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Letter to the editor

Neostigmine induced anaphylaxis in the wake of surgery

Anaphylaxis during the course of an anaesthesia procedure remains a major problem. Anaphylaxis is a severe systemic reaction mediated by specific IgE antibodies; it has occurred in 1/13,000 anaesthesia procedures in France [1]. The latter number is approximate because not all anaphylactic reactions are referenced and not all patients reported as having had anaphylaxis subsequently have positive diagnostic exams after the event (only half of these patients are addressed to an allergist after the event [2]). The most frequently incriminated drugs are neuromuscular blocking drugs [3], but any of the drugs used in anaesthesia can provoke an anaphylactic reaction. Only one case of anaphylaxis due to neostigmine was published in 2000 in the English speaking literature [4]. Here, we report a second case.

A 69-year-old woman (150 cm, 75 kg) was admitted for incisional hernia 1 year after a rectal surgery. Past medical history consisted of: appendectomy (aged 11), clean urinary incontinence (aged 67), cataract (aged 67), and colonoscopy (aged 68). She also suffered from hypercholesterolemia, depression, chronic low back pain and osteoporosis. Her medications were Simvastatine, Citalopram and Fosavance. No past history of allergy was known.

One year before, she underwent rectal surgery for rectal cancer. The drugs used for anaesthesia were: propofol, remifentanil, atracurium, ketamine and desflurane. At the present time, for the incisional hernia, she received gabapentine 300 mg and alprazolam 0.25 mg 2 hours before surgery. She was pre-oxygenated and anaesthesia was induced with propofol (200 mg), sufentanil (15 μg) and ketamine (15 mg). The patient was intubated without incident. We performed a transabdominal plane blockade with 225 mg of naropeine. After calibration of monitoring, neuromuscular paralysis was induced 30 min later with atracurium (50 mg). Anaesthesia was maintained with nitrous oxide, oxygen and desflurane.

Surgery proceeded uneventfully and was complete within approximately 90 min. The response to train-of-four was 4 on 4, with a percentage of 11%. At this moment, blood pressure was 156/82, heart rate 68/min, fraction expired of CO_2 39 mmHg and oxygen saturation 99%. For reversal of the neuromuscular blockade, 1 mg of atropine and 2.5 mg of neostigmine were administered intravenously. Within 5 min, the patient developed a generalized rash, bronchospasm (oxygen saturation: 89% and fraction expired of CO_2 43 mmHg) and the blood pressure dropped (79/43) with a pulse of 100 b/min. Fifteen mg ephedrine was administered intravenously without success (blood pressure 75/48), followed by 8 mg of dexamethasone and finally 0.2 mg epinephrine. This injection achieved a blood pressure of 106/63, an oxygen saturation of 98%, 40 mmHg of fraction expired of CO_2 and a pulse of 94 b/min. The modifications of the various measures are presented on Figs. 1 and 2.

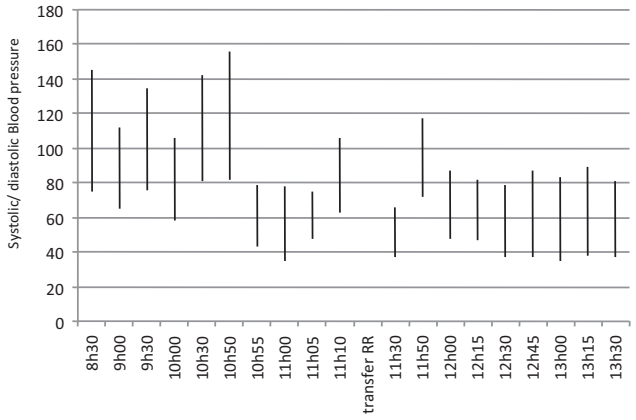

Fig. 1. Blood pressure variation during the operation and in the recovery room.

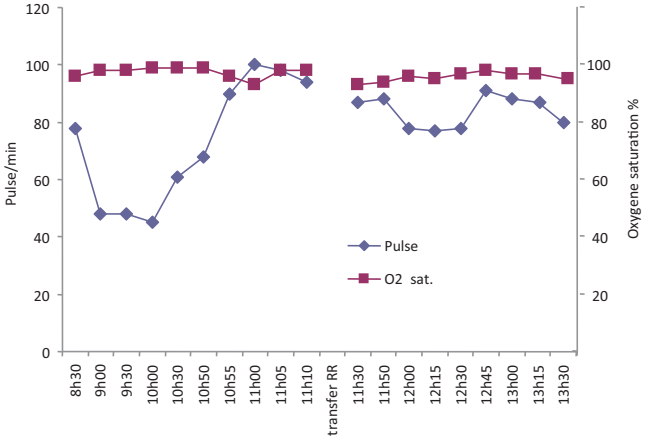

Fig. 2. Pulse and O_2 saturation variation during the operation and in the recovery room.

The patient was extubated in the operating room, but a blood pressure drop (66/37) and bronchospasm (93%) reoccurred in the postoperative recovery room. Epinephrine was again injected intravenously (0.1 mg twice) and via two sprays (1 mg then 5 mg) associated with 120 mg methylprednisolone. After 2 hours in the postoperative recovery room, blood pressure was 89/38, heart rate 87/min and oxygen saturation 97%. The patient was stabilized and was hospitalized in the surgical department. She was discharged 4 days later.

