
CASE REPORT

ANAPHYLAXIS DURING ANESTHESIA – ROLE OF SKIN PRICK TESTING IN DIAGNOSING MULTIPLE SENSITIVITIES

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ABSTRACT

The true incidence of anaphylactic reactions and their associated morbidity and mortality remain poorly defined. This is due to uncertainties in reporting accuracy and exhaustivity. A 23 years old male developed severe anaphylaxis under general anesthesia with cardiovascular collapse, bronchospasm and angio-edema. He was promptly managed with intravenous Adrenaline, Hydrocortisone, colloid solutions and Promethazine. The temporal relation suggested Atracurium to be the cause. However, skin prick test, performed 8 weeks later, showed a very strong (+++) positive test for Atracurium and mild sensitivity (+) with Suxamethonium. No sensitivity to Nalbuphine, Thiopentone or Pancuronium was noted. The relevant information was endorsed in patient's medical record sheet for his future exposure.

KEY WORDS: *Atracurium. Muscle relaxants. Anaphylaxis. Anesthetic adverse drug reactions.*

INTRODUCTION

Anesthesiology represents a pharmacologically unique practice of medicine, with patient's exposure to a large number of drugs and substances over a relatively short period of time. Any drug administered during the peri-operative period can produce potentially life-threatening immune-mediated anaphylaxis. Prick testing is a reliable method for picking up the culprit drug from the polypharmacy given during General Anesthesia (GA).

The true incidence of anaphylactic reactions and their associated morbidity and mortality remains poorly defined. This is due to uncertainties over reporting accuracy and exhaustivity. Most reports on the incidence of anaphylaxis originate in Australia, France, the United Kingdom and New Zealand and USA.¹⁻⁵ No such data has yet been compiled for Pakistan. Here we present a case of severe anaphylaxis with Atracurium that was later confirmed by the skin prick test.

CASE REPORT

A 23 years old male was referred to our department for pre-anesthetic assessment for a pyelolithotomy under GA. He was a non-smoker, non-addict without previous history of asthma, hypertension, or diabetes mellitus. There was a positive history of mild allergic skin rash with co-trimoxazole. Weight of the patient was 64 kgs and pre-operative blood parameters and chemistry were normal with no abnormality in Electrocardiograph (ECG) and chest X-rays.

On the day of surgery, in the operating room, he had a regular pre-induction pulse of 82 per minute and a blood pressure of 127/78 mmHg. Pre-induction, 5mg of intravenous Nalbuphine was given as an analgesic followed by

Thiopentone 375mg and Suxamethonium 100mg intravenously. With direct laryngoscopy, cuffed endotracheal tube of 8.0 mm was passed and no cardiovascular stress response was noted. Anesthesia was maintained with controlled ventilation (IPPV) using 1.0% Isoflurane + 40% Oxygen in nitrous oxide (N₂O). Patient was positioned right laterally and his tube re-checked for any mal-positioning due to movement. Once the effect of Suxamethonium waned off, he was given intravenous Atracurium 25 mg slowly. Within seconds the airway pressure increased above 40 cm H₂O and the next BP reading showed 58/30 mmHg. Keeping the diagnosis of anaphylaxis in mind, patient was immediately placed back in supine position and his legs were raised. Isoflurane and N₂O were turned off and IPPV with 100% oxygen was started. At the same time, Adrenaline 0.5 mg (1:1000) was given intramuscularly in an attempt to improve his circulatory status along with 500mg intravenous Hydrocortisone. Patient did not show any sign of improvement even after waiting for about 1 - 1½ minutes. 50 µg of 1:400'000 adrenaline was given intravenously that raised the BP to 84/45 mmHg and his bronchospasm was also relieved. Meanwhile 1000ml of colloidal solution were pushed intravenously. The blood pressure improved within next 7-8 minutes and the patient regained consciousness and was later shifted to intensive care unit (ICU) for observation. In the ICU, he had mild bronchospasm that was treated with salbutamol nebulization. His BP was 125/75 mmHg and pulse 118 per minute; while oxygen saturation (SpO₂) was 97% and ECG showed no signs of any abnormality. He developed peri-orbital and peri-oral puffiness that subsided with a single 25 mg dose of intravenous Promethazine and Hydrocortisone 100 mg intravenous 6 hourly for next 24 hours. After 48 hours, his vital signs were within normal limits; his chest examination revealed no signs of bronchospasm and angio-edema was completely gone.

