CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20984

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA 20-984
Name of drug: Raplon (rapacuronium, Org 9487)
Applicant: Organon
Indication: Neuromuscular blocking agent
Documents reviewed: volumes 1.1, 1.3, 1.77-1.162
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Reviewer: Thomas Permutt

INTRODUCTION

Raplon (rapacuronium, Org 9487) is a new molecular entity in the steroid class of nondepolarizing neuromuscular blocking agents. Neuromuscular blockers are used in surgery to suppress reflexive movement, to relax the vocal cords and jaw to facilitate tracheal intubation, and in intensive care to facilitate mechanical ventilation. Succinylcholine, a depolarizing agent, has a very fast onset and does not last long, but it has undesirable side effects. Rapacuronium is the latest in a series of nondepolarizing agents intended to approach succinylcholine in onset and duration without the side effects of a depolarizing agent.

Such fast and short action is especially sought for rapid-sequence intubation. In emergency surgery, for example, where the patient has not fasted, the anesthetic agent may cause the patient to vomit and choke. Tracheal intubation is needed to protect the airway. Intubation requires neuromuscular blockade, but conscious patients cannot be paralyzed without distress. The rapid sequence therefore consists of administration of a fast-acting hypnotic followed quickly by a neuromuscular blocker and intubation within 60 to 90 seconds.

The effect of neuromuscular blockers is obvious and is not seen with placebo: patients are paralyzed. There is consequently no statistical problem in determining that an agent is effective. The effects can be characterized quantitatively, however, and it is in this characterization that some statistical considerations arise. This review focuses on these quantitative issues:

1. comparison of intubating conditions with succinylcholine;
2. characterization of onset and duration of action;
3. characterization of potency, including demographic effects.

INTUBATING CONDITIONS

Intubating conditions with rapacuronium and succinylcholine were compared in the three largest trials in the NDA. These studies were designed and analyzed as noninferiority trials, with a prespecified criterion of clinical equivalence. The design and analysis were discussed in meetings between the sponsor and the reviewing division and in correspondence related to the review of protocols. There was agreement on the methods of statistical analysis, but not on the criterion of equivalence.

STUDY 070007

Study 070007 was a randomized, parallel-group trial at five centers in the United States. Elective surgery patients were preoxegenated and then anesthetized with a combination of nitrous oxide, fentanyl and propofol after optional premedication with midazolam or lorazepam. Intubation was attempted 60 seconds after administration of rapacuronium or succinylcholine (but about five minutes after administration of fentanyl and one to two minutes after propofol, not a rapid sequence), and again 30 seconds later if the first attempt failed. As is usual for safety reasons in studies of neuromuscular blocking agents, the administering anesthesiologist was not blind to the treatment assignment. Instead, laryngoscopy and intubation were performed by a second, blinded anesthesiologist. This is the nearest to double-blind technique that can be achieved in such studies. However, because succinylcholine may have visible side effects different from nondepolarizing agents, the assessor is not always truly blinded.

The protocol called for recruitment of 56 subjects at each site, 12 to be over 65, randomized in equal numbers to the two treatments. It was amended to allow four of the sites to enroll an additional 14 patients each because of a large number of protocol violations at the other center. Intubating conditions were scored as excellent, good, fair or impossible according to a standard (Viby-Mogensen) scoring system involving position and movement of the vocal cords, ease of laryngoscopy, airway reaction such as coughing, and movement of the limbs. The protocol specified as the primary outcome, "acceptable" intubating conditions at 60 seconds, lumping excellent and good, and proposed a noninferiority test with a difference of 10 percent in the proportion of acceptable conditions to be considered clinically insignificant. FDA reviewers of the protocol commented that neither the lumping of good and excellent conditions nor the margin of 10 percent was well justified with respect to a claim of therapeutic equivalence.

One hundred of 336 patients were excluded from the per-protocol analysis, including all but one patient at center 1. The principal protocol violation was a longer time than was specified between administration of fentanyl and of the blocking agent. The applicant argues that a longer interval can affect the intubating conditions, and therefore considers the per-protocol analysis more informative than the intent-to-treat analysis. As the violations occurred before the administration of the test drug and as the clinician was not blinded, I agree that there is no reason to think the intent-to-treat analysis would be less subject to bias. In any case, the results of the two analyses were not substantially different.

