The Risk of Anaphylactic Reactions to Rocuronium in the United States Is Comparable to That of Vecuronium: An Analysis of Food and Drug Administration Reporting of Adverse Events

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Published reports from France and Norway suggest a frequent incidence of anaphylaxis to rocuronium and have raised concerns about its safety. We hypothesized that the Food and Drug Administration Adverse Event Reporting System could be used to confirm whether there has been an unusual incidence of anaphylactic events for rocuronium in the United States (U.S.) and whether the reporting patterns differ within and outside of the U.S. We queried the Food and Drug Administration Adverse Event Reporting System for 1999 through the first quarter of 2002 for all adverse events for the drugs rocuronium and vecuronium and then searched on the terms considered to represent possible anaphylaxis using proprietary software. We compared the frequency of these terms in data both for rocuronium and vecuronium. We then assessed the occurrence of reports of anaphylaxis-related terms in reports from the U.S. compared with reports originating outside of the U.S. For rocuronium, the database contained 311 reports, 166 domestic and 145 from foreign sources. Fifty percent of the foreign reports contained an anaphylaxis term versus 20% of the domestic reports (P < 0.001). For vecuronium, the comparable figures were 17% and 19% (not significant) and the total number of reports was 243. The incidence of the reports containing anaphylaxis terms did not differ between vecuronium and rocuronium in the U.S. but were significantly different for foreign reports (P < 0.001). These data confirm that U.S. anesthesia providers have not observed a significant difference in anaphylactic reactions between the two commonly used intermediate-acting muscle relaxants and suggest that frequency of reports of anaphylaxis may be significantly influenced by the area from which the reports originate.


A naphylactic or anaphylactoid reactions occur in 1 in 1000 to 20000 anesthetics (1–5). Neuromuscular blocking drugs (NMBDs), latex, and antibiotics have been the agents most commonly thought to cause anaphylactic reactions during anesthesia (6–8), and NMBDs contribute to over 60% of these (6,9). Interestingly, when specific immunoglobulin E was tested in 68 patients referred to an allergy center in Denmark for presumed intraoperative anaphylaxis, only one patient actually had antibodies to a NMBD (10).

Based on wholesale sales reports, rocuronium is the most commonly used intermediate-acting muscle relaxant in the United States (U.S.) (Table 1). Studies from France and Norway have suggested a frequent rate of anaphylaxis with rocuronium (8,11,12). When interpreting these results, the frequency of use of different NMBDs in clinical anesthesia (the denominator data) must be considered. This is estimated from a market share survey for the various NMBDs (6). Some authors suggest that the incidence of anaphylactic reactions to rocuronium merely reflects its market share.
including "anaphylactic reaction," "anaphylactic shock," terms considered to represent possible anaphylaxis, in-
and vecuronium, and then searched specifically on the
of foreign report is not recorded. The country of origin
tative, must be sent to the FDA. The data are reported
erature reports, direct contact, or via a sales represen-
Any serious adverse event not in the package labeling
reaches the MedWatch system
first quarter of 1999 through the first quarter of 2002.

We requested and received, under the Freedom of
Methods

Allergy testing provides one avenue for assessing
the incidence of adverse reactions to a medication, but
correlations with clinical adverse reactions can be
highly variable. One important source for drug safety
reporting is the Food and Drug Administration (FDA)
Adverse Event Reporting System (AERS). We hypoth-
esized that the AERS could be used to determine
whether there had been an unusually large number of
anaphylaxis or anaphylactoid reactions to rocuronium
and whether the reports from France and Norway
correspond with reports from the U.S. domestic market.

