

Case Report

Severe ranitidine-induced anaphylaxis: a case report and literature review

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SUMMARY

What is known and Objective: Ranitidine is a generally well-tolerated drug, and serious side effects are rare. However, ranitidine-induced anaphylaxis has been reported on rare occasions. We report on such a case and review other cases reported in the literature.

Case summary: A 36-year-old man with no history of other medications, illnesses or allergic diseases, especially to drugs, consulted our emergency department because of renal colic and epigastric discomfort. He was given 50 mg of ranitidine as a slow intravenous bolus and 20 mg of piroxicam intramuscularly. Within the first minute, the patient developed a cold sweat, trembling, dyspnoea and deterioration of his consciousness. The condition was considered as an anaphylactic shock, and cardiopulmonary resuscitation and inotropic support were immediately commenced. Two days later, he was weaned off the ventilator as he was haemodynamically stable. He was discharged after 7 days. Four weeks later, skin prick tests to ranitidine and piroxicam were performed on the forearm of the patient. He reacted strongly to ranitidine about 10 min later but not to piroxicam. To assess cross-reactivity to other H₂- and H₁-receptor antagonists in our patient, we subsequently performed prick tests to famotidine, cimetidine and desloratadine and all were negative.

What is new and Conclusion: We re-emphasize a potentially serious, albeit very rare, adverse effect of ranitidine and summarize other reported cases. This case demonstrates that commonly used, generally safe drugs may on occasions cause serious adverse effects.

What is known and Objective

Ranitidine is a specific, long-acting H₂-receptor antagonist that is indicated for gastroduodenal ulcer, gastroesophageal reflux and hypersecretory states.¹ It has an excellent safety profile. Reported side effects of ranitidine are headache, rash, fatigue, diarrhoea and, more rarely, elevated transaminases.² Some sporadic cases of ranitidine-induced anaphylaxis have been

described in the medical literature. As this medication is often used intravenously, the anaphylactic reactions can be life-threatening. As a provocation test is dangerous, skin tests to ranitidine is a reliable tool for establishing causality in the presence of concomitant drugs. We report herein a clinical observation of a severe ranitidine-induced anaphylaxis confirmed by a skin test, and we review reported cases of such a side effect.

Details of the Case

A 36-year-old man with no history of illnesses, allergic diseases or reactions, especially to drugs, consulted our emergency department because of renal colic and epigastric discomfort. He had no fever, and the physical examination revealed an exacerbation of abdominal pain upon palpation. The abdominal X-ray and ultrasonography revealed no evidence of renal or abdominal lithiasis. The complete blood counts and blood biochemistry were within normal limits. The patient was given 50 mg of ranitidine as a slow intravenous bolus and 20 mg of piroxicam intramuscularly. Within the first minute of drug administration, the patient developed a cold sweat, trembling and dyspnoea and lapsed into a coma. Blood pressure was not detectable. The condition was considered as an anaphylactic shock, and cardiopulmonary resuscitation was immediately commenced. The patient was intubated and was resuscitated by the administration of intravenous fluid, adrenaline and hydrocortisone. He was kept in our department for ventilatory and inotropic support. Two days later, he was weaned off the ventilator and by then he was haemodynamically stable without inotropic support. He made a full recovery and was discharged 7 days later. After four weeks, skin prick tests to ranitidine (25 mg/mL) and piroxicam (20 mg/mL) were performed on the patient's forearm. Histamine 10 mg/mL and 0.9% normal saline were used as positive and negative skin prick test controls, respectively. About ten minutes later, the patient had a strong reaction to ranitidine but not to piroxicam. A prick test to ranitidine performed on two healthy controls according to the same procedure applied on the patient was negative. To assess cross-reactivity to other H₂-receptor antagonists in our patient, we subsequently performed prick tests to famotidine, cimetidine and desloratadine that were negative at 20-min reading. No systemic reactions were noticed after these tests.

A clear temporal relationship was observed between ranitidine administration and the onset of symptoms. Symptoms and signs subsided after drug withdrawal. The radioallergosorbent

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test (RAST) for ranitidine was not available in our country, and a specific IgE test was not performed. Based on the Naranjo algorithm, it is probable that the reaction manifested by the patient was because of ranitidine.³ Anaphylactic shock, also called anaphylaxis, is the most severe form of allergic reaction. However, although allergic reactions are common, anaphylaxis is very rare. In adults, medication seems to be the most common culprit. Liew *et al.*⁴ reported that age-specific hospitalization rates for drug-induced anaphylaxis were highest in the 55–84 age group (3.8/100 000 population). Similarly, fatal anaphylaxis in the UK, Australia and New Zealand has been reported to be mainly due to medication (44%, 57% and 56%, respectively).⁵ Anaphylaxis-inducing drug categories most frequently reported in the literature are antibacterials and non-steroidal anti-inflammatory drugs.⁶ Conversely, H₂-receptor antagonists are rarely responsible. Only a few isolated case reports of severe anaphylaxis elicited by these drugs have been reported. Ranitidine is considered to be an extremely well-tolerated drug, as it does not have any of cimetidine's most serious