Intubating conditions, per-protocol group

	Rapacuronium N = 124	Succinylcholine N = 112
Excellent	53 (43%)	74 (67%)
Good	55 (44%)	32 (29%)
Poor	16 (13%)	4 (4%)
Impossible	0	2 (2%)
Acceptable	108 (87%)	106 (95%)
Unacceptable	16 (13%)	6 (5%)

After applicant's table 15

A ninety-five percent confidence interval for the difference in proportion of acceptable conditions (normal approximation) was 0.1 to 15 percent. Thus, the noninferiority criterion was not met, and the proportions were in fact significantly different. In addition, about two thirds of the acceptable scores were excellent rather than good with succinylcholine, compared to only half with rapacuronium.

Substantial center effects were noted, with one site having 100 percent acceptable conditions with succinylcholine compared to 76% for rapacuronium, and two other sites having nearly equal proportions for the two treatments. Intubating conditions were generally slightly better with both treatments in elderly patients:

Intubating conditions, per-protocol group, over 65

	Rapacuronium N = 26	Succinylcholine N = 28
Excellent	13 (50%)	22 (79%)
Good	12 (46%)	6 (21%)
Poor	1 (4%	0
Impossible	0	0
Acceptable	25 (96%)	28 (100%)
Unacceptable	1 (4%)	0

After applicant's table 16

STUDY 174308

Study 174308 was conducted at four centers in France. The design was generally similar to study 070007, just described. Thiopental was used rather than propofol for induction of anesthesia. Also, the centers were not required to recruit equal numbers: the intent-to-treat groups ranged from 44 to 83 patients. The per-protocol group included 266 of 282 patients treated, and the results for the per-protocol and intent-to-treat groups were not substantially different. An additional five patients in each per-protocol group were eliminated from analysis,

three because of missing primary data and seven because of impossible intubation due to anatomical malformation.

Intubating conditions, per-protocol group

	Rapacuronium N = 128	Succinylcholine N = 128
Excellent	39 (30%)	61 (48%)
Good	71 (55%)	52 (41%)
Poor	11 (9%)	12 (9%)
Impossible	7 (5%)	3 (2%)
Acceptable	110 (86%)	113 (88%)
Unacceptable	18 (14%)	15 (12%)

After applicant's tables 17, 18

A one-sided 95% upper confidence bound for the inferiority in acceptable conditions of rapacuronium to succinylcholine was 9.2 percent; a two-sided 95% confidence interval was (−5.6%, 10.3%). The protocol-defined noninferiority criterion of no more than a 10 percent difference with 95 percent confidence (one-sided) was therefore met. I do not believe this justifies a claim of therapeutic equivalence, however. There was a clear difference in the distributions of acceptable conditions between excellent and good. Also, a difference of 10 percent would represent a near doubling of the 12% failure rate with succinylcholine to 22 percent. Again, while the noninferiority criterion was proposed in the protocol, FDA reviewers questioned its appropriateness at that time.

Again, there were substantial center effects. One center rated most of the acceptable conditions as good, regardless of treatment, whereas the others divided them more evenly between good and excellent, with more excellent ratings in the succinylcholine group. Again, elderly patients were more likely than younger adults to have excellent conditions on either treatment, but in this case they were also more likely to have unacceptable conditions with rapacuronium:

Intubating conditions, per-protocol group, over 65

	Rapacuronium N = 25	Succinylcholine N = 26
Excellent	8 (32%)	16 (62%)
Good	12 (48%)	9 (35%)
Poor	1 (4%)	0
Impossible	4 (16%)	1 (4%)
Acceptable	20 (80%)	25 (96%)
Unacceptable	5 (20%)	1 (4%)

After applicant's table 16

STUDY 174303

Unlike the previous two studies, study 174303 was a trial of rapid-sequence intubation. Two different induction techniques were used, at random, either fentanyl and thiopental or alfentanil and propofol. In either case the injection of rapacuronium or succinylcholine was begun a few seconds after the injection of the hypnotic was finished. It was intended to recruit equal numbers of obese and nonobese patients, 40 each at each of four centers in Germany. Recruitment difficulties caused amendment of the protocol to provide for more normal than obese patients, a fifth center, and larger enrollments at centers that could recruit more patients; in fact the number of patients per center ranged from 32 to 113. The per-protocol set comprised 316 of 335 patients randomized.