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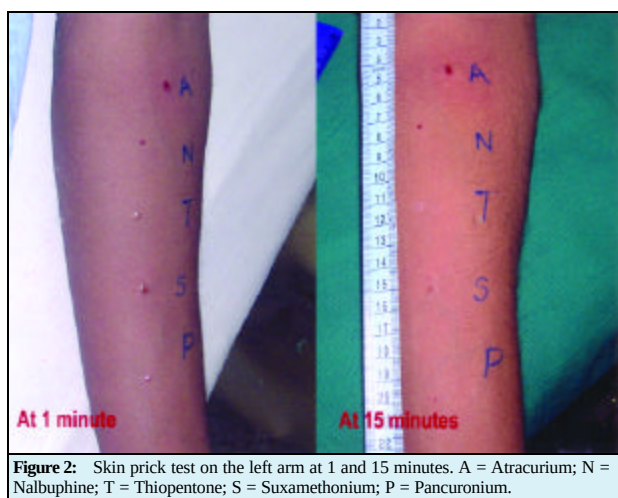
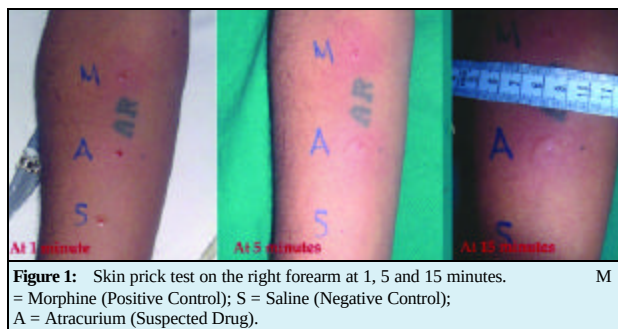
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He was discharged from the ICU to general ward and finally sent home. The follow-up after 4 weeks revealed no residual effects. Patient was counseled regarding his hypersensitivity and called again for follow-up after further 4 weeks. At this time, he was admitted as a day case in the high dependency unit and skin prick test was performed. The volar aspect of right forearm was pricked with Morphine, normal saline and Atracurium, where Morphine was used as a positive and saline as negative controls. To rule out the possibility of hypersensitivity due to other agents used at the time of anaphylaxis, the left forearm was pricked with Atracurium, Nalbuphine, Thiopentone, Suxamethonium and Pancuronium. Within one minute, the morphine site showed a weal of about 2mm with a surrounding flare while Atracurium site showed just flare and saline remained normal (Figure 1). After 5 minutes, the excessive fluid was blotted and a weal appeared around Atracurium and after 15 minutes, Atracurium showed a weal more than 10 mm while saline remained normal (Figure 1). On the left side, after 15 minutes, Atracurium showed a weal of about 10mm while Suxamethonium had a weal of around 3mm (Figure 2). Thiopentone showed an area of mild skin necrosis around 2-3 mm whereas Nalbuphine and Pancuronium showed no reaction (Figure 2). The skin prick test for other non-depolarizing muscle relaxants like Rocuronium and Vecuronium couldn't be performed due to non-availability of these drugs.

The patient was given a detailed follow-up card including the account of the anaphylactic reaction and result of the skin prick test. The relevant information was also endorsed in his medical record sheet.



DISCUSSION

The term "anesthetic adverse drug reactions" (AADR) is used for any drug effect that is not of therapeutic, diagnostic or prophylactic benefit to the patient. It has been classified as type A and B; whereas type 'B' being uncommon, not dose-related, more severe on re-exposure and having signs and symptoms of drug allergy. An anaphylactic reaction (anaphylaxis) is an exaggerated response to a substance to which an individual has become sensitized, in which Histamine; Serotonin and other vasoactive substances are released from basophils and mast cells in response to an IgE mediated reaction. This causes systemic symptoms which can include pruritus, erythema, flushing, urticaria, angio-odema, nausea, diarrhea, vomiting, laryngeal edema, bronchospasm, hypotension, cardiovascular collapse and death, anaphylactic reactions are type B adverse reactions.⁶

The introduction of Atracurium in the early 1980's⁷ revolutionized clinical practice by providing relaxation with little or no dependence on the kidney for elimination; faster onset; a more rapid, measurable recovery; and faster and more complete antagonism of residual block than in the case of the then available longer-lasting drugs like pancuronium.