side effects. The PubMed database (MeSH terms: ranitidine, anaphylaxis) includes 14 case reports of ranitidine-induced anaphylaxis^{7–19} (Table 1). Most were severe cases that required ventilatory support and cardiovascular resuscitation as was the case in our patient. Only one case of fatal ranitidine-induced anaphylaxis has been reported.¹⁹ It is well known that anaphylactic reactions are usually more dramatic when the drug is given by injection than when given orally. Indeed, whenever ranitidine was given intravenously (seven cases), the induced anaphylaxis was severe and required cardiovascular and/or pulmonary resuscitation. In contrast, all cases of anaphylaxis induced by oral ranitidine were moderate. This could explain the severity of the reaction in our patient. Interestingly, in this case, ranitidine anaphylaxis was diagnosed with a skin prick test to this drug, which was immediately and strongly positive. This suggests an IgE-mediated mechanism for the anaphylactic reaction. Koh *et al.*¹³ detected serum-specific IgE reacting to ranitidine. Skin tests, such as prick and intradermal tests, are classical means of testing for the immediate type of drug hyper-

Table 1. Reported anaphylactic reactions induced by ranitidine

Publication	Administration route of ranitidine	Severity of the reaction	Outcome of the patient	Confirmatory study	Cross-reactivity
Walker <i>et al.</i> (7)	Oral	Did not require cardiopulmonary resuscitation	Recovery without sequelae	Positive prick and provocation tests	Not assessed
Foti <i>et al.</i> (8)	Intravenous	Required cardiopulmonary resuscitation	Recovery without sequelae	Positive intradermal test	Not assessed
Castro <i>et al.</i> (9)	Oral	Did not require cardiopulmonary resuscitation	Recovery without sequelae	Positive prick test	Negative prick and intradermal tests to cimetidine and famotidine
Rethnam and Yesupalan (10)	Intravenous	Required cardiopulmonary resuscitation	Recovery without sequelae	Not performed	Not assessed
Thurot-Guillon <i>et al.</i> (11)	Intravenous	Required mask ventilation	Recovery without sequelae	Positive intradermal test	Positive intradermal test to hydroxyzine and dexchlorpheniramin
Demirkan <i>et al.</i> (12)	Oral	Did not require cardiopulmonary resuscitation	Recovery without sequelae	Positive prick test	Negative intradermal test to famotidine
Demirkan <i>et al.</i> (12)	Intravenous	Required nasal oxygen therapy	Recovery without sequelae	Positive provocation test	Not assessed
Koh <i>et al.</i> (13)	Oral	Did not require cardiopulmonary resuscitation	Recovery without sequelae	Positive prick intradermal and provocation tests Positive specific IgE	Negative prick, intradermal and provocation tests to cimetidine and famotidine
Kaneko and Maruta (14)	Intravenous	Required cardiopulmonary resuscitation	Recovery without sequelae	Not performed	Not assessed
Powell and Maycock (15)	Intravenous	Required cardiopulmonary resuscitation	Recovery without sequelae	Positive intradermal test	Not assessed
Lazaro <i>et al.</i> (16)	Oral	Did not require cardiopulmonary resuscitation	Recovery without sequelae	Positive prick and provocation test	Negative prick, intradermal and provocation tests to cimetidine, famotidine and nizatidine
Barry <i>et al.</i> (17)	Oral	Did not require cardiopulmonary resuscitation	Recovery without sequelae	Not performed	Not assessed
Greer and Fellows (18)	Oral	Required mask ventilation	Recovery without sequelae	Not performed	Not assessed
Oliva <i>et al.</i> (19)	Intravenous	Required cardiopulmonary resuscitation	Death	Not performed	Not assessed

sensitivity; but their specificity and sensitivity in diagnosing ranitidine-induced anaphylaxis are not fully established. However, when performed on patients with suspected ranitidine-induced anaphylaxis (eight cases), these tests (prick and/or intradermal tests) were positive. Provocation tests performed in three of these patients were all positive, denoting good specificity of the skin tests for ranitidine. Drug skin tests are also useful for assessing cross-reactivity between chemically similar drugs such as H₂-receptor antagonists. The prick test to famotidine, cimetidine and desloratadine was negative in our patient, suggesting a selective reaction to ranitidine. Among the 14 published cases, cross-reactivity between ranitidine and other H₂- or H₁-receptor antagonists was assessed by skin tests in five. Only one patient, who developed anaphylaxis after ranitidine injection, had a positive intradermal test to ranitidine,

dexchlorpheniramine and hydroxyzine, but not to cetirizine, loratadine and cimetidine.¹¹ Koh *et al.* and Lazaro *et al.*^{13,16} have conversely reported negative oral provocation tests to cimetidine, nizatidine, famotidine and nitrofurantoin in two patients with ranitidine-induced anaphylaxis.

What is new and Conclusion

A new case of severe ranitidine-induced anaphylaxis is reported with use of added to the skin prick testing for diagnosis. Lack of cross-reactivity between ranitidine and other H₂-receptor antagonists is demonstrated. This case demonstrates that commonly used, generally safe drugs may on occasions cause serious adverse effects.

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