Author's response to reviews

Title: Fatal injection of Ranitidine: a case report

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Author's response to reviews: see over
We are most grateful to the reviewers for their kind remarks and excellent suggestions. We have made every effort to address each of these in the revised manuscript.

REVIEWER #1

1) It would be useful to have more actual data about the prevalence of serious adverse events with ranitidine and a discussion of this. There is none at present.

A brief background regarding adverse effects of Ranitidine has been included in the text (see page n. 2).

2) A section on the use of ranitidine (number of prescriptions would be helpful).

Tables 1 and 2 respectively with the recommended oral, IM and IV dosages in adults have been included.

3) How often is i/v ranitidine used?

This medication is often used intravenously in the operating room and during the recovery in surgical departments or ICU (Intensive Care Unit), while in oral route in medical departments. Moreover recent studies showed that the indications for use of ranitidine is the most frequently accounted in percentual for the prophylaxis and the prevention of non steroidal anti-inflammatory drug–induced ulcer.

References


4) It would be useful to have more information about the actual incident. How long after surgery did it take place?

Ranitidine was administered intravenously 24 hours after the surgery.
5) What other drugs had been administered in the previous 24 hours?

We have included in the text some of the following informations:

Complexively in the previous 24 hours the following therapy was administered:

**Before the hospitalization the patient was treated with alfuzosin**, *alpha 1A receptor antagonists*, used to treat the symptoms of **enlarged prostate** (*benign prostatic hyperplasia* - BPH). Alfuzosin helps to relax the muscles in the prostate and the opening of the bladder. This helps to improve urine flow and decrease symptoms of BPH. **After the patient’s hospitalization this medication was suspended.**

**Post-surgery therapy was:**

- Lactated Ringer's solution
- Antibiotic: Cefodizime (Modivid)

No significant interaction exists for these two drugs, even with ranitidine.

6) Was the patient on antibiotics?

The patient was on antibiotic “Modivid” (cefodizime). It is a cephalosporin of third generation. Third-generation cephalosporins have a broad spectrum of activity and further increased activity against gram-negative organisms. They may be particularly useful in treating hospital-acquired infections, although increasing levels of extended-spectrum beta-lactamase are reducing the clinical utility of this class of antibiotics. Often reduced activity against Gram-positive organisms. Common ADRs (≥ 1% of patients) associated with cephalosporin therapy include: diarrhea, rash, electrolyte disturbances, and/or pain and inflammation at injection site. Infrequent ADRs (0.1-1%) include: vomiting, headache, dizziness, oral and vaginal candidiasis, pseudomembranous colitis, superinfection, eosinophilia, and/or fever. Hence, it is commonly stated that they are contraindicated in patients with a history of severe, immediate allergic reactions (urticaria, anaphylaxis, interstitial nephritis) to penicillins, carbapenems or cephalosporins.

6) Have you considered that the reaction could have been due to a reaction to other constituents in the injection rather than ranitidine?

A testimony by the Chief Nursing Office of the Hospital to the Court and the official clinical documentation of the patient unequivocally corroborated that the injection’s constituents administrated to the patient were as follows: 1 phial of Zantac 50 mg,
intravenous in normal saline solution. Ranitidine shows compatibility with all solutions commonly used for intravenous administrations.

7) Have you looked into what the other constituents are?

Please read previous answer.

8) VERY IMPORTANT AND MAY BE HARD TO PROVE-IT WOULD BE NICE TO KNOW THAT THE MANUFACTURERS HAVE BEEN INVOLVED AS THIS AS SERIOUS IMPLICATIONS

We will notify this case to the pharmaceutical company of the product.

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REVIEWER #2

1) Concomitant medications and the relative timing of administration- this is crucial to accepting that ranitidine could have been causal in death.

Before the hospitalization the patient was treated with alfuzosin, alpha 1A receptor antagonists, used to treat the symptoms of enlarged prostate (benign prostatic hyperplasia - BPH). Alfuzosin helps to relax the muscles in the prostate and the opening of the bladder. This helps to improve urine flow and decrease symptoms of BPH. After the patient’s hospitalization this medication was suspended.

Post-surgery therapy was:

- Lactated Ringer's solution
- Antibiotic: Cefodizime (Modivid)

No significant interaction exists for these two drugs, even with ranitidine.

