Skin Reactions to Intradermal Neuromuscular Blocking Agent Injections

A Randomized Multicenter Trial in Healthy Volunteers

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Background: Numerous reports confirm the performance of intradermal tests for the diagnosis of anaphylaxis during anesthesia; however, there is controversy over their diagnostic value regarding the newer neuromuscular blocking agents (NMBAs).

Methods: One hundred eleven healthy volunteers were randomly assigned to receive intradermal injections of two NMBAs, at five increasing concentrations. A concentration was considered as a reactive concentration when it led to a positive reaction in more than 5% of the subjects. These concentrations were compared with the maximal concentration recommended for the diagnosis of sensitization to NMBAs.

Results: The maximal nonreactive concentrations were \(10^{-3}\) m for suxamethonium; \(10^{-4}\) m for pancuronium, vecuronium, rocuronium, and cisatracurium; and \(10^{-5}\) m for atracurium and mivacurium. Except for mivacurium, these nonreactive concentrations were close to the maximal concentrations used for the diagnosis of sensitization against NMBAs. For mivacurium, the nonreactive concentrations were higher than the maximal concentration currently recommended in clinical practice.

Conclusion: The aminosteroidal NMBAs pancuronium, vecuronium, and rocuronium and the benzylisoquinoline cisatracurium have a similar potency to induce a nonspecific skin reactivity. If the criteria for positivity and the maximal concentrations of the commercially available compounds recommended by French practice guidelines are used, the risk of false-positive results is limited, and only minor modifications of these recommendations could be suggested. A slight reduction in the maximal concentration used for rocuronium from 1:100 to 1:200 and an increase from 1:1,000 to 1:200 for mivacurium can be proposed.

Additional material related to this article can be found on the ANESTHESIOLOGY Web site. Go to http://www.anesthesiology.org, click on Enhancements Index, and then scroll down to find the appropriate article and link. Supplementary material can also be accessed on the Web by clicking on the “ArticlePlus” link either in the Table of Contents or at the top of the Abstract or HTML version of the article.

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intradermally on the forearm and the back to determine a concentration-response relation. These dose-response relations obtained in control subjects were compared with the maximal concentration recommended by the recent French guidelines for the diagnosis of sensitization to NMBAs by intradermal skin tests in subjects who have experienced a suspected anaphylactic reaction during general anesthesia.32-33


table 1. Product Characteristics

<table>
<thead>
<tr>
<th>NMBA</th>
<th>Presentation, mg/ml</th>
<th>Molecular Weight</th>
<th>Molar Concentration, M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rocuronium bromide</td>
<td>10</td>
<td>609.70 (salt)</td>
<td>1.640 × 10⁻²</td>
</tr>
<tr>
<td>Rapacuronium bromide</td>
<td>20</td>
<td>597.92 (active moiety)</td>
<td>3.345 × 10⁻²</td>
</tr>
<tr>
<td>Vecuronium bromide</td>
<td>2</td>
<td>637.74 (salt)</td>
<td>3.138 × 10⁻³</td>
</tr>
<tr>
<td>Pancuronium bromide</td>
<td>10</td>
<td>732.68 (salt)</td>
<td>2.730 × 10⁻³</td>
</tr>
<tr>
<td>Atracurium (di)besylate</td>
<td>2</td>
<td>1,243.49 (salt)</td>
<td>8.042 × 10⁻³</td>
</tr>
<tr>
<td>Cisatracurium (di)besylate</td>
<td>2</td>
<td>929.17 (active moiety)</td>
<td>2.152 × 10⁻³</td>
</tr>
<tr>
<td>Mivacurium (di)chloride</td>
<td>2</td>
<td>1,029.27 (active moiety)</td>
<td>1.943 × 10⁻³</td>
</tr>
<tr>
<td>Succinylcholine (di)chloride</td>
<td>20</td>
<td>361.31 (salt)</td>
<td>5.536 × 10⁻²</td>
</tr>
</tbody>
</table>

NMBA = neuromuscular blocking agent.
Assessments
The diameters of the initial wheals (within 1 min, hereinafter referred to as “the wheal at 1 min”) and of the wheals at 15 min were recorded as the mean value of the maximum and perpendicular measured diameter. The reaction to the negative control was considered as normal if there was no increase of the wheal at 15 min as compared with the wheal at 1 min and if there was no flare at 15 min. The reaction to the positive control was considered as normal if there was an increase of the wheal at 15 min as compared with the wheal at 1 min and if a flare was present at 15 min.

