

REVIEW

The risk of allergy related to general anaesthesia

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For a long time, the nature of reactions occurring within minutes after the intravenous induction of anaesthesia, has been misunderstood. Following the research done by Paton, the idea of non-specific histamine release has been considered, particularly concerning D-tubocurarine and muscle relaxants (MR) [1]. From 1970 onwards, the concept of shock related to non-specific histamine release towards numerous anaesthetic substances has been supported by considerable studies carried out by the German School with W. Lorenz and A. Doenicke [2].

The allergic risk of general anaesthesia has long been ignored. After the very first report of a case by Jerums in 1967 [3] of an anaphylaxis to suxamethonium, only about 20 shocks considered as of allergic nature were published until 1972. From then onwards, studies performed by Fisher, by the Nancy team, and by Vervloet emphasize the role of anaphylaxis [4–7]. The diagnosis method used by the three teams has proven the main part played by MR in post-induction shocks, and the high frequency of crossed anaphylaxis between the various MR [8].

Baldo's research has identified the epitopes of MR, which are quaternary ammonium ions, and definitively confirmed the existence of specific IgE [9]. Some time later, IgE antibodies towards thiopentone, morphine, codeine and other narcotics, and propofol were identified [10–12].

In 1976, a third mechanism linked to complement activation was described for alphaxalone (Althesin) by Watkins [13]. It is no longer thought to be involved in reactions with anaesthetic agents, but is involved in reactions to protamine, dextrans and vascular prostheses. Thus, the general term of anaphylactoid shock (AS) for clinical accidents can rightly be selected according to Watkins as long as the anaphylactic mechanism has not been clearly established by the immunoallergic tests [14].

For 20 years, studies in Australia, France and the U.K. have reported a great number of cases of post-induction AS, whereas this situation is hardly known in other countries [15]. Many specialized consultations in France have been set by the collaboration of anaesthesists and allergologists allowing epidemiological surveys. A recent

one has registered 1585 patients having experienced a shock during GA in 1990 and 1991. The incidence of anaphylactoid shocks is estimated to be 1:3500 anaesthetics, and anaphylaxis has been diagnosed in 52% of cases (1:6500 anaesthetics) [16].

In 1992, the substances responsible for anaphylaxis are primarily MR (70%) followed by latex (12.6%) [17–19]. The major part played by suxamethonium has been confirmed in the U.K. and U.S.A. [15]. Alcuronium is the main cause of anaphylactic shocks in Australia. These figures should be corrected for the relative amounts of each MR used in each country. In France, the increase of shocks involving vecuronium is linked to its increasing use. Hypnotics are rarely involved: propanidid (which is no longer used in France), thiopentone, and latterly propofol.

Latex is the main cause of shocks in children [17–20]. Children with spina bifida are particularly at risk [20,21]. In a retrospective study of 7386 surgical procedures in children, 11 cases of anaphylaxis were detected in 10 children, mostly suffering from spina bifida: an allergy to latex was found in eight cases [19]. Indeed the latter present a high incidence of sensitization [22]. Clinical symptoms only appear 30–60 min after the induction, and such reaction time does suggest allergy to latex.

The most frequent signs of anaesthesia induced anaphylactoid shocks involve the skin and mucous membranes, and include tachycardia and arterial hypotension. Bronchospasm was only found in 39% of cases. Cardiac dysrhythmias are not uncommon and may lead to haemodynamic failure. It would seem that, for atracurium, bradycardia, just like tachycardia, is also a sign of histamine release. Usually, using specific treatment, signs regress within 1 hr without any sequelae. However, in some cases, bronchospasm is particularly serious and difficult to treat, which may result in cerebral anoxia and its consequences. Previous treatment with β -blockers may explain the lack of tachycardia or bradycardia, as well as the resistance of the arterial hypotension to adrenaline [16].

The impressive number of shocks due to MR suffered by women is left unexplained. What is the high frequency of anaphylaxis to MR linked to? A major reason could be the divalence of molecules. Baldo's studies have shown

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that all MR possess two or three quaternary ammonium ions [9]. In the case of an ordinary drug, a small part of it binds to proteins and is able to bridge specific IgE. Most of it remains free, and can act as a monovalent hapten which is able to saturate antibody sites, and prevent bridging. This phenomenon described by De Weck as the in built inhibition represents the most efficient protection [23]. The divalent MR molecules are able to bridge specific IgE leading to a massive histamine release even if the level of specific IgE is low.