Like all other Benzylisoquinolines, Atracurium also tends to cause release of histamine but it is considered to be less than Mivacurium and Metocurine by the electron-withdrawing effect of the carboxyl groups in the chains. This histamine release may be further reduced by slower injection (30-60 sec) or administration of smaller or divided doses of the relaxant.⁸

Neuromuscular blocking agents are responsible for 60-75% of serious AADR, more than half of which occur on first contact with the drug.⁶ However, the quaternary ammonium group found in muscle relaxants is widely present in other drugs, foods, cosmetics, and hair care products. This could explain why anaphylaxis to muscle relaxants is five to ten times more common in females. Benzylisoquinolones (Atracurium, Cis-atracurium, Mivacurium) and Suxamethonium are responsible for a greater number of AADR than aminosteroids (pancuronium, vecuronium, rocuronium).⁹ Cross-sensitivity between neuromuscular blocking drugs occur in upto 60% of patients.¹⁰

The clinical features of anaphylaxis are cardiovascular collapse (88%); bronchospasm (36%); angio-oedema-commonly of the face, eg. periorbital and perioral (24%); generalised oedema 7%; and cutaneous signs such as rash (13%), erythema (45%) and urticaria (8.5%).⁶ Though its safety has widely been debated, adrenaline remains the mainstay of treatment. Intramuscular route has shown higher plasma concentration compared to the subcutaneous route. The intravenous route is reserved for severe, non-responding cardiovascular collapse.¹¹ Slow administration (over 1 minute) of 50 µg of 1:10000 Adrenaline has been recommended by the Association of Anaesthetists of Great Britain and Ireland.⁶

Investigating an anaphylaxis occurring during anesthesia is difficult as multiple drugs are given at the same time and this polypharmacy makes it impossible to incriminate drug clinically. Moreover, more than one drug may be responsible. In our patient, the temporal events suggested Atracurium as the possible cause but on prick testing, Suxamethonium also gave a positive response.

Serum tryptase evaluation is sensitive only if the sample is taken within 30-120 minutes of anaphylaxis. Tryptase is the principal protein content of mast cell granules and is released, together with Histamine and other amines, in anaphylactic and anaphylactoid reactions. The basal plasma tryptase concentration is 0.8 - 1.5 ng/ml. The half life of the analyte is approximately 2.5 hours with maximum concentrations at approximately 1 hour. Thus, elevated concentrations can be detected for 12 - 14 hours even in the event of death. Plasma tryptase concentrations of >20 ng/ml may be seen after anaphylactic reactions. *In vitro*, tryptase is a stable protein. Plasma or serum may be stored at -20°C for long periods before laboratory analysis. Radioallergosorbent test (RAST) for antigen specific IgE antibodies are currently helpful only in confirming Suxamethonium and latex allergy and have a low sensitivity.

The diagnosis of AADR depends on Skin Prick Test (SPT) or Intradermal Testing (IDT). In proven muscle relaxant anaphylaxis, no laboratory test has been shown to compare for specificity and sensitivity. Skin testing will probably be diagnostic in anaphylaxis, but not in anaphylactoid reactions.⁹ Skin Prick Test (SPT) has been shown to be more sensitive than Intradermal Testing (IDT).¹² When a neuromuscular blocking drug is incriminated as the cause of a reaction, a Skin Prick Test (SPT) for other muscle relaxants is carried out to find a safe muscle relaxant for future anesthesia.¹³ Though a drug not producing a positive skin tests is considered safe but cases have been described in whom false negative skin tests led to a second severe anaphylactic reaction to another neuromuscular blocking drug.¹⁴

It is important to keep in mind that there is no support at present for routine screening of patients for specific drug antibodies before anesthesia. Similarly, there is no valid predictor of drug anaphylaxis. Claims that any form of screening will predict anaphylaxis are without foundation. A history of previous exposure is not necessary for an anaphylactic reaction. Routine testing is not indicated before a first or subsequent exposure to drugs used previously without incident. The use of test doses of intravenous drugs is not an appropriate method of testing for anaphylaxis. Anaphylaxis has resulted from very small doses.⁶ Prick testing after an anaphylactic reaction during GA is an important investigation as it may reveal and confirm the true combination of sensitivities among the multiple drugs given during anesthesia.

Management, once anaphylaxis has occurred, is of extreme importance in order to avoid fatalities. It is highly recommended that every anesthetist should know an 'anaphylaxis drill'. This should be agreed by departments of anesthesia as a standard operating procedure and be available immediately in all rooms where anesthetics are given. The anesthetists should rehearse a simulated

'anaphylaxis drill' at regular intervals including members of staff who would be called upon to assist. The standard procedure should include advice about investigation of the reaction and advice to be given to the patient.

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