The results of the NMBA groups were interpreted 15 min after injection as a positive or nonpositive reaction according to the guidelines of the Société Française d’Anesthésie et de Réanimation (SFAR) and the Société Française d’Allergologie et d’Immunologie Clinique (SFAIC). The criteria for positivity are commonly used in the literature and have been proposed by several authors and an expert panel. A test result was used in the literature and have been proposed by several authors and an expert panel.32 These criteria for positivity are commonly used in the literature and have been proposed by several authors and an expert panel.32 A test result was considered as positive if the mean of the maximum and perpendicular diameter of the wheal at 15 min was at least 8 mm and was at least two times the diameter of the wheal at 1 min. All assessments were performed while the assessor was blinded to the NMBA injected.

Statistical Analysis
Demographic data were summarized by NMBA group. For the positive skin reactions at 15 min, frequency distributions were made for each NMBA, by concentration and location of injection. The size of the wheals at 15 min was summarized for the controls and for each NMBA, by concentration and location of injection. The percentage change in mean wheal diameter at 1 and 15 min after injection was compared statistically for each of the NMBA concentrations. All comparisons were performed with the paired Student t test after testing for normality. Statistical testing was two-sided, at a significance level of 0.05. Estimates, with corresponding two-sided 95% confidence intervals, were calculated using the t distribution.

Reactive Concentrations
During investigators’ meetings, consensus was reached about the concentrations to be considered as “reactive concentrations” able to induce a positive cutaneous response in healthy subjects. Concentrations leading to a positive skin test result (mean of the maximum and perpendicular diameter of the wheal at 15 min was at least 8 mm and was at least two times the diameter of the wheal at 1 min) in more than 5% of the subjects (i.e., 2 subjects or more tested positive per NMBA) were considered as reactive concentrations leading to an unacceptable risk of false-positive results for patients in clinical practice. These concentrations, initially expressed as molar dilutions of each NMBA, were converted into the corresponding ponderal dilution of commercially available compounds. The resulting concentrations considered as able to induce a nonspecific histamine release in healthy subjects were compared with the maximal concentration recommended to be used for intradermal skin testing of patients having presented a suspected anaphylactic reaction during anesthesia recommended in France by the SFAR and the SFAIC.32

Results
Demographic Data
The mean age of the volunteers was similar in all NMBA groups (table 2). Male/female distribution did not vary much in the different NMBA groups, except in the groups tested with rocuronium and vecuronium, where the sex distributions were 70%/30% and 30%/70%, respectively.

Skin Reactions
One of the two criteria for determining a reaction as being positive was a wheal size of at least 8 mm 15 min after injection. Results for the different controls and NMBA dilutions are presented separately for the reactions on the forearm and on the back in figures 1 and 2. Additional information regarding this is available on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org. The largest reactions to the highest concentrations were with mivacurium and then rapacuronium, followed by atracurium, cisatracurium, and rocuronium.

The mean wheal at 15 min was statistically significantly larger on the back than on the forearm for both control and NMBA dilutions (P < 0.01). At 10⁻¹⁰ m, a mean wheal exceeding 8 mm was observed only with mivacurium on both the forearm and the back. A mean wheal exceeding 8 mm was also observed with rapacuronium, but only on the back.

The other criterion that must be fulfilled for determining a reaction as being positive was an increase in wheal size of at least 8 mm 15 min after injection as compared with the wheal at 1 min and if there was no flare at 15 min. The reaction to the positive control was considered as normal if there was no increase of the wheal at 15 min as compared with the wheal at 1 min and if a flare was present at 15 min.

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Table 2. Summary of Demographic Data per NMBA

<table>
<thead>
<tr>
<th>NMBA</th>
<th>n</th>
<th>Mean (SD)</th>
<th>Range</th>
<th>Female n (%)</th>
<th>Male n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rocuronium</td>
<td>28</td>
<td>28 (7)</td>
<td>21–45</td>
<td>9 (32)</td>
<td>19 (68)</td>
</tr>
<tr>
<td>Rapacuronium</td>
<td>28</td>
<td>24 (5)</td>
<td>18–43</td>
<td>11 (39)</td>
<td>17 (61)</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>27</td>
<td>27 (7)</td>
<td>18–45</td>
<td>19 (70)</td>
<td>8 (30)</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>28</td>
<td>25 (5)</td>
<td>19–39</td>
<td>13 (48)</td>
<td>15 (52)</td>
</tr>
<tr>
<td>Atracurium</td>
<td>28</td>
<td>26 (6)</td>
<td>18–45</td>
<td>13 (46)</td>
<td>15 (54)</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>27</td>
<td>26 (4)</td>
<td>18–38</td>
<td>14 (52)</td>
<td>13 (48)</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>28</td>
<td>27 (7)</td>
<td>19–45</td>
<td>17 (61)</td>
<td>11 (39)</td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>28</td>
<td>26 (5)</td>
<td>20–42</td>
<td>15 (54)</td>
<td>13 (46)</td>
</tr>
</tbody>
</table>

