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Onset of Maximum Neuromuscular Block Following Succinylcholine or Vecuronium in Four Age Groups

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Background: **Increasing age appears to be associated with a slower onset of neuromuscular blockade, but such an effect has not been studied with the same doses of the same drugs across pediatric and adult age groups.**

Methods: **The authors measured the evoked compound action potential of the adductor pollicis muscle in response to 0.1-Hz stimulation of the ulnar nerve, during fentanyl-thiopental-oxygen anesthesia, in 160 patients aged 1–3 yr, 3–10 yr, 20–40 yr, or 60–80 yr. Subparalyzing doses of vecuronium (0.03 mg/kg) or succinylcholine (0.3 mg/kg), or paralyzing doses of vecuronium (0.1 mg/kg) or succinylcholine (1.0 mg/kg), were administered to ten patients in each age group.**

Results: **Onset time, defined as the time from injection to maximum depression of response with a subparalyzing dose or the time from injection to ablation of visible response with a paralyzing dose, varied with age in all groups ($P < 0.001$). For 0.3 mg/kg succinylcholine, it increased from 49 ± 6 s in 1–3-yr-old patients, to 104 ± 9 s in 60–80-yr-old patients ($P < 0.00001$). For 0.03 mg/kg vecuronium, onset time was 3.6–5.9 times longer than for succinylcholine, increasing from 219 ± 15 s in 3–10-yr-old patients to 473 ± 30 s in 60–80-yr-old patients ($P < 0.00001$ by linear regression). For paralyzing doses, succinylcholine 1.0 mg/kg had an onset time of 58 ± 7 s and 95 ± 7 s, in 1–3-yr-old and 60–80-yr-old patients, respectively ($P < 0.001$). For 0.1 mg/kg vecuronium, onset time varied between 125 ± 19 s in 1–3-yr-old patients to 295 ± 31 s in 60–80-yr-old patients ($P < 0.00001$), and was 2.1–3.3 times longer than 1 mg/kg succinylcholine.**

Conclusions: **Increasing age is associated with slower onset for both succinylcholine and vecuronium. When equipotent, subparalyzing doses of succinylcholine and vecuronium are compared, onset time is 4.5 times as long with vecuronium. (Key words: Age: succinylcholine; vecuronium. Monitoring: electromyogram. Neuromuscular blockade: onset time. Neuromuscular relaxants: succinylcholine; vecuronium.)**

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ONE of the most important features of a muscle relaxant is its speed of onset, which may, in turn, be influenced by potency,[1,2] dose,[3,4] cardiac output,[5] and muscle blood flow.[6] These last two factors may depend on age.[6,7] In one study,[7] onset time for vecuronium was found to increase with age, but only adult patients were tested. If cardiac output and muscle blood flow changes associated with age can affect vecuronium onset time, the same is expected to be true for the shorter-acting succinylcholine. In the dose range 2–5 times ED95, which corresponds to the doses normally given for tracheal intubation, measured onset time is dose dependent.[3,4] Thus, when comparing the onset times of two relaxants, an important bias may be introduced if the intubating doses that are chosen are not equipotent. However, with subparalyzing doses, time to maximum blockade is independent of dose,[3] and measured onset time is a function of the agent given, instead of the dose administered.

The purpose of this study was to evaluate the speed of onset and intensity of maximum blockade with succinylcholine and vecuronium during thiopental-opioid-oxygen anesthesia in four age groups. To make comparisons between relaxants, equipotent subparalyzing (ED50-ED90) and paralyzing (2–3 × ED95) doses of succinylcholine and vecuronium were chosen. To determine the effect of age on onset time, the same doses were given to patients 1–80 yr of age. Finally, to standardize the measurements, the method of monitoring and the anesthetic were the same for all patients.

