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Rocuronium: high risk for anaphylaxis?

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Patients suspected of anaphylaxis during anaesthesia have been referred to the senior author's clinic since 1974 for investigation. Since release of rocuronium on to the worldwide market, concern has been expressed about its propensity to cause anaphylaxis. We identified 24 patients who met clinical and laboratory (intradermal, mast cell tryptase and morphine radioimmunoassay) criteria for anaphylaxis to rocuronium. The incidence of rocuronium allergy in New South Wales, Australia has risen in parallel with sales, while there has been an associated fall in reactions to other neuromuscular blocking drugs. Data from intradermal testing suggested that rocuronium is intermediate in its propensity to cause allergy in known relaxant reactors compared with low-risk agents (e.g. pancuronium, vecuronium) and higher-risk agents (e.g. alcuronium, succinylcholine).

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Anaphylaxis during anaesthesia is a significant contributor to morbidity and mortality during the perioperative period. It has been estimated to be of the order of 1:980 to 1:20 000 by the Boston Collaborative Drug Surveillance Survey,[1] but published international figures vary within this range.

Rare adverse effects of drugs, such as anaphylaxis, do not usually become apparent until the drug is established in clinical usage. It may be misrepresented (higher or lower) by small numbers of reactors until the drug has been observed extensively after release on to the market. In addition, estimation of prevalence requires knowledge of both numbers of reactors and total numbers of doses given in the population. Estimation of the number of reactors is hampered by difficulty in definitive diagnosis and referral of reactors, while the number of doses of a drug given is at best an estimate from drug sales data.

Another method of assessing the relative likelihood of a new neuromuscular blocking drug (NMBD) to cause anaphylaxis is to determine cutaneous sensitivity in a population of patients known to be relaxant reactors.[2]

Rocuronium was introduced in Australia in 1996. It is a monoquaternary NMBD that shares its aminosteroid structure with pancuronium and vecuronium, which are less likely to produce anaphylaxis than other NMBDs.[2 3] In addition, rocuronium causes less direct histamine release than the benzylisoquinolinium-derived NMBDs, such as atracurium and mivacurium.[4] An early French study[5] of cutaneous sensitivity in NMBD reactors suggested that rocuronium may be more likely to cause anaphylaxis than the other aminosteroid drugs. Subsequently, three anaphylactic reactions were reported in 2000 uses in the UK.[6] Concern has been expressed in Australia regarding an apparently high number of anaphylactic reactions to rocuronium.

Methods and patient selection

Patients were referred to the senior author's clinic after having being suspected of anaphylaxis during anaesthesia.

Criteria for anaphylaxis

Patients were suspected to have had an anaphylactic event when the condition was life-threatening and involved two or more of the classic signs of anaphylaxis: hypotension, bronchospasm, dermatological signs (erythema, rash or urticaria) and angio-oedema. The diagnosis was regarded as confirmed if results of intradermal testing, radioimmunoassay (RIA) or mast cell tryptase (MCT) testing were positive.[7] Mast cell tryptase is the single most useful test to confirm an anaphylactic event,[8–10] whereas the most valuable test to determine the identity of the responsible agent is intradermal testing. RIA testing can also help to identify a responsible agent, especially when intradermal tests are negative.[8] Patients whose reactions were severe and clinically likely to be anaphylaxis but whose reactions

involved a single organ system were admitted to the database only if there was supporting laboratory evidence.

Testing

Intradermal testing,[8 11] MCT testing[12] and morphine RIA testing for IgE antibodies to NMBDs[13] were performed according to published protocols.

