



Perioperative Anaphylaxis to Ranitidine: A Case Report of a Rare Event of a Safe Drug

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Abstract

Perioperative anaphylaxis is a rare event with an incidence of 1 in 10,000 to 1 in 20,000. It is fatal in 0.65% to 2% of cases, if not recognized and treated promptly. It is difficult to identify the culprit agent as multiple drugs are given simultaneously. Ranitidine hydrochloride is a well-tolerated, widely used drug for perioperative prophylaxis for stress ulcers. It has been extensively studied and reported to have an excellent safety profile with rare occurrence of severe hypersensitivity reactions. We report a case of ranitidine-induced perioperative anaphylaxis, during excision of an epididymal cyst, which was successfully managed upon early recognition of anaphylaxis and subsequently referred to the allergy services. We confirmed ranitidine to be the culprit agent with a positive skin prick and immediate intradermal skin test. Therefore, awareness of this rare but fatal hypersensitivity reaction to a commonly used drug with excellent safety profile is vital to ensure that it is not overlooked when investigating drug allergy.

Keywords: Histamine H2 antagonists; Ranitidine; Perioperative anaphylaxis

Introduction

Anaphylaxis is an acute, rapidly evolving potentially life threatening immune mediated multi-system clinical syndrome that involves the release of mast cells and basophil derived immune mediators, mostly on re-exposure of a specific antigen i.e. a drug [1-4]. Within the perioperative setting, anaphylaxis is rare with an incidence of 1 in 10,000 to 1 in 20,000 [5]. However, it is fatal in 0.65% to 2% of cases if not recognized and treated promptly [6]. Identification of the culprit agent is challenging as multiple drugs are administered in quick succession. The 6th National Audit Project on perioperative anaphylaxis, the largest ever prospective study related to anesthesia and surgery identified the commonest causes of perioperative anaphylaxis to be antibiotics (47%), neuromuscular blockers (33%), chlorhexidine (9%), and patent blue V dye (5%). Ranitidine hydrochloride (Zantac) is a well-tolerated competitive and reversible H₂-receptor antagonist that is widely used for treatment of common gastrointestinal pathologies including gastro-oesophageal reflux disease, peptic ulcers and as perioperative prophylaxis for stress ulcers. It blocks the action of histamine on gastric parietal cells therefore inhibiting acid production. It also indirectly decreases gastrin and acetylcholine-induced gastric acid secretion. Since its introduction in 1981, ranitidine has been extensively studied and is reported to have an excellent safety, with rare occurrence of anaphylaxis profile [7]. We present one case of ranitidine-induced perioperative anaphylaxis during excision of an epididymal cyst, which was successfully managed resulting in completion of surgery.

Case Presentation

We report a case of a 40 year-old man with known history of Crohn's disease, who was referred to allergy clinic following an incident of perioperative anaphylaxis during elective excision of an epididymal cyst under general anesthesia. Induction and maintenance of anesthesia was achieved with propofol and alfentanil. He was given Hartmann's Intravenous (IV) fluids and a ProSeal Laryngeal Mask Airway (LMA) was inserted for airway maintenance. Neuromuscular blockers were not administered. Ten minutes after induction, flucloxacillin 1 g was given, followed by skin preparation using Travasept (chlorhexidine acetate 0.015% and cetrimide 0.15%). Fifteen minutes following induction, a slow infusion of paracetamol 1 g, ondansetron 4 mg, dexamethasone 8 mg and ranitidine 50 mg were administered and immediately afterwards, the patient was hypotensive (from 120/90 mmHg to 100/60 mmHg). Forty minutes after induction of anesthesia, he was profoundly hypotensive (55/30 mmHg), with mild tachycardia (90 bpm to 110 bpm) and

