The Response of Newborns to Succinylcholine and d-Tubocurarine

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The durations of action of succinylcholine and *d*-tubocurarine in newborns and adults were compared. Patients were given similar doses on the basis of body surface area, *d*-tubocurarine, 4 mg/m², and succinylcholine, 40 mg/m². Duration of action was evaluated by observing muscle response to nerve stimulation. We found little difference between the durations of action of succinylcholine in newborns and adults. Newborns, on the other hand, were more sensitive to *d*-tubocurarine than adults.

In 1955, Stead reported that newborns and adults respond differently to the action of muscle relaxants. Using ventilatory depression to assess the responses to these agents, he concluded: 1. the neonate requires at least two times the dose of succinylcholine in mg/kg to produce depression comparable to that in the adult; 2. the neonate is more sensitive to the effects of *d*-tubocurarine than the adult.[1]

Churchill-Davidson and Wise studied the same problem by evaluating the effects of the muscle relaxants using electromyographic techniques. In their initial report they concluded that the newborn was resistant to the action of the depolarizing relaxant, decamethonium. To attain paresis in the hand muscles equal to that in the adult, the newborn required two to three times the adult dose of this drug, in mg/kg.[2] In a second report they said they were unable to confirm Stead's finding regarding higher sensitivity of the newborn to *d*-tubocurarine. When they gave equal doses of *d*-tubocurarine (by body-weight calculation) to adults and newborns, they found equal degrees of weakness in the hand muscles.[3]

The purpose of our study was to compare the effects of relaxants in newborns and adults when similar doses based on body surface area were given. We have used the nerve stimulator and force-displacement strain gauge to measure responses to these relaxants.

Methods

Seventy-three patients having operations under general anesthesia were included in this study. Sixty were adults who served as controls to determine the usual durations of action of *d*-tubocurarine and succinylcholine. Moderate doses of barbiturates and/or narcotics and belladonna alkaloid were given for premedication. Anesthesia was induced with thiamylal or thiopental, 200–300 mg, or nitrous oxide and oxygen. For maintenance, nitrous oxide, 2 l/min, oxygen 2 l/min, and halothane, 0.5 to 1.5 per cent, were given.

Needles were placed subcutaneously overlying the ulnar nerve at the wrist. A Block-Aid® Monitor stimulated the nerve supramaximally at a rate of one shock/4 sec. Supramaximal stimulation was assured by increasing the voltage output of the stimulator beyond the point of maximum muscle response. Force of adduction of the thumb was measured by a technique previously described.[4]

During the anesthesia 20 patients were given succinylcholine, 40 mg/m² body surface area, and 40 patients were given *d*-tubocurarine, 4 mg/m². These doses were chosen because the response of the adult patient to the absolute dose is familiar to anesthesiologists (succinylcholine, 68 mg; *d*-tubocurarine, 7 mg). Body surface area was estimated from height and weight using the Dubois nomogram. The degree and duration of neuromuscular block were determined by noting the change in force of thumb adduction that followed administration of the relaxant.

Thirteen of the patients were less than 40 days old and had had 15 operations. Information relevant to this group is listed in table 1. In these patients, anesthesia was induced and maintained with nitrous oxide, oxygen and halothane. During anesthesia, similar doses of either succinylcholine and/or *d*-tubocurarine, on the basis of body surface area, were given.

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TABLE 1. Data for 13 Patients Less Than 40 Days Old

