Intraoperative Ephedrine Allergy in a Patient Who Received Chemotherapy and Perioperative Hypersensitivity Reactions

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Anaesthesia represents a specific set-up in respect to pharmacology, and during this time, early hypersensitivity reactions or anaphylaxis may occur in patients who are exposed to a great number of foreign substances. Intravenous ephedrine (5 mg) was applied to a 37-year-old patient due to the development of intraoperative hypotension in a total abdominal hysterectomy operation. After application, hyperaemia was seen in the track of the intravenous catheter of that extremity. Approximately 15 minutes later, urticarial plaques were observed extensively in the abdomen and in both extremities. Methylprednisolone (100 mg+100 mg) and pheniramine (45.5 mg) were given with an increasing infusion rate of intravenous crystalloid. The patient was extubated without any problem and removed to the recovery unit for observation. After the total disappearance of lesions at postoperative 60 minutes and because of the stability of vital signs, the patient was removed to the service. In the follow-up of surgery, no complication developed, and the patient was discharged on postoperative day 2.

Keywords: Ephedrine, intraoperative, hypersensitivity reactions

Introduction

Allergic drug reactions comprise 6%–10% of all undesirable effects related to drugs. The World Allergy Organization defines drug reaction as a drug allergy if it occurs with IgE- or T-cell-mediated hypersensitivity reactions. Drug allergy most commonly manifests itself via skin findings (1).

It is known that an allergic reaction is observed in patients who are sensitive to various factors such as general anaesthetics, local anaesthetics, muscle relaxants, opioids, antibiotics, volume expanders from intravenous fluids and blood products. It is difficult to determine the responsible agent given that during anaesthesia, various drugs that can be responsible for an anaphylaxis or anaphylactoid reaction are used together. Among these drugs, an allergic reaction is most commonly observed against muscle relaxants. In fact, anaphylactic reactions due to Sugammadex that is used to reverse the effect of muscle relaxants are also detected (2). In this case report, we aimed to present a drug allergy caused by ephedrine, which had no prior reported case during anaesthesia, and to discuss the topic of perioperative hypersensitivity.

Case Presentation

The 37-year-old patient underwent an operation for total abdominal hysterectomy. Her medical history revealed that she underwent a caesarean section, thyroidectomy because of multinodular goitre, mastectomy because of breast cancer and general anaesthesia for breast reconstruction; there were no complications and she was not allergic to any drugs. Furthermore, she received chemotherapy because of breast cancer and was using 20 mg tamoxifen once a day. The patient was admitted to the operating room and standard monitorization was performed. Intravenous access was established, and 0.9% isotonic sodium chloride infusion was started. Prior to induction, the heart rate was 108 beats min⁻¹, non-invasive blood pressure was 110/68 mmHg, SpO₂ 100%, and endotracheal intubation was performed to the patient using propofol 2 mg kg⁻¹, fentanyl citrate 1 µg kg⁻¹ and rocuronium 0.6 mg kg⁻¹.

In the maintenance of anaesthesia, 50% N₂O+50% O₂ and sevoflurane were administered. Because hypotension (77/46 mmHg) developed 50 min after the start of the operation, intravenous 5 mg ephedrine was administered. After the ad-

Figure 1. Urticarial lesions in bilateral lower extremities

ministration, redness was observed in the venous trace of the same extremity where the intravenous cannula was placed. Approximately 15 min later, in both extremities, urticarial plaques that were widespread in the abdomen were observed (Figure 1). The patient's hypotension persisted; therefore, her intravenous crystalloid infusion rate was increased. Methylprednisolone (100+100 mg) and pheniramine (45.5 mg) were intravenously administered. Regression was observed in the patient's urticarial plaques and her vital signs became stable. Intervention lasted 90 min, and she was extubated after all the airway reflexes returned to normal; she was kept under observation in the postoperative care unit. Upon her lesions completely disappearing in the 60th postoperative minute, she was discharged to the service because her vital signs were also stable. Her postoperative IgE value was measured to be 443 IU L⁻¹ (0–100 IU L⁻¹). No problems developed in the patient's follow-up, and she was discharged with full recovery 2 day later.

Discussion

Anaesthesia represents a pharmacologically-specific situation and during this period, hypersensitivity reactions or anaphylaxis can develop in patients who were exposed to anaesthetics, analgesics, antibiotics, antiseptics, blood products, heparin, polypeptides and intravenous volume expanders (3). Agents that cause allergic reactions in the perioperative period are shown in Table 1 (4).

Allergic reactions are defined as four types. Type 1 (immediate hypersensitivity) reactions occur with an IgE antibody and are generally related with mast cells and basophiles. Historically, true anaphylaxis is started with the IgE-dependent activation of these cells. Type 2 reactions are cytotoxic. These reactions are resulted from IgG or IgM antibodies against a cell surface antigen that activates the complements causing cell lysis. Circulating soluble antigen and IgG or IgM antibody complexes cause the Type 3 reaction. In the presence of a complement, these complexes damage the walls of the blood vessel and the integrity of the membrane. Type 4 reactions involve sensitized lymphocytes instead of antibodies. Following the sensitization of a drug or an antigen, lymphocytes react with lymphokine secretion that me-

Table 1. Agents causing allergic reactions in the perioperative period

Anaesthetic agents

Induction agents (chromophore-soluble drugs, barbiturates, etomidate, propofol)

Local anaesthetics (para-aminobenzoic ester agents)

Muscle relaxants (succinylcholine, gallamine, pancuronium, d-tubocurarine, metocurine, atracurium, vecuronium, mivacurium, doxacurium)

