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Severe Perioperative Anaphylaxis With Positive Skin Tests to Midazolam and Rocuronium During Breast Cancer Surgery: A Case Report

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Abstract

Midazolam is an uncommon suspect when perioperative anaphylaxis follows the administration of several drugs at induction. We report a 50-year-old woman with allergic asthma who, within minutes of induction for breast cancer surgery, developed hypotension, tachycardia, generalized erythema, severe bronchospasm, and desaturation (peripheral oxygen saturation nadir 70%). Ceftriaxone 2 g had been given before induction with midazolam 2 mg, propofol 100 mg, fentanyl 100 µg, and rocuronium 40 mg; sevoflurane was used for maintenance. The first arterial blood gas showed a pH of 7.164, a partial pressure of arterial carbon dioxide ($PaCO_2$) of 69.5 mmHg, and a partial pressure of arterial oxygen (PaO_2) of 44.1 mmHg. She was treated with 100% oxygen, ventilatory support, intravenous epinephrine, inhaled and intravenous salbutamol, corticosteroids, and chlorphenamine. Surgery was postponed, and she required overnight intensive care, during which rocuronium was re-administered by infusion without a renewed reaction. Serial videolaryngoscopy showed laryngeal edema that resolved before extubation on day 1. Skin tests on day 14 were positive to rocuronium at 0.05 mg/mL and midazolam at 0.5 mg/mL and negative to propofol, fentanyl, sevoflurane, and latex; tryptase was not measured. The midazolam concentration was 10 times the European Academy of Allergy and Clinical Immunology (EAACI) maximum non-irritant intradermal concentration (0.05 mg/mL), so an irritant false-positive result cannot be excluded, and ceftriaxone was not specifically tested. On day 28, general anesthesia with propofol, fentanyl, remifentanil, and sevoflurane, avoiding midazolam, neuromuscular blocking agents, and beta-lactams, was uneventful. The case highlights the need to include benzodiazepines in perioperative allergy work-ups, to use validated test concentrations and timing, to measure tryptase, and to avoid all suspected agents after the reaction.

Categories: Anesthesiology
Keywords: breast cancer surgery, bronchospasm, drug hypersensitivity, midazolam, perioperative anaphylaxis, rocuronium, skin tests

Introduction

Perioperative anaphylaxis is uncommon but potentially fatal. In the UK 6th National Audit Project (NAP6), life-threatening reactions occurred in approximately one in 10,000 anesthetics, with a mortality of about 4%; antibiotics and neuromuscular blocking agents (NMBAs) were the most frequently identified culprits, followed by chlorhexidine and patent blue [1]. Identifying the responsible exposure is difficult because several drugs are given within minutes at induction. The investigation relies on an acute serum tryptase compared with a baseline sample obtained at least 24 hours later and on skin-prick and intradermal testing performed ideally four to six weeks after the event using validated maximum non-irritant concentrations [2]. Skin testing has imperfect sensitivity, particularly when performed early, and irritant concentrations can cause false-positive results; results must therefore be interpreted together with the clinical timeline [2]. Midazolam is an infrequent culprit, but skin-test-supported reactions have been reported [3-5].

We describe severe perioperative anaphylaxis during attempted breast cancer surgery, followed by positive skin tests to rocuronium and midazolam. Beyond the concurrent positive tests, the case illustrates three practical points. The midazolam result was obtained at a concentration 10 times the current European Academy of Allergy & Clinical Immunology (EAACI) maximum non-irritant intradermal concentration. Rocuronium was inadvertently re-administered by infusion in the intensive care unit (ICU) before the allergy work-up. The patient subsequently underwent uneventful general anesthesia avoiding midazolam, NMBAs, and beta-lactams, which clinically confirmed the negative skin tests to propofol, fentanyl, and sevoflurane.

Case Presentation

A 50-year-old woman weighing 50 kg was admitted for planned quadrantectomy and sentinel lymph node biopsy for a right breast malignancy. Her history included allergic asthma with inhalant sensitization (skin-prick testing in 1999 had been positive to *Alternaria*; horse, cat, and dog epithelia; and olive and birch pollen) and light smoking. She used a salmeterol/fluticasone propionate combination inhaler, recorded as as-needed at the preanesthetic visit and described as almost daily at the later allergy consultation, and took

an estradiol valerate/dienogest oral contraceptive. She had never received general anesthesia, reported previous uneventful local anesthesia for dental procedures, and had no known drug or food allergy. The preanesthetic assessment classified her as American Society of Anesthesiologists physical status II.

