Author's response to reviews

Title: Fatal injection of Ranitidine: a case report

Authors:

  Antonio Oliva (antonio.oliva@rm.unicatt.it)
  Sara Partemi (spartemi@yahoo.it)
  Vincenzo Arena (arena@libero.it)
  Fabio De Giorgio (fdegiorgio@ticani.it)
  Catia Colecchi (colecchi@tiscali.it)
  Nadia Fucci (n.fucci@rm.unicatt.it)
  Vincenzo L. Pascali (vincenzo.pascali@rm.unicatt.it)

Version: 2 Date: 15 November 2007

Author's response to reviews: see over
Fatal injection of Ranitidine: a case report

Antonio Oliva MD PhD¹, Sara Partemi MD¹, Vincenzo Arena MD³, Fabio De Giorgio MD¹, Catia Colecchi MD¹, Nadia Fucci PhD², Vincenzo L. Pascali MD PhD¹ Full Professor

¹Institute of Legal Medicine
²Forensic Toxicology Laboratories
³Institute of Pathology
Catholic University, School of Medicine, Rome, Italy

Corresponding Author:
Antonio Oliva MD PhD
Research Scientist
Institute of Legal Medicine, Catholic University, School of Medicine, Rome, Italy
Email: antonio.oliva@rm.unicatt.it
Phone: +39-0630154249, Fax: +39-0635507033

Abstract: Ranitidine hydrochloride (Zantac®), class $H_2$–receptor antagonist, is a widely used medication with an excellent safety record. Anaphylactic reaction to ranitidine is an extremely rare event and the related death has never been described in the Literature. We present the clinical history, histologic and toxicological data of a 51-years-old man, with negative anamnesis for allergic events, who suddenly died after the intravenous administration of 1 phial of Zantac® 50 mg prescribed as a routine postsurgery prophylaxis stress-ulcer.

Keywords: Anaphylaxis, drug-induced, Ranitidine, Adverse drug Reactions
Background:

Ranitidine hydrochloride (Zantac®) belongs to class $H_2$–receptor antagonist medications used in peptic ulcer disease therapy, acute stress ulcers, gastroesophageal reflux and related disorders. As this medication has an excellent safety record $^{1,2}$, we could not find any report of fatalities related to this drug in Literature, although the incidence of anaphylactic reaction to H2 receptor antagonists and proton pump inhibitors together has been reported as 0.3% - 0.7$^3$.

Case Report:

A 51-years-old man was admitted to the Hospital for treatment of a benign prostatic hyperplasia. The patient’s anamnesis was negative for allergic events. He underwent transurethral resection of the prostate (TURP) with regular post-surgery recovery, followed by the prescription of routine prophylaxis stress-ulcer (1 phial of Zantac® 50 mg, intravenous). Few minutes after the administration, the patient suddenly developed a combination of wheezing, dyspnea and hypotension followed by loss of conscience. Despite intensive resuscitation, no cardiac activity reappeared and death was certified 30 minutes later. Because the circumstances of death appeared suspicious to the treating emergency physician, a forensic investigation was initiated as the Public prosecutor ordered a forensic necropsy. The autopsy revealed pulmonary congestion with upper airway widespread oedema, presence of petechial haemorrhages and brain swelling with diffused petechial haemorrhages. There was no evidence of recent myocardial infarction, nor other structural heart diseases. The rest of the organs were unremarkable. Histological sections confirmed the presence of widespread ipolaryngeal and pharyngeal mucosal and submucosal oedema with inflammatory cells and abundance of mast cells (figure 1A - 1B). Toxicological analyses on blood performed using a gas chromatography-mass spectrometry (GC/MS) technique revealed the presence of ranitidine [<10 nanograms/milliliter (LOQ)] (figure 2). No other drugs were found.
Death was attributed to anaphylactic shock due to an adverse reaction caused by Ranitidine intravenous injection, suggestive for a pathogenic mechanism of immediate-type hypersensitivity reaction Type I, according to Gell and Coombs Classification System.