Patient	Age at Operation (days)	Diagnosis	Operation	Temperature During Operation (C)	Preoperative Electrolytes (mEq/l)				Succinylcholine				d-Tubocurarine	
									Recovery Times (min)					
					HCO_3^-	Cl	Na	K	Dose (mg)	10 Per Cent	50 Per Cent	90 Per Cent	Dose (mg)	Recovery Time (min) 10 Per Cent
1	1	meningomyelocele	closure meningomyelocele	36–37									0.78	23
2	1	imperforate anus	colostomy	36–38					7.2	11	12	14	0.72	>78
3	3	tracheoesophageal fistula	repair of tracheoesophageal fistula	34–35									0.68	51
4	3	megacolon	colostomy	37					7.0	8	9	11		
*5	10	hydrocephalus	ventricular atrial shunt	36–37					8.0	12	14	17	0.80	11
**6	10	wound dehiscence	closure of wound dehiscence	35	24.7	101	139	5.3					0.70	12
7	10	preauricular mass	excisional biposy of mass	35–37					0.6	6	7	10	0.96	20
8	20	chronic diarrhea	rectal biopsy	34–35	24.9	99	137	4.0	8.8	22	26	31	0.88	17
9	20	pyloric stenosis	pyloromyotomy	35–37	28.0	101	140	6.2					0.92	21
10	24	pyloric stenosis	pyloromyotomy	35–36	25.6	110	145	5.1	8.0	5	6	7	0.90	>35
11	28	pyloric stenosis	pyloromyotomy	37	23.4	98	138	4.0	8.0	4	5	6	0.80	35
12	30	premature closure of cranial sutures	strip craniectomy	32									1.10	>49
13	36	neuroblastoma	liver biopsy and adrenalectomy	37									1.10	>75
14	37	pyloric stenosis	pyloromyotomy	37	19.2	98	138	4.0	9.0	5	6	7	0.90	>37
15	38	pyloric stenosis	pyloromyotomy	35–36	23.8	108	143	6.0	6.7	5	6	7		

* Reoperation of patient 1. ** Reoperation of patient 4.

TABLE 2. Recovery from Succinylcholine (40 mg/m² b.s.a.)

	No. of Patients	Mean Age	Mean Dose (mg)	Mean Recovery Time and S.D. (min)		
				10 Per Cent	50 Per Cent	90 Per Cent
Adults	20	40 years	68	7 ± 1.3	8.5 ± 1.6	10 ± 2.4
Infants	8	18 days	8	7 ± 3.0	8.3 ± 3.0	10 ± 3.8

TABLE 3. Recovery from d-Tubocurarine (4 mg/m² b.s.a.)

	No. of Patients	Mean Age	Mean Dose (mg)	Median 10 Per Cent Recovery (min)	Mean Twitch Depression (Per Cent)
Adults	40	42 years	7	8.4	67
Infants	13	17 days	.85	35	99

A nomogram modified for infants was used for estimation of body surface area.[5] The method of evaluating responses to muscle relaxants was that described for the adult.

During the 15 operations on infants, nine studies of succinylcholine and 13 studies of *d*-tubocurarine were done. In seven patients in whom both drugs were given, succinylcholine was given first. *d*-Tubocurarine was not administered until there had been complete recovery from succinylcholine, as evidenced by responses to nerve stimulation. We have shown in a previous investigation that the duration of action of *d*-tubocurarine is unaltered by prior use of succinylcholine.[6]

The mean 10, 50 and 90 per cent twitch-force recovery times following succinylcholine were determined in the newborn and compared with the mean times for attainment of the same end points in the adults.

The duration of relaxation in the newborn following *d*-tubocurarine was prolonged. In only eight were we able to determine the time to 10 per cent recovery before the termination of the operation necessitated antagonizing the relaxation with neostigmine. Since the missing values were those of the patients in whom the drug had the most prolonged response, we were able to obtain the median time for 10 per cent recovery. This value was compared with the median 10 per cent recovery time in adults.

Results

Mean age of the 60 adult patients was 41 years. The group given succinylcholine received an average of 68 mg (range 54–83) of drug. All patients had 100 per cent depression in twitch force. Recovery times to 10, 50 and 90 per cent of control values averaged 7.0, 8.5, and 10 minutes, respectively. Adults given *d*-tubocurarine received an average of 7 mg (range 5.5–9.0) of the drug, which produced a mean depression in twitch force of 67 per cent from control values. The median time to 10 per cent recovery was 8.4 minutes.

The average age of the newborns was 18 days. Those given succinylcholine, mean dose 8 mg, had 100 per cent twitch depression. As in the adults, recovery averaged 7.0, 8.3, and 10 minutes to 10, 50 and 90 per cent of control twitch force values. Results from Patient 8 were omitted because of inordinately prolonged neuromuscular block. Recovery times to 10, 50 and 90 per cent were 22, 26 and 31 minutes. The possibility of atypical plasma cholinesterase was suspected in this child. Because he was critically ill with wasting diarrhea, we deemed testing for plasma cholinesterase inappropriate to his care. Had we included the results from this patient, it would have changed the mean values but would not have resulted in a statistically significant difference between adult and newborn groups.

