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The Neuromuscular Response of Infants to a Continuous Infusion of Succinylcholine

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The response of the adductor of the thumb to ulnar nerve stimulation (0.1 Hz) was evaluated during continuous infusion of succinylcholine (SCh) in 20 infants anesthetized with halothane (1%) and N_2O/O_2. Train-of-four stimulation (2 Hz for 2 s) was used to differentiate between phase I and phase II block. Some infants were very resistant to the neuromuscular effects of SCh. These infants (Group 1) were younger in age, 57 ± 15 days (mean ± SE) and required 24.6 ± 3.3 $mg \cdot kg^{-1}h^{-1}$ SCh to achieve more than 90% depression of the twitch. Older infants (Group 2), 188 ± 33 days, required significantly less ($P < 0.001$) SCh (8.7 ± 0.5 $mg \cdot kg^{-1}h^{-1}$) to achieve the same degree of twitch suppression. Group 1 infants recovered from the effects of SCh very rapidly. After 10 mg/kg SCh, the train-of-four ratio in Group 1 infants recovered to 75% in 4.7 ± 0.6 min, whereas it took 34 ± 10 min in Group 2 infants ($P < 0.01$). Tachyphylaxis developed in infants after 3.6 ± 0.3 mg/kg (mean ± SE) and phase II block after 5.3 ± 0.7 mg/kg ($P < 0.05$) SCh. Combining the data of infants with that of children from a previous study conducted in a similar fashion[1] resulted in significant correlation ($P < 0.001$) between the log age and SCh requirement. The rate of administration of a continuous infusion of SCh in infants should be based upon the response of infants and not on a fixed dose ($mg \cdot kg^{-1} \cdot h^{-1}$). (Key words: Neuromuscular relaxants: succinylcholine. Anesthesia: pediatric. Monitoring: stimulator, nerve.)

SUCCINYLCHOLINE can be administered as in a continuous infusion to provide neuromuscular relaxation. Side effects of this technique are the development of tachyphylaxis and Phase II block. In a previous study[1] we demonstrated that children 1–15 yr old anesthetized with halothane and N_2O develop tachyphylaxis after a mean (±SE) intravenous dose of SCh 3.0 ± 0.4 mg/kg and Phase II block (train-of-four ratio less than 50%) after 4.1 ± 0.6 mg/kg.[1] The dose at which infants develop tachyphylaxis and Phase II block has not been defined previously.[2]

The present study was undertaken to evaluate the neuromuscular response of infants during the continuous administration of SCh by recording the force of contraction of the adductor of the thumb in response to supramaximal ulnar nerve stimulation at the wrist. A stimulus of 0.1 Hz was used to determine the degree of neuromuscular relaxation, and train-of-four stimulation was used to differentiate between Phase I and Phase II block.

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Methods

The protocol for this study was approved by the Subcommittee on Human Studies, Committee on Research, of our institution.

Twenty ASA I infants, 4 days to 11 months, undergoing a variety of elective abdominal procedures, were studied. None of the patients were premature and none had neuromuscular disease. The infants did not receive antibiotics and had no evidence of electrolyte imbalance. Infants older than 9 months were premedicated with rectal methohexital (20–25 mg/kg). No premedication was given to the younger infants. Anesthesia was induced by a face mask with N_2O/O_2 and halothane; after tracheal intubation, patients were maintained at 1% inspired halothane in N_2O and O_2 (2:1 ratio).

A blood pressure cuff, precordial and/or esophageal stethoscope, oral temperature probe, and ECG were used to monitor the infants. Intravenous fluids consisted of 5% dextrose in lactated Ringer's solution infused through a hand vein. Rates of fluid administration were calculated according to our standard formulas.[3]

The force of contraction of the adductor pollicis was measured using a Grass FT-03 force displacement transducer and a Grass polygraph (Model 7C). Supramaximal square wave stimuli of 0.2 ms duration at a frequency of 0.1 Hz were delivered to the wrist through surface electrodes. Electrical impulses were generated by a Grass S88 stimulator through an isolation unit (Grass SIU5). Intermittently, every 1–3 min, train-of-four stimuli (2 Hz for 2 s) were used to measure train-of-four ratios (T4/T1).