Intubating conditions, per-protocol group

	Rapacuronium N = 160	Succinylcholine N = 156
Excellent	81 (51%)	114 (73%)
Good	62 (39%)	38 (24%)
Poor	17 (11%)	4 (3%)
Acceptable	143 (89%)	152 (97%)
Unacceptable	17 (11%)	4 (3%)

After applicant's table 22

Apparently no patients were classified as impossible to intubate. Acceptable intubating conditions were significantly ($p < 0.01$, Cochran-Mantel-Haenszel test stratified by obesity, center and anesthetic technique) more frequent with succinylcholine than with rapacuronium, and the noninferiority criterion was clearly not met. In addition, acceptable conditions were excellent rather than good substantially more often with succinylcholine than with rapacuronium. The study report concludes that succinylcholine and rapacuronium were different with respect to intubating conditions.

Again, variation across centers was notable. No substantial differences were noted between obese and normal patients nor between the two anesthetic techniques.

SUMMARY—INTUBATING CONDITIONS

When excellent and good conditions were lumped as "acceptable," rapacuronium produced similar results to succinylcholine in one of three studies. In that one study (174308), while the rates for rapacuronium and succinylcholine were similar to each other, succinylcholine had an unusually low rate of acceptable conditions compared to the other two studies and, according to the medical reviewer, compared to clinical experience. Furthermore, even in that study the conditions were substantially more often excellent with succinylcholine than with rapacuronium. In two other studies, the rate of acceptable conditions was substantially and statistically significantly lower with rapacuronium than with succinylcholine.

The proposed labeling includes the following text and tables under "pharmacodynamics":

Table 1 presents intubating conditions from one US study of 236 and a European study with 256 adult patients (≥ 18 yrs) with intubation initiated at 50 seconds following 1.5 mg/kg RAPLON™ (rapacuronium bromide) for Injection or 1 mg/kg succinylcholine under the following conditions: premedicated with midazolam, induced with fentanyl and propofol for the US study and premedicated with midazolam, induced with fentanyl and thiopental in the European study. Table 2 presents the intubating conditions of the geriatric patients in these two studies.

Table 1. Intubation Scores in Adults (≥ 18 yrs) With Laryngoscopy Initiated at 50 Seconds

	Drug IV over 5 seconds	Number (%) of patients with acceptable (excellent or good) intubating conditions	Estimated difference in acceptable intubating conditions (succinylcholine - RAPLON□)	95% Confidence Interval
US Study[a]	RAPLON□ 1.5 mg/kg (n=124)	108 (87%)	7.6%	[0.1%, 15.2%]
	succinylcholine 1.0 mg/kg (n=112)	106 (95%)		
European Study[b]	RAPLON□ 1.5 mg/kg (n=128)	110 (86%)	2.3%	[-5.9%, 10.5%]
	succinylcholine 1.0 mg/kg (n=128)	113 (88%)		

a=In the US study excellent intubating conditions were present in 53 (43%) RAPLON□ treated patients and 74 (66%) patients treated with succinylcholine.

b=In the European study excellent intubating conditions were present in 39 (30%) RAPLON□ treated patients and 61 (48%) patients treated with succinylcholine.