Other factors could play an aggravating role: MR are polycationic substances. The interaction with membranar receptors for polycations has been reported to potentiate IgE-dependent histamine release [24]. Suxamethonium, as a structural analog for acetylcholine, might also bind to membranar cholinergic receptors, leading to the activation of GMP and potentiating HR. The divalence of MR molecules accounts for the high sensitivity of skin tests whether by pricks or by intradermal tests, but equally for the frequency of crossreactivity. However, the length and flexibility of the chain between ammonium ions play a major role. Drugs with a rigid cyclic structure, such as pancuronium and vecuronium are less crossreactive than molecules with a flexible chain [25].

The cause of sensitivity to MR has not been found out. Only in 70% of cases, has an MR been previously used. A sensitization to cosmetics and other substances containing ammonium ions has been supposed. The high frequency of females with AS to MR invites us to suggest the existence of auto-immune specific IgE towards natural constituents containing quaternary ammonium ions: first of all, acetylcholine and different membranar phospholipids. Antibodies towards food lecithins from soy, egg, etc. could alternately be hypothesized.

Diagnosis has greatly improved in recent years. The diagnosis of anaphylactoid shock is supported by increased blood histamine and methylhistamine concentrations within the first hour of shock, and by the increased tryptase level, in the next 6 hr [26]. The first serum sample may also be screened for specific IgE. This process could be of legal medical value if the patient dies.

The post-operative testing takes place within 2 months. Prick-tests and intradermal tests have a specificity and sensitivity higher than 95% towards muscle relaxants, with a reproducibility of 88% several years later [8, 16, 25] (Fig. 1). The sensitivity is good for gelatins, about 50% for propofol, poor for barbiturates, opiates and benzodiazepines (Fig. 2).

The detection of specific IgE against alcuronium choline and latex may be carried out with commercial tests [27]. Different teams have been working to increase the sensitivity of detection. RIAs carried out with substances having a tertiary ammonium group, such as

triethylamine and trimethylamine, are relatively sensitive for detecting these antibodies [28]. Another technique uses the binding of a quaternary ammonium group (choline chloride) on sepharose by ether linkage. This is more sensitive than RIAs for alcuronium or choline on epoxy active sepharose: 88.9% *vs* 66.7% for the choline radio-allergosorbent test, and 40.7% for the alcuronium radio-allergosorbent test [29]. The greatest degree of inhibition obtained with this RIA is caused by the MR responsible for the shock. On the other hand, the smallest degree of inhibition is a result of MR when both skin tests and leucocyte histamine release tests were negative. The coupling procedure of thiopentone to sepharose may produce some drawbacks, due to the degradation of thiopentone into products with exposed ammonium groups. False positive RIA to thiopentone have been observed in some subjects allergic to MR [30].

The leucocyte histamine release may be used for every kind of drug: its sensitivity is 71% for MR, unknown for other substances [16]. Almost 100% of cases can be detected by the simultaneous use of skin tests, QAS-RIA and LRH [16,29].

A matter of present interest is certainly predictive tests. As IgE antibodies against MR remain present for a long time, and prick-tests are very sensitive with these drugs, pre-anaesthetic screening for anaphylaxis to MR may be carried out [31]. It is for the same reasons that predictive prick-tests for latex allergy are advised [32]. Every anaesthetist should practise predictive prick tests to MR. The technique is easy. The lack of any skin reaction is the rule and requires no particular skill. Similarly prick tests to latex are from now on systematically advised in children with spina bifida. We think that they should be applied to every atopic patient, and to all members of surgical and medical staff, all workers using latex gloves or manufacturing latex devices. Indeed, atopy and frequent exposure to latex considerably increase the risk of sensitization [20].

Another point of interest is the institution of wide prospective studies using prick tests, in order to know the incidence of sensitization in a random population, and to determine the exact importance of various factors of risk focused upon by retrospective studies concerning large series of AS: sex, atopy, previous general anaesthetics, frequent exposure to latex, systemic reactions to drugs (SDR). For example, the frequency of previous AS to MR and of SDR is surprisingly high in patients having experienced AS to propofol [12]. One might suppose that certain subjects could be prone to synthesize specific IgE towards chemicals, in parallel with atopic patients whose specific IgE are directed towards natural proteins. One might also hypothesize chemical peculiarities of IgE molecules in certain subjects, enabling non-specific inter-