On the day of surgery (day 0), blood pressure was 120/70 mmHg and heart rate was 80 beats/min, and her general condition was considered good. Relevant preoperative laboratory results are shown in Table *1*. The preoperative eosinophil count was within the reference interval; this does not exclude drug sensitization.

Parameter	Timing	Result	Units	Reference interval
Blood pressure	Preinduction / nadir	120/70 / ≈75-80/40	mmHg	N/A
Heart rate	Preinduction / peak	80 / ≈110	beats/min	N/A
SpO_2	Preinduction / nadir	99 / 70	%	N/A
White blood cells	Day -4 / Day 1 / Day 26	6.45 / 8.20 / 7.45	10^3/µL	3.60-10.00
Eosinophils	Day -4 / Day 1 / Day 26	5.4 / 0.1 / 3.9	%	0.5-6.0
Eosinophils, absolute	Day -4 / Day 1 / Day 26	0.35 / 0.01 / 0.29	10^3/µL	Up to 0.80
Hemoglobin	Day -4	13.5	g/dL	11.5-16.0
Platelets	Day -4	218	10^3/µL	150-450
Creatinine	Day -4	0.80	mg/dL	0.52-1.04
C-reactive protein	Day -4	<0.50	mg/L	Up to 3.30
pH	12:59 / 13:12 / Day 1	7.164 / 7.133 / 7.438	N/A	7.35-7.45*
$PaCO_2$	12:59 / 13:12 / Day 1	69.5 / 68.8 / 38.0	mmHg	35-45*
PaO_2	12:59 / 13:12 / Day 1	44.1 / 217 / 126	mmHg	80-100 (room air)*
PaO_2/FiO_2 (FiO_2 1.0)	12:59 / 13:12	≈44 / ≈217	mmHg	>400*
SaO_2	12:59 / 13:12 / Day 1	65.9 / 99.7 / 98.8	%	95-99*
Lactate	12:59 / 13:12 / Day 1	1.3 / 1.2 / 0.9	mmol/L	<2.0*
Total IgE	Day 18	447	IU/mL	Up to 100
Specific IgE, ampicilloyl / amoxicilloyl	Day 17	0.140 / 0.170	kUA/L	0-0.099
Specific IgE, penicilloyl G / penicilloyl V / cefaclor	Day 17	0.000 / 0.050 / 0.030	kUA/L	0-0.099
Serum tryptase	-	Not measured	-	-

TABLE 1: Vital signs, relevant laboratory results, serial arterial blood gases, and immunological findings

Vital signs were read from the handwritten anesthetic chart; nadir and peak values are approximate. *Arterial blood gas printouts do not report reference intervals; conventional adult values are given for orientation. The day 1 sample was obtained after extubation with oxygen by nasal cannula at 2 L/min. Other preoperative chemistry and coagulation tests (day -4) were within reference intervals except urea 45.8 mg/dL (15.0-45.0), sodium 135 mEq/L (136-148), alkaline phosphatase 30 U/L (36-126), and prothrombin activity 125% (70-120), which were not considered clinically relevant.

Day 0: day of the reaction; Day -4: preoperative testing; Day 26: readmission

SpO_2: peripheral oxygen saturation; $PaCO_2$: partial pressure of arterial carbon dioxide; PaO_2: partial pressure of arterial oxygen; FiO_2: inspired oxygen fraction; SaO_2: arterial oxygen saturation; IgE: immunoglobulin E; kUA/L: kilounits of allergen per liter; N/A: not applicable

Ceftriaxone 2 g was administered intravenously for antibiotic prophylaxis before induction (charted at approximately 12:20-12:30). At 12:35, anesthesia was induced with midazolam 2 mg, propofol 100 mg (single bolus), fentanyl 100 µg (with a further 50 µg at approximately 12:45), and rocuronium 40 mg, and the trachea was intubated; sevoflurane (approximately 2%) in oxygen and air was used for maintenance. Within a few minutes of induction, the patient developed sudden hypotension (charted nadir approximately 75-80/40 mmHg), tachycardia (approximately 110 beats/min), desaturation (peripheral oxygen saturation nadir

70%), extreme thoracic rigidity with poor chest expansion, bronchospasm, and a generalized erythematous rash. Because all agents were given within about 15 minutes, a separate latency for each could not be calculated. The interval was approximately 10-20 minutes for ceftriaxone and a few minutes for the induction agents.