Table 2. Intubation Scores in Geriatrics (≥ 65 yrs) with Laryngoscopy Initiated at 50 Seconds

	Drug IV over 5 seconds	Number (%) of patients with acceptable (excellent or good) intubating conditions
US Study[a]	RAPLON□ 1.5 mg/kg (n=26)	25 (96%)
	succinylcholine 1.0 mg/kg (n=28)	28 (100%)
European Study[b]	RAPLON□ 1.5 mg/kg (n=25)	20 (80%)
	succinylcholine 1.0 mg/kg (n=26)	25 (96%)

a=In the US study excellent intubating conditions were present in 13 (50%) RAPLON□ treated patients and 22 (79%) patients treated with succinylcholine.
b=In the European study excellent intubating conditions were present in 8 (32%) RAPLON□ treated patients and 16 (62%) patients treated with succinylcholine.

The style of the tables, with acceptable vs. unacceptable conditions in the body of the table and excellent vs. good in a footnote, was prospectively agreed in meetings between the sponsor and the division. However, those discussions were focused on how to present data showing equivalence with respect to acceptable conditions but not with respect to excellent conditions. It turned out that conditions were not equivalent even when good and excellent were lumped, so that the need for such an approach is not clear.

The justification for including studies 070007 and 174308 but not study 174303 in this section is not apparent. The results of study 174303 were less favorable to Raplon, so that the two chosen studies do not give a balanced view of the experience in clinical trials. Furthermore, while the label wording is not explicit, these data may appear to the reader to have a bearing on use in rapid-sequence intubation, and study 174303 was the only one of the three trials in which a rapid sequence was used.

The data from these three studies, considered together, suggest that rapacuronium may be a useful though not equivalent alternative to succinylcholine. I recommend that all three studies be included in labeling, and that the tables be simplified to show the Viby-Mogensen scores (excellent, good, poor, impossible) directly rather than acceptable/unacceptable.

ONSET AND DURATION OF ACTION

The proposed labeling describes rapacuronium as having a "rapid onset and short duration of action." These terms were given a definite meaning in this context by Bedford, then acting division director, in an article in Anesthesiology, which is referred to in the application. "Rapid onset" is defined as less than five minutes, and "short duration" means less than 20 minutes. There remain two problems in application of these standards. One is that these measurements will vary somewhat from patient to patient, and Bedford did not address the question of what parameters of the distribution needed to be less than five or 20 minutes. The other problem became apparent in the first application of the standards, which was to the drug rocuronium, and was discussed by Bedford. The difficulty is that both the onset and duration might vary with the dose. While it has been customary in labeling to use these terms in the introduction to the label as a characterization of the drug, they may in fact apply to some but not to other doses. It is even possible that a drug would have "rapid onset" at one dose but "short duration" only at a different dose.

ONSET

Onset of a neuromuscular blocker has been defined as the time from administration to the maximum depression of the thumb-twitch reflex. The ulnar nerve is stimulated electrically in the "train-of-four" pattern: four shocks over 1.5 seconds. Normally this produces four distinct twitches of the thumb, designated T_1 through T_4. With increasing blockade the later twitches disappear and T_1 is reduced in magnitude, usually measured by the force the thumb exerts. Onset is defined as the time to the maximum reduction in T_1, which with rapacuronium was almost always the absence of any twitch at all.

Adults 18-64

	Study	N	Onset (s) Mean ± s.d.
1.5 mg/kg	070003	10	62 ± 10
	070005	22	100 ± 52
	174201	10	101 ± 19
	174203	32	97 ± 30
	174301	4	108 ± 22
	174306	52	83 ± 25
	174309	6	91 ± 28
2.5 mg/kg	070005	19	72 ± 24

After ISE tables 22, 23

The precise measurement of force requires a period of calibration. Accordingly, this measurement was not carried out in the largest studies in the NDA, in which the aim was to study intubation, more or less rapid, under nearly realistic conditions. Rather, the application summarizes onset data from several much smaller studies.

The mean time in each study was far below the five-minute standard for "rapid onset." Furthermore, given the standard deviations, the great majority of individual patients must have had times less than five minutes. Clearly the onset of action of rapacuronium 1.5 or 2.5 mg/kg can be described as rapid by the Bedford criterion.

DURATION

The duration of action of neuromuscular blocking agents has been defined as the time until the T_1 force returns to 25% of its baseline value. Alternatively, when force is not measured, the time to the reappearance of T_3 has been considered to be an approximately equivalent measure.

