

Crossreactions to Muscle Relaxants in the Operating Room

D. A. Moneret-Vautrin

*Department of Clinical Immunology and Allergology, University Hospital,
Av. de Lattre de Tassigny, 54035 NANCY Cedex France*

Introduction

Anaphylactic shock caused by anesthetic substances is a well-recognized fact. The frequency in France, evaluated by successive epidemiologic studies, is estimated to be 1 in 3500 (1). Sixty percent of these occurrences are of proven immunologic origin, and are related to the presence of IgE antibodies (2); 59% of the cases of anaphylactic shock in the operating room (OR) are due to muscle relaxants (MR) (2). All of these molecules share quaternary ammonium radicals (QAR), and it is these radicals that have been shown to be the antigenic epitopes (3,4). Some of these agents have two QARs and are therefore divalent: suxamethonium, alcuronium, atracurium, mivacurium, pancuronium, D-tubocurarine, and rocuronium. Gallamine is trivalent, and vecuronium has one QAR and one tertiary ammonium group. It has been clearly demonstrated that the crossreactivity of IgE antibodies to these muscle relaxants is based on their structural similarity (5). Other drugs that contain a tertiary ammonium group (e.g., morphine and codeine) have been shown to crossreact with muscle relaxant-specific IgE antibodies (6). These data appear to justify the theoretical possibility of crossreactions between muscle relaxants being the cause of anaphylaxis in some cases, which has been shown to be true for the β -lactamines. This leads us to pose several questions: is there evidence that cases of anaphylaxis owing to crossreactions between these agents actually occur? What is the *in vitro* evidence for their crossreactivity? How does such evidence relate to the possibility of inducing histamine release from sensitized basophils and mast cells? Can the risk of anaphylaxis to these agents be predicted?

*Author to whom all correspondence and reprint requests should be addressed.

Crossed Anaphylaxis

Crossed anaphylaxis is said to have occurred when the recurrence of anaphylaxis in the OR is caused by a different MR than that which caused the first episode. Cases have been described in which decamethonium, then suxamethonium (7); pancuronium, then vecuronium (8); D-tubocurarine, then vecuronium (9); and suxamethonium, then pancuronium (personal case) were responsible for recurrent anaphylaxis in the OR. This indicates that one should logically be able to predict the occurrence of anaphylactic shock when a new curare derivative is commercialized, even before it has been administered to patients (10).

Likewise, when shock occurs during the induction of anesthesia that includes a curarizing agent, it is usually possible to determine retrospectively that the patient had been exposed previously to another of these agents. This leads to the hypothesis that immunologic hypersensitivity to agent A can be responsible for an anaphylactic reaction to agent B, that this phenomenon is the result of crossreacting antibodies induced by agent A, and that clinical reactions of this nature might occur frequently in the OR. It therefore becomes necessary to consider what means should be used to study this problem in order to be able to predict the risk of recurrence of anaphylactic shock owing to immunologic crossreactivity between muscle relaxants.

Crossreactivity In Vitro

Crossreactivity is the result of a biochemical event that results from the similarity of molecular structures, so that one molecule is likely to bind to an IgE antibody that is specific for a different molecule—one with a closely similar structure. Crossreactions of such antibodies with molecules containing tertiary or quaternary ammonium radicals can be observed regularly when the substances are fixed to a solid support; they are allowed to react with serum from patients who have had an anaphylactic reaction to any one of them. Binding to specific IgE can be demonstrated with respect to all the muscle relaxants—likewise with simple substances such as triethylamine and trimethylamine, and with certain drugs such as codeine and morphine (6–11). In addition, all these substances are capable of specifically inhibiting the binding of specific IgE to MR fixed to a solid support (2). The inhibition is more pronounced with divalent molecules than with monovalent molecules, such as triethylamine, *N*-methylnmorpholinium sulfate, citidylcholine, or ethamsylate (6,11,22). In comparing the results of inhibition tests with clinical data, the strongest inhibition is usually obtained with the substance responsible for the anaphylactic shock. This implies that the affinity of the anti-QAR IgE antibody for these drugs depends not only on the presence of these antigenic determinants, but also on adjacent

regions of the molecule (5). It has been hypothesized that a low degree of inhibition by a given MR should mean a lower risk of inducing a classic crossreaction with that substance (11). However, it was recently reported that rocuronium, a new muscle relaxant, was able to inhibit the binding of a different muscle relaxant—one that had caused a clinical reaction to the specific IgEs in affected patients sera. This inhibition was greater with rocuronium than it was to the original muscle relaxant itself, even when the skin test to rocuronium was negative (13). Therefore, one is led to conclude that tests based on inhibition of the binding of a substance containing QARs to specific IgEs by various MR will be of no help to clinicians wanting to evaluate the risk that a given MR will cause anaphylaxis in patients who already are sensitized.

Crossreactivity In Vivo

The mechanism of anaphylaxis involves the liberation of mediators from sensitized mast cells and basophils, histamine in particular. Cell activation leading to histamine release is secondary to bridging of specific IgEs on the surface of these cells by the corresponding antigenic molecules. This event can be examined either by in vitro leukocyte (basophil) histamine release or by skin tests that explore the release of histamine from cutaneous sensitized mast cells.