Intradermal testing was performed 4–6 weeks after the reaction using appropriate dilutions of drugs that have been found to be unlikely to produce local false-positive reactions as a result of direct histamine release. Concentrations of the drugs used are presented in Table 1. The skin was lightly cleaned with isopropyl alcohol, the skin beneath the test site also being cleaned with isopropyl alcohol to exclude sensitivity to the skin preparation. A syringe with the drug dilution was attached to a 25 gauge needle, which was introduced through the skin at an angle of 10° with the bevel uppermost, until the lumen was covered. Sufficient solution was then injected to raise a 1–2 mm weal (0.01–0.02 ml). Normal saline was used as a control to exclude dermatographism, while 0.001% morphine sulphate in normal saline, which gives a weal and flare in all patients with normal cutaneous responsiveness, was used to assess whether a negative test was a result of impaired responsiveness. The intradermal test was recorded as positive when a weal of more than 0.8 cm arose within 10 min and persisted for 30 min or longer.

There was one departure from the intradermal testing protocol. This patient had an anaphylactic reaction to vecuronium with a positive skin test to vecuronium and a negative skin test to rocuronium. This patient had anaphylaxis to rocuronium at a subsequent anaesthetic and was tested a second time on the back rather than the forearm. A 1:1000 dilution of rocuronium 10 mg ml^{-1} in saline was used as the initial dilution. This patient has been described in detail previously.[13]

MCT assays were performed using commercially available kits (Pharmacia, Sydney, Australia). Each patient had blood taken by the referring anaesthetist and the serum was forwarded to our laboratory for testing. Because tryptase levels begin to rise within 30 min of an anaphylactic

Table 1 Drug dilutions used for intradermal testing

Drug	Standard dilution (1:1)	Dilution for testing
Rocuronium	10 mg ml^{-1}	1:1000
Pancuronium	2 mg ml^{-1}	1:1000
Vecuronium	4 mg ml^{-1}	1:1000
Atracurium	10 mg ml^{-1}	1:10 000
Cisatracurium	2 mg ml^{-1}	1:1000
Alcuronium	5 mg ml^{-1}	1:1000
Mivacurium	2 mg ml^{-1}	1:1000
Succinylcholine	50 mg ml^{-1}	1:1000
Alcuronium	5 mg ml^{-1}	1:1000
Gallamine	40 mg ml^{-1}	1:1000
Decamethonium	2 mg ml^{-1}	1:1000
Tubocurarine	10 mg ml^{-1}	1:10 000

Table 2 Diagnostic criteria and clinical features of 24 patients with anaphylaxis to rocuronium. CVS=cardiovascular system; Pos=positive; Neg=negative; ND=not done; Y=yes; N=no; U=unknown; M=male; F=female

Patient	Sex	Features						Past	Testing		
		CVS collapse	Pulmonary oedema	Bronchospasm	Angio-oedema	Rash	Flushing	exposure	Peak MCT	RIA	Intradermal
1	F	Y	N	N	N	N	Y	N	Pos	Pos	Pos
2	F	Y	N	Y	N	N	N	N	ND	Pos	Pos
3	F	Y	N	Y	N	N	N	N	Pos	Pos	Pos
4	F	Y	Y	Y	N	Y	N	U	Pos	Pos	ND
5	M	Y	N	N	N	N	Y	N	Pos	Pos	Pos
6	F	Y	N	N	N	Y	Y	N	Pos	Pos	Pos
7	F	N	N	Y	N	N	Y	N	Neg	Pos	Neg
8	M	Y	N	N	N	Y	N	U	Neg	Neg	Pos
9	F	Y	N	Y	N	N	Y	N	Pos	Pos	Pos
10	F	Y	N	Y	N	N	N	N	Pos	Pos	Pos
11	F	Y	N	Y	N	N	Y	N	ND	Pos	Pos
12	F	Y	N	N	N	N	N	Y	Neg	Neg	Pos
13	F	Y	N	N	N	N	N	N	Pos	Pos	Pos
14	M	Y	N	N	Y	Y	N	N	Pos	Pos	Pos
15	M	Y	N	N	N	N	N	N	Pos	Pos	Pos
16	F	Y	N	Y	N	N	Y	N	Pos	Pos	Pos
17	F	Y	N	N	Y	Y	N	N	Pos	Pos	Pos
18	F	Y	N	N	Y	N	Y	N	Pos	Pos	Pos
19	F	Y	N	Y	Y	Y	N	Y	Pos	Pos	Pos
20	F	Y	N	N	N	N	Y	N	Pos	Pos	Pos
21	F	Y	N	Y	N	N	N	N	Pos	Pos	Pos
22	M	N	N	Y	N	N	Y	N	ND	ND	Pos
23	F	Y	N	N	N	N	N	N	Pos	Pos	Pos
24	F	Y	Y	Y	N	N	Y	N	Pos	Pos	Pos