Adults 18-64, per protocol, without reversal agents

	Study	N	Duration (min) Mean ± s.d.
1.5 mg/kg	070001	16	15 ± 6
	070003	10	13 ± 3
	070005	20	14 ± 5
	070010	11	17 ± 5
	174201	10	10 ± 3
	174203	30	11 ± 3
	174301	4	11 ± 2
	174302	59	16 ± 4
	174306	25	20 ± 5
	174309	5	20 ± 7
2.5 mg/kg	070001	18	26 ± 10
	070005	17	23 ± 9
	070010	10	24 ± 8

After ISE tables 24, 25

At 1.5 mg/kg, the mean duration was always 20 minutes or less. The variability, however, was such that many individual patients had durations more than 20 minutes. According to the sponsor's pooled analysis (Table 26), 154 of 190 patients (81 percent) had clinical duration of less than 20 minutes. As noted above, Bedford was not explicit about what statistical parameter had to be less than 20 minutes for duration to be called "short." It is clear, however, that the duration of action of rapacuronium 1.5 mg/kg was short both on average and in most individual patients.

As noted above, the largest studies in the NDA did not make mechanomyographic determinations of clinical duration because the calibration period would have interfered with the simulation of realistic clinical conditions for intubation. In two of the intubation studies (070007 and 174308), however, the time to return of the third twitch in the train-of-four was recorded. This has also been used as a measure of clinical duration. In study 070007 the mean (± s.d.) time was 13 ± 6 min, and in study 174308 it was 10 ± 4 min. Again, the times are well within the range of "short" duration, both on average and in most individual patients.

At 2.5 mg/kg, the duration was clearly "intermediate." The draft labeling principally recommends a dose of 1.5 mg/kg, partly for this reason. In cesarean section, however, 2.5 mg/kg is recommended. The labeling fairly describes the variation of duration of action with dose.

It seems to me, therefore, that rapacuronium is correctly described as having a rapid onset and a short duration of action. The duration depends on the dose, however, and it is not short at some doses within the recommended range.

POTENCY AND DEMOGRAPHIC EFFECTS

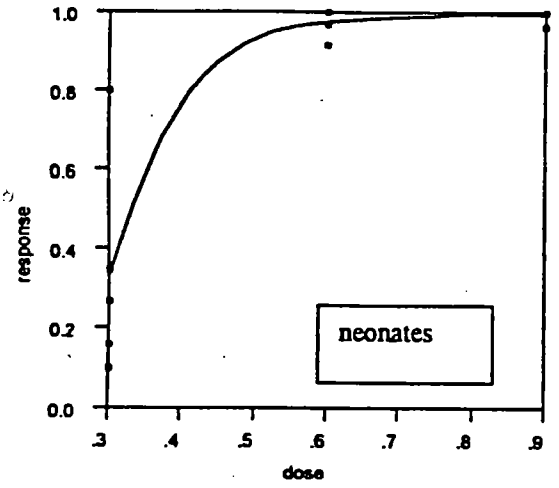
It has been customary to characterize the potency of neuromuscular blocking agents in terms of partially effective doses ED_{50}, ED_{90} and especially ED_{95}. The application says, "These are the estimated doses to produce a 50%, 90% and 95% depression of twitch at the adductor pollicis muscle of the thumb, in response to stimulation of the ulnar nerve." However, the operational definition of these terms has been somewhat ambiguous. With binary outcomes, ED_{50} (for example) would be defined as the dose that produced the outcome in 50 percent of subjects. What constitutes a "50% . . . depression of twitch," though, depends on how the twitch is measured and on how those measurements are combined across subjects. In this application it has been defined as follows. For each patient the force of the thumb twitch was measured by mechanomyography repeatedly, at intervals of ten seconds. The minimum of all these measurements was divided by a "baseline" value; there were also repeated baseline measurements, and it is not clear how they were combined to get this single value. The quotient, subtracted from one and then expressed as a percentage, was the "depression" for the individual patient. The ED_{50} was the dose at which the mean depression (across patients) was expected to be 50 percent. The draft labeling refers to two studies in which ED_{50} was estimated, study 070002 in pediatrics and study 070004 in adults, including elderly patients.