Because per volunteer the skin reaction to two neuromuscular blocking agents (NMBA)s was tested, each volunteer is presented twice in the above table.
The diameter of at least 100% (i.e., twice the diameter of the initial wheal) at 15 min as compared with 1 min after injection. This is presented in figure 3 for the five different NMBA dilutions, together with the mean percentage change after injection of the negative control (phenol physiologic diluent). The wheal diameter was statistically significantly larger at 15 min for all NMBAs at the highest concentration (10⁻³ log molar dilution of vecuronium, pancuronium, atracurium, cisatracurium, and mivacurium, and 10⁻² log molar dilution of rocuronium, rapacuronium, and succinylcholine; P < 0.001), but the estimated difference was below 100% for vecuronium, pancuronium, and succinylcholine injected on the forearm and for pancuronium and succinylcholine injected on the back. When the next lower concentration (10⁻⁴ log molar dilution of vecuronium, pancuronium, atracurium, cisatracurium, and mivacurium, and 10⁻⁵ log molar dilution of rocuronium, rapacuronium, and succinylcholine) was injected, the wheal diameter was statistically significantly larger at 15 min for all NMBAs except for vecuronium, cisatracurium, and succinylcholine injected on the forearm. The estimated difference, however, was more than 100% for mivacurium only.

A skin test was considered as positive when both criteria detailed in the Materials and Methods section were fulfilled. The numbers of patients presenting with a reaction considered as positive for each of the concentrations studied are listed on table 3. In addition, we also reported the NMBA concentrations that induced a statistically significant percentage increase in wheal size at 15 min. To the three lowest NMBA concentrations, an occasional positive reaction (< 5% of cases) was seen either on the forearm or on the back, but not on both, as illustrated in table 3. To the next higher concentration (10⁻³ log molar dilution of vecuronium, pancuronium, atracurium, cisatracurium, and mivacurium, and 10⁻⁵ log molar dilution of rocuronium, rapacuronium, and succinylcholine), there were more positive reactions, particularly to rapacuronium, atracurium, and mivacurium. To the highest concentrations, there were positive...
reactions to all NMBAs in more than 5% of the volunteers. At this concentration, positive skin reactions were seen most frequently to rocuronium, rapacuronium, atracurium, cisatracurium, and mivacurium. The results of these tests were similar on the forearm and the back, except for vecuronium, for which no positive reaction was observed at 10^-4 M on the forearm, whereas two positive reactions were observed on the back.

In addition, Table 4 shows the molar dilutions and the corresponding ponderal dilutions of commercially available compounds found to induce a positive skin test result in 5% or more of healthy subjects and the maximal ponderal dilutions recommended to be used for the diagnosis of anaphylaxis in patients having presented an immediate hypersensitivity reaction during anesthesia according to the practice guidelines recommended in France by the SFAR and the SFAIC.

Safety

There were three cases of pruritus after injection of one of the control or test substances. In one subject, this occurred after injection of histamine on the back. Two subjects had pruritus after injection of the highest concentration of atracurium. In one subject, this occurred both on the forearm and on the back. All of these events were mild to moderate and were self-limiting.

Discussion

This is the first study in which all available NMBAs were tested intradermally in five increasing log molar concentrations, in healthy, anesthesia-naive volunteers. The interpretation of the results was based on the criteria recommended by the French Societies of Allergology and of Anesthesiology, which define a positive reaction as a wheal of at least 8 mm in diameter and doubling of the initial wheal, assuming that intradermal injection of

Table 3. Frequency Table of Positive Skin Reactions

<table>
<thead>
<tr>
<th>NMBA</th>
<th>Forearm, n (%)</th>
<th>Back, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n 10^-7</td>
<td>10^-6</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>Rapacuronium</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>Atracurium</td>
<td>28</td>
<td>1 (4)*</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>28</td>
<td>0</td>
</tr>
</tbody>
</table>

Because per volunteer the skin reaction to two neuromuscular blocking agents (NMBAs) was tested, each volunteer is presented twice in the above table.