reaction and remain high for approximately 6 h, blood samples were taken between half an hour and 6 h after the reaction. In six patients with either a negative MCT or no MCT result, a convincing clinical picture of anaphylaxis together with a positive morphine RIA or intradermal test was considered sufficient to establish the diagnosis. It has been observed that tryptase assays can be elevated by causes other than anaphylaxis, such as vancomycin administration. In our study, however, all patients with a positive MCT also had corroborating clinical and laboratory evidence of anaphylaxis to rocuronium.

Morphine RIA testing was performed using morphine sulphate coupled to Sepharose to detect anti-quaternary ammonium IgE in serum. Morphine RIA is the most appropriate *in vitro* test for the detection of IgE antibodies that cross-react with substituted ammonium ions and hence for the *in vitro* diagnosis of NMBD-induced anaphylaxis.[8]

Results

In the period from 1997 to 1999 inclusive, we investigated 54 patients suspected to have had anaphylactic reactions to rocuronium and, of these, 24 fulfilled our criteria for anaphylaxis and admission to the database. Over many years, 386 other patients have been entered into the database after demonstrated anaphylaxis to other NMBDs, taking the total number of NMBD reactors to 410. The details of these 24 patients and the criteria for diagnosis are shown in Table 2. The clinical signs recorded resulted from detailed written descriptions of the suspected anaphylactic event by the anaesthetist attending the patient during the incident. Over the same period there were 10 other patients in New South Wales who fulfilled diagnostic criteria for anaphylaxis to rocuronium but were not admitted to the database as they were investigated by others. Only two of the 24 patients included were known to have received rocuronium previously.

Figure 1 shows the number of anaphylactic reactions attributed clinically and by testing to allergy to rocuronium by year from patients referred from within New South Wales. Anaphylaxis to rocuronium in New South Wales was first reported in 1997, the year after its release, and since then there has been an increase in the number of reports annually. This increase in reactions closely parallels the increase in usage. Equally, the observed reduction in the frequency of anaphylaxis caused by other NMBDs during this period is in keeping with the steady fall in market share of the other commonly used NMBDs.

Table 3 shows the incidence of skin test cross-reactivity to rocuronium in patients who reacted to other NMBDs. Figure 2 shows the relative propensity of each NMBD to cause positive intradermal tests in a population of known NMBD reactors. Table 4 gives the incidence of positive skin tests for other NMBDs in patients who reacted to rocuronium. Three patients showed cutaneous sensitivity to pancuronium, vecuronium and rocuronium but not to any other NMBD.

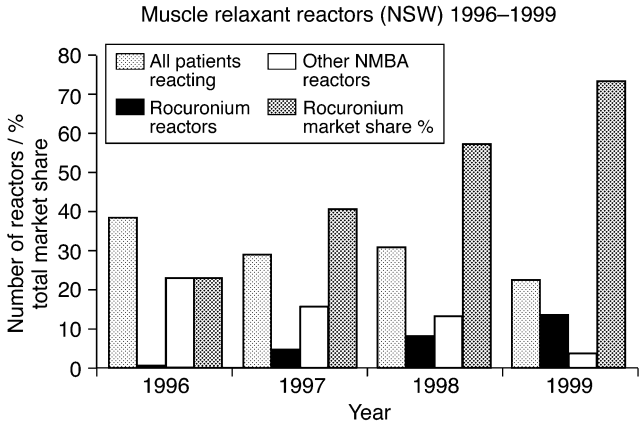

Fig 1 Anaphylaxis by year for rocuronium and other neuromuscular blocking drugs (as referred to senior author's clinic), and rocuronium market share in New South Wales, 1996–1999.