2) Furthermore, the timing of death relative to the administration of general anaesthetic is not stated. Presumably, other drugs could have been administered to cause anaphylaxis.

The patient underwent transurethral resection of the prostate (TURP) with epidural anesthesia. Ranitidine was administered intravenously approximately 24 hours after the anesthesia and surgery. We do not have any proof regarding a causal correlation between the anaesthesia and death of the patient, especially in terms of timing. Anyway the anesthesia generally is responsible of a variety of neurological symptoms such as
headache, parestesias, low back pain. These symptoms were completely absent in our patient.

3) Similarly it would be expected that the patient had received a blood transfusion during TURP. Can the Authors be certain that death was not due to a transfusion reaction?

The patient had received a blood transfusion one day after the surgery. The authors are certain that death was not due to a transfusion’s reaction because the blood was autologous.

In Italy, since 1967, all the activities regarding immunohaematology and blood transfusion are regulated by government law which has been updated over the time until now in agreement with the Recommendations of Council of Europe. Although not completely risk free, autologous blood is the safest form of Blood transfusion. Exclusive use of a patient’s own blood eliminates reactions due to donor recipient incompatibility and precludes exposure to transfusion transmitted infection. Between the various methods of recovery blood, our patient was subjected to the following: Preoperative autologous Blood [PABD -units of Blood are drawn from a patient usually starting (in the short term case) three to five weeks before an elective surgical procedure and stored for transfusion at the time of the surgery]. Moreover in Literature doesn’t exist any reaction of anaphylaxis by autologous blood transfusion.

4) Lab data should be included in the manuscript to show whether metabolic disturbance or sepsis could have contributed to death.

No significant variations of metabolic parameters or signs of sepsis were noted on laboratory data.

5) How was the phial of Zantac made up and administered?

The administration was intravenous. A testimony to the Court by the Chief Nursing Office of the Hospital and the official clinical documentation of the patient unequivocally demonstrated that the injection administrated to the patient was as follows: 1 phial of Zantac 50 mg, intravenous in normal saline solution. Ranitidine shows compatibility with all solutions commonly used for intravenous administrations.

6) The post-mortem findings are noted, but these in themselves do not confirm that ranitidine was the cause of death. For example, many of the findings could be explained by intensive resuscitation.
We did not observed any artefacts of resuscitation like haemorrhage of subcutaneous tissues and pectoral muscles and/or contusions of lungs or retinal haemorrhages, which are classically signs of the increase in intracranial pressure. Moreover the autopsy did not revealed any typical signs of death consequent to asphyxia. On the other side the autopsy revealed pulmumary congestion with upper airway widespread oedema, presence of petechial haemorrhages and brain swelling with diffused petechial haemorrhages. Furthermore we found the presence of widespread ipolaryngeal and pharyngeal mucosal and submucosal oedema with inflammatory cells and abundance of mast cells: according to international specialized Literature (Pumphrey RS, Roberts IS.: Postmortem findings after fatal anaphylactic reactions 2000;53;273-276 J. Clin. Pathol.), both autopsy and histologic investigations showed the most common post-mortem findings related to anaphylaxis.

7) Specific mention should be made regarding autopsy examination of the lungs and pulmonary vessels. The symptoms preceding death could have been caused by pulmonary embolism which clearly needs to have been excluded as a cause of death following TURP

In our case no signs of tromboembolism were noted nor macroscopically nor microscopically at the necropsy.

Indeed from the Literature it is well known that “Although perioperative pulmonary thromboembolism (PTE) is a common complication of surgery, intraoperative pulmonary thromboembolism is unusual.”

Moreover: “Clinical thromboembolic complications following TURP are rare. TURP patients have a low risk for DVT, but an intermediate risk for pulmonary emboli. Pulmonary emboli may occur without identifiable risk factors and despite TED stocking prophylaxis.”


8) Was a serum total IgE measured?

Testing for specific IgE antibodies and mast cell tryptase was not performed because of post-mortem degradation of the serum. Despite these limitations, we do believe that our findings (clinical history, autopsy, histological and toxicological analyses) are highly suggestive of anaphylactic reaction caused by Ranitidine