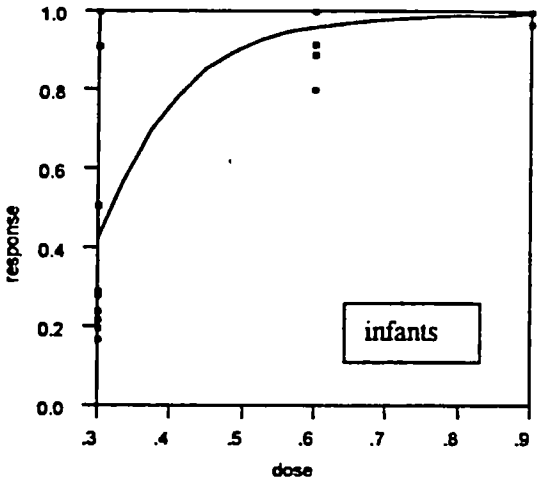
PEDIATRICS—STUDY 070002

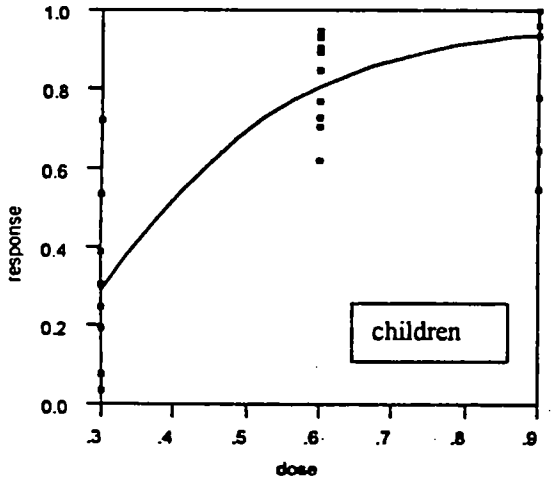
A report of study 070002 was submitted to the IND, and I reviewed it. (My review is attached.) The NDA report contains a new analysis, however. In addition to the "probit" analysis proposed in the protocol and the linear interpolation suggested in my review, the parameters α and β in the Hill equation

$$Y = \frac{X^{\beta}}{\alpha^{\beta} + X^{\beta}}$$

were estimated by least squares, with fractional depression of twitch as Y and dose as X. The Hill equation is not given any theoretical justification in the application but is used empirically as a fairly simple function with a sigmoid shape. The figures (prepared by me from data submitted electronically) show the fitted equations.







In each case the fitted line crosses the horizontal line at 0.5 (50% response) between the doses of 0.3 and 0.6 mg/kg. Thus, the ED_{50} is estimated by this method to be between 0.3 and 0.6 mg/kg in each case, as would also be the case with linear interpolation between these two doses. The estimates are lower by the nonlinear method, because the fitted function is curved.

As a general method, fitting the Hill equation suffers some but not all of the same defects as the probit method. In particular, it allows responses in one part of the dose range to influence the fit in a different part, without a clear justification of the functional form. This can lead to speculative extrapolations outside the dose range tested, as well as to absurd results inside the range as I discussed for the probit model. In this case, the responses at 0.9 mg/kg affect mainly the curvature of the function between 0.3 and 0.6 mg/kg.