Results

Vercuronium and rocuronium together accounted for
approximately 80% of the U.S. market for intermediate-acting muscle relaxants during the years
studied (Table 1). The frequencies of U.S. and non-U.S.
Individual Safety Reports related to rocuronium are
shown in Table 2. Twenty percent (n = 33) of the U.S.
Individual Safety Reports for rocuronium were for an
event containing an anaphylaxis-related term com-
pared with 50% (n = 72) of the non-U.S. reports (Table
2, P < 0.01). The frequency of U.S. and non-U.S. Individual
Safety Reports for vecuronium did not differ in
the two markets and is shown in Table 3. Seventeen
percent (n = 20) of the reports for adverse reaction to
vecuronium were for anaphylaxis in the U.S. as com-
pared to 19% (n = 23) outside the U.S. (Table 3).

The frequency of reports of anaphylaxis to vecuro-
nium was similar to that for rocuronium in the U.S.
An incidence of 1 case of anaphylaxis per 1,008,000
vials of rocuronium sold in the U.S., and 1 case per
1,107,250 vials of vecuronium was noted. Reports of
anaphylaxis to vecuronium were more common than
that for vecuronium in the non-U.S. reports (P < 0.001).

Table 1. Market Share in the United States for the 4 Most Commonly Used Nondepolarizing Neuromuscular Blocking Drugs During the Period 1999–2002

<table>
<thead>
<tr>
<th></th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rocuronium</td>
<td>9280</td>
<td>7225</td>
<td>8288</td>
<td>8531</td>
</tr>
<tr>
<td>Vercuronium</td>
<td>4303</td>
<td>9618</td>
<td>3906</td>
<td>4318</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>2607</td>
<td>1424</td>
<td>2075</td>
<td>1640</td>
</tr>
<tr>
<td>Atracurium</td>
<td>852</td>
<td>844</td>
<td>1031</td>
<td>1074</td>
</tr>
</tbody>
</table>

The numbers shown are unit volume in 1000 vials. Data are for generic and brand name of NMBD together.
Table 2. Individual Safety Reports for Rocuronium (Generic and Brand Name)

<table>
<thead>
<tr>
<th>Preferred term (PT)</th>
<th>U.S. reports</th>
<th>Non-U.S. reports</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylactic reaction</td>
<td>1</td>
<td>11</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Anaphylactic shock</td>
<td>22</td>
<td>59</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Anaphylactoid reaction</td>
<td>10</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Total reports with “anaphylaxis” term</td>
<td>33</td>
<td>72</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total number of reports</td>
<td>166</td>
<td>145</td>
<td></td>
</tr>
</tbody>
</table>

NS = not significant.

Table 3. Individual Safety Reports for Vecuronium (Generic and Brand Name)

<table>
<thead>
<tr>
<th>Preferred term (PT)</th>
<th>U.S. reports</th>
<th>Non-U.S. reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylactic reaction</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Anaphylactic shock</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Anaphylactoid reaction</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Total reports with “anaphylaxis” term</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>Total number of reports</td>
<td>121</td>
<td>122</td>
</tr>
</tbody>
</table>

P = not significant.

Discussion

Our analysis of FDA AERS database found that either the pattern of reporting adverse drug reactions to vecuronium and rocuronium is different between U.S. and non-U.S. anesthetics or providers or there is an actual dramatic difference in the true incidence. Could the differences between the U.S. and non-U.S. reports be real and related to genetic predisposition to anaphylaxis to rocuronium and not to other steroid-based NMBDs? Though possible, this seems unlikely. Norway reports a frequent incidence of rocuronium reactions, whereas the Danish experience does not, despite the similar genotypes of Danes and Norwegians; this supports the concept that it is reporting that varies rather than incidence. The Danish experience with specific immunoglobulin E actually suggests the anaphylaxis frequency to any NMBD may be far less than previously reported (10).

Although early reports from Norway suggested a frequent incidence of anaphylaxis to rocuronium, an analysis by an expert panel of the Norwegian Medicines Agency reviewed the data and indicated that there was no evidence to support a more frequent rate of anaphylaxis with rocuronium than with other NMBDs (20). This contrasted with earlier Norwegian concerns about the drug that led the Norwegian Medicines Agency in 2000 to recommend use of rocuronium only if there was a clear positive indication. At the same time, a prospective monitoring plan was put in place to assess whether there was a true increased incidence—and the answer appears to be no. These data corroborate the U.S. experience and demonstrate the potential reporting bias of AERS.