**Discussion:**

The Ranitidine, a H2 receptor antagonist, which is commonly used to treat peptic ulcer and gastroesophageal reflux diseases, is associated with a low incidence of adverse reactions. Most of the patients reported were obstetric patients and we found also a case of severe anaphylaxis to ranitidine in a patient with pancreatitis. The review of Literature didn’t show any report of fatalities related to this drug. In the present case patient’s death was due to ranitidine; clinical symptoms were a combination of wheezing, dyspnea and hypotension followed by loss of conscience that the patient suddenly showed few minutes after the administration of the medication. He had negative anamnesis for allergic events and no another drugs were administered. Despite intensive resuscitation, no cardiac activity reappeared and death was certified 30 minutes later.

What lessons might be learned from this case? Physicians can hardly pick up a medical journal today without reading about some new medication, and how it promises to completely change the course of a disease or symptoms. Indeed the wonders of pharmacology are numerous, as nowadays, old or new medications are a double-edged sword. Much of the recent research on problems with medications has focused primarily on errors in medication use, which are important, but adverse drug reactions (ADRs) that are not preventable, given our current state of knowledge, are a more common problem with a greater human burden. The question is whether tracking non-preventable drug-related injuries is important, especially after it is known that a specific drug can cause a specific reaction. It is, for several reasons: first, avoiding administration of the same medication to the patient in the future requires knowing and documenting that the patient had a previous allergy or sensitivity. When a patient develops an allergy or sensitivity, it is often not recorded, and patients receive drugs to which they have known allergies or sensitivities: could this have happened in our case? Until the use of electronic medical records becomes ubiquitous, other partnerships must be undertaken.
to lower the incidence of ADRs. Health plans and pharmacy benefit managers must work together to take effective steps to increase ADR monitoring and reporting and to proactively avoid ADRs through pharmacy management tools. An other important issue, related to the previous one, is that hospitals have had strong incentives not to identify too many of these events. Reporting large numbers of adverse events and any serious preventable event brings intense scrutiny from regulators and the public. Thus, most hospitals have relied on spontaneous reporting, which only identifies about 1 in 20 adverse reactions and leads to the perception that injuries from ADRs are less common than they really are. For all these reasons areas of ongoing research need to be improved directed toward diagnostic precision and accurate monitoring of adverse drug reactions including further understanding of the immunochemistry of allergenic medications, improvement of the reproducibility and sensitivity of relevant IgE in vitro assays, and further validation of computer-assisted evaluation of adverse drug events. Moreover the positive and negative predictive values for these diagnostic tests need to be better defined, whenever possible. At present, the primary diagnostic tool for properly assessing immunologic drug reactions remains a meticulous and detailed history obtained by an astute, knowledgeable, and motivated physician.

**Conclusion:**
We described the only one deadly reaction related to Ranitidine in Literature. It’s a very rare reaction to this extensively used drug in clinical practice. However, this case suggest that, although the incidences of anaphylactic reactions related to ranitidine are low, caution needs to be exercised on administration of this drug. In addition, further study is needed to define strategies for the prevention of ADRs in hospitalized patients.

**Competing interest:**
The authors declare that they have no competing interests.

**Authors’ contributions:**
AO and SP performed the autopsy examination and are responsible of the conception
and design of the manuscript; VA performed the histological analysis; NF provided the toxicological results; FDG and CC performed the review of the literature, VLP is the supervisor of the manuscript, All the authors have read and approved the final manuscript.

Consent
We certify that written informed patient consent has been obtained for publication of the present report and for the accompanying images.

References

Legend to the figures

**Histological examination: Figure 1 (panel 1A - 1B)**
Histological sections from lungs shows the presence of inflammatory cells and mast cells.

**Toxicological analysis: Figure 2**
Gas chromatography-mass spectrometry (GC/MS) analysis shows the presence of ranitidine at the following concentrations: <10 nanograms/milliliter (LOQ).