Table 3 Incidence of cross-reactivity of rocuronium with other NMBDs as determined by intradermal testing with rocuronium in patients allergic to another NMBD

Patients known to be allergic to	Number tested	Positive to rocuronium
Succinylcholine	44	10
Vecuronium	10	4
Atracurium/cisatracurium	13	0
Pancuronium	2	1
Alcuronium	1	1
Mivacurium	1	0

Discussion

As the incidence of anaphylactic reactions during anaesthesia is low, determining the risk of anaphylaxis to individual NMBDS would require a study of over 30 million patients.[2] Furthermore, for an individual drug, the estimated incidence of anaphylactic reactions will depend on the criteria for anaphylaxis used and the method and accuracy of determining drug usage and the number of reactions.

Fundamentally, the incidence of anaphylaxis to any particular NMBD will be determined by the market share (or number of uses) of the drug and the size of the population who are allergic, i.e. the number who have IgE antibodies to the drug.

The incidence of anaphylaxis to rocuronium closely follows the increase in usage of this NMBD (Fig. 1); the overall number of reactions and the number of reactions to other relaxants appears to be falling. This is reflected in data on patients seen at the Anaesthetic Allergy clinic between January and June 2000, among whom there were eight reactions to rocuronium and only three to all other NMBDs.

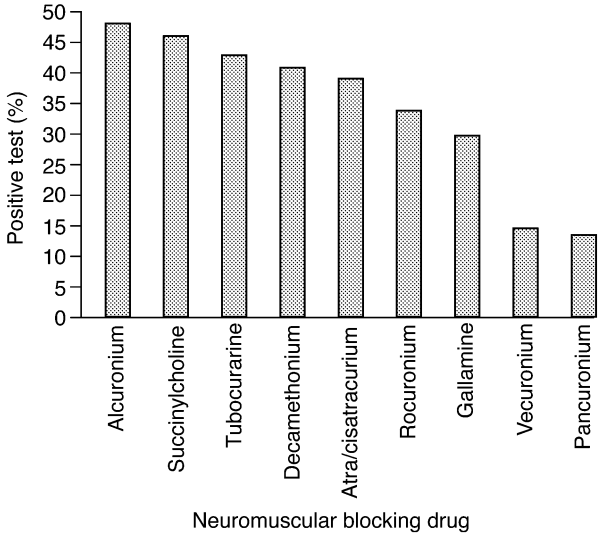

Fig 2 Incidence of positive intradermal tests to rocuronium and other neuromuscular blocking drugs in patients allergic to a neuromuscular blocker.

Table 4 Rocuronium reactors: positive skin tests to other NMBDs

NMBD	Tested	Positive	%
Succinylcholine	23	4	17.4
Vecuronium	23	4	17.4
Pancuronium	23	5	21.7
Atracurium/cisatracurium	23	11	47.8
Mivacurium	23	12	52.2

The reduction in reactions to other NMBDs is not a phenomenon reported or observed previously and is an important consideration in the relative safety of NMBDs. One would expect that if a drug of intermediate risk of producing anaphylaxis gained such a proportion of the market and displaced higher-risk drugs such as succinylcholine, the overall incidence of anaphylaxis should fall, and we suspect this is occurring with the increasing use of rocuronium in Australia.

