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Safety of Inhalational Anesthesia in Patients with Multiple Drug Allergies Presenting for Major Surgeries under General Anesthesia

[Sunil Rajan](#), [Jacob Mathew](#), [Pulak Tosh](#), and [Manu Sudevan](#)

Department of Anaesthesiology, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, Kochi, Kerala, India

Address for correspondence: Dr. Manu Sudevan, Department of Anaesthesiology, Amrita Institute of Medical Sciences, Kochi, Kerala, India. E-mail: msudevan@gmail.com

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Abstract

The prevalence of perioperative anaphylaxis is 1 in 1250–20,000 anesthetics. Inhalational anesthesia is considered safe in patients with multiple drug allergies, as there have been no reports of anaphylaxis to volatile inhalational agents. Anesthetic management of six patients with documented allergy to all commonly used anesthetic drugs who underwent major surgeries under general anesthesia is described as a case series. The plan of anesthesia in these patients was an anesthetic gas-based general anesthesia without using muscle relaxants but with the use of intravenous fentanyl if patient was not allergic to it. Sevoflurane 8% in oxygen was used for induction. Following cessation of breathing and on attaining an end-tidal concentration of >4% sevoflurane, direct laryngoscopy and intubation were performed. Anesthesia was maintained with sevoflurane in nitrous oxide and oxygen mixture maintaining a lower end-tidal carbon dioxide. Hypotension and/or bradycardia were managed with intermittent intravenous boluses of adrenaline 20 µg. At the end of surgery, all anesthetic gases were cutoff, and patients were extubated when awake. No muscle relaxant was used in any of the cases. Two patients received fentanyl before induction, whereas others were given oral paracetamol 2 h before induction. Postoperative analgesia was provided with oral paracetamol which was given 2–4 h after surgery. Intraoperative period was uneventful for these patients. In patients with multiple drug allergies, inhalational agent-based general anesthesia can be considered as a safe alternative to regular anesthetic practice involving polypharmacy, with a reduced risk of perioperative adverse events.

Keywords: Anaphylaxis, drug allergy, general anesthesia, inhalational

INTRODUCTION

Anaphylaxis is an unanticipated reaction which, without a high degree of suspicion and prompt management, can rapidly progress to a life-threatening condition with a mortality ranging from 3% to 9%. [1] The prevalence of perioperative anaphylaxis varies widely across the globe with an incidence of 1 in 1250–20,000 anesthetics. [2] Inhalational anesthesia is considered safe in patients with multiple drug allergies, as there have been no reports of anaphylaxis to volatile inhalational agents. [3,4,5,6]

Anesthetic management of six patients with documented allergy to almost all commonly used anesthetic drugs [Table 1], who underwent major surgeries under general anesthesia with endotracheal intubation, is described in this case series.

CASE REPORTS

The patients' details are described below individually, while the anesthetic management is discussed together, as all patients had skin test positivity of more than 10 × 10 mm induration for all the commonly used anesthetic agents hence they received general anesthesia mainly based on inhalational agents alone without the use of muscle relaxants.

Case 1

A 25-year-old female, known case of papillary carcinoma of thyroid, was posted for total thyroidectomy. She gave a history of multiple drug allergies with a history of angioedema after consuming diclofenac. Skin allergy test revealed allergy to almost all antibiotics, general and local anesthetic drugs. She used to take oral paracetamol when febrile.

Case 2

A 64-year-old female, a case of multinodular goiter, was posted for total thyroidectomy. Hysterectomy was done 30 years back under spinal anesthesia. As she gave a history of drug allergy to many drugs, skin allergy testing was done which showed allergy to almost all analgesics, local anesthetics, muscle relaxants, sedatives, premedicants, antihistamines, anticholinergics, neostigmine, and antibiotics.

Case 3

A 58-year-old male, known case of hypertension, diabetes mellitus, dyslipidemia, and status postexcision biopsy of suspected alveolus lesion, during which there were some intraoperative adverse events manifested with urticarial lesions and hypotension which were managed with adrenaline, hydrocortisone, and antihistamines. After the procedure, intradermal allergy testing was done which showed multiple anesthetic drug allergies but was not sensitive for fentanyl. Biopsy was positive for squamous cell carcinoma, and the patient was posted for alveolar resection, neck dissection, and free fibular bone flap under general anesthesia.

Case 4

A 69-year old female with multinodular goiter was scheduled to undergo total thyroidectomy. She was a known case of coronary artery disease, hypertensive on nebivolol, dyslipidemic on atorvastatin, and had osteoarthritis of bilateral knees. She gave a history of itching, redness, heartburn, and regurgitation on consuming all pain killers except oral paracetamol. Skin allergy testing showed sensitivity to all commonly used anesthetic drugs except fentanyl.

