



Original Contribution

Intraoperative medications associated with hemodynamically significant anaphylaxis^{☆,☆☆}



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Abstract

Study objective: To facilitate the identification of drugs and patient factors associated with hemodynamically significant anaphylaxis.

Design: Using an existing database containing complete perioperative records, instances of hemodynamically significant anaphylaxis were identified using a physiologic and treatment-based screening algorithm. All cases were manually reviewed by 2 clinicians, with a third adjudicating disagreements, and confirmed cases were matched 3:1 with control cases. Intraoperative medications given in instances of hemodynamically significant anaphylaxis and patient risk factors were compared with control cases.

Setting: University of Michigan Hospital, a large, tertiary care hospital.

Patients: All adult patients undergoing surgery between January 1, 2004, and January 5, 2015.

Interventions: None.

Measurements: Incidence of hemodynamically significant anaphylaxis during anesthesia. Patient risk factors and intraoperative medications associated with hemodynamically significant anaphylaxis.

Main results: Hemodynamically significant anaphylaxis occurred in 55 of 461 986 cases (1 in 8400). Hemodynamically significant anaphylaxis occurred in 52 patients, with 1 patient experiencing 3 instances and another patient 2 instances. Only 1 drug was associated with an increased risk of hemodynamically significant anaphylaxis: protamine (odds ratio, 11.78; 95% confidence interval, 1.40-99.26; $P = .0233$). No category of drugs was associated with increased risk. Of patient risk factors, only personal history of anaphylaxis was associated with an increased risk (odds ratio, 77.1; 95% confidence interval, 10.46-567.69; $P = <.0001$). Postoperative follow-up and evaluation of patients were low at our institution. A serum trypsin level was sent in only 49% of cases, and 41% of levels were positive, an overall positive rate of 20% of cases. Following instances of hemodynamically significant anaphylaxis, only 29% of patients were seen and evaluated by an allergist at our institution.

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Conclusions: Hemodynamically significant anaphylaxis is a rare complication of anesthesia, with an incidence consistent with the existing literature. Contrary to most existing literature, only protamine was associated with increased risk. A personal history of anaphylaxis appears to best predict risk of hemodynamically significant anaphylaxis.

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1. Introduction

Depending on the definition of anaphylaxis used, anywhere from 1 in 3180 to 1 in 20 000 surgical cases are complicated by anaphylaxis [1-3]. Numerous substances commonly used in the perioperative setting have been implicated, including drugs, latex, and disinfectants [4-7]. Among drugs, antibiotics and neuromuscular blocking drugs (NMBDs) have been most commonly reported as causes of anaphylaxis, although recent work has downplayed the role of NMBD-induced anaphylaxis in North America in favor of antibiotics [8,9]. Among NMBDs, quaternary amines have been increasingly implicated in causing anaphylaxis, with rocuronium thought to cause more than half of instances of NMBD anaphylaxis [10]. Patient risk factors for anaphylaxis are relatively poorly defined, with a history of atopy commonly identified as a risk factor [1,11]. According to a recent study, 68% of patients who experienced anaphylaxis in the operating room had a history of atopic reactions [12].

Accurate identification of anaphylaxis presents a significant clinical challenge to anesthesiologists, as many physiologic changes normally encountered in anesthesiology may mimic those of anaphylaxis and are much more likely. A 2001 study from Denmark used simulated cases of anaphylaxis to show that every one of 21 teams of trained anesthesiologists failed to recognize anaphylaxis within 10 minutes [13]. Furthermore, even the criteria used to define anaphylactic shock are controversial [14].

Early identification of anaphylaxis allows for the prompt administration of epinephrine, which is widely considered to be the first-line therapy, although the dosage used in clinical practice varies widely [5,15]. Effective secondary therapies include intravenous fluids, antihistamines, and glucocorticoids [16-18]. The mortality of intraoperative anaphylaxis is estimated at 0%-1.4% [19,20]. There is evidence from the nonperioperative literature that delaying epinephrine treatment may result in increased mortality [21]. As a result, objective data identifying compounds at highest risk for inciting intraoperative anaphylaxis and high-risk patients could expedite prompt clinical diagnosis and treatment of suspected anaphylaxis. According to the World Allergy Organization, anaphylaxis may be immunoglobulin E (IgE)-mediated or non-IgE-mediated [22]. However, both have identical clinical presentations, and treatment recommendations are the same for both entities. Evidence of increased tryptase concentration or positive skin test is generally used to differentiate IgE- from non-IgE-mediated anaphylaxis [14,23].

We hypothesize that the retrospective application of epidemiologic methods to a large institutional database may facilitate the identification of drugs or patient factors associated with hemodynamically significant anaphylaxis in adult patients undergoing surgery. In doing so, we would hope to enable the prospective early identification of anaphylaxis and prompt administration of epinephrine.

2. Materials and methods

2.1. Institutional research board statement

University of Michigan Institutional Research Board approval was granted for this project. The patient informed consent requirement was waived because this study presented minimal risk to participants (IRB # HUM00069050).

2.2. Screening methodology

The primary outcome was hemodynamically significant anaphylaxis: grade III and IV anaphylaxis (Table 1) [24]. *Grade III anaphylaxis* is defined as shock and/or life-threatening smooth muscle spasm. *Grade IV anaphylaxis* is defined as cardiac and/or respiratory arrest. The University of Michigan Anesthesia Information Management System database (Centricity; General Electric Healthcare, Waukesha, WI) was retrospectively queried for possible instances of hemodynamically significant anaphylaxis from January 1, 2004, through January 5, 2015, using a 2-step approach intended to best approximate the Ring and Messmer criteria (Table 2) [24]. All adult cases were eligible for inclusion, including cardiac cases. Our screening process was as follows: We looked for hypotension followed by treatment suggestive of anaphylaxis. First, “hemodynamically significant” adult

Table 1 The severity scale for quantification of intensity of anaphylactoid reaction, adapted from Ring and Messmer [23]

| Grade | Symptoms |
|-------|---|
| I | Cutaneous symptoms and/or mild fever |
| II | Non-life-threatening cardiovascular, gastrointestinal, and/or respiratory disturbance |
| III | Shock, life-threatening smooth muscle spasm |
| IV | Cardiac and/or respiratory arrest |

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