For surgical relaxation, an I MED (Model 92Z0) volumetric infusion pump was used to administer 0.2% SCh (2 mg/ml.) The initial infusion rate was 5.0 $mg \cdot kg^{-1} \cdot h^{-1}$ (83 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Depending on the twitch response of the patient, the infusion rate was increased by increments of 2.5 $mg \cdot kg^{-1} \cdot h^{-1}$ (41 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or 5.0 $mg \cdot kg^{-1} \cdot h^{-1}$. The slow rate of incremental increase (2.5 $mg \cdot kg^{-1} \cdot h^{-1}$) was used if the twitch was less than 50% of control in response to the initial infusion. The faster rate of incremental increase was used if the patient was resistant to the neuromuscular effects of SCh. The infusion rate was adjusted to maintain a twitch height at less than 10% of control.

Tachyphylaxis was defined as being present when the twitch height started to recover and its amplitude increased to more than 10% of the basal value despite the continuous infusion of SCh at a constant rate. Phase II

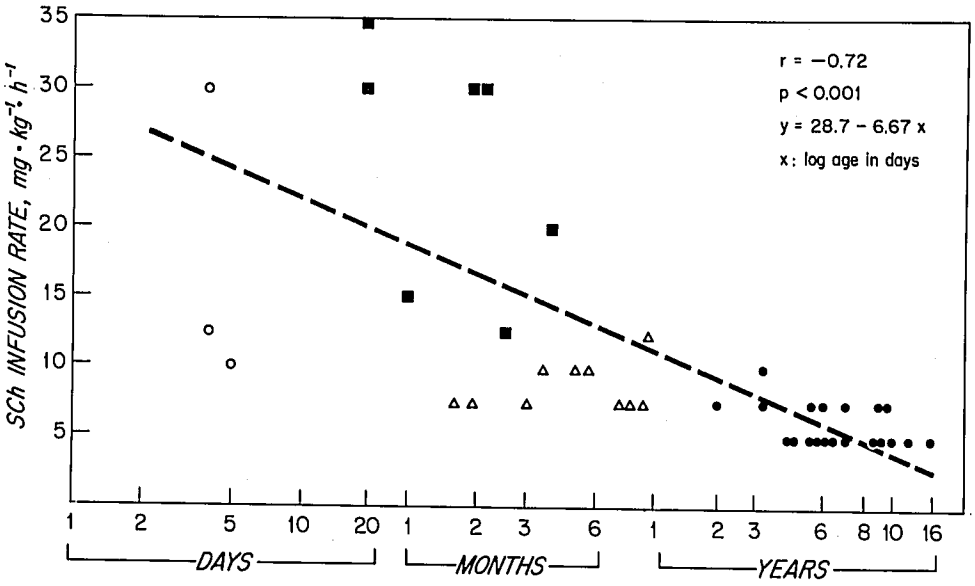

FIG. 1. The age of infants and children in relation to the infusion rate of SCh required to maintain more than 90% depression of twitch response. Data of children are from our previous study.[1] (O = neonates, ■ = infants Group 1, Δ = infants Group 2, ● = children.)

block was defined as being present when the train-of-four ratio was less than 50% (T4/T1 < 50%).

Statistical analysis was performed using the noncorrelated Student's *t* test and the correlation coefficient. The data were considered significantly different when the *P* values were less than 5%.