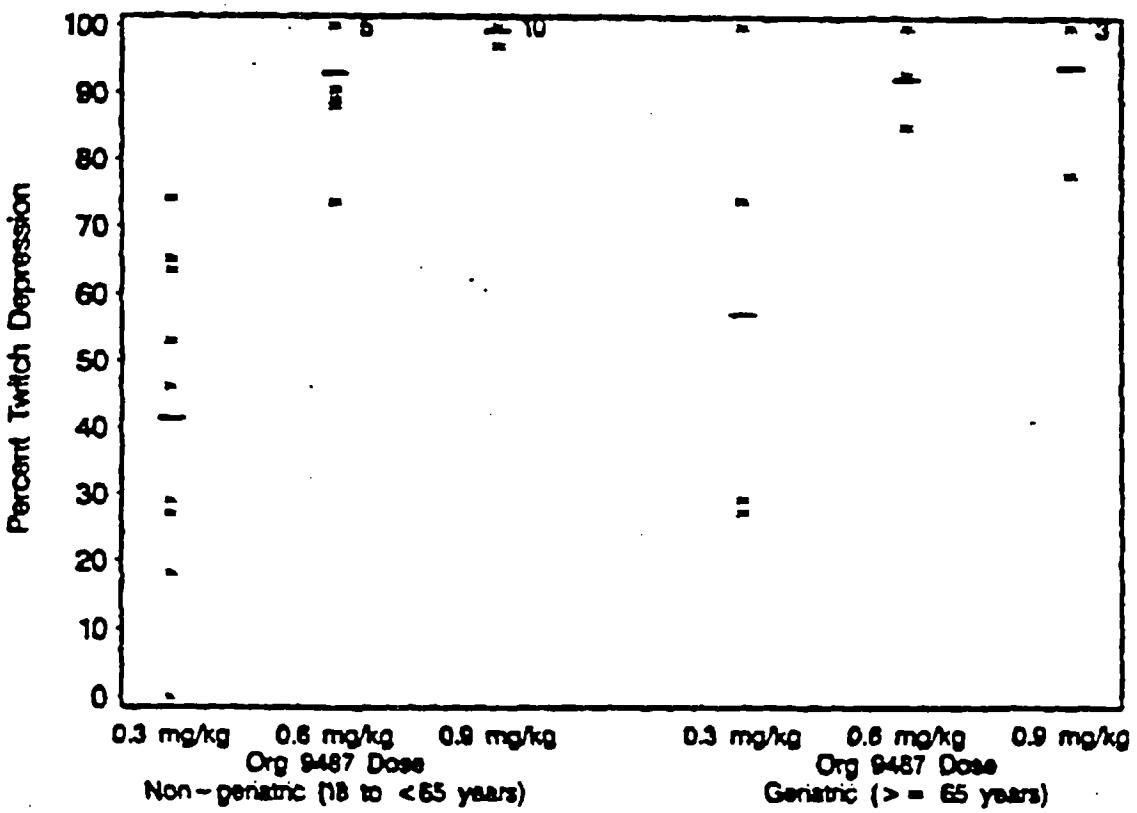
For this study, however, I think the estimates by the Hill-equation method are the most reasonable of the three methods. The dose-response function undoubtedly *is* curved between 0.3 and 0.6 mg/kg, because it is steep there (on average) and flat between 0.6 and 0.9 mg/kg. The piecewise linear function I suggested fitting has no theoretical justification, either, and is obviously less realistic here. It is useful, as I suggested before, as a check on the other methods, as it is not subject to extreme errors because it does not extrapolate, it only interpolates.

The estimated ED_{50} by this method was 0.33 in neonates, 0.32 in infants and 0.39 in children. As I said in my earlier review, these estimates are subject to wide uncertainty, and the evidence

for a real difference in ED_{50} between age groups is weak. However, it does appear that children may require a higher dose than infants or neonates to produce complete blockade. This information would be reasonably conveyed to the practitioner by the labeling proposed in the application: "The ED50 for pediatric patients (1 to 12 years) is 0.4 mg/kg and for neonates (< 1 mo) and infants (1 mo to < 1 yr) is 0.3 mg/kg."

ADULTS– STUDY 070004

Study 070004 was a randomized, open-label study in adults undergoing elective surgery. The protocol called for 30 patients under 65 and 30 patients over 65, but only 43 patients were recruited, three of whom were withdrawn before administration of the drug. Of the 40 patients treated, 11 were over 65. The figure (volume 82, page 0061) shows the responses in the two age groups separately. (Horizontal lines mark the mean response for each group, and numbers indicate multiple patients with the same value.)