Materials and Methods

After approval by the Hospital's Ethics Committee, 160 patients, ASA physical status 1 or 2, were studied after induction of anesthesia for various elective surgical procedures. Patients with diseases of neurologic or muscular systems were excluded, as were those treated with drugs that can alter neuromuscular response. An equal number (40) of subjects in each of

the four age groups, 1–3 yr, 3–10 yr, 20–40 yr, and 60–80 yr of age, was studied. Within each age group, patients were randomized into four subgroups of ten to receive approximately equipotent subparalyzing doses (between ED50 and ED90) of either 0.3 mg/kg succinylcholine,[8,9] 0.03 mg/kg vecuronium,[10,11] or full paralyzing doses (2–3 × ED95) of 1.0 mg/kg succinylcholine or 0.1 mg/kg vecuronium.

No premedication was given. On arrival in the operating room, each patient's ECG, arterial blood pressure, and oxygen saturation were monitored. An intravenous infusion was then established and 0.006–0.01 mg/kg atropine or 0.003–0.005 mg/kg glycopyrrolate with 1–2 μg/kg fentanyl was given intravenously. Anesthesia was induced with 4–7 mg/kg thiopental intravenously. When the lid reflex disappeared, the lungs were ventilated with 100% oxygen *via* a face mask. Supplementary doses of 1–2 mg/kg thiopental intravenously were administered, as necessary, to maintain unconsciousness.

After induction of anesthesia, the integrated electromyographic response (EMG) of the adductor pollicis muscle, in response to supramaximal stimulation of the ulnar nerve, was recorded using a Relaxograph/Datex 221 NMT monitor. Single-twitch stimulation (pulse width 0.1 ms, constant current, up to 70 mA) was given every 10 s using the nerve stimulator unit incorporated into the Relaxograph. Stimulating and recording surface electrodes were infant- or adult-size Red Dot. The test hand was immobilized in supination to an arm board. After calibration and obtaining a 30-s baseline measurement, the relaxant was injected into a rapidly running intravenous infusion. Recordings were continued until maximum blockade was observed. Maintenance of the anesthetic was then left to the discretion of the anesthesiologist. The time from injection of the drug to maximum blockade, and the intensity of maximum blockade (the lowest percent of control), were measured.

Results are presented as means ± SEM. Onset time *versus* age relationships were calculated for every dosage regimen using linear regression analysis and *t* statistics evaluation. Comparisons between age groups were also made using one-way ANOVA and Tukey's *post hoc* test for between-group comparisons. Comparisons between vecuronium and succinylcholine were made for either subparalyzing or paralyzing doses in each age group with the unpaired, two-tailed Student's *t* test. Because of the large discrepancy in standard deviation between the vecuronium and succinylcholine groups, a logarithmic transformation was made. The onset time ratio, defined as the onset time for vecuronium divided by the onset time for succinylcholine, with 95% confidence limits, was then calculated. This calculation was made for both paralyzing and subparalyzing doses to estimate by how much the onset time of vecuronium exceeded that of succinylcholine. A P value of less than 0.05 was considered to indicate a statistically significant difference.

Results

Demographic data are shown in table 1. There were no significant differences within each age group with respect to age or body weight, but males predominated among children and females among adults.

In every age group, onset of maximum blockade was significantly slower after vecuronium than succinylcholine, both after subparalyzing ($P < 0.0000005$), and full paralyzing ($P < 0.0005$) doses (table 2). Twitch height depression obtained with subparalyzing doses of 0.3 mg/kg succinylcholine was similar to that obtained with 0.03 mg/kg vecuronium. Similarly, no significant difference was observed in maximum blockade between 1.0 mg/kg succinylcholine and 0.1 mg/kg vecuronium (table 2). The onset of maximum blockade, and relationship to age, is presented in figures 1–4. For both dosages of both drugs, onset time varied with age ($P < 0.01$ by ANOVA). Linear regression of the data indicated that onset time increased with age ($P < 0.001$). For all four drug regimens studied, there was an approximately twofold difference in onset time over the age range studied. However, there was no statistically significant difference between the two pediatric age groups for any of the drug regimens studied (table 2).

For subparalyzing doses, onset time for vecuronium was 3.6–5.9 times that required for succinylcholine, depending on the age group (table 2). For paralyzing doses, this ratio was less (2.1–3.3).