Results

From the data of the present study we noticed that the requirement of succinylcholine in infants was extremely variable. The range of initial infusion rate to maintain more than 90% depression of the twitch was 7.5 $mg \cdot kg^{-1} \cdot h^{-1}$ to35 $mg \cdot kg^{-1} \cdot h^{-1}$. However, there was a tendency for the requirement of SCh to diminish with age. When the data of the present study were pooled with the data of our previous study in children,[1] conducted with the same techniques (equipment and anesthesia) under the supervision of the same researcher (NG), a high degree of correlation was found ($r = 0.72$; $P < 0.001$) between the log age in days of the infants and children and the dose of SCh to maintain at least 90% depression of the twitch response (fig 1).

We had the opportunity to study three neonates (less than 10 days). One of them was resistant to the neuromuscular effect of SCh, requiring 30 $mg \cdot kg^{-1} \cdot h^{-1}$ and the other two were relatively sensitive requiring 10–12.5 $mg \cdot kg^{-1} \cdot h^{-1}$. Since the number of neonates was small in the present study and their response did not fit any specific pattern, we report their data separately (tables 1–3).

Infants in this study exhibited two types of response to SCh. One group (Group 1) was extremely resistant to the neuromuscular effects of the drug. These infants required more than 12.5 $mg \cdot kg^{-1} \cdot h^{-1}$ to maintain more than 90% twitch depression, and they recovered very rapidly (less than 10 min after 10 mg/kg). A dose of 12.5 $mg \cdot kg^{-1} \cdot h^{-1}$ was used as a cutoff point because it represents more than twice the mean dose of SCh that produced at least 90% depression of twitch in children.[1]

The response of the second group of infants (Group 2) was comparable to that of older children.[1] These infants required less than 12.5 $mg \cdot kg^{-1} \cdot h^{-1}$ of SCh and recovered more slowly from its effect (>11 min). Infants in Group 1 were younger (20–130 days), whereas those in Group 2 were older (48–340 days). We also calculated the requirement of these infants according to body surface area. Group 1 infants required 424 ± 52 $mg \cdot m^{-2} \cdot h^{-1}$, a significantly higher amount of SCh than the Group 2 infants who required 174 ± 15 $mg \cdot m^{-2} \cdot h^{-1}$ ($P < 0.001$).

Neither the dose of SCh required to produce tachyphylaxis nor the duration of SCh infusion to induce Phase II block was significantly different between the two groups of infants in the present study and the children of the previous study (Table 3).[1] However, Phase II block occurred after a slightly larger dose (5.5 ± 0.5 mg/kg) in infants of Group 1 than in infants of Group 2 (3.6 ± 0.6 mg/kg) ($P < 0.05$) (Table 2).

The recovery time of train-of-four was also significantly faster in the infants of Group 1 relative to Group 2 (Table 3). Recovery time of the train-of-four from 25% to 50% was 1.4 ± 0.3 min for Group 1 and 8.1 ± 2.7 min for Group 2 ($P < 0.05$); from 50% to 75% it was 2.4 ± 0.5 min for Group 1 and 21.8 ± 4.6 min for Group 2 ($P < 0.005$).

Discussion

The results of the present study and those of our previous study of children indicate that the dose of SCh

TABLE 1. The Age, Weight, Infusion Rate of Succinylcholine and Maximum Twitch Depression Achieved in Infants and Children

	Age	Weight (kg)	Infusion Rate That Produced >90% Depression of Twitch $mg \cdot kg^{-1} \cdot h^{-1}$	Maximum Twitch Depression Achieved %
Neonates n = 3	4.4 ± 0.3 days (4–5)	3.3 ± 0.4 (2.6–4)	17.5 ± 6.3 (10–30)	96 ± 1.1 (94–98)
Group 1 n = 7	57 ± 15 days (20–130)	5.1 ± 0.4 (4–6.6)	24.6 ± 3.3* (12.5–35)	93 ± 1.1 (90–96)
Group 2 n = 10	188 ± 33 days (48–340)	6.9 ± 0.5 (5–9.3)	8.7 ± 0.5*† (7.5–12.5)	96.2 ± 0.9 (90–100)
Mean for all infants n = 20	115 ± 22 days	5.6 ± 0.4	15.4 ± 2.2†	95 ± 0.7
Children n = 22	6.4 ± 0.8 yr (1–15)	14.4 ± 2.7 (7.4–75)	6.47 ± 0.3† (5–7.5)	96.5 ± 1.2 (90–100)

Values shown are mean ± SE error. Range is shown in parentheses.
Data of children are from our previous study DeCook and Goudsouzian.[1]

* $P < 0.001$ between Groups 1 and 2 infants.
† $P < 0.005$ between infants and children.