An arterial sample obtained at 12:59, approximately 20 minutes after onset, showed a pH of 7.164, partial pressure of arterial carbon dioxide ($PaCO_2$) of 69.5 mmHg, partial pressure of arterial oxygen (PaO_2) of 44.1 mmHg, arterial oxygen saturation (SaO_2) of 65.9%, and lactate of 1.3 mmol/L. A repeat sample at 13:12 showed a pH of 7.133, $PaCO_2$ of 68.8 mmHg, PaO_2 of 217 mmHg, SaO_2 of 99.7%, and lactate of 1.2 mmol/L, indicating improved oxygenation with persistent ventilatory impairment (Table *1*). The inspired oxygen fraction (FiO_2) field on the analyzer printouts (21%) was an operator-entered default rather than a measured value; the anesthetic chart documents an FiO_2 of 1.0 from the onset of the reaction. Assuming an FiO_2 of 1.0, the PaO_2/FiO_2 ratio was approximately 44 mmHg in the first sample and 217 mmHg in the second.

Management was recorded on the anesthetic chart. The FiO_2 was increased from 0.5 to 1.0, and the patient was ventilated manually and then with protective settings and recruitment maneuvers; sevoflurane was continued. Epinephrine was given intravenously as three boluses of 50 µg between approximately 12:45 and 13:00 (cumulative 150 µg). Salbutamol was given as four doses of two metered-dose puffs through the breathing circuit between 12:45 and 13:15, followed by an intravenous bolus of 25 µg and an infusion of 10 µg/mL at 18 mL/h (180 µg/h). Hydrocortisone 1 g intravenously (IV) (infused from approximately 12:45 to 13:05), chlorphenamine 10 mg IV (12:45), and methylprednisolone 40 mg IV (approximately 13:05) were administered, together with Ringer's lactate (2 × 500 mL). Respiratory volumes recovered gradually, peak airway pressures decreased, and gas exchange improved. Following discussion with the surgical team and family, the operation was postponed, and the patient was transferred to the ICU at 13:55, intubated and sedated.

ICU care included pressure-controlled ventilation, propofol sedation, continuation of the intravenous salbutamol infusion, central venous catheterization, invasive arterial pressure monitoring, and serial blood gases. Neuromuscular blockade was maintained with a rocuronium infusion (500 mg/50 mL) at 30 mg/h from 15:00, discontinued at 18:33 because ventilation and gas exchange were adequate (approximately 105 mg in total). This re-exposure preceded the allergy investigation. No renewed anaphylactic episode was documented, and mild overnight hypotension did not require vasoactive support.

Serial videolaryngoscopic assessment documented marked laryngeal edema on day 0, a reduction on day 1, and clinical resolution before extubation (Figure *1*). By day 1, gas exchange had improved, and sedation was reduced; the patient became awake, cooperative, and able to follow commands. After a spontaneous breathing trial, she was extubated and received nebulized epinephrine (1 mg), beclomethasone (0.8 mg), and salbutamol, with oxygen through nasal cannulae at 2 L/min. A supine portable chest radiograph obtained in the operating room at 13:05 on day 0 showed no acute consolidative parenchymal abnormality or pleural effusion (Figure *2*), and a follow-up radiograph on day 1 was unchanged. She returned to the breast surgery ward on day 1 and was discharged home on day 3.

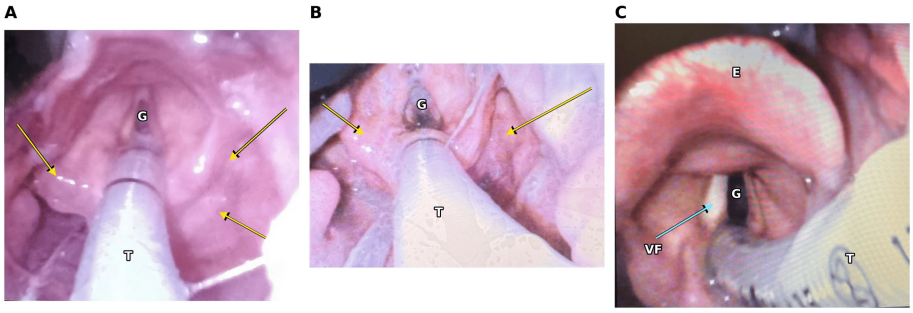


FIGURE 1: Serial videolaryngoscopic evolution of the laryngeal edema

(A) Marked edema on day 0, the day of the perioperative reaction. (B) Reduced edema on day 1. (C) Later examination on day 1, before extubation, when clinical resolution was confirmed by the treating clinician. Photographs of the videolaryngoscope display were cropped without altering tissue appearance; different angles, lighting and magnification preclude quantitative comparison.