Discussion

This study demonstrates that the onset times of both succinylcholine and vecuronium neuromuscular blockade are markedly age dependent, both for subparalyzing and paralyzing doses. Onset times varied by a factor of two in the age range 1–80 yr. Furthermore, succinylcholine has a markedly faster onset of action

Table 1. Demographic Data of the Patients

Group	Dose (mg/kg)	N	Male/Female Ratio	Age (yr)	Weight (kg)
1–3 yr (n = 40)	Vec 0.03	10	5/5	2.1 ± 0.2	12.1 ± 0.5
	Sux 0.3	10	8/2	2.3 ± 0.2	13.5 ± 0.6
	Vec 0.1	10	7/3	2.1 ± 0.1	12.8 ± 0.4
	Sux 1.0	10	6/4	2.0 ± 0.2	12.7 ± 0.5
3–10 yr (n = 40)	Vec 0.03	10	7/3	5.1 ± 0.4	17.9 ± 1.0
	Sux 0.3	10	7/3	5.1 ± 0.2	18.3 ± 0.3
	Vec 0.1	10	6/4	6.3 ± 0.1	24.8 ± 2.9
	Sux 1.0	10	4/6	5.5 ± 0.2	20.9 ± 0.7
20–40 yr (n = 40)	Vec 0.03	10	3/7	28.6 ± 1.9	65.0 ± 4.2
	Sux 0.3	10	3/7	32.0 ± 1.5	69.2 ± 3.1
	Vec 0.1	10	1/9	32.3 ± 1.9	60.6 ± 3.2
	Sux 1.0	10	2/8	31.7 ± 1.8	63.3 ± 5.1
60–80 yr (n = 40)	Vec 0.03	10	3/7	69.0 ± 1.7	64.7 ± 4.0
	Sux 0.3	10	4/6	65.6 ± 1.2	69.5 ± 3.2
	Vec 0.1	10	7/3	65.6 ± 1.4	74.0 ± 5.0
	Sux 1.0	10	6/4	66.9 ± 1.7	74.9 ± 4.2

Values are presented as mean ± SEM. Vec = vecuronium; Sux = succinylcholine.

than vecuronium does in all age groups. Comparisons obtained with subparalyzing doses allow vecuronium onset time to be quantified with respect to succinylcholine. Across all age groups, onset time for vecuronium was found to be, on average, 4.5 times greater than that for succinylcholine.

Vecuronium was chosen in this study because it can be injected quickly without the risk of hypotension[12] and histamine release,[13] and the duration of surgery did not allow use of a longer-acting agent. Integrated EMG of the adductor pollicis muscle was measured, because it correlates well with measurement of force,[14]

Table 2. Onset Time and Intensity of Maximal Blockade

Group	Dose (mg/kg)	N	Onset Time (s)	Vec/Sux Onset Time Ratio	Minimal Twitch Height (% Control)
1–3 yr (n = 40)	Vec 0.03	10	260 ± 15*†	5.9	39.2 ± 6.9
	Sux 0.3	10	49 ± 6*†	(4.5–7.6)	27.1 ± 8.7
	Vec 0.1	10	125 ± 19*†	2.1	0.4 ± 0.4
	Sux 1.0	10	58 ± 7‡	(1.8–2.4)	7.8 ± 5.2
3–10 yr (n = 40)	Vec 0.03	10	219 ± 15*†	4.2	40.2 ± 9.1
	Sux 0.3	10	63 ± 11*†	(3.6–5.0)	37.6 ± 7.0
	Vec 0.1	10	162 ± 18†	2.8	0.4 ± 0.3
	Sux 1.0	10	60 ± 8†	(2.6–3.0)	5.4 ± 3.4
20–40 yr (n = 40)	Vec 0.03	10	366 ± 27†‡§	3.6	38.5 ± 3.2
	Sux 0.3	10	102 ± 9‡§	(3.0–4.3)	29.9 ± 4.8
	Vec 0.1	10	222 ± 14‡	3.3	1.3 ± 0.4
	Sux 1.0	10	71 ± 8	(3.1–3.5)	1.0 ± 0.3
60–80 yr (n = 40)	Vec 0.03	10	473 ± 30*‡§	4.6	40.5 ± 8.2
	Sux 0.3	10	104 ± 9‡§	(4.0–5.3)	41.0 ± 7.7
	Vec 0.1	10	295 ± 31‡§	3.0	3.4 ± 1.6
	Sux 1.0	10	95 ± 7‡§	(2.9–3.2)	3.9 ± 1.2

