RESPIRATORY COMPLICATIONS ASSOCIATED WITH THE USE OF MUSCLE RELAXANTS IN YOUNG INFANTS

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RECENT reports have suggested that the response of the newborn and of the young infant to the administration of skeletal muscle relaxants may differ from that of the adult. Stead [1] stated that the neonate resembles a patient with myasthenia gravis in his relative resistance to succinylcholine and increased sensitivity to *d*-tubocurarine. Rees [2] recommended the avoidance of the non-depolarizing drugs in the neonatal period. He also pointed out that the neonate might show the so-called "dual response" when given succinylcholine over a long period of time. Other authors [3, 4, 5] also have reservations regarding the use of *d*-tubocurarine in the young infant. Telford and Keats [6] presented data showing that children are more resistant to the effects of succinylcholine than are adults. On the other hand, Foldes [7] implies that, with correct dosage, both the depolarizing and non-depolarizing drugs may be used safely in the infant.

The present study consists of a review of a series of consecutive, unselected cases for the purpose of (a) establishing whether or not actual clinical experience showed that the infant responded differently from the adult to the administration of muscle relaxants and (b) whether or not this behavior, if present, could be related to any of the following: (1) age of the infant, (2) changes in body temperature, and (3) duration of anesthesia.

MATERIAL

The cases analyzed consisted of infants less than 13 weeks of age who had undergone a variety of surgical procedures during a two year period (1957–59). The infants were divided into two groups of almost equal number; one group of 114 children did not receive a muscle relaxant during the anesthesia, while a second group of 106 children was given succinylcholine and/or *d*-tubocurarine. Most of the infants who were given *d*-tubocurarine also had received a prior dose of succinylcholine for the purpose of facilitating endotracheal intubation. Because *d*-tubocurarine was given always *after* the return of adequate respirations, it was considered reasonable to separate the entire group into three categories: (1) those who did not receive a relaxant, (2) those who were given only succinylcholine, and (3) those who received *d*-tubocurarine.

The weights of the infants varied from 1.5 to 7.5 kg. (3.3 to 16.5 pounds). The total individual doses of succinylcholine ranged from 5 to 50 mg. intravenously and 15 to 65 mg. intramuscularly; those for *d*-tubocurarine ranged from 0.25 to 4.5 mg. intravenously. A variety of anesthetic agents and techniques were used.

Each record was reviewed for evidence of postoperative respiratory insufficiency. For the purpose of this study, respiratory insufficiency was defined as any ventilatory inadequacy, occurring during the immediate postoperative period, which, on clinical evaluation, required the assistance of respiration. For purposes of comparison, the patients were separated into four age categories: 0–7 days, 1–4 weeks, 5–8 weeks, and 9–12 weeks.

RESULTS

Two hundred and twenty cases were reviewed. Twenty-nine (13 per cent) were thoracic operations, 92 (42 per cent) were abdominal procedures and 99 (45 per cent) were operations outside the major body cavities. A majority of the patients were either seriously ill or presented major anesthetic problems.

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TABLE 1

RESPIRATORY COMPLICATIONS

	Number of Cases	Respiratory Complications	Incidence (Per Cent)
Patients without Relaxant	114	14	12
Patients with Relaxant	106	29	27*
Totals	220	43	20

* $P < 0.01$.

Tables 1 and 2 show the incidence of respiratory complications in the entire series (20 per cent), in the nonrelaxant group (12 per cent), in the relaxant group (27 per cent) and in the various age categories. Table 3 indicates that both those infants who were given succinylcholine alone and those who were given *d*-tubocurarine had an increased complication rate as compared to the infants who were given no relaxant. The increased incidence in the *d*-tubocurarine group was of statistical significance ($P < 0.01$), as determined by the Chi-square method.

TABLE 2

RESPIRATORY COMPLICATIONS BY AGE GROUP

	Number of Cases	Respiratory Complications			
		Without Relaxant	With Relaxant	Totals	Incidence (Per Cent)
0–7 days	60	6	14	20	33*
1–4 weeks	29	1	3	4	14
5–8 weeks	90	4	9	13	14
9–12 weeks	41	3	3	6	15
Totals	220	14	29	43	20

* $P = 0.03$.

TABLE 3

DISTRIBUTION OF RESPIRATORY COMPLICATIONS IN NONRELAXANT, SUCCINYLCHOLINE AND *d*-TUBOCURARINE GROUPS

	Number of Cases	Respiratory Complications	Incidence (Per Cent)
No Relaxant	114	14	12
Succinylcholine	89	18	20*
d-Tubocurarine	17	11	65†
Totals	220	43	20

* $P = 0.20$.
† $P < 0.01$.