T: endotracheal tube; G: glottic opening; E: epiglottis; VF: vocal fold; yellow arrows: edematous periglottic tissue

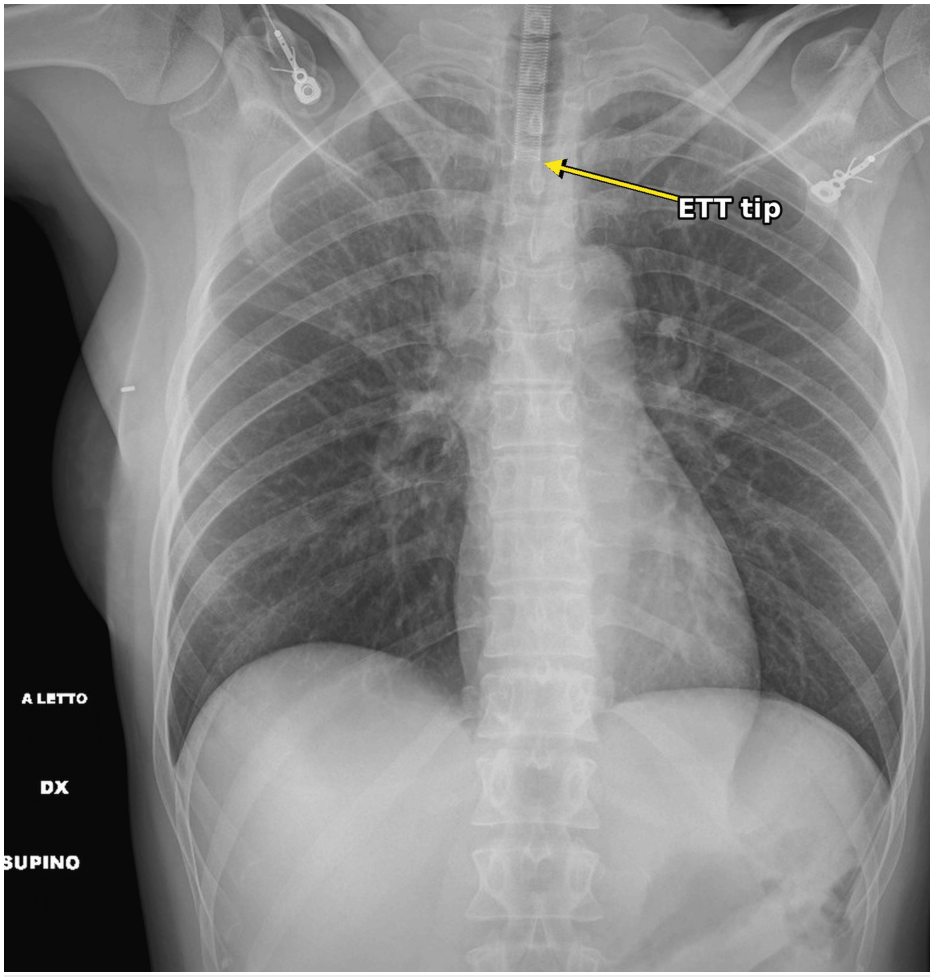


FIGURE 2: Supine portable chest radiograph obtained in the operating room on day 0

The radiograph was obtained at 13:05, approximately 30 minutes after onset, while the patient was intubated, and shows no acute consolidative parenchymal abnormality or pleural effusion. The arrow indicates the tip of the reinforced endotracheal tube; electrocardiographic electrodes are visible. Identifying information was removed by cropping; no image detail was enhanced.