Values are expressed as mean ± SEM. Values in parentheses are 95% confidence limits. Vec = vecuronium; Sux = succinylcholine.

* Significantly different from same drug and dose given to 20–40-yr-olds.

† Significantly different from same drug and dose given to 60–80-yr-olds.

‡ Significantly different from same drug and dose given to 1–3-yr-olds.

§ Significantly different from same drug and dose given to 3–10-yr-olds.

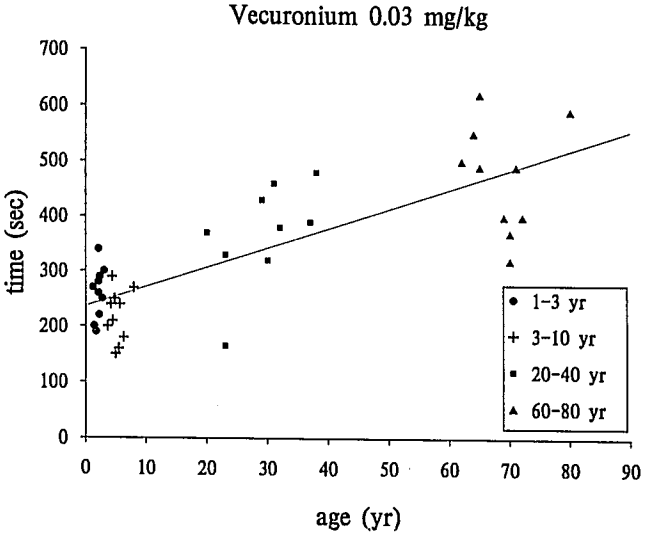

Fig. 1. Relationship between onset time to maximal blockade and age with a subparalyzing dose of vecuronium ($P < 0.00001$ by linear regression).

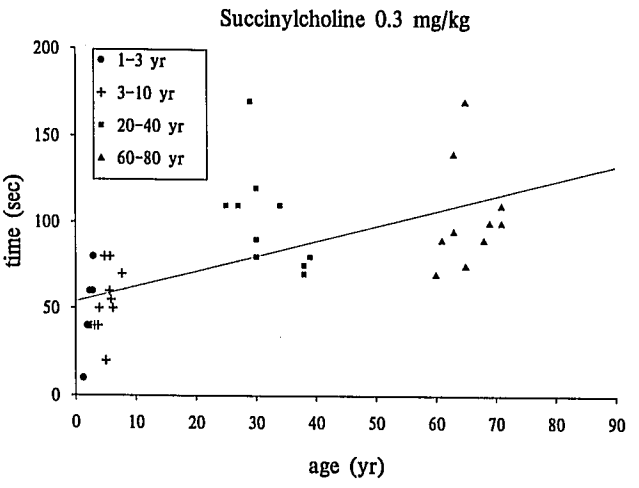

Fig. 3. Relationship between onset time to maximal blockade and age with a subparalyzing dose of succinylcholine ($P < 0.00001$ by linear regression).

but is simpler to use, and the same equipment can be used in all patients regardless of age.[15] In the four age groups studied, maximum blockade by vecuronium and succinylcholine was approximately the same. Children were reported to require approximately the same dose of succinylcholine[8] or vecuronium[16] for a similar degree of blockade as adults. In elderly patients, the vecuronium dose response was found to be the same as in young adults.[10]

