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.

(Anesth Analg 2005;101:819–22)

Anaphylactic 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

Supported, in part, by the Office of Research and Development, Department of Veterans Affairs, Seattle, WA.

Disclosure: Michael Bishop and James O'Donnell receive unrestricted grant funding from Organon, Inc.

Presented, in part, at the annual meeting of the American College of Clinical Pharmacology, Phoenix, Arizona, October 3–5, 2004.

Accepted for publication March 29, 2005.

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DOI: 10.1213/01.ANE.0000175213.87556.D8

0003-2999/05

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

	1999	2000	2001	2002
Rocuronium	9280	7225	8288	8531
Vecuronium	4303	9618	3906	4318
Cisatracurium	2607	1424	2075	1640
Atracurium	852	844	1031	1074

The numbers shown are unit volume in 1000 vials. Data are for generic and brand name of NMBD together.

(clinical use), (13,14) but it remains uncertain whether these reports represent the experience of the larger anesthesiology community.

The diagnosis of anaphylaxis is confirmed by a variety of tests, including serum tryptase levels, skin testing (intradermal or prick test), or detection of specific immunoglobulin E by radioimmunoassay. Skin testing is often considered the standard procedure, (15,16) but the prevalence of sensitivity to NMBDs based on skin testing or presence of specific immunoglobulin E can be as frequent as 9.3% (17). A study concerning allergy testing by Garvey et al. (10) in Denmark does not suggest a more frequent incidence of sensitivity to rocuronium, and mast cell activation patterns do not differ significantly between rocuronium and vecuronium during skin testing (18). Skin testing is fraught with difficulties and can result in frequent false-positive results (16,19).

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 hypothesized 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 correlated with reports from the U.S. domestic market.

Methods

We requested and received, under the Freedom of Information Act, 3.25 yr of FDA AERS data from the first quarter of 1999 through the first quarter of 2002. Reports of adverse events reach the MedWatch system either directly from a doctor or via the manufacturer. Any serious adverse event not in the package labeling that is reported to the manufacturer, whether via literature reports, direct contact, or via a sales representative, must be sent to the FDA. The data are reported to MedWatch as U.S. or foreign. The country of origin of foreign report is not recorded.

We searched for all AERs for the drugs rocuronium and vecuronium, and then searched specifically on the terms considered to represent possible anaphylaxis, including "anaphylactic reaction," "anaphylactic shock," and "anaphylactoid reaction." Duplicate reports or duplicate use of the terms were eliminated. These terms are from the Medical Dictionary for Regulatory Activity (Northrop Grumman Mission Systems, Reston, VA) "Preferred Terms" (PT) for indexing adverse drug reactions. Searches were conducted using proprietary software created by Corel Corporation (Ottawa, Canada) for Pharmaconsultants, Inc. (Palatine, IL) to facilitate searching the FDA records. The proportion of all adverse events that were anaphylactic reactions were compared using a χ^2 test for rocuronium versus the second most commonly used intermediate-acting muscle relaxant, vecuronium. We then assessed the frequency of reports of anaphylaxis in the U.S. versus outside of the U.S., using χ^2 test or Fisher's exact test as appropriate.

The market share for the various NMBDs for the U.S. for the years 1999–2002 was requested from IMS Health (Fairfield, CT). The market share for the various NMBDs over the years was used to estimate the relative usage of the various intermediate-acting NMBDs in the U.S..

Results

Vecuronium 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 compared 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 compared to 19% ($n = 23$) outside the U.S. (Table 3).

The frequency of reports of anaphylaxis to vecuronium 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 rocuronium were more common than that for vecuronium in the non-U.S. reports ($P < 0.001$).

Table 2. Individual Safety Reports for Rocuronium (Generic and Brand Name)

Preferred term (PT)	U.S. reports	Non-U.S. reports	*P* Value
Anaphylactic reaction	1	11	<0.01
Anaphylactic shock	22	59	<0.01
Anaphylactoid reaction	10	2	NS
Total reports with "anaphylaxis" term	33	72	<0.01
Total number of reports	166	145	–

NS = not significant.

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

Preferred term (PT)	U.S. reports	Non-U.S. reports
Anaphylactic reaction	5	5
Anaphylactic shock	8	14
Anaphylactoid reaction	7	4
Total reports with "anaphylaxis" term	20	23
Total number of reports	121	122

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. anesthesia 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 can not 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 MedWatch 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 database 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 Report number may appear more than once if a MedWatch Report lists, for example, anaphylaxis, hypotension, or drug hypersensitivity. When this duplication occurs all of the listings are grouped together and counted as one report rather than three. We cannot be absolutely sure that we eliminated all duplicates, but the cases identified were reviewed individually, 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 cardiovascular 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 postmarketing period. The widely differing results in reported 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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