An allergy consultation on day 7 considered ceftriaxone among the possible triggers, advised its avoidance, and recommended testing of the anesthetic drugs and antibiotics. Inhalant skin-prick testing on day 11 confirmed sensitization to dog and cat epithelia, *Alternaria*, and cypress; latex prick testing was negative. Drug skin testing on day 14, reported as performed according to the European Academy of Allergy and Clinical Immunology (EAACI)/European Network of Drug Allergy (ENDA) Drug Allergy Interest Group recommendations, included propofol, midazolam, fentanyl, sevoflurane, rocuronium, and latex and was positive to midazolam at 0.5 mg/mL and rocuronium at 0.05 mg/mL. Skin tests to levofloxacin, azithromycin, and clarithromycin were negative. The report did not specify whether the positive results arose from prick or intradermal tests, and wheal diameters, control responses, and dilution steps were not included. These findings are summarized in Table *2*.

Agent or assessment	Documented finding	Interpretation within this report
Rocuronium	Positive skin test at 0.05 mg/mL (day 14); 40 mg at induction; ICU infusion (≈105 mg over 3.5 hours) without renewed reaction	Most robust positive result (recommended EAACI intradermal concentration); ICU tolerance under sedation, steroids and antihistamine does not exclude sensitization
Midazolam	Positive skin test at 0.5 mg/mL (day 14)	Ten times the EAACI 2019 maximum non-irritant intradermal concentration (0.05 mg/mL); possible irritant false positive
Propofol, fentanyl, sevoflurane	Skin tests negative (day 14)	Early testing; negative results confirmed by uneventful use on day 28
Ceftriaxone	Given 10-20 minutes before onset; not skin-tested; avoidance advised	Possible culprit; not excluded
Penicillin determinants, cefaclor	Specific IgE: ampicilloyl 0.140 and amoxicilloyl 0.170 kUA/L; penicilloyl G, penicilloyl V and cefaclor negative	Low-level sensitization; not ceftriaxone-specific
Levofloxacin, azithromycin, clarithromycin	Skin tests negative	Clarithromycin tolerated as prophylaxis on day 28
Latex	Negative prick test (day 11)	Latex allergy unlikely
Total IgE	447 IU/mL (day 18)	Consistent with atopy; does not identify the culprit
Tryptase (acute and baseline)	Not measured	No biochemical confirmation of mast-cell activation

TABLE 2: Documented allergy findings and limits of causal interpretation

Skin-test modality, wheal diameters and control responses were not reported.

EAACI: European Academy of Allergy and Clinical Immunology; ICU: intensive care unit; IgE: immunoglobulin E; kUA/L: kilounits of allergen per liter

The allergy service concluded that the patient had perioperative anaphylaxis with immunoglobulin E (IgE)-mediated hypersensitivity to rocuronium and midazolam. It recommended avoidance of midazolam, rocuronium, other NMBAs (pending further investigation if their use became necessary), ceftriaxone, (provisionally) other beta-lactams, and proposed premedication with cetirizine, methylprednisolone, and chlorphenamine for any future surgery. Total IgE was 447 IU/mL. Specific IgE to penicilloyl G (0.000 kilounits of allergen per liter (kUA/L)), penicilloyl V (0.050 kUA/L), cefaclor (0.030 kUA/L), and formaldehyde (0.010 kUA/L) were below the laboratory threshold of 0.1 kUA/L, whereas ampicilloyl (0.140 kUA/L) and amoxicilloyl (0.170 kUA/L) were marginally elevated. No ceftriaxone-specific skin or in vitro test was performed, serum tryptase was not measured during or after the reaction, and basophil activation testing was not performed.

The patient was readmitted on day 26, and on day 28 she underwent right breast quadrantectomy with radioguided sentinel lymph node biopsy under general anesthesia. Following the allergy recommendations, midazolam, NMBAs, ceftriaxone, and beta-lactams were avoided, and clarithromycin (skin-test negative) was used for antibiotic prophylaxis. Premedication consisted of oral cetirizine 10 mg daily from two days before surgery, and chlorphenamine 10 mg IV and methylprednisolone 40 mg IV on the morning of surgery; the methylprednisolone dose planned for the previous evening was not given because the drug was unavailable. Anesthesia was induced with propofol 140 mg and fentanyl 100 µg and maintained with sevoflurane 2.8% and a remifentanil infusion. The trachea was intubated without an NMBA (7.0 tube, Macintosh 3 blade), and dexamethasone 8 mg and ibuprofen 600 mg were given. Anesthesia (about 1.5 hours) and surgery were uneventful. Intraoperative frozen section of the sentinel node was negative, and she was discharged the next day. The clinical timeline is shown in Figure *3*.