* NMBA concentrations inducing a statistically significant percentage increase in wheal size at 15 min as compared with 1 min.
0.03 ml causes an initial wheal of 4 mm. These criteria have been defined according to the currently available literature and have been proposed by several authors and an expert panel.

Skin tests for immune-mediated hypersensitivity reactions are based on the observation of the local consequences of histamine release by sensitized cutaneous mast cells induced by the allergen. Cell activation results from bridging of specific immunoglobulin E (IgE) by at least divalent allergens. This could explain why skin tests for the diagnosis of IgE-dependent allergies to protein allergens, which usually contain numerous epitopes, are considered as more efficient than for the diagnosis of allergy to drugs whose epitopes are usually unknown and could be only monovalent. However, NMBAs carry two quaternary ammonium ions that are considered as the main epitopes involved in anaphylaxis to these drugs. This is probably why the performance of skin tests for the diagnosis of sensitization against NMBAs has been considered as excellent by most of the authors. Its excellent reproducibility as well as persistence of positivity with time has also been confirmed. Therefore, when a neuromuscular blocking drug is incriminated as the cause of a reaction, it has been shown that the negativity of intradermal tests to other NMBAs allows for a subsequent safe use of these negative drugs. Nevertheless, no diagnostic investigation can be considered as 100% reliable, and some cases of false-negative results of intradermal tests leading to re-exposure of patient to these NMBAs and renewed adverse reactions have been reported. However, these authors used a 10⁻³ dilution of the commercially available NMBAs to increase the specificity of their diagnostic procedure.

Intradermal tests to NMBAs can be performed either on the anterior aspect of the forearm or on the back, and there is no consensus at this time. Nevertheless, mast cell distribution varies significantly between trunk and distal body sites, and skin sensory innervation is not uniform. Some authors favor intradermal tests on the back because the skin is less exposed to and modified by physical agents. However, in a report regarding a prick test, the skin reactivity was less notable on the forearm than on the back for both histamine and allergens. At that time, such data were lacking for intradermal tests and NMBAs. In our series, the overall results of intradermal tests were similar on the forearm and the back, except for vecuronium, for which no positive reaction was observed to 10⁻⁴ on the forearm, whereas two positive reactions were observed on the back. However, the mean wheal at 15 min was statistically significantly larger on the back than on the forearm for both control and NMBAs dilutions.

In this study, interpretation was based on the SFAR criteria, which define a positive reaction as a wheal of at least 8 mm in diameter and doubling of the initial wheal, assuming that intradermal injection of 0.03 ml causes an initial wheal of 4 mm. Indeed, intradermal tests consist of an injection, at a 0.5- to 1-mm depth, of a volume between 0.02 and 0.05 ml to obtain an injection papula of 3–5 mm. However, in routine practice, it is difficult to fix a strict volume using an intradermal syringe. In our study, however, we found an initial wheal of 5 mm in most cases. This clearly emphasizes the importance of taking into account not only the final wheal diameter obtained 15 min after the injection, but also the ratio between this wheal and the initial papula diameter obtained at the time of injection to interpret intradermal test results. The measurement of the initial wheal and the requirement that the wheal is doubled are essential and should not be disregarded. Failure to fulfill these requirements would result in diminished specificity and hence a higher level of false-positive results.

One of the limitations of intradermal tests for the diagnosis of sensitization to NMBAs comes from their ability to induce histamine release from mast cells within the skin through non-IgE-mediated mechanisms. Thus, false-positive results may occur, depending on the maximal concentration used, but this concentration will vary from one compound to another, according to their respective nonspecific histamine-releasing properties. This difficulty has long been recognized in reports that demonstrated the limited predictive value of skin tests used as screening tests.

Two studies have been reported in which the skin reactions to log molar concentrations of intradermally injected NMBAs were evaluated in healthy volunteers, but these series only investigated cisatracurium and rocuronium. Our series is the only one investigating all NMBAs commercially available. Although positivity criteria in previous studies differ from the SFAR criteria, in all of these three studies, increasing NMA concentrations resulted in increasing wheal diameters. In previous reports, depending on the criteria used, positivity was observed at a 10⁻³ log molar concentration for rocuronium and at a 10⁻⁴ log molar concentration for cisatracurium. In our series, using the more restrictive SFAR criteria, a significant number of positive reactions (> 5% of reacting subjects) were observed only at a 10⁻³ log molar concentration for both rocuronium and cisatracurium. Therefore, histamine releasing properties within the skin seem to be similar for the most recent NMBAs (table 4).