Bridging depends on the existence of antibody-combining sites (paratopes) specific for the QAR and, as demonstrated with sensitized basophils, it also depends on several other conditions. First, the antigen must be divalent (i.e., it must have at least two identical epitopes). One sees, for example, that when in vitro leukocyte histamine release is positive with the MR responsible for the anaphylaxis, it is negative with monovalent haptens such as ethamsylate and citidylcholine and with aliphatic chains that have only a single ammonium group (10,14). Because a tertiary nitrogen group can bind to anti-QAR IgE antibody sites, vecuronium, which has only a single NH_4^+ group, behaves like a divalent molecule (6). Second, bridging also depends on the distance between epitopes. By using ammonium salts with different chain lengths, it has been found that histamine release does not occur if the distance between two ammonium groups is less than 6.2 Å (14,15). Based on the results of skin tests with benzylpenicilloyl hapten derivatives in patients allergic to penicillin, Levine and Redmond showed that bridging occurs when the distance between epitopes is at least 4.5, and it is optimal when this distance is from 8 to 13 Å (16). With respect to the MR, the distance between the QARs is of the same order: 10.7 Å for D-tubocurarine and 11.1 Å for pancuronium (17). Furthermore, bridging depends on the overall structure of the molecule because, in 20 patients allergic to a given MR, leukocyte histamine release was observed in 11 cases but only once with a different curare derivative

(18). It appears, therefore that the antibody binding site corresponds in part to regions of the MR molecule that are adjacent to the QARs. A fourth condition for binding depends on the degree of flexibility of the molecule, allowing a variable distance to occur between the QARs. This has been studied mainly by means of skin tests. Crossreactivity between aliphatic molecules (gallamine, suxamethonium) is much more frequent than crossreactivity of aliphatic molecules with cyclic molecules such as the aminosteroids atracurium and mivacurium (15,19). Likewise, crossreaction among the three aminosteroids—pancuronium, vecuronium, and rocuronium—is very frequent (13). The requirement that these different conditions for bridging be present predicts, therefore, that on the one hand, crossreactivity that can produce histamine release from mast cells or basophils is less frequent than crossreactivity that can be demonstrated by binding to IgE antibody free in serum. On the other hand, there appear to be so many individual differences that crossreactivity is eminently variable from one patient to the next.

What is the frequency of crossreactivity that results in the liberation of histamine? Crossreactivity having been observed by means of skin tests since 1979 (20,21) has since been the object of systematic investigation, using standard concentrations of reagents in skin tests in patients who have experienced an anaphylactic reaction to an MR (19). Crossreactivity with one or several curare derivatives can be demonstrated by skin testing in 84% of patients tested; 10% of them will react to six different agents (19). In a recent premarketing study of rocuronium, for example, 16% of the patients tested reacted to rocuronium, plus five other curare derivatives: suxamethonium, gallamine, atracurium, pancuronium, and vecuronium; 80% reacted to at least one of these agents, whereas 4% had no crossreaction, responding only to the agent responsible for their anaphylactic reaction (13).

Can Anaphylaxis Caused by a Crossreaction be Prevented?

In a patient who has a serious anaphylactic reaction induced by a MR and who must be given one of these agents, prevention depends on two possible observations. The first is the demonstration of a negative intradermal skin test reaction with a different MR and the absence of histamine release when this agent is reacted in vitro with the patient's leukocytes (18,22,23). With such evidence, the subsequent administration by an anesthesiologist of the agent that was tested is perfectly well-tolerated by the patient in question. It can be seen that each new MR increases the possibilities for patients with this type of problem, given that a prior skin test carried out to ascertain that no crossreactivity will occur (13).

The second observation that can be made requires the use of a monovalent hapten that is able to saturate the antibody-binding sites before injection of the curarizing agent. Consequently, saturation of these sites prevents the possibility of bridging (25). One could imagine that such a mechanism of protection might exist for atracrium, since this molecule is rapidly hydrolyzed in vivo to two monovalent half molecules, limiting the ability of the native molecule to form bridges. It is indeed astonishing to note that the frequency of anaphylactic shock caused by vecuronium—it is responsible for 37% of curare-induced anaphylactic shock—corresponds to the frequency of its use; whereas, for a comparable volume of use, atracrium is responsible for only 15% of the cases of curare-induced anaphylaxis (2). Theoretically, several drugs contain a single QAR and could behave as monovalent haptens. Because of the lower affinity of a monovalent molecule compared to a divalent molecule, a molar excess of the monovalent hapten relative to a MR is necessary, which limits the choice of substances that could act in this way. It has been demonstrated that citidylcholine and ethamsylate combined with MR are able to inhibit in vitro leukocyte histamine release induced by MRs, when the test is performed on the blood obtained up to three hours after a 30-min iv infusion of one of these monovalent haptens. It has also been demonstrated that the combination of a monovalent hapten with a reactogenic MR inhibits the skin reactivity to the MR (22).