Case 5

A 52-year-old female presented with papillary carcinoma thyroid posted for total thyroidectomy under general anesthesia. She was a known case of atopic dermatitis and asthmatic on salbutamol and budesonide inhalers. Earlier history of anaphylaxis during lymph node biopsy under local anesthesia was elicited. She also gave a history of allergy to multiple drugs including paracetamol, which was confirmed with intradermal skin allergy testing.

Case 6

A 48-year-old female patient with a history of multiple drug allergies was diagnosed to have carcinoma breast and was posted for mastectomy with axillary clearance. History of food allergy and allergy to drugs with wheezing and urticaria was elicited. Skin allergy test revealed sensitivity to all tested opioids, muscle relaxants, analgesics, anticholinergics, neostigmine, and antihistamines. There was no reaction to ondansetron. She gave a history of allergy to paracetamol also.

Anesthetic management of the cases

All patients were assessed in the preanesthesia clinic with a detailed history and relevant investigations. Intradermal allergy test results were documented. All the six patients were sensitive to commonly used drugs during anesthesia as described in [Table 1](#). Two patients were not allergic to fentanyl and others used

to take oral paracetamol without side effects. Some had documented allergy even to antihistamines. All patients were allergic to most of the antibiotics as well.

They were admitted on the day prior to surgery and were kept fasting for 6 h for solids and 2 h for clear fluids. No premedication was administered on night prior to surgery. On the day of surgery, those who were not allergic to paracetamol were given 1 g of paracetamol with sips of water 1 h before surgery.

The plan of anesthesia in these patients was an anesthetic gas-based general anesthesia without using muscle relaxants but with use of intravenous fentanyl if patient was not allergic to it. In the operation theater, all emergency drugs and equipment were kept ready for resuscitation. Adrenaline was diluted and loaded as 10 µg/mL and 100 µg/mL solutions in syringes and infusion pumps. All patients received hydrocortisone 100 mg and dexamethasone 8 mg intravenously on arrival to the operation theater. Steroids were used to reduce the risk of recurring or protracted anaphylaxis as well as for supplemental analgesic and antiemetic effects. After attaching preinduction monitors such as electrocardiogram, noninvasive blood pressure monitor, and pulse oximeter, those who were not allergic to fentanyl received 10 µg of fentanyl intravenously initially as a slow bolus. After 5 min, if there was no itching, urticaria, tachycardia, hypotension, or difficulty in breathing, the remaining fentanyl (2 µg/kg) was also given over 5 min. Two of the above-mentioned patients (Case numbers 3 and 4) received fentanyl preoperatively without any adverse events.

Patients were informed about inhalation induction and were asked to maximally inhale and exhale through a tight-fitting face mask. Sevoflurane 8% in oxygen was used for induction with a gas flow rate of 6 L/min. When the patients lost consciousness, 50% nitrous oxide was added to anesthetic mixture and as depth of anesthesia became deeper and respiration became shallower, breaths were assisted by gentle bag ventilation synchronizing with patients effort till they became apneic. Heart rate and blood pressures were closely monitored for the development of hypotension or bradycardia. None of our patients except one developed hypotension, which was managed with adrenaline 20-µg bolus intravenously. Following cessation of breathing and on attaining an end-tidal concentration of >4% sevoflurane, direct laryngoscopy and intubation were performed. Case 3 was intubated nasally and others orally with 7.0-mm internal diameter cuffed endotracheal tube. Laryngoscopy was easy in all patients, but two patients (Cases 5 and 6) had mild cough while the tube was passed through the larynx. There was no evidence of bronchospasm and both were managed by hyperventilating with sevoflurane 8% dial setting.

Anesthesia was maintained with sevoflurane (end-tidal concentration between 2% and 4%) in oxygen and nitrous oxide (1:2) mixture. All patients were mechanically ventilated with a tidal volume of 6–8 ml/kg body weight and at higher respiratory rate (14–16 min⁻¹) so as to maintain an end-tidal carbon dioxide (EtCO₂) level of 25–30 mmHg. A lower EtCO₂ was maintained to reduce spontaneous respiratory efforts during surgery. Any attempt at breathing was managed by hyperventilating with bag and temporarily increasing sevoflurane concentration by 1%–2%. Hypotension and/or bradycardia were managed with intermittent intravenous boluses of adrenaline 20 µg. If hypotension was persistent, adrenaline infusion (0.05–0.5 µg/kg/min) was started and titrated to maintain desired hemodynamic levels. Cases 3 and 4, both hypertensives on medication, required adrenaline infusion to maintain blood pressure. The patients were monitored for development of skin rashes on exposed parts of the body, and any increase in airway pressures suggestive of anaphylaxis. Although the plan was to manage the condition with adrenaline, none of our patients developed those signs intraoperatively.