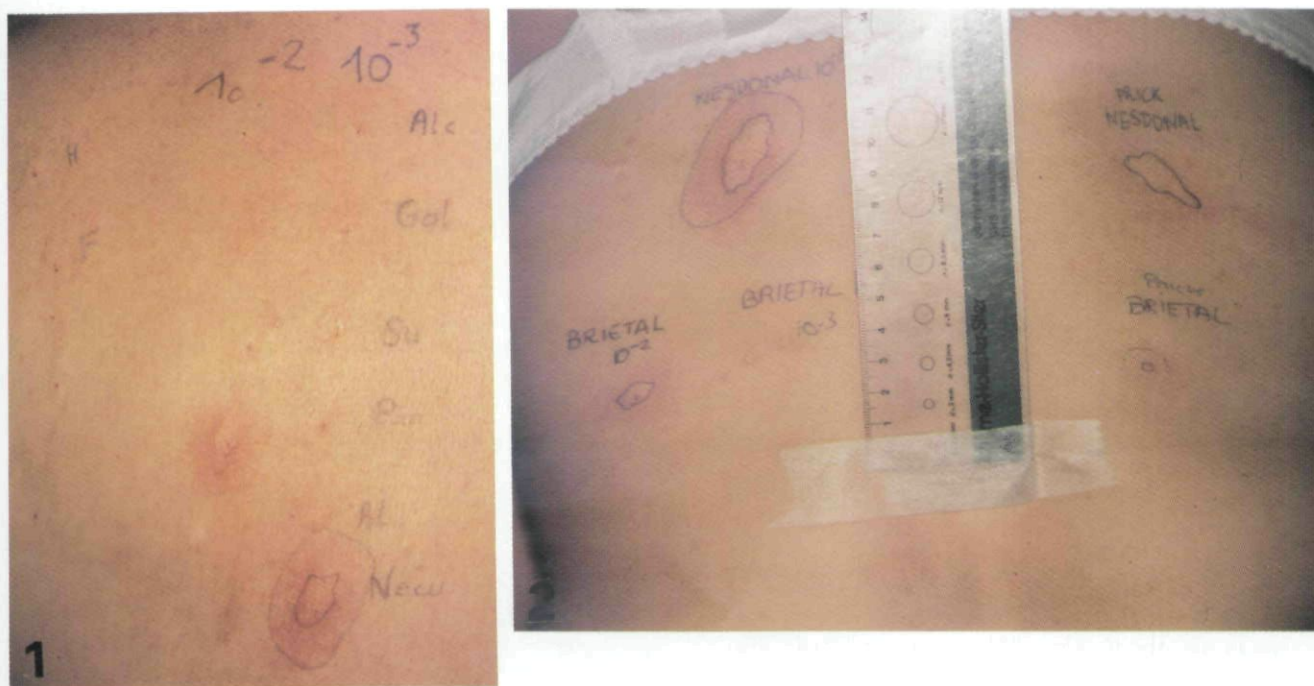


Fig. 1. Intradermal tests to diluted solutions of alcuronium (Alc), gallamine (Gal), suxamethonium (Su), pancuronium (Pan), atracurium (At) and vecuronium (Vecu). IDT is positive for vecuronium (10^{-3}) with a crossreactivity towards pancuronium (10^{-2}).

Fig. 2. Right, prick-tests to thiopentone (Nesclonal®) and methohexital (Brietal®). Left, intradermal tests to thiopentone (10^{-3}) and methohexital (10^{-2}). Tests in a patient with an anaphylaxis to thiopentone, confirmed by RIA and LHR. A crossreactivity with methohexital is demonstrated.

actions between these IgE and various kinds of drugs to occur [12].

In spite of unknown facts, the anaesthetist is now aware that occupational exposure to latex, food allergy to banana or avocado, may account for a hypersensitivity to latex [33]. Previous SDR could be a factor of risk of allergy to an anaesthetic drug. He must consider with the greatest care an asthma and an atopy. It has been shown that basophils from atopic or asthmatic patients are more prone to histamine release, with respect to intravenous anaesthetic drugs [34–36]. He is now able to choose an anaesthetic protocol offering little risk of histamine release or to use alternatives for a muscle relaxant. In any case, anaesthetic drugs should always be diluted and injected slowly. He can associate an anti- H_1 premedication to prevent the effects of non-specific histamine release. The use of an anti- H_2 is of no further value. No drug can prevent the triggering of an anaphylactic reaction. When there is arterial hypotension, the usual treatment of shock with vasoplegia must be started at once: quick fluid loading with cristalloid solutions, associated with adrenaline and a β -adrenergic agonist when there is combined bronchospasm. Surgery should

be stopped as soon as possible, so that anaesthesia may be discontinued as quickly as possible [37]. The patient should then be informed, and sent to a unit where an allergological diagnosis may be made within 6 weeks after shock.