There were 20 females and four males in our study, a female preponderance similar to that in patients allergic to other NMBDs in our database. This marked preponderance of females, usually of the order of 4:1, has been noted in other studies of anaphylaxis to NMBDs.[2 5 14 15]

RIA testing for morphine antibodies has now simplified RIA testing for NMBD allergy, as the single substituted ammonium group is common to the structures of both morphine and NMBDs. As a result, it is much more efficient to use the morphine RIA to test for IgE antibodies to NMBDs as a group than to use specific NMBD RIAs.[8]

A previous study[2] examined individual cutaneous relaxant sensitivity in a population of patients who reacted to NMBDs, and the results suggested that in Australia succinylcholine and alcuronium were high-risk drugs (over 40% of the NMBD-allergic population were sensitive) and vecuronium and pancuronium were low-risk drugs (fewer than 10% of NMBD-allergic patients were sensitive). These data appeared to reflect the described incidences of severe clinical reactions in the two large published series in Australia and France.[2 3]

Data from our analysis (Fig. 2) confirm these general trends. We have divided the NMBDs into high-, intermediate- and low-risk drugs in the population of relaxant-sensitive patients. These divisions, of course, are arbitrary and exact percentages of reaction depend very much on the sample size (number tested) for each drug. With the possible exception of decamethonium (only 10 tested, four positive) the numbers tested give a good indication of the relative risk of each agent. NMBDs with a high risk (>40%) of causing anaphylaxis in the relaxant-sensitive population were alcuronium, succinylcholine, *d*-tubocurarine and decamethonium. Intermediate-risk (20–40%) agents were atracurium/cisatracurium, rocuronium, mivacurium and gallamine. As expected, the two low-risk agents were vecuronium and pancuronium.

Allergy to NMBDs is due to the cross-linking of cell-bound IgE molecules by the substituted ammonium groups that provide the neuromuscular blocking effects of these drugs.[14] It is not, therefore, surprising that cross-sensitivity between NMBDs occurs. Indeed, it is more difficult to determine why patients allergic to one NMBD are not allergic to all NMBDs, yet of 410 patients allergic to NMBDs in the database only two had cutaneous sensitivity to all NMBDs tested.

The length of the carbon chain between active groups, the three-dimensional structure and the nature of binding of immunoglobulin may partially explain differences between individual agents. Differences in antigen–antibody binding strength may vary, but why this strength should be different when the antigen is so similar remains unclear. From previous data, cross-sensitivity between NMBDs has been estimated to occur in up to 60% of patients.[16 17]

We tested only a small number of reactors to other NMBDs with rocuronium to ascertain cross-sensitivity (Table 3). It is not possible to draw conclusions from these data, as the numbers tested were too small. It is interesting to observe, however, that the NMBDs with which there was some cross-reactivity included other members of the aminosteroid class of relaxants (such as vecuronium, pancuronium), to which rocuronium is most closely related structurally, and not the benzylisoquinolinium group, which includes atracurium, cisatracurium and mivacurium, which are structurally dissimilar to rocuronium.

When the known rocuronium reactors underwent skin tests to other NMBDs (Table 4), the results were not as expected. The incidence of cross-sensitivity to relaxants of the aminosteroid family was lower than that to the benzylisoquinolinium family. Structural similarity was

expected to result in rocuronium reactors reacting most frequently with other relaxants of the aminosteroid family.

These results differ substantially from those of Laxenaire *et al*.,[5] which showed a very high incidence of cross-sensitivity using a 10^{-1} dilution of rocuronium (10 mg ml^{-1}) administered on the back. Levy *et al*.[18] studied weal and flare responses to cisatracurium and rocuronium on the forearm, and showed that concentrations such as those used by Laxenaire *et al*. produce a high incidence of false positives. It is generally believed that greater concentrations should be used on the back than on the forearm. However, in our experience there is minimal difference. Skin testing on the back using the same dilutions as those recommended for testing on the forearm is the standard method in New Zealand.

In conclusion, our experience suggests no cause for alarm about anaphylaxis to rocuronium. Our database shows that the rate of anaphylaxis is rising in proportion to usage of the drug, not out of proportion to it. Rocuronium is intermediate in reactivity in relaxant-sensitive patients.

The structure of rocuronium closely resembles that of the other aminosteroid NMBDs—vecuronium and pancuronium. Whilst rocuronium is not a high-risk agent in terms of anaphylaxis in the relaxant-sensitive population, it is significant that there is a distinct variation from its nearest relatives in its propensity to cause anaphylaxis in this population.