TABLE 2. Dose and Duration of Succinylcholine Infusion for Onset of Tachyphylaxis and Phase II Block

	Dose of SCh to Onset of Tachyphylaxis (mg/kg)	Duration of SCh Infusion to Onset of Tachyphylaxis (min)	Dose of SCh to Onset of Phase II Block (mg/kg)	Duration of SCh Infusion to Onset of Phase II Block (min)
Neonates	4.7 ± 0.8 (3.2–6.1)*	16 ± 2.7 (11–20)	8.6 ± 4.3 (3–17)	16.3 ± 3.9 (9–22)
Group I	3.9 ± 0.3 (3–5)	14.6 ± 1.8 (7–22)	5.5 ± 0.5† (3.5–8)	17.8 ± 2.4 (10–30)
Group II	3.1 ± 0.5 (2–6.5)	16.8 ± 2.3 (12–35)	3.6 ± 0.6† (2–6.3)	22.5 ± 4 (14–40)
Mean for all infants	3.6 ± 0.3	15.8 ± 2.3	5.3 ± 0.7	20.2 ± 2
Children	3.0 ± 0.4 (0.8–6.2)	23 ± 2 (8–44)	4.1 ± 0.6 (1.6–12.8)	29 ± 5 (9–68)

Values shown are mean ± SE.
* Range is shown in parentheses.

† $P < 0.05$ between Group 1 and 2 infants.

TABLE 3. Times To Recovery (in minutes) of Train-of-four Ratio after Discontinuation of Succinylcholine Infusion

	Total Dose of SCh Administered	Duration of SCh Infusion	Lowest T-of-4 Recorded %	Lowest T-of-4 to 25%	25–50%	50–75%
Neonates	10.5 ± 0.2 (10–11)*	31 ± 16 (39–52)	5 ± 3.5 (1–12)	6 ± 4.1 (1–14)	4 ± 0.6 (1–22)	17.3 ± 6.8 (4–24)
Group 1	9.8 ± 0.2 (8–12)	35.4 ± 3.9† (26–52)	12.8 ± 5.4 (1–40)	1.2 ± 0.1 (1–2)	1.4 ± 0.3‡ (1–3)	2.4 ± 0.5§ (1–5)
Group 2	9.3 ± 0.7 (8.5–12)	53 ± 3.4† (47–64)	13.1 ± 5.7 (1–34)	5.4 ± 3.3 (1–19)	8.1 ± 2.7‡ (2–20)	21.8 ± 4.6§ (8–36)
Mean of all infants	9.8 ± 0.3	43.4 ± 2.9	11.5 ± 3.2	3.6 ± 1.5	5.8 ± 2	8.4 ± 2.9†
Children	10.3 ± 0.6 (4.8–13.4)	71 ± 5 (26–105)	12 ± 5 (1–50)	3.4 ± 0.5 (1–9)	11.6 ± 3 (1–27)	25 ± 5† (2–45)

Values shown are mean ± SE.
The data in children are from previous study.[1]
* Range is shown in parentheses.

† $P < 0.01$.
‡ $P < 0.05$.
§ $P < 0.005$.

required to produce more than 90% depression of twitch height is related to age, the requirement being higher in younger infants and diminishing with age ($r = 0.72$; $P < 0.001$) (fig. 1). In older children the dose requirement is more uniform, whereas it is more diverse in younger infants. Neonates less than 10 days old were the most unpredictable. The younger infants (57 ± 15 days) who required larger doses (24.6 $mg \cdot kg^{-1} \cdot h^{-1}$) recovered more rapidly from the neuromuscular effects of SCh than the older infants (188 ± 33 days) who required a slower infusion rate (8.7 $mg \cdot kg^{-1} \cdot h^{-1}$).