The preliminary studies in our team indicate the possibility of prevention of anaphylaxis to MR by monovalent haptens [38]. Such research might be successfully developed by pharmaceutical companies, as has already been done for dextran.

Anaesthetics, muscle relaxants and other substances used during surgical procedures (latex, protamine, antibiotics) without any doubt induce anaphylactoid reactions. However, this knowledge should not be used to hide errors in anaesthetic techniques. It is essential, therefore, that allergologists should be clearly informed of such problems in order to achieve the best diagnosis. Thus, it will be possible to carry out epidemiological studies giving a precise idea on the importance of allergic risk in anaesthesia. Besides, the marketing of new drugs should from now on take into account the anaphylactoid risk and any incident or accident should be investigated by well trained teams. One of the most intriguing facts in

1992 is certainly that this pathology still remains unknown in certain economically and scientifically well developed countries.

References

- 1 Paton WDM. Histamine release by compounds of simple chemical structure. *Pharmacol Rev* 1957; 9:269-328.
- 2 Lorenz W, Doenicke A, Feifel G *et al*. Histamine release in man by propanidid, gelatin (Haemacel), Histalog, Pentagastrin and Insulin. *Naunyn Schmiedebergs Arch Pharmacol* 1970; 266:396-7.
- 3 Jerums G, Whittingham S, Wilson P. Anaphylaxis to suxamethonium. *Br J Anaesth* 1967; 39:73-6.
- 4 Fisher MM. Intradermal testing in the diagnosis of allergic reactions to intravenous drugs. *Anaesth Intensive Care* 1976; 4:97-104.
- 5 Belotti JJ. Choc anaphylactique provoqué par les curarisants. Thèse Med, Nancy 1973, 133 pp.
- 6 Sigiel M, Laxenaire MC, Moneret-Vautrin DA, Condi M, Jacob F, Picard JM. Trois cas de choc anaphylactique à la Célocurine. *Anesth Analg (Paris)* 1975; 32:447-62.
- 7 Vervloet D, Arnaud A, Vellieux P, Kaplanski, Charpin J. Accidents de type anaphylactique imputables aux myorelaxants au cours de l'anesthésie générale. *Presse Med* 1977; 6:725-8.
- 8 Birnbaum J, Vervloet D. Allergy to muscle relaxants. *Clin Rev Allergy* 1991; 9:281-93.
- 9 Baldo BA, Fisher MM. Substituted ammonium ions as allergenic determinants in drug allergy. *Nature* 1983; 306:262-4.
- 10 Baldo BA, Fisher MM, Harle DG. Allergy to thiopentone. *Clin Rev Allergy* 1991; 9:295-308.
- 11 Fisher MM, Harle DG, Baldo BA. Anaphylactoid reactions to narcotic analgesics. *Clin Rev Allergy* 1991; 9:309-18.
- 12 Laxenaire MC, Mata-Bermejo E, Moneret-Vautrin DA, Guéant JL. Life-threatening anaphylactoid reactions to propofol (Diprivan®). *Anesthesiology* 1992; 77:725-80.
- 13 Watkins J, Clark A, Appleyard TN, Padfield A. Immune-mediated reactions to Althesin (alphaxolone). *Br J Anaesth*, 1976; 48:881-6.
- 14 Watkins J, Udnoon S, Taussig PE. Mechanisms of adverse response to intravenous agents in man. In: *Adverse response to intravenous drugs*. London: Academic Press. New York: Grune and Stratton, 1978.
- 15 Mosciki RA, Sockin SM, Corsello BF, Ostro MG, Bloch KJ. Anaphylaxis during induction of general anesthesia. Subsequent evaluation and management. *J Allergy Clin Immunol* 1990; 86:325-32.
- 16 Laxenaire MC, Moneret-Vautrin DA. Le risque allergique en anesthésie-réanimation. Collection d'Anesthésiologie et de Réanimation. Edited by F Lemaire, JM Desmots. Paris: Ed Masson, 1990; 17:1-154.
- 17 Gold M, Schwartz JS, Braude BM, Dolovich J, Shandling B, Gilmour RF. Intraoperative anaphylaxis: an association with latex sensitivity. *J Allergy Clin Immunol* 1991; 87:662-6.