Opioids (meperidine, morphine, fentanyl)

Other agents

Antibiotics (cephalosporins, penicillin, sulphonamides, vancomycin)

Aprotinin

Blood products (complete blood, erythrocyte suspension, fresh frozen plasma, thrombocyte suspension, cryoprecipitate, fibrin glue, gamma globulin)

Bone cement

Chymopapain

Corticosteroids

Cyclosporine

Products added to the agent (protectives)

Furosemide

Insulin

Mannitol

Non-steroid anti-inflammatory drugs

Protamine

Methylmethacrylate

Radiocontrast agents

Latex (natural rubber)

Streptokinase

Vascular graft material

Vitamin K

Colloidal volume expanders (dextrans, protein fractions, albumin, HES)

diates the inflammatory response to an antigen (5). A pseudoallergic reaction is clinically similar to an allergic reaction but (e.g. due to histamine secretion) lacks immunological features. Risk factors for pseudoallergic reactions are emotional stress, atopy, increased sensitivity to histamine and female gender (6). In anaesthetized patients cardiovascular collapse due to vasodilation and decreased venous return is life threatening.

Dewachter et al. (7) reported that neuromuscular blockers and antibiotics are the most common drugs that trigger perioperative anaphylaxis. Mertes et al. (8) reported that the most frequent allergic reactions in anaesthesia are against neuromuscular blockers and that this is followed by latex and an-

tibiotics. Unexplained intraoperative cardiovascular collapse is linked to anaphylaxis triggered by latex (natural rubber). In fact, it is reported that vascular graft materials also cause an intraoperative reaction (9). Allergic skin reactions against the preparations that involve sympathomimetic, which are used in the symptomatic treatment of the upper respiratory tract infection, are reported in the past (10). However, there are no reported cases similar to our own that involve intraoperative ephedrine use.

Barash et al. (9) determined that the risk of an allergic reaction against many drugs was 1%–3%, and 5% of adults in the U.S.A. had allergies to one or more drugs. However, Hung et al. (5) reported that even though more than a fourth of the surgical patients have allergies to one or more drug, only 50% of drug allergies are true drug allergies.

Allergic drug reactions are reactions mediated by specific antibodies or lymphocytes. These reactions are defined as the first of four hypersensitivity reactions. Type 1 reactions are an important cause of mortalities and morbidities during anaesthesia. Drug reactions are observed primarily in young and middle-aged adults and women. Furthermore, genetic factors are reported to be important. The estimated rate of the incidence of Type 1 hypersensitivity reactions among all anaesthesia cases is 1:1,250 and 1:10,000 (11). In most series, Type 1 reactions account for at least 60% of all hypersensitivity reactions observed in the perioperative period. According to French databases, it is estimated that IgE-mediated (Type 1) allergic reactions are observed 100.6 times in every million interventions (12). The estimated death rate is reported to be 3%–9% (13). Our patient's postoperative serum IgE level is 443 IU L⁻¹ (0–100 IU L⁻¹), and it is thought to be consistent with IgE-mediated Type 1 reaction because of the prevalent skin lesions that were observed 15 min after administering ephedrine.

Traditional *in vivo* or *in vitro* diagnostic tests required for the allergic reaction of most anaesthetic drugs are either not present or not viable. The most important diagnostic factor is the doctor's awareness that an observed adverse effect may be due to a drug (9). In the few minutes following the antigen delivery in the intradermal skin test, localized oedema forms due to histamine vasodilatation secreted from the mast cells in the skin and also an increase in vascular permeability. Fisher (14) presented a simple, safe and practical method that can be performed on most of the patients that experience an anaphylactic reaction in the perioperative period. Observing a drug-specific IgE antibody is considered as evidence that there will be a risk of anaphylaxis if the drug is administered (9). Sympathomimetic-specific IgE antibodies cannot be observed in our country. Furthermore, serum tryptase measurements are recommended in guidelines for diagnosing allergic reactions. An increase in serum tryptase only demonstrates mast cell degranulation. Even though it does not discriminate between allergic and non-allergic anaphylaxes, it is suggested

that the serum tryptase level is above 25 mc L⁻¹ in IgE-mediated reactions (8). The serum tryptase level must be measured within 1–6 h because its biological half-life is 2 h. Because the serum tryptase measurements are not performed in our hospital, we were unable to measure this parameter in this patient.

In the treatment of allergic reactions, inhibiting mediator production and secretion by cutting its contact with the responsible antigen and modulating the effects of free mediators are the goals to be reached (6). Furthermore, as recommended by all published articles, epinephrine and fluid therapy are the keystones in the treatment of hypersensitivity reactions during anaesthesia. During anaesthesia, the patient is monitored and intravenous access is established for administering rapid intravenous epinephrine, and being under the supervision of anaesthesiologist enables early diagnosis. However, the intensity of the reaction and the response to treatment can vary greatly; therefore, the administration of epinephrine must be shaped with the intensity of the symptoms (8). Fluid replacement, corticosteroids, antihistaminics and bronchodilators can be used as supports for treatment. In our case, we performed steroid therapy because of the presence of skin reactions and an inability to observe an anaphylaxis picture; we observed that lesions disappeared.

Conclusion

Ephedrine, which is widely used in anaesthesia practices, may cause a hypersensitivity reaction. Among the diagnostic methods of hypersensitivity reactions, apart from skin tests, serum tryptase, specific IgE measurement and basophil activation tests are used. Chemotherapy may change the response of the immune system (15). Therefore, it should not be overlooked that it can result in consequences ranging from skin lesions to anaphylaxis against the drugs that are used in the anaesthesia of patients that undergo chemotherapy.

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