The mean response at 0.3 mg/kg was 42 percent in nongeriatric patients and 57 percent in geriatric patients. These numbers both being close to 50 percent, the estimated ED_{50} cannot be far from 0.3 mg/kg. The Hill equation estimates were 0.32 and 0.27 mg/kg. Linear interpolation gave 0.35 mg/kg for nongeriatric patients, while the probit analysis gave 0.33. As in the pediatric study, I think the curvilinear fit is more realistic, so that 0.32 mg/kg is probably the best estimate. For geriatric patients, the response was more than 50 percent at all doses

tested, so that the estimated ED_{50} must be an extrapolation, but only a short one from 57 percent at 0.3 mg/kg. The Hill equation gave 0.27 mg/kg while the probit analysis gave 0.20 mg/kg. The proposed labeling is, "The ED50 (dose required to produce 50% suppression of the first[T1] mechanomyographic [MMG] response of the adductor pollicis muscle to indirect supramaximal train-of-four stimulation of the ulnar nerve) during opioid/nitrous oxide/oxygen anesthesia is approximately 0.3 mg/kg in adult (18 to 65 yrs) and geriatric (≥ 65 yrs) patients." I think this wording is appropriate.

OTHER DEMOGRAPHIC EFFECTS

The two studies just discussed give the clearest indication of changes in the effects of rapacuronium with age. In particular, there is an indication, though not clear evidence, that children over the age of one year, but not infants or neonates, may require a slightly higher dose by body weight than adults. There is also a very weak indication that patients over 65 may be slightly more sensitive to rapacuronium than younger adults.

It is appropriate here to consider other evidence of systematic variation in effect across patients. The integrated summary of efficacy collects information on time to onset and duration by age, sex and ASA class (a measure of general condition used by anesthesiologists). Also, as noted above, obese and nonobese patients were compared in study 174303. There was no overall analysis by race, although the U.S. studies included substantial numbers (from about 20 to 100 percent) of non-Caucasian patients.

AGE

Duration of action was observed to increase with age in adult subjects at higher doses. Several slightly different analyses support this conclusion, the following one perhaps most clearly (clinical duration, pooled studies 070001, 070003, 070005, 070010; after ISE Table 53).

Age	18-30	31-40	41-50	51-64	Over 65
Duration > 30 min	2/9 (22%)	3/17 (18%)	0/9 (0%)	3/10 (30%)	6/13 (46%)

In pediatric patients, a longer mean onset time (190 s) was noted in neonates (N=4) than in infants (84 s) or children (53 s) at a dose of 2.0 mg/kg. However, the times for neonates were highly variable (s.d. 261 s), and a paradoxical dose response was observed in neonates, with a mean onset time of 98 s at 1.0 mg/kg. The variability, the small number of patients and the paradoxical dose response all suggest that the observed difference between age groups may not be reliable.

SEX

Duration of action may have been somewhat longer for women than for men at a dose of 2.5 mg/kg (pooled studies 070001, 070003, 070005, 070010; ISE Table 57): 12 of 46 (26%) of women and 2 of 12 (17%) of men had clinical duration longer than 30 minutes. This comparison, being based on very few patients, may not be reliable.

ASA CLASS

No differences were noted in pooled analyses of onset and duration by ASA class. These analyses, however, involve no patients worse than ASA class 3, and only 14 patients in ASA class 3. There is thus little indication either way as to the possibility of different pharmacodynamics in sicker patients.

CONCLUSIONS

Rapacuronium has been shown to be an effective neuromuscular blocking agent. (Safety is discussed in the medical officer's review.) At a dose of 1.5 mg/kg its onset can be properly characterized as "rapid" and its duration of action as "short," but at higher doses the duration is longer. While rapacuronium may be useful in some cases where succinylcholine is presently used, a claim of equivalence to succinylcholine is not justified. The application is approvable from the standpoint of statistics.

/S/ 4/3/99

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/S/ 2/4/99

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archival: NDA 20-984
cc:
HFD-715/Nevius, Welch
HFD-170/Samanta, Cortinovis, Rappaport, McCormick, Permutt
HFD-170/division file