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desaturation (87%). There was a drop in his tidal volume to 150 ml to 200 ml respectively and he became difficult to ventilate by hand. There was no evidence of bronchospasm and wheeze clinically. Generalized erythema was also noted. Anaphylaxis was promptly recognized and successfully managed with ephedrine, metaraminol, chlorphenamine, hydrocortisone and IV fluids, with improvement both clinically and hemodynamically, within 10 min. Surgery was completed. Serum tryptase level at 3 h was 24 ng/ml. Postoperatively, fentanyl, codeine and Ketorolac were administered for postoperative pain without further reactions. A few months later he attended allergy clinic where skin prick and immediate intradermal skin testing was undertaken to a panel of anesthetic drugs and all index drugs administered perioperatively. Normal saline and histamine were used as negative and positive controls, respectively for skin prick testing. Skin prick and intradermal skin tests to ranitidine (25 mg/ml) at dilutions of 1:1 and 1:1000 respectively, were positive. Bloods showed a normal baseline tryptase (5 ng/ml) and negative specific IgE to chlorhexidine, latex, morphine, pholcodine, ampicilloyl, amoxicilloyl, penicilloyl V & G. Commercial assay for specific IgE to ranitidine was not available. The patient then had a cautious oral challenge to ondansetron and flucloxacillin and a topical challenge to chlorhexidine gluconate, following a written consent, which he tolerated. The positive skin test to ranitidine confirmed a diagnosis of ranitidine-induced perioperative anaphylaxis.

Discussion

There are only three published cases of perioperative anaphylaxis to ranitidine [8-10], all requiring resuscitation. On the contrary, various authors have reported cases of oral ranitidine-induced anaphylaxis of moderate severity, not requiring inotropic and ventilatory support [10]. In 2006, [11] reported the incidence of anaphylaxis to both H₂-receptor blockers and proton pump inhibitors to be low, 0.3% to 0.7%. The pathogenesis of ranitidine-induced anaphylaxis encompasses both IgE-mediated or non-immunological mechanisms [12]. It can occur either at first exposure or after sensitization [13]. To investigate the culprit agent in drug allergy, all drugs administered are investigated with *in-vitro* tests (skin prick and immediate intradermal skin tests) and *in-vivo* tests with specific IgE serology, but this depends on the availability of commercial assays. Direct Provocation Testing (DPT) is advocated as gold standard for diagnosis of drug allergy. However, the decision to proceed with DPT is based on risk-benefit analysis and should be communicated with patient(s), as there is potential risk of fatalities. According to the literature, there are no validated skin test dilutions for ranitidine. To establish the validity of the ranitidine skin test dilutions and reduce the risk of false positives (irritant reactions), we undertook Skin Prick (SPT) and Intradermal (IDT) skin testing, on eight healthy controls and found adequate skin test dilutions for ranitidine (25 mg/ml) to be 1:1 for SPT and 1:1000 for IDT. The patient's SPT and IDT skin test to ranitidine yielded positives with 4 mm weal and 12 mm weal, respectively. Skin tests to other H₂-receptor antagonists were not carried. Specific IgE serology to ranitidine was not undertaken due to lack of ranitidine commercial assay. Direct provocation testing to ranitidine was not undertaken due to the severity of the index reaction. There is evidence for cross-reactivity amongst H₂-receptor antagonist drugs. However, the data on cross-reactivity phenomenon is controversial. A literature review in 2011 by Song on cross reactions amongst H₂-receptor antagonist, and demonstrated that most cross-reactions occur between famotidine, ranitidine and nizatidine and rarely with cimetidine. It is postulated that differences

in the side chains and ring structures of the H₂-receptor antagonists, underpin the underlying cross-reactivity [14]. For instance, famotidine, ranitidine and nizatidine have similar side chains on the rings structures. However, there are some published reports demonstrating no cross-reactivity between H₂-receptor antagonists, on skin testing and oral challenge [15]. Nonetheless, due to greater evidence for cross-reactivity amongst H₂-receptor antagonists and the severity of the index reaction, the patient was advised to avoid all H₂-receptor antagonists. Proton pump inhibitors were recommended as alternatives and he tolerated them.

Conclusion

In summary, we report a fourth case of perioperative anaphylaxis to ranitidine - a widely used drug for a wide range of gastric acid-related disorders and for perioperative prophylaxis for stress-induced gastric ulcers. This case raises awareness that commonly used drugs with excellent safety profile can cause life threatening anaphylaxis. It highlights to role of allergy services and the importance of investigating all drugs given perioperatively to avoid overlooking "common" drugs. We have established validated skin test dilutions for ranitidine 25 mg/ml - 1:1 dilution for skin prick testing and 1:1000 dilution for intra-dermal skin testing.

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