

Negative association between previous allergy and intradermal tests for rocuronium and cisatracurium: what about additional tests?

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In a retrospective analysis published in the *Korean Journal of Anesthesiology* [1] concerning the relationship between intradermal tests for neuromuscular blocking agents in patients with history of allergy to various anesthetic agents, no association between allergy history and positive skin test was found.

This report raises the following important issues with respect to anaphylaxis during anesthesia, rocuronium-sugammadex complex, additive anaphylactic effect of anesthetic agents, and additional diagnostic tests in anesthesia:

1. Anaphylaxis during anesthesia constitutes a severe adverse event, rendering its identification and early treatment imperative, and partially explains its causality, pathophysiology, and mortality. The incidence of hypersensitivity reactions during anesthesia varies from 1 : 3,180 to 1 : 10,000 based on several prospective studies; however, this incidence might be underestimated [2]. Multiple causative factors have been implicated, including drugs, liquids, metal devices, materials, and procedures

during anesthesia. The incidence of perioperative reactions in Spain was 1 : 381, involving mild skin reactions (48%) and cases of anaphylaxis (52%). On rare occasions, skin rash might be absent, as seen with drug reactions in eosinophilia and Kounis syndrome.

2. Sugammadex induces selective reversal of aminosteroidal non-depolarizing neuromuscular blockers acting as muscle relaxants, such as rocuronium and vecuronium. Sugammadex is a modified gamma cyclodextrin with eight carboxyl thio ether groups at the sixth carbon positions, creating a cavity that can encapsulate the rocuronium molecule and further produce the rocuronium-sugammadex complex. The rocuronium-sugammadex complex can induce anaphylactic reactions, and is also suggested to induce Kounis syndrome [3]. Notably, during anesthesia, patients may be exposed to various agents such as propofol, remifentanyl, rocuronium, fentanyl, and sugammadex, all able to induce immunological changes.

3. In a recent report [4], a 46-year-old male patient developed tachycardia with ST elevation in the inferior leads and shock without cutaneous manifestations following propofol, remifentanyl, rocuronium, fentanyl, and sugammadex administration during anesthesia for laparoscopic surgery. Two years later, a similar anaphylactic reaction occurred, this time accompanied by generalized erythema, following perioperative administration of rocuronium and sugammadex. Serum histamine and tryptase levels were increased, whereas skin prick tests were negative for rocuronium and sugammadex but positive for histamine and rocuronium-sugammadex complex. The authors wondered how rocuronium-sugammadex complex formation could induce im-

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munological changes and allergic reactions. In another report [5] of anaphylactic shock induced by the rocuronium-sugammadex complex after cesarean section, intradermal skin tests were negative for sugammadex and positive for rocuronium. A follow-up skin prick test with pre-mixed rocuronium-sugammadex complex revealed a strong positive reaction, but a test with only rocuronium was negative.

4. It is well known that simultaneous exposure to several drugs, acting as antigens, can produce more extensive symptoms than mono-sensitization. Furthermore, immunoglobulin E (IgE) antibodies with different specificities can have an additive effect, and even small amounts of corresponding antigens can further trigger mediator release in cases of exposure.

5. Determination of the appropriate examinations to elucidate the pathogenesis and etiology of anaphylaxis in order to establish risk-reduction strategies seems to be of paramount importance. We suggest, therefore, that apart from intradermal skin tests, serum histamine, serum tryptase, eosinophils, and

total IgEs, the following tests would be of additional value [6]:

- a. Serum-specific IgE measurements for the suspected drug;
- b. Radioallergosorbent testing, enzyme-linked immunosorbent assay or fluoroenzyme immunoassay.
- c. Drug provocation test, which is a controlled challenge with the drug suspected of causing the hypersensitivity reaction; and
- d. Basophil activation test, which is a cytometry method of measurement of drug-induced activation of basophil markers CD63 or CD203c.

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