When administered to facilitate tracheal intubation, 0.1 mg/kg vecuronium and 1.0 mg/kg succinylcholine are commonly used as full paralyzing doses (2–3 × ED95). Subparalyzing doses of 0.3 mg/kg succinylcholine used in our study were between the ED50 (0.184–0.240 mg/kg) and ED90 (0.352–0.420 mg/kg) values reported during N_2O-opioid anesthesia by Meakin *et al.*[8] in children, and Smith *et al.*[9] in adults. Similarly, the dose of vecuronium, 0.03 mg/kg, was between its ED50 (0.020–0.026 mg/kg) and ED90 (0.033–0.044 mg/kg) values reported by O'Hara *et*

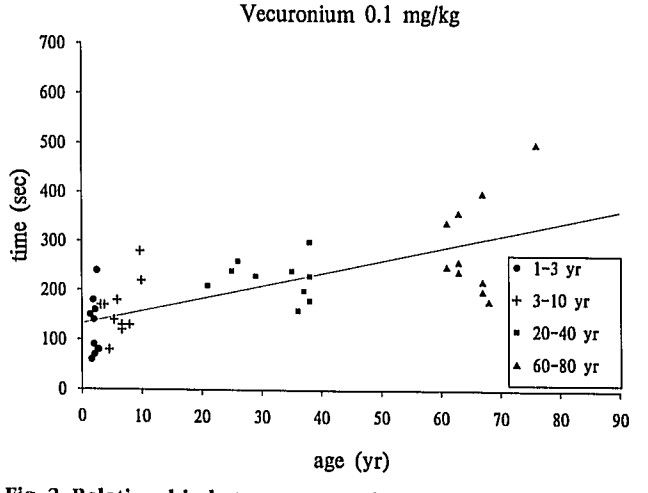

Fig. 2. Relationship between onset time to maximal blockade and age with a paralyzing dose of vecuronium ($P < 0.00001$ by linear regression).

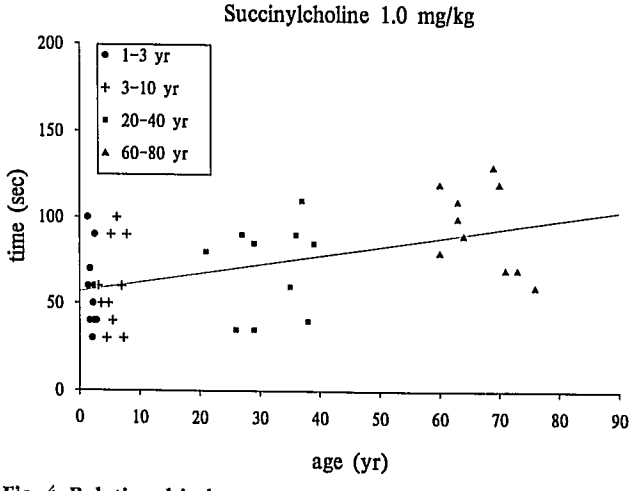

Fig. 4. Relationship between onset time to maximal blockade and age with a paralyzing dose of succinylcholine ($P < 0.001$ by linear regression).

al.[10] and Fiset *et al.*[11] in adults under similar anesthetic conditions. In this study, 0.3 mg/kg succinylcholine produced a similar intensity of blockade as 0.03 mg/kg vecuronium in all age groups (table 2). Therefore, succinylcholine has approximately one-tenth the potency of vecuronium.

The time to maximum block for both drugs and dosages increased with age. Previous studies reported shorter onset of nondepolarizing block in children 1–3 yr of age compared with that in older children,[17,18] and in young adults compared with elderly patients.[7] In the current investigation, there was no difference in onset times between 1–3 and 3–10-yr-old children. It is unclear whether the discrepancy with the previous study was caused by the different drugs and dosages used, or by the relatively small number of patients per group (ten) in the current study. This age-related effect is probably caused by circulatory factors, because both drugs, which have different mechanisms of action, are affected to the same extent. Generally, cardiac output, expressed per kilogram of body weight, decreases, and circulation time increases, as age increases, and this probably accounts for the slower onset in older individuals.

