legends

Figure 1. The study algorithm.

KIDS-KAERS, Korea Institute of Drug Safety-Korea Adverse Event Reporting System database; ADR, adverse drug reaction; N, number of patients

Figure 2. Ranitidine and its conjugation compounds for specific IgE (sIgE) detection. A, ranitidine; B, indirectly conjugated ranitidine and human serum albumin (iRNT-HSA); C, directly conjugated ranitidine-human serum albumin (dRNT-HSA); D, A 2-site ELISA for the detection of sIgE in indirect and direct ranitidine-human serum albumin conjugates (iRNT-HSA and dRNT-HSA).

HSA, human serum albumin; ELISA, enzyme-linked immunosorbent assay

Figure 3. Drugs used safely in ranitidine anaphylaxis patients (N = 12).

PPI, proton pump inhibitors; OPT, oral provocation test

Figure 4. Chemical structures of H₂ receptor antagonists and proton pump inhibitors.

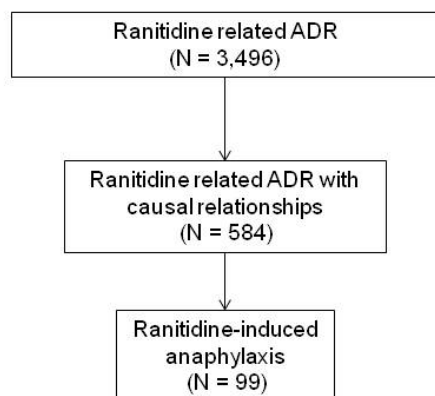
Figure S1. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) of ranitidine-HSA compounds.

HSA, human serum albumin

Figure 1.

Pharmacovigilance data of KIDS-KAERS database

2007 January 1 to 2014 June 30



Pharmacovigilance data of Severance hospital

2007 January 1 to 2015 May 31

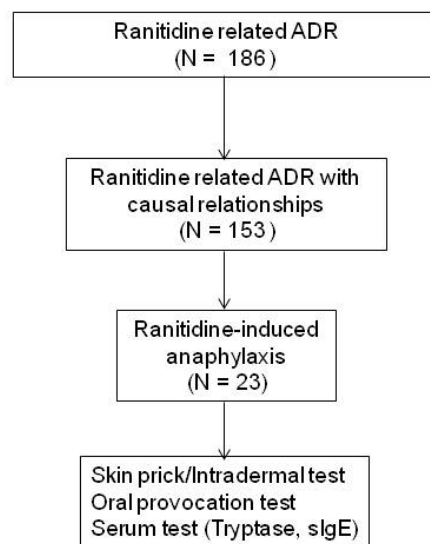


Figure 2.

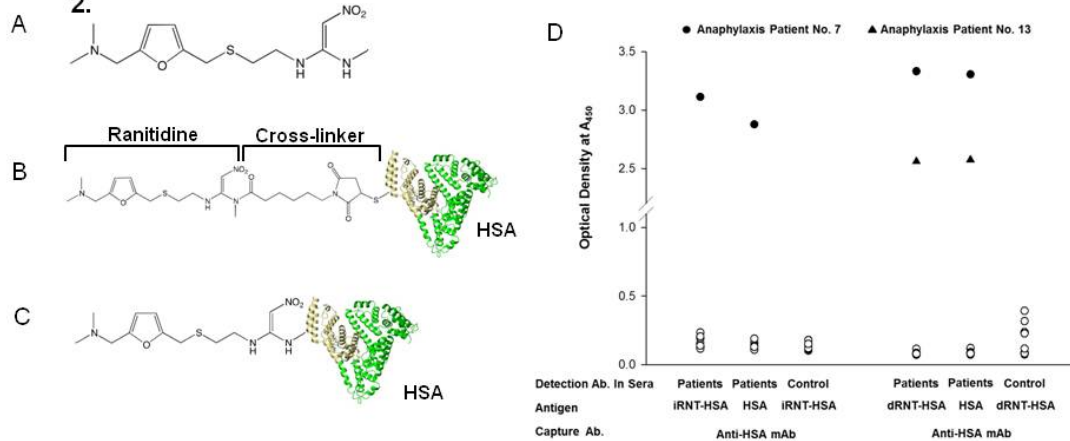


Figure 3.