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References

1 Beard K, Jick H. Cardiac arrest and anaphylaxis with anesthetic agents [letter]. *J Am Med Assoc* 1985; **254**: 1742

2 Fisher MM, Baldo BA. The incidence and clinical features of anaphylactic reactions during anaesthesia in Australia. *Ann Fr Anesth Reanim* 1993; **12**: 97–104

3 Laxenaire MC, Moneret-Vautrin DA, Widmer S, *et al*. Substances anesthesiques responsables de chocs anaphylactiques. Enquete multicentrique francaise. Anaesthetic drugs responsible for anaphylactic shock. French multi-center study. *Ann Fr Anesth Reanim* 1990; **9**: 501–6

4 Levy JH, Davis GK, Duggan J, *et al*. Determination of the hemodynamics and histamine release of rocuronium (ORG 9426) when administered in increased doses under N_2O/O_2-sufentanil anesthesia. *Anesth Analg* 1994; **78**: 318–21

5 Laxenaire MC, Gastin I, Moneret-Vautrin DA, Widmer S, Gueant JL. Cross reactivity of rocuronium with other neuromuscular blocking agents. *Eur J Anaesthesiol* 1995 (Suppl.); **11**: 55–64

6 Neal SM, Manthri PR, Gadiyar V, Wildsmith JA. Histaminoid reactions associated with rocuronium. *Br J Anaesth* 2000; **84**: 108–11

7 Fisher MM. Clinical observations on the pathophysiology and treatment of anaphylactic cardiovascular collapse. *Anaesth Intensive Care* 1986; **14**: 17–21

8 Fisher MM, Baldo BA. Immunoassays in the diagnosis of anaphylaxis to neuromuscular blocking drugs: the value of morphine for the detection of IgE antibodies in allergic subjects. *Anaesth Intensive Care* 2000; **28**: 167–170

9 Laroche D, Vergnaud MC, Sillard B, Soufarapis H, Bricard H. Biochemical markers of anaphylactoid reactions to drugs. Comparison of plasma histamine and tryptase. *Anesthesiology* 1991; **75**: 945–9

10 Fisher MM, Baldo BA. The diagnosis of fatal anaphylactic reactions during anaesthesia; employment of immunoassays for mast cell tryptase and drug-reactive IgE antibodies. *Anaesth Intens Care* 1993; **21**: 353–7

11 Fisher MM. Intradermal testing after anaphylactoid reaction to anaesthetic drugs; practical aspects of performance and interpretation. *Anaesth Intens Care* 1984; **12**: 115–20

12 Fisher MM, Baldo BA. Mast cell tryptase in anaesthetic anaphylactoid reactions. *Br J Anaesth* 1998: **80**: 26–9

13 Fisher MM, Merefield D, Baldo BA. Failure to prevent an anaphylactic reaction to a second anaesthetic drug during anaesthesia. *Br J Anaesth* 1999; **82**: 770–3

14 Laxenaire MC, Moneret-Vautrin DA, Guéant JL, *et al*. Drugs and other agents involved in anaphylactic shock occurring during anaesthesia. A French multicentre epidemiological enquiry. *Ann Fr Anesth Reanim* 1993; **12**: 91–6

15 Youngman PR, Taylor KM, Wilson JD. Anaphylactoid reactions to neuromuscular blocking agents: a commonly undiagnosed condition? *Lancet* 1983; **2**: 597–9

16 Baldo BA, Fisher MM. Substituted ammonium ions as allergenic determinants in drug allergy. *Nature* 1983; **306**: 262–6

17 Fisher M, Munro I. Life threatening anaphylactoid reactions to muscle relaxants. *Anesth Analg* 1983; **62**: 559–66

18 Levy J, Gottge M, Szlam F, Zaffer R, McCall C. Wheal and flare responses to rocuronium and atracurium in humans. *Br J Anaesth* 2000; **85**: 844–9