Onset time was defined as the interval between injection and maximum measured depression of response. When subparalyzing doses are given, the time corresponding to maximum blockade presumably coincides with the peak drug concentration at the neuromuscular junction. When paralyzing doses are given, measured blockade becomes 100% when the drug concentration at the neuromuscular junction is large enough to decrease adductor pollicis response below the limit of sensitivity of the measuring device, which, in this study, was 1–2%. This implies that, when depression of response is measured as 100%, the concentration of relaxant at the neuromuscular junction may increase further. Such an increase in drug concentration is not accompanied by an increase in measured blockade, because maximum measurable effect (100%) is reached. Thus, for paralyzing doses, measured onset time depends on the accuracy of the device used to measure twitch depression, although concentration at the neuromuscular junction may increase after a twitch response is no longer detectable. It follows that, although paralyzing doses are normally used clinically, the time to peak effect of a relaxant drug is best obtained with subparalyzing doses, because a measurable effect, different from 100% twitch depression, is obtained at all times.

As expected, onset time was markedly decreased by increasing the vecuronium dose from 0.03 mg/kg to 0.1 mg/kg. However, there was little difference between onset time for 0.3 and 1.0 mg/kg succinylcholine for tracheal intubation. For all age groups combined, mean onset time was 79.5 s with 0.3 mg/kg, and 71.0 s with 1 mg/kg succinylcholine (table 2). The reason for dose-independent onset time is probably related to the relative importance of circulation time for a short-acting drug such as succinylcholine. Onset time may be thought of as the sum of circulation time and time for development of blockade. Circulation time may be defined as the interval between injection and first appearance of the drug at the site of action. It depends largely on circulating factors and, thus, is independent of dose and drug. The time for development of blockade is the interval from the first appearance of the drug at the neuromuscular junction and attainment of sufficient concentrations for maximum effect. For succinylcholine, circulation time is an important fraction of onset time, because blockade develops rapidly. Thus, dose-dependent variations in onset time are small.

With full paralyzing doses, vecuronium onset time was 2.1–2.8 times that required with succinylcholine in children, and 3.0–3.3 times that in adults. This is similar to the ratios of 2.0–2.6, found by Reynolds *et al.*[19] in children aged 2–13 yr, and 3.3, reported by Martin *et al.*[20] in adults aged 23–72 yr. Despite similar results, the methods used in those studies were different. Larger doses of succinylcholine (1.5 mg/kg) were given in both studies. Volatile anesthetics, which potentiate both vecuronium and succinylcholine blockade,[21,22] were employed in Reynolds' study. Visual evaluation of twitch disappearance, which probably correlates with 95–98% block,[23] was used by Martin *et al.*[20] Train-of-four (TOF) stimulation employed in the same study has been reported to decrease onset time, probably by augmentation of muscle blood flow, which, in turn, increases delivery of relaxant to neuromuscular junction.[24] Nitrous oxide, used in all these studies, potentiates succinylcholine-induced block[25] and, in clinical practice, nitrous oxide is often not administered before the neuromuscular blocking drug given at induction. In this study, no inhaled anesthetic was administered, and we used a standard stimulation pattern with single stimuli 0.1 Hz. Furthermore, the relaxant was injected within 30 s of the first stimulus, to avoid the effect of repeated stimulation.[24]

In the evaluation of new or existing nondepolarizing neuromuscular relaxants, it is important to make valid

comparisons of onset times with those of succinylcholine. To achieve this, equipotent doses must be given, and, in this regard, subparalyzing doses are preferred, because onset time is independent of the degree of blockade attained. Results obtained in patients of a certain age group may not apply to younger or older subjects. In the current study, onset time for vecuronium is 4.5 times that for succinylcholine. Considerable narrowing of this ratio would be required for a nondepolarizing drug before it can be considered to have onset characteristics approaching those of succinylcholine.

In conclusion, onset times for both vecuronium and succinylcholine become progressively longer with advancing age. Comparing the onset of a nondepolarizing relaxant with succinylcholine, equipotent subparalyzing doses of both drugs should be used in patients of the same age.

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