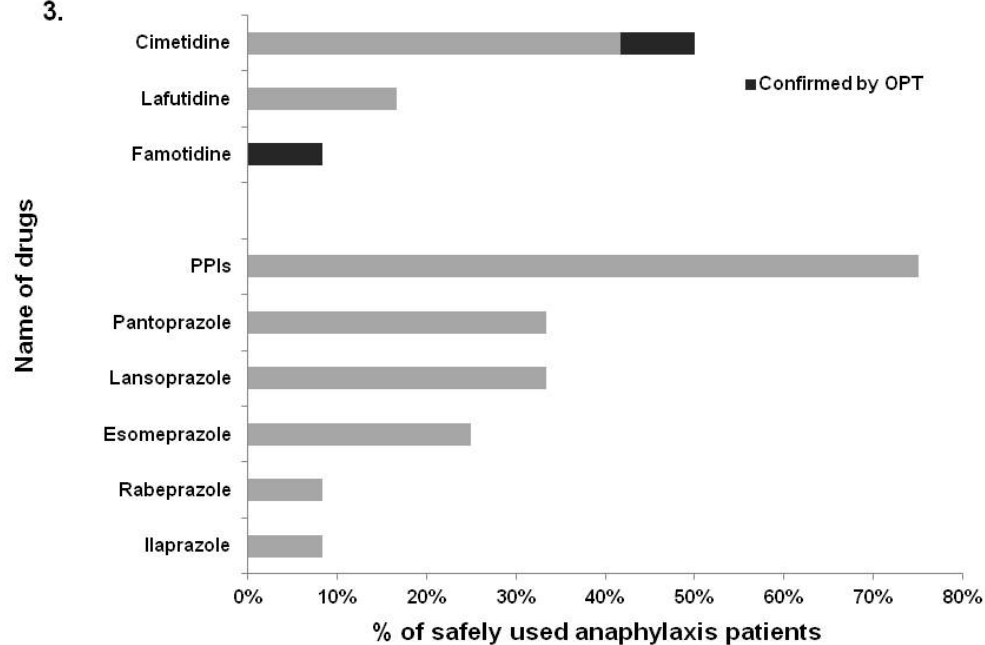
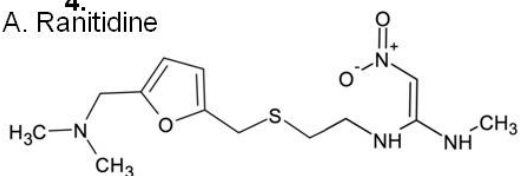
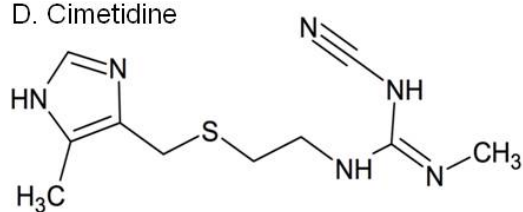


Figure 4.

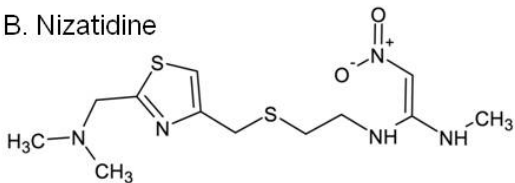
A. Ranitidine



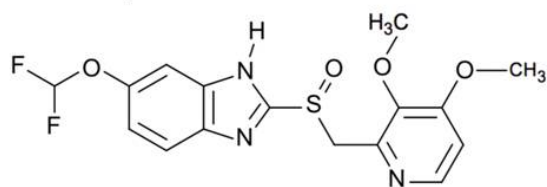
D. Cimetidine



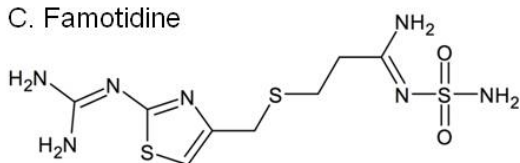
B. Nizatidine



E. Pantoprazole



C. Famotidine



F. Lansoprazole