The mean dose of *d*-tubocurarine was 0.85 mg. Eleven of 13 patients had 100 per cent depression in twitch force. The remaining two had more than 95 per cent twitch force depression. Median 10 per cent twitch force recovery took 35 minutes. The results are summarized in tables 2 and 3. As a result of these studies, we conclude that newborns respond to succinylcholine similarly to adults and that most newborns are more sensitive to the action of *d*-tubocurarine than adults.

Discussion

Several differences between adults and neonates might be implicated in their different responses to *d*-tubocurarine. The anesthesia in many of the adults was induced with a barbiturate. We excluded this as an important reason by inducing anesthesia in eight of the adults with nitrous oxide, oxygen and halothane. The durations of action of *d*-tubocurarine in these eight patients were not different from the durations in the other 32.

The second factor which might account for some of the increased magnitude and prolonged response to *d*-tubocurarine in the infants was the higher concentration of halothane necessary to maintain an equal level of surgical anesthesia. Gregory, Eger and Munson have shown that the minimum alveolar anesthetic concentration of halothane in the neonate is nearly 40 per cent greater than in the minimum alveolar anesthetic concentration in the adult.[7] It is probable that at increased depth of anesthesia halothane will have greater synergism with *d*-tubocurarine, although this synergism has not been measured.

Our findings are in close agreement with those of Churchill-Davidson and Wise, but our conclusions are not. We have arrived at different conclusions because they chose an infant dose based on body weight. We, on the other hand, chose a dose based on body sur-

face area. Had we given succinylcholine on a weight basis, approximately 1 mg/kg, our infants would have received an average of 3.2 mg, not 8 mg. Like Churchill-Davidson and Wise, we would have concluded that the infant requires two to three times the adult dose to produce the same degree of neuromuscular block. Had they given a dose based on body surface area instead of weight in their *d*-tubocurarine study, they might have agreed that the newborn is more sensitive to the action of *d*-tubocurarine.

Clinical observation of the effects of most drugs has shown that infants given doses scaled down on the basis of weight from adult therapeutic doses will be undertreated. Likewise, finding a therapeutic dose in the infant and scaling this on a weight basis for the adult will result in overdosage.[5, 9]

Recently, pediatricians have come to accept body size rather than weight as a means of measuring drug dosage. A firm foundation for this practice was established in 1949, when Crawford *et al.* studied blood concentrations of acetylsalicylate and sulfadiazine in infants, children and adults. They demonstrated similar blood levels of drug when equal doses on the basis of body surface area were given. In a further study that included a variety of other medications, their clinical results suggested that this method of dose calculation offered greater accuracy than calculations based on a unit of body mass.[5]

In addition to its use in determining drug dosage, the surface-area rule has simplified fluid and electrolyte therapy. Under ordinary circumstances only one dosage value is necessary for infants, children and adults. Although the surface-area rule works well in older infants and children, in the neonate the systems of detoxification and elimination of drugs are poorly developed and all rules may fail.[10]

The two relaxants we chose to study, by coincidence, behave in a manner that will satisfy those who believe that weight is the best measure of relative dose, as well as those who prefer the surface-area measurement. If the choice be weight, as was Churchill-Davidson's and Wise's, doses of *d*-tubocurarine scaled in mg/kg will have equal potency in the neonate and the adult. To be consistent, however, the conclusion would be that the neonate is resistant to the depolarizing muscle relaxants. If, as we believe, the surface-area rule is proper, the conclusion would be that succinylcholine behaves similarly in the neonate and the adult, and that the neonate is quite sensitive to *d*-tubocurarine. It is not possible to conclude that neonates are both sensitive to curare and resistant to succinylcholine.

The practicing anesthesiologist can rightfully ask, "How much relaxant shall I give?" The answer comes from the results of both studies. Giving a neonate 0.5 mg of *d*-tubocurarine produces a degree of relaxation equivalent to that produced by 12 mg in the average adult. Giving a neonate 8 mg of succinylcholine will result in a degree of relaxation equivalent to that produced by giving an adult 60 to 70 mg.

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