The tryptase and histamine levels 1 hour after the beginning of the reaction were at normal levels. The level of latex specific IgE was negative, contrary to quaternary ammonium IgE that was at 11.87% (normal < 2%).

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Allergy tests were performed 8 weeks after the reaction. The intradermic test was positive for neostigmine at a 1/100 dilution (a negative control was performed with a subject having never received neostigmine): 4 mm immediate wheal, 10 mm after 30 minutes with a 40 mm erythema. At the same time, a positive control had a 4 mm immediate wheal, 6 mm after 30 minutes with a 21 mm erythema. Skin tests for latex were negative. There was also a strong positive reaction to suxamethonium in skin prick tests and intradermic tests with a 1/1000 dilution (4 mm immediate wheal, 10 mm after 30 minutes with a 30 mm erythema), whereas the other neuromuscular blocking agents like atracurium were negative (4 mm immediate wheal, none after 30 minutes without erythema).

In the French and Anglo-Saxon literature published since 1980, we find more than 4500 cases of anaphylaxis per anaesthesia documented by an allergological test [5]. Neuromuscular blocking agents are the most frequently drug incriminated, representing 69.2% of the cases published, followed by latex (12.1%), preventive antibiotherapy (8%), hypnotics (3.7%), colloids (2.7%), and opioids (1.4%). Other substances were sometimes incriminated such as aprotinin, protamine and methylene blue [6,7]. In contrast, we could note the rarity of local anaesthetic allergies with only 29 indisputable cases published during the last 20 years [8]. Finally, no publication reported anaphylaxis per anaesthesia reactions implicating inhaled anaesthetic agents.

The classification of Gell and Coombs divides anaphylactic reactions into four types: types I (immediate, related to IgE), II (delayed, related to IgM and/or IgG), III (delayed related to IgG and/or IgM immune complexes) and IV (delayed hypersensitivity, related to cell-mediated immune responses). Between 1997 and 2004, 70% of anaphylactic reactions during anaesthesia were related to IgE, and 30% were not. Anaphylaxis was predominant in females (72.5%). Mortality was between 2 and 6% [9]. Skin tests with immediate readings were indicated for patients reporting reactions that evoked immediate hypersensitivity. Their diagnostic and predictive values are good for neuromuscular blocking drugs, latex, and certain antibiotics.

Skin tests consist of prick tests and of intradermic tests when prick tests are negative. The maximal concentrations not to be exceeded are well established for certain drugs and biological substances (like neuromuscular blocking drugs in particular). For others, it is advisable to systematically perform tests on control subjects in order to determine the appropriate concentration for the test [10].

Prick tests are carried out on the forearm or on the back. To limit false positive tests, skin prick tests have to be spaced out by 4 cm and avoid skin zones close to the elbows. The reading of pricks is made after 15 minutes and consists of the measure of the wheal in millimeters. "Positivity" and "negativity" of the test are retained by comparison to the measure of a control wheal performed at the same time.

Intradermic tests consist of the injection of a measurable quantity of the explored molecule put directly into the dermis. Such tests are particularly adapted to the clinical detection of the various mechanisms of hypersensitivity. The tests consist of the injection of 0.04 mL of the diluted drug on the external faces of arms or in the back. Usually, drug dilution is empirical and begins at a low dosage to limit the incurred risks. The maximal concentrations have to be considered in order to avoid false positives. If possible, a negative control is performed with the same solvent. Positive controls, which provoke an immediate wheal of about 5 mm, are also necessary with the exception of publication of recommended dilutions.

The readings are repeated at 30 minutes, 6 hours and 24 hours and in some cases at 72, 96 hours and a week after injection. For immediate readings, positivity is retained for a wheal superior or equal to 10 mm [11].

In our case, the patient was allergic to neostigmine. The chronology of the events during the surgery was not in favour of an atracurium-centered hypothesis or other drugs used for the induction of anaesthesia. In our department, we are used to omitting curare usage at induction when patients have a history of easy intubation. This practice was chosen to limit curare injection to a single dose for short-term planned interventions. This patient, who was multi-operated, would have been able to present a delayed allergy to latex. This was unlikely because of the timing, severity and speed of onset of the reaction. The negative latex IgE level and the negative skin test confirmed our clinical conclusions.

On the other hand, the discovery of a positive skin prick test and intradermic test for suxamethonium is probably completely fortuitous but explains the positive level of quaternary ammonium IgE observed in this patient. Neostigmine is an anticholinesterase drug used for the reversal of non-depolarizing neuromuscular blockades. Currently only one case of anaphylaxis related to neostigmine injection was reported in the English speaking literature. However, neostigmine was reported to be the potential cause of one of anaphylactic event in a series of 443 cases during anaesthesia [12]. In its information leaflet on the drug, the laboratory indicates some rare cases of hypersensibility. The frequency of anaphylactic reaction is considered as rare to exceptional ($< 1/10{,}000$).

This patient is not the first case of an anaphylactic reaction to neostigmine. But, because of the few publications on this subject, it seemed important to inform anaesthetists of the risks associated with this drug. In addition, the discovery of another allergy (suxamethonium) during allergic exams underlines the importance of such systematic testing after an episode of anaphylactic reaction.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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