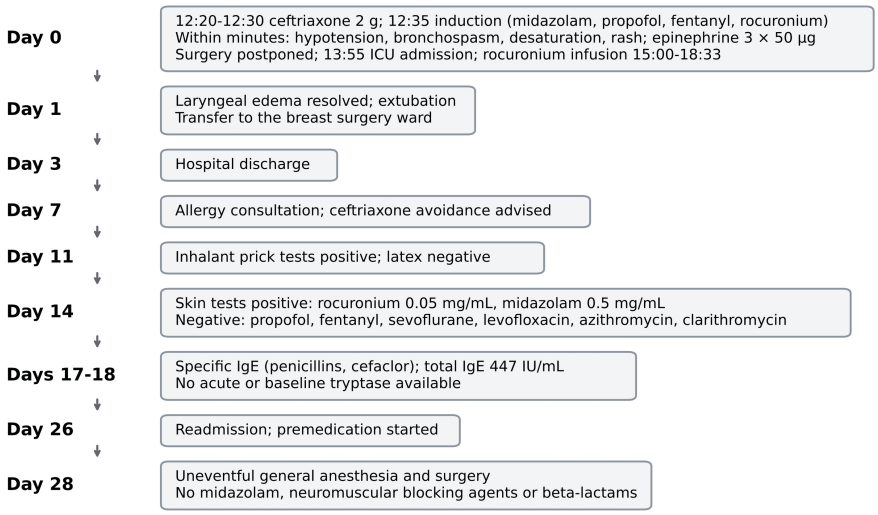


FIGURE 3: Timeline of the reaction, recovery, allergy investigation, and subsequent surgery

Day 0 denotes the day of the reaction. Clock times are taken from the anesthetic and intensive care records.

ICU: intensive care unit; IgE: immunoglobulin E

Discussion

The combination of abrupt cardiovascular instability, generalized erythema, and severe bronchospasm after induction was clinically consistent with anaphylaxis [6]. Serial videolaryngoscopy also documented upper-airway edema and its subsequent resolution before extubation. These findings complement the lower-airway and gas-exchange abnormalities, although laryngeal swelling alone does not identify the culprit drug or exclude a contribution from airway instrumentation. The respiratory component was particularly prominent: hypercapnia, acidemia, markedly impaired oxygenation, and difficult ventilation required continued intubation and ICU care. Allergic asthma could have contributed to the severity of airway obstruction, but isolated asthma or airway instrumentation would not adequately explain the accompanying rash and circulatory disturbance. Other considerations include opioid-associated rigidity, mechanical airway obstruction, and the hemodynamic effects of induction drugs. These alternatives do not exclude anaphylaxis and may overlap with it.

Published midazolam reactions encompass severe systemic events and localized reactions. Jeon et al. described hypotension and bronchospasm with subsequent positive intradermal testing [3]. Nucera et al. reported five skin-test-supported cases with differing clinical phenotypes [4]. Funabiki et al. showed that midazolam can be implicated even when deterioration occurs after other induction agents [5]. Midazolam therefore deserves a place in the investigation even when more familiar suspects are present, but the present case does not justify a claim of exclusive midazolam-induced anaphylaxis.

Three methodological issues affect interpretation. First, testing was performed 14 days after the event, earlier than the four to six weeks generally recommended [2]. Early testing mainly increases the risk of false-negative results, so the negative results to propofol, fentanyl, and sevoflurane needed clinical confirmation; this was provided by their uneventful use four weeks later. Second, the report does not specify the test modality, but the rocuronium concentration of 0.05 mg/mL corresponds to the EAACI intradermal step (the prick concentration being 10 mg/mL), which suggests that the positive results were intradermal. Third, and most importantly, the 2019 EAACI position paper lists maximum non-irritant concentrations for midazolam of 5 mg/mL for prick testing and 0.05 mg/mL for intradermal testing [2]. The midazolam result reported here (0.5 mg/mL) was therefore obtained at ten times the recommended intradermal limit. This concentration corresponds to the intradermal concentration (a 1:10 dilution of the 5 mg/mL solution) of the earlier ENDA/EAACI Drug Allergy Interest Group position paper on skin test concentrations [7], which the allergy service followed, and has been used in previous midazolam investigations [4,5]. However, it may produce non-specific irritant reactions. By contrast, Funabiki et al. documented a positive intradermal result at 0.05 mg/mL [5]. The rocuronium result was obtained at the recommended non-irritant intradermal concentration and is therefore the more reliable of the two positive tests. Wheal diameters and control responses were not reported, which prevents independent validation of either result.