At the end of surgery, all anesthetic gases were cutoff, and patients were bag ventilated till they regained spontaneous breathing and were generating adequate tidal volume. Extubation was performed on the table for all patients except Case 3, when patients were awake with return of protective airway reflexes. Case 3 was tracheostomized, and on regaining spontaneous respiration, the patient was treated with oxygen supplementation through T-piece. All surgeries lasted for 1.5–2 h except Case 3 which lasted for 8 h. No muscle relaxant was used in any of the cases. Cases 3 and 4 received fentanyl before induction, but intraoperatively, only Case 3 received intermittent boluses of intravenous fentanyl.

Postoperative analgesia was provided with oral paracetamol which was given 2–4 h after surgery. For Case 3, fentanyl infusion (10 µ/h) was given for 48-h postoperatively and then changed to enteral paracetamol through Ryle's tube. No antiemetic was administered to any patient. Administration of dexamethasone preoperatively might have had a blunting effect on postoperative pain and emesis in all the patients. Case 6

developed postoperative nausea 4 h after surgery and received ondansetron 4 mg intravenously since she was not allergic to it as per allergy testing. However, soon after drug administration, she developed urticarial lesions all over the body with hypotension and wheezing. This was managed with adrenaline 200 µg and she required adrenaline infusion for 4 days postoperatively; as whenever infusion was stopped, urticarial lesions reappeared though there was no hypotension or wheezing after the initial bolus. Case 3 also remained in postoperative intensive care unit for 5 days, but due to surgical reasons such as free-flap vascularity monitoring. All other patients were shifted to the ward 24 h after surgery.

All patients were kept warm in the intra- and postoperative period using forced-air warming devices to prevent postoperative shivering. Intravenous fluid warmers were also used. All received intravenous dexamethasone 8 mg thrice daily in the 1st-postoperative day, twice daily on the 2nd-postoperative day, and once on the 3rd day and then it was stopped. All patients except Case 6 had an unremarkable postoperative period.

DISCUSSION

As an anesthesiologist, it is important to know about two entities namely anaphylaxis and anaphylactoid reactions. Anaphylaxis is an immune (IgE)-mediated Type-1 hypersensitivity reaction where there is always a prior exposure to the allergen, whereas anaphylactoid reaction is nonimmune mediated, without any previous exposure to allergen.[7] However, the clinical manifestations of both are similar. On exposure to allergen, there is release of the preformed mediators inside mast cells (histamine, serum tryptase, eosinophilic chemotactic factor, and neutrophilic chemotactic factor), followed by release of mediators synthesized after mast cell activation (leukotrienes, TXA₂, cytokines, prostaglandins, and platelet activating factor).[8] Anaphylaxis presents clinically with profound hypotension due to vasodilation and increased capillary permeability; there will be bronchospasm manifesting as raised peak airway pressures, urticarial lesions, and cutaneous flushing along with angioedema, and in more severe cases, laryngeal edema, cardiovascular collapse, and laryngospasm as well.[9]

The most common anesthetic agents implicated in the occurrence of intraoperative anaphylaxis are neuromuscular blocking agents (NMBAs) (70%). Among which higher chance of anaphylaxis is for succinylcholine, vecuronium (anaphylaxis), followed by atracurium (anaphylactoid). The allergy is mainly secondary to the quaternary ammonium compound and hence there is a high incidence of cross-reactivity among NMBAs.[7] The second most common allergen is latex (12.6%), followed by colloids (4.7%) (gelatin > dextran > albumin), intravenous induction agents (3.6%, thiopentone > propofol > etomidate), and antibiotics (2.6%, cephalosporins, carbapenems, and vancomycin). There have been reports of allergy to benzodiazepines and opioids (morphine and meperidine); however, reaction to synthetic opioids like fentanyl is rare. Allergy to local anesthetics (esters > amides) is less, but when it occurs, it is mainly due to the added preservative (benzoates and metabisulfite) in amide group and due to para amino benzoic acid (PABA) moiety in ester group. Delayed Type-4 hypersensitivity is more common than Type-1 hypersensitivity with local anesthetics.[7] It is important to note that allergy to blood products, atropine, protamine, and bone cement has also been documented. Anaphylactoid reactions are most commonly due to radiocontrast agents.