- 18 Warpinski JR, Folger J, Cohen M, Bush RK. Allergic reaction to latex: a risk factor for unsuspected anaphylaxis. *Allergy Proc* 1991; 12:95-102.
- 19 Setlock MA, Kelly KJ. Anaphylaxis on induction of anesthesia associated with latex allergy (Abstract). *Anesthesiology* 1991; 75(suppl):1043.
- 20 Slater JE. Allergic reactions to natural rubber. *Ann Allergy* 1992; 68:203-9.
- 21 Moneret-Vautrin DA, Laxenaire MC, Bavoux F. Allergic shock to latex and ethylene oxide during surgery for spina bifida. *Anesthesiology* 1990; 73:556-8.
- 22 Moneret-Vautrin DA, Mata E, Guéant JL, Turgeman D, Laxenaire MC. High risk of anaphylactic shock during surgery for spina bifida. *Lancet* 1990; 335:865-6.
- 23 De Weck AL. Drugs as allergens. *J Allergy Clin Immunol* 1986; 78:1047-50.
- 24 Tobin MC, Karns BK, Anselmino LM, Thomas LL. Potentialisation of human basophil histamine release by protamine: a new role for a polycation recognition site. *Mol Immunol* 1986; 23:245-53.
- 25 Leynadier F, Dry J. Anaphylaxis to muscle-relaxant drugs: study of cross-reactivity by skin tests. *Int Arch Allergy Appl Immunol* 1991; 94:349-53.
- 26 Laroche D, Vergnaud MC, Sillard B, Soufarapis H, Bricard H. Biochemical markers of anaphylactoid reactions to drugs. *Anesthesiology* 1991; 75:945-9.
- 27 Assem ESK. Anaphylactic anaesthetic reactions. The value of paper radioallergosorbent tests for IgE antibodies to muscle relaxants and thiopentone. *Anaesthesia* 1990; 45:1032-8.
- 28 Harle DG, Baldo BA, Fisher MM. Immunoassays employing substituted ammonium compounds other than neuromuscular blocking drugs in increase the detection of IgE antibodies to these drugs. *Mol Immunol* 1990; 27:1039-45.
- 29 Guéant JL, Mata E, Monin B *et al*. Evaluation of a new reactive solid phase for radioimmunoassay of serum specific IgE against muscle relaxant drugs. *Allergy* 1991; 46:452-8.
- 30 Baldo BA, Harle DG. Drug allergenic determinants. In: Baldo BA, ed. *Molecular approaches to the study of allergens*. Monogr Allergy Basel, Karger, 1990; 28:11-51.
- 31 Moneret-Vautrin DA, Laxenaire MC. Concept and limitations of predictive tests in anaesthesiology. *Ann Fr Anesth Reanim* 1993; 12:212-8.
- 32 Moneret-Vautrin DA, Laxenaire MC. Routine testing for latex allergy in patients with spina bifida. Reply. *Anesthesiology* 1991; 74:391-2.
- 33 M'Raihi ML, Charpin D, Pons A, Bongrand P, Vervloet D. Cross-reactivity between latex and banana. *J Allergy Clin Immunol* 1991; 87:129-30.
- 34 Marone G, Stellato C, Mastronardi P, Mazzarella B. Non-specific histamine-releasing properties of general anesthetic drugs. *Clin Rev Allergy* 1991; 9:269-80.
- 35 Laxenaire MC, Mata E, Guéant JL, Moneret-Vautrin DA, Haberer JP. Basophil histamine release in atopic patients after in vitro provocation with thiopental, diprivan® and chlormethiazole. *Acta Anaesthesiol Scand* 1991; 35:706-10.
- 36 Guldager H, Sondergaard I. Histamine release from baso-

- phil leukocytes in asthma patients after in vitro provocation with various neuromuscular blocking drugs and intravenous anaesthetic agents. *Acta Anaesthesiol Scand* 1987; 31:728-9.
- 37 Eon B, Paparian L, Gouin F. Management of anaphylactic and anaphylactoid reactions during anesthesia. *Clin Rev Allergy* 1991; 9:415-29.
- 38 Moneret-Vautrin DA, Motin J, Mata E *et al.* Preventing muscle relaxant anaphylaxis with monovalent haptens. A preliminary study. *Ann Fr Anesth Reanim* 1993; 12:190-202.

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