Conclusion

One can be assured that the diagnosis of an anaphylactic reaction to a curare derivative can be considered with much greater confidence than was the case just 15 yr ago. The diagnosis can now be made with well-established methods. Tests for crossreactivity leads to assume the safe use of one or more other MR in 84% of cases. The systematic search for the protective effect of the two monovalent haptens mentioned above is likely to provide, in certain cases, additional protection, assuring an even higher degree of security. It is logical to foresee that, in the future, all injections of MR in patients at risk will be preceded by premedication with an intravenous monovalent hapten, such as has been accomplished with dextran. This should be an attractive area of research for drug companies that produce and sell muscle relaxants.

References

1. Moneret-Vautrin, D. A. and Laxenaire M. C. (1993), *Clin. Exp. Allergy* **23**, 629–633.
2. Laxenaire, M. C. et al. (1996), *Ann. Fr. Anesth. Réa.* **15**, 1211–1218.
3. Baldo, B. A. and Fisher, M. M. (1983), *Mol. Immunol.* **20**, 1393–1400.
4. Baldo, B. A. and Fisher, M. M. (1983), *Nature* **306**, 262–264.

5. Harle, D. G., Baldo, B. A., and Fisher, M. M. (1985), *J. Immunol. Methods* **78**, 293–305.
6. Harle, D. G., Baldo, B. A., and Fisher, M. M. (1990), *Mol. Immunol.* **27**, 1039–1990.
7. Fisher, M. M. and Chan, M. C. Y. (1982), *Anaesth. Intens. Care* **10**, 153–155.
8. Conil, C., Bornet, J. L., Jean-Noel, M., Conil, J. M., and Brouchet, A. (1985), *Ann. Fr. Anesth. Ranim.* **4**, 241–243.
9. Farrell, A. M., Gowland, G., Mc Dowell, J. M., Simpson, K. H., and Watkins, J. (1988), *Anaesthesia* **43**, 207–209.
10. Moneret-Vautrin, D. A., Laxenaire, M. C., and Mouton, C. (1984), *Ann. Fr. Anesth. Ranim.* **3**, 467.
11. Guéant, J. L., Mata, E., Monin, B., Moneret-Vautrin, D. A., Kamel, L., Nicolas, J. P., and Laxenaire, M. C. (1991), *Allergy* **46**, 452–458.
12. Moneret-Vautrin, D. A., Kanny, G., Guant, J. L., Widmer, S., and Laxenaire, M. C. (1995), *Int. Arch. Allergy Immunol.* **107**, 172–175.
13. Laxenaire, M. C., Gastin, I., Moneret-Vautrin, D. A., Widmer, S., and Guéant, J. L. (1995), *Eur. J. Anaesth.* **12** (Suppl. 11), 55–64.
14. Didier, C. A., Cadot, D., and Bougrand, P. (1987), *J. Allergy Clin. Immunol.* **79**, 578–584.
15. Vervloet, D., Arnaud, A., Didier, A., Furstoss, M., and Charpin, D. (1985), in *Proceedings of the XII International Congress of Allergology and Clinical Immunology*, Washington, DC, pp. 69–74.
16. Levine, B. B. and Redmond, A. P. (1968), *J. Clin. Invest.* **47**, 555–567.
17. Iollenaere, J. P., Moereels, H., and Raymaekers, L. A. (1979), *Atlas of the Three-Dimensional Structure of Drugs*. Elsevier, Amsterdam, pp. 56–59.
18. Mata, E., Guéant, J. L., Moneret Vautrin, D., Bermejo, N., Gérard, N., Nicolas, P., and Laxenaire, M. C. (1992), *Allergy* **47**, 471–476.
19. Moneret-Vautrin, D. A., Guéant, J. L., Kamel, L., Laxenaire, M. C., El Kolty, S., and Nicolas, J. P. (1988), *J. Allergy Clin. Immunol.* **82**, 745–752.
20. Fisher, M. (1980), *Anaesth. Intens. Care* **8**, 211, 212.
21. Vervloet, D., Arnaud, A., Vellieux, P., Kaplanski, S., and Charpin, J. (1979), *J. Allergy Clin. Immunol.* **63**, 348–353.
22. Moneret-Vautrin, D. A., Mouton, C., and Widmer, S. (1985), *Ann. Fr. Anesth. Réa.* **4**, 186–191.
23. Moneret-Vautrin, D. A., Laxenaire, M. C., and Guéant, J. L. (1989), in *Progress in Allergy and Clinical Immunology*, Pichler, W. Y., Stadler, B. M., Dahinden, C. A., Pécoud, A. R., Frei, P., Schneider, C., and de Weck, A. L., eds., Hogrefe-Huber, Bern, pp. 450–454.
24. Occeili, G., Amedeo, J., Raucoules, M., Cassuto, J. P., and Grimaud, D. (1992), *Thérapie* **47**, 423–427.
25. de Weck, A. L. (1993), *Ann. Fr. Anesth. Réa.* **12**, 126–130.