The exact age or weight at which infants converted from being resistant to sensitive could not be delineated. Two infants of practically the same age (2 months) and weight (5 kg) had very different responses to SCh. One required little (7.5 $mg \cdot kg^{-1} \cdot h^{-1}$) while the other required a large dose (30 $mg \cdot kg^{-1} \cdot h^{-1}$). Dosage calculations based on body weight or surface area would not have predicted the requirement of these infants. Therefore, the dose in infants should be based upon their response.

Previous studies have shown that infants are more resistant than children to a single intravenous dose of SCh. In infants, 2 mg/kg is equipotent to 1 mg/kg in children.[4,5] After intramuscular administration, a decreased requirement with age also has been reported.[6] However, these single-dose studies[4–6] did not demonstrate this marked (threefold) resistance. This is probably due to the fact that a 1 mg/kg dose in children[5] or adults[7] consistently produces 100% depression of the twitch, whereas a relatively constant level of twitch depression is maintained with continuous infusion, and thus pharmacologic differences can be detected more easily.

Previous studies have suggested that the high SCh requirements of infants is due to their large extracellular fluid space compared with that of older children.[1,4] Since succinylcholine is a small, readily diffusible molecule that is distributed rapidly in the ECF, differences in extracellular volume might explain the general trend of decreased requirement with age. However, this does not explain the marked threefold difference in the SCh requirement between young infants and older ones or among young infants of the same age.

A simple explanation of our observations would be that the resistant infants (Group 1) have a higher level of plasma pseudocholinesterase and thus hydrolyze the drug rapidly; hence, their requirement would be higher and recovery would be rapid. However, it has been demonstrated clearly that the cholinesterase levels of infants less than 6 months is about half that of adults.[4,8,9]

Another explanation of this high requirement by some infants is that their myoneural junction is relatively immature and thus behaves differently. In previous studies, we demonstrated that infants less than a month old had lower train-of-four values and tetanus-twitch ratios than infants older than 2 months of age.[10] Studies with nondepolarizing relaxants have shown a wide variation in their effect.[11,12] In one study, some neonates required three times the average plasma level of *d*-tubocurarine to achieve the same degree of neuromuscular relaxation as other neonates.[13] However, in these studies the evidence of immaturity was seen only in neonates less than 2 months old. The present study indicates that marked differences in the neuromuscular response to relaxants might occur up to 4 months of age. If any of our infants were premature at birth or had serious electrolyte imbalance, one could have suggested that these factors might alter their response. However, all our infants were full-term ASA Class I babies, and all were in electrolyte balance.

In this study the dose of SCh that led to the development of tachyphylaxis in Group 1 infants was not different from that in Group 2, or to that in the children of the previous study.[1] The smaller infants required a slightly larger dose before developing Phase II block. It is logical to assume that the development of Phase II block is a function of their higher requirement for maintenance.

Since the neuromuscular response of small infants to SCh is extremely variable, it is imperative to follow their response throughout the administration of relaxant. A neuromuscular monitor is invaluable in this respect as well as in differentiating between Phase I and Phase II response. An easy way to detect these sensitive infants from the resistant ones is to discontinue the infusion of SCh for a very short interval. If the twitch and the train-of-four start to recover quickly to 50% in 2 min (Table 3), then the patient is most probably resistant to the drug and the infusion can be resumed. However, if recovery is slow it becomes important to discontinue the infusion early to allow sufficient time for spontaneous recovery.

In conclusion, we found that the requirement of SCh in infants and children decreases with age. Some infants up to the age of 4 months can be very resistant to the neuromuscular effects of SCh and also recover quickly from its effect. We recommend that the rate of administration of SCh be based on the neuromuscular response of the patient.

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