It is also possible that the non-U.S. practitioners have observed a large number of anaphylactic reactions to rocuronium because they use rocuronium for tracheal intubation (for the larger dose and rapid administration) as opposed to the U.S. providers who may be using rocuronium to maintain intraoperative muscle relaxation (tracheal intubation with succinylcholine). Alternatively, more rapid tracheal intubation by providers in high-reporting areas could be causing bronchospasm during light anesthesia and subsequent hypotension as a result of decreased venous return. The lack of immunoglobulin E specific antibodies in the Garvey et al. study (10) certainly raises the possibility that some of the reports of apparent anaphylaxis actually represent a confluence of relatively common clinical findings (hypotension, vasodilation, and bronchospasm) that do not have an immunologic basis.

Drug reporting is inherently biased because people may be more likely to report things if they have heard that others have a similar problem. Spontaneous reports are rarely complete. Because the underlying population of patients exposed to the drug (the denominator data) is unknown, one cannot estimate the risk or incidence of an adverse reaction (21). Although the market share can be used to estimate the relative frequency of use of a NMBD in a year, the lack of data on wasted drug, expired drug, or drug inventory makes this estimate unreliable. The highest peak in the reporting of adverse reactions to a drug generally occurs in the second year after its approval, a phenomenon known as the Weber effect, (22) and the reporting peaks periodically. Although we did not analyze the reactions by the year of origin, it is conceivable that the peak in non-U.S. reports of adverse reactions to rocuronium may be a part of this phenomenon.

We used the three terms considered to represent possible anaphylaxis, including “anaphylactic reaction,” “anaphylactic shock,” and “anaphylactoid reaction.” To investigate the possibility that U.S. reporters used the terms “hypotension” or “bronchospasm” when non-U.S. reporters might have used an anaphylaxis term, we also performed searches on these two terms and found no difference between U.S. and non-U.S. reporters for either rocuronium or vecuronium.

Because there is no truly accurate denominator for our data, we compared the incidence of anaphylaxis reports to the total number of reports for a drug. This is similar to the technique used in the ASA Closed Claims Database studies, using the total number of reports as a denominator (23,24).

Because the MedWatch program is open to any observer, more than one drug name may be entered into the database for an identical chemical substance and be assigned a separate Individual Safety Report...
number. For example, a physician might make a Med-
Watch report and list rocuronium as a suspected drug
and describe the reaction observed as bronchospasm.
A nurse or patient relative might report the same
event listing the suspected drug as Zemuron and the
adverse event as wheezing. As a result, the database
must be searched for each commonly used drug name
and the results combined. This combined list may
include duplicate reports of the same event. The da-
tabase organization calls up each drug reaction PT,
which also lists the name entered in the search so that
a single report with one unique Individual Safety Re-
port number may appear more than once if a Med-
Watch Report lists, for example, anaphylaxis, hypo-
tension, or drug hypersensitivity. When this
duplication occurs all of the listings are grouped to-
gether and counted as one report rather than three.
We cannot be absolutely sure that we eliminated all
duplicates, but the cases identified were reviewed indi-
vidually, and cases that appeared to be identical
were removed.

The AERS has come under recent criticism because
of its failure to detect the increased risk of cardiovas-
cular incidents with cyclooxygenase-2 inhibitors (25).
For less common events, the “signal to noise” ratio
should be clearer and the AERS system is considered
critical for detecting such events during the post-
marketing period. The widely differing results in re-
ported anaphylaxis-like reactions is difficult to explain
and suggests the need for prospective monitoring of
outcomes to ascertain the safety of widely used drugs
while also making sure that relatively safe drugs are
not lost to the market.

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