Prick tests, which are performed by perforating the skin approximately 1 mm deep, through a drop of test solution with a needle or a special device, are also largely used to investigate skin reactivity to NMBAs.
However, these tests have been considered as less sensitive than intradermal tests by some authors. Their specificity has recently been questioned in a study investigating skin sensitivity to rocuronium and vecuronium in healthy volunteers. On the contrary, in another series investigating cisatracurium and rocuronium, no positive response was observed even with undiluted solution in healthy volunteers. Systematic investigation of the maximal reactive and nonreactive concentrations for all NMBAs in healthy volunteers would be interesting.

It is of special interest to establish a dose-related skin reaction curve in healthy subjects for all NMBAs used in standard clinical practice. However, one should be aware of the different conclusions that should be drawn from results obtained from healthy subjects, when designing a diagnosis procedure that will be used for patients. Indeed, the predictive value of a test depends not only on the performance of the test itself but also on the prevalence of the disease in the population tested.

If the test is used to screen patients for anesthetic allergy in the absence of any abnormal reaction, the prevalence of the disease is low and the predictive value of the test will be minimized. In such situations, a false-positive rate of 5% will be unacceptable. Therefore, skin tests are not recommended before anesthesia in apparently healthy subjects without any specific risk factors.

The situation for patients having presented a suspected immediate hypersensitivity reaction during anesthesia is completely different. In this population, the prevalence of the disease is high and the predictive value is maximized. That is why, in our series, a rate of less than 5% positive reaction in healthy subjects has been considered as an acceptable threshold to determine the maximal concentrations that should be used for the diagnosis of anaphylaxis in patients having presented an immediate hypersensitivity reaction during anesthesia.

One should also notice that there is no accepted standard diagnostic method, such as a challenge test, for the diagnosis of sensitization to NMBAs. Therefore, our aim will be to obtain the highest possible degree of clinical safety for each individual who is referred to an anesthesiology consultation. Therefore, a diagnosis of IgE-mediated immediate hypersensitivity will not be determined by a single test criterion, but by a weight of evidence that includes the description of the reaction and test results.

We can compare both reactive and nonreactive concentrations obtained in healthy subjects to the maximal concentration recommended in France for patients with a history of suspected anaphylaxis during anesthesia (table 4). In standard clinical practice, allergologists do not use molar dilution of NMBAs but a 10-fold dilution of the commercially available concentration of the drugs. Therefore, log molar concentrations have been converted into the corresponding 10-fold dilutions of commercial compounds.

It seems that the maximal dilutions recommended in the SFAR and SFAIC practice guidelines are close to the maximal concentrations considered as negative in healthy volunteers (suxamethonium 1:100 vs. 1:55, rocuronium 1:100 vs. 1:164, vecuronium 1:10 vs. 1:31, pancuronium 1:10 vs. 1:27, atracurium 1:100 vs. 1:804) and clearly below the concentrations considered as positive (table 4). However, concentrations recommended for aminosteroidal compounds are slightly higher than those showed as negative in healthy volunteers, whereas the reverse is true for benzylisoquinoline compounds. Therefore, if one wishes to obtain a similar picture for both compound families, a slight modification in the recommendation could be proposed, leading to the following maximal concentrations: rocuronium 1:200 (instead of 1:100), vecuronium 1:50 (instead of 1:10), pancuronium 1:50 (instead of 1:10), and mivacurium 1:200 (instead of 1:1,000). However, one should keep in mind that the current study refers to the histamine-releasing properties of NMBAs within the skin in healthy subjects, not the diagnostic predictive value in patients with a history of immediate hypersensitivity reaction during anesthesia. The risk of increased false-negative results when using overdiluted concentrations does exist, and the maximal concentrations used to perform intradermal tests must represent the best compromise between sensitivity and specificity of the diagnostic procedure.

Conclusion

All NMBAs are able to induce a nonspecific cutaneous wheal response, depending on the concentration used. Therefore, determination of the maximal nonreactive concentration for each drug within healthy subjects seems to be of importance to determine the maximal concentrations that should be used for the diagnosis of anaphylaxis. Our results show that the various commercially available aminosteroidal NMBAs pancuronium, vecuronium, and rocuronium and the benzylisoquinoline cisatracurium have a similar potency in producing positive cutaneous responses. If the criteria for positivity and the maximal concentrations recommended by current practice guidelines in France are used, the risk of false-positive results is limited, and only minor modifications of these recommendations should be proposed.

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