TABLE 4

INCIDENCE OF HYPOTHERMIA IN NONRELAXANT AND RELAXANT GROUPS

	Number of Cases	Number of Infants 95.8 F. or below	Incidence of Hypothermia (Per Cent)
Nonrelaxant Group	86	32	37
Relaxant Group	82	50	61*
Totals	168	82	49

* $P < 0.01$.

Tables 4, 5, and 6 correlate the incidence of respiratory complications with the immediate postoperative rectal temperature. Eighty-two (49 per cent) of the 168 infants in whom the temperature was recorded had a postoperative temperature of less than 96 F.; 29 (35 per cent) of these hypothermic infants had respiratory difficulties. In 86 infants the body temperature remained at 96 F. or above; only 10 (12 per cent) of these more or less "normothermic" infants developed postoperative complications. The incidence of hypothermia in those infants who did not receive a relaxant was 37 per cent as compared to an incidence of 61 per cent in those children who did receive a relaxant. The difference

TABLE 5

INCIDENCE OF RESPIRATORY COMPLICATIONS IN "NORMOTHERMIC" INFANTS

	Number of Cases	Number of Respiratory Complications	Incidence (Per Cent)
Patients without Relaxant	54	7	13
Patients with Relaxant	32	3	9
Totals	86	10	12

TABLE 6

INCIDENCE OF RESPIRATORY COMPLICATIONS IN HYPOTHERMIC INFANTS

	Number of Cases	Number of Respiratory Complications	Incidence (Per Cent)
Patients without Relaxant	32	5	16
Patients with Relaxant	50	24	48
Totals	82	29	35

TABLE 7

EFFECT OF DURATION OF ANESTHESIA UPON THE INCIDENCE OF RESPIRATORY COMPLICATIONS

Duration of Surgery	Number of Cases	Number of Respiratory Complications	Incidence (Per Cent)
2 hours or less	115	19	16
More than 2 hours	65	21	32*

* $P = 0.02$.

was statistically significant. The incidence of respiratory complications in the children who did not receive a relaxant was 16 per cent in the hypothermic group and 13 per cent in the "normothermic" group. In those infants who did receive a relaxant, the incidence of respiratory complications was 48 per cent in the hypothermic group and 9 per cent in the "normothermic" group.

The average duration of anesthesia per case for the entire series was two hours. Table 7 shows that the infants who had more than two hours of anesthesia had a 32 per cent complication rate as compared to 16.5 per cent in those who had two hours or less. This difference was of borderline significance ($P = 0.02$).

DISCUSSION

The increased incidence of respiratory depression in those infants who received *d*-tubocurarine may have been due to one or more of the following effects: (a) a direct drug effect in the presence of a myasthenic-like state, as suggested by Stead; (b) simple overdose in the presence of a normal neuromuscular mechanism; (c) the combined effects of the muscle relaxant and hypothermia upon respiration.

Neither hypersensitivity nor the myasthenic-like state described by Stead could be excluded by the data. However, 6 of the 17 infants who were given *d*-tubocurarine responded in a normal manner, indicating that in these infants, at least, there was no grossly altered myoneural function.

Overdosage with *d*-tubocurarine was, of course, a possible etiologic cause of the respiratory problems seen in those infants who received the drug. Most authors [5, 7, 8] recommended initial doses of about 0.22 mg. per kilogram of body weight. In our series of cases, the *total* intravenous dose per patient averaged 0.42 mg. per kilogram. The 6 infants who exhibited a normal response to *d*-tubocurarine had an average *total* dose of 0.23 mg. per kilogram of body weight, while the 11 infants who showed evidence of postoperative respiratory depression had an average total dose of 0.54 mg. per kilogram, usually given as an initial larger dose followed by one or two smaller ones. However, 6 of the 11 infants who developed respiratory depression actually received total doses of *d*-tubocurarine of less than 0.23 mg. per kilogram of body weight. In these infants it was difficult to relate the postoperative respiratory problem to *d*-tubocurarine overdose.

The depressant effect of hypothermia upon respiration has been amply documented.[9, 10, 11] It is our impression that this effect summates with the effect of the muscle relaxant upon the breathing mechanism.

Bigler and McQuiston [12] presented data showing that children below the age of 6 months tend to become hypothermic during general anesthesia. Harrison, Bull and Schmidt [13] have pointed out that in the modern air-conditioned operating room the small infant may have precipitous and sharp falls in body temperature if no attempts are made to maintain body heat. Premature babies show this tendency quit markedly.[14, 15] In our study 49 per cent of the infants in whom a postoperative rectal temperature was recorded had a temperature of less than 96 F.