It is important to recognize anaphylaxis immediately, and management involves stopping the implicated agent immediately followed by administering 100% oxygen, intravenous epinephrine 5–10 mcg boluses, or intramuscular 0.5–1 mg (1:1000 doses). Other supportive measures include adequate intravenous crystalloids up to 2–4 L for adults, antihistamines (chlorpheniramine 10–20 mg), corticosteroids (hydrocortisone 100–500 mg), and bronchodilators (salbutamol, albuterol). Sometimes, continuous infusion of epinephrine will be required in the postoperative period and vasopressin can be used in cases of refractory hypotension.[9]

Proper documentation of anaphylaxis is important, and further evaluation for causative allergen by *in vitro* methods (RAST, serum tryptase, and serum IgE levels) and *in vivo* methods (skin prick/intradermal skin tests/provocation or challenge tests) has to be done.[7] Serum tryptase is used as a measure to differentiate anaphylaxis and anaphylactoid reactions when levels < 15 ng/mL (anaphylactoid/mild anaphylaxis), and

when levels >20 ng/mL, anaphylaxis is confirmed. Ideally, three samples should be taken, first at the onset of reaction, then 1–2 h after reaction, and the third value 6–24 h after the initial reaction. Ratio of tryptase during reaction to baseline tryptase >2 is suggestive of anaphylaxis (TDR/BT >2).

Anaphylaxis to volatile agents has not been reported so far. However, there have been reports of immune-mediated (IgG) hepatic toxicity toward a trifluoroacetyl metabolite of halothane. Prior administration of halothane increases incidence and severity of hepatitis.[3] Enflurane and isoflurane have also been associated with immune-mediated hepatic injury without prior exposure to halothane.[3] Therefore, we used sevoflurane as it is not metabolized to trifluoroacetyl metabolites and will not cause immune-mediated hepatitis.[3] Moreover, it has a pleasant smell and is associated with a smooth, rapid induction, and recovery following discontinuation of anesthesia. It has been also noted that maintenance of anesthesia with sevoflurane resulted in less patient movement and more favorable hemodynamic responses intraoperatively.[10,11]

It had been shown that sevoflurane induction can provide good intubating conditions without use of muscle relaxants.[12,13,14] Inhalation induction with 6%–7% sevoflurane in 66% nitrous oxide and 28% oxygen by face mask, the time for achieving acceptable tracheal intubating conditions following manual hyperventilation by mask was 4.7 min (3.7–5.7) in adult patients.[15] Addition of nitrous oxide to sevoflurane has the advantage of deepening the plane of anesthesia which will provide more favorable intubating condition in the absence of relaxants. However, the margin of safety may be reduced in an apneic patient if encountered with a difficult airway. None of our patients had anticipated difficult airway, and although one patient required a nasal intubation, there was no desaturation while securing the airway. Although emergence delirium and agitation were documented to be more following sevoflurane anesthesia,[16] in our patients, though extubation time was delayed by 5–10 min, we did not come across any troublesome agitation or delirium.

Although minimum alveolar concentration (MAC) for intubation of sevoflurane is only 2.9%, [17] we intubated our patients when end-tidal concentration of sevoflurane was $>4\%$ even after adding 50% nitrous oxide to the mixture. We did so because MAC intubation denotes immobility of only 50% of patients to tracheal intubation. We used higher concentration to ensure that no patient moved or developed spasm during intubation so as to avoid the need for administration of drugs to treat any such adverse events. The availability of Bispectral Index monitoring would have provided more reliable information on the depth of anesthesia and might have helped us to titrate sevoflurane concentration to more optimal levels.

CONCLUSION

Anaphylaxis is a life-threatening complication that should be anticipated in a patient with multiple drug allergies, such patients have to be evaluated for causative allergens prior to surgery and anesthesia. In these patients, inhalational agent-based general anesthesia can be considered as a safe alternative to regular anesthetic practice involving polypharmacy, with a reduced risk of perioperative adverse events.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Figures and Tables

Table 1Intradermal skin test positivity ($\geq 10 \times 10$ mm)

Agents	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Midazolam	+	+	+	+	+	+
Glycopyrrolate	+	+	+	+	+	+
Atropine	-	+	+	+	+	-
Neostigmine	-	+	+	+	+	+
Ondansetron	+	+	+	+	+	-
Metoclopramide	+	+	+	+	+	+
Morphine	+	+	+	+	+	+
Fentanyl	+	+	-	-	+	+
Buprenorphine	+	+	+	+	+	+
Paracetamol	-	-	-	-	+	+
Pethidine	+	+	+	+	+	+
Pentazocine	+	+	+	+	+	+
Propofol	+	+	+	+	+	+
Thiopentone	+	+	+	+	+	+
Ketamine	+	+	+	+	+	+
Suxamethonium	+	+	+	+	+	+
Atracurium	+	+	+	+	+	+
Vecuronium	+	+	+	+	+	+
Pancuronium	+	+	+	+	+	+
Lidocaine	+	+	+	+	+	+
Bupivacaine	+	+	+	+	+	+
Antihistamines	-	-	-	-	-	+

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+Sensitive, -Not sensitive to drug

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