Concurrent positivity to midazolam and rocuronium creates an attribution problem rather than proof that both drugs triggered the reaction. The allergy service's diagnosis is reported as documented, but its

evidentiary limits must remain explicit. Rocuronium, a recognized high-risk agent [1], was given as a 40 mg bolus at induction and again by infusion in the ICU (approximately 105 mg over 3.5 hours) without a renewed reaction. This apparent tolerance occurred under deep sedation, mechanical ventilation, high-dose corticosteroids, an antihistamine and a salbutamol infusion, which could attenuate or mask clinical signs, and therefore does not exclude sensitization. It nevertheless illustrates an avoidable risk: after suspected perioperative anaphylaxis, all potential culprits should be avoided until investigation is complete [1,2]. Ceftriaxone was given shortly before induction and was not skin-tested; it was explored only indirectly with penicillin-determinant and cefaclor-specific IgE, so its involvement cannot be excluded. No drug provocation test was performed.

Epinephrine is the central treatment for anaphylaxis; oxygen, fluid resuscitation, and ventilatory support address the associated physiological failure, and bronchodilators supplement treatment of persistent bronchospasm, whereas antihistamines and corticosteroids do not replace epinephrine [6]. In this patient, treatment was started within minutes of onset: epinephrine (three 50-µg intravenous boluses, consistent with recommended titrated dosing for severe reactions [1,6]), inhaled salbutamol, chlorphenamine and hydrocortisone were all charted by approximately 12:45, followed by intravenous salbutamol and methylprednisolone. Doses and times were reconstructed from a handwritten chart with approximately five-minute resolution, so the exact interval between onset and each intervention cannot be stated more precisely.

The subsequent uneventful anesthesia has practical value. It confirms clinical tolerance of propofol, fentanyl, and sevoflurane, the drugs whose negative skin tests were least reliable because of early testing, and it shows that a balanced technique without benzodiazepines or NMBAs is feasible for this type of surgery. Because corticosteroid and antihistamine premedication does not reliably prevent IgE-mediated anaphylaxis, the main protective measure was avoidance of the suspected agents rather than premedication [2,6].

The diagnosis of anaphylaxis in this patient is clinical. It is based on the charted combination of generalized erythema, hypotension, tachycardia, and severe bronchospasm with hypoxemia within minutes of drug administration, which meets World Allergy Organization criteria [6] and corresponds to Ring and Messmer grade III [8]. The data do not allow identification of a single culprit or biochemical confirmation of mast-cell activation. No acute or baseline tryptase was measured, skin testing was early and incompletely reported, midazolam was tested at a supra-recommended intradermal concentration, and ceftriaxone was not specifically tested. The airway images are photographs of a videolaryngoscope display acquired at different angles; they illustrate the clinician-confirmed progression but do not allow quantitative measurement of airway caliber or edema. Long-term oncological outcomes were outside the scope of this report. Accordingly, this report presents severe clinical anaphylaxis with positive skin tests to two peri-induction agents, of which the rocuronium result is the more reliable, followed by safe anesthesia with the agents that had tested negative.

Conclusions

Severe (Ring and Messmer grade III) perioperative anaphylaxis occurred shortly after induction for breast cancer surgery and was followed by positive skin tests to rocuronium and midazolam. The rocuronium result was obtained at the recommended intradermal concentration. The midazolam result was obtained at ten times the EAACI maximum non-irritant intradermal concentration and may be an irritant false positive. Ceftriaxone, given shortly before induction, was not specifically tested and cannot be excluded, and rocuronium was re-administered in the ICU without a renewed reaction. In the absence of tryptase measurements, the event is a clinical diagnosis, and no single culprit can be established. Four weeks later, general anesthesia avoiding midazolam, NMBAs and beta-lactams was uneventful. Perioperative allergy work-ups should include benzodiazepines, use validated non-irritant concentrations and appropriate timing, and be accompanied by acute and baseline tryptase sampling. All suspected agents should be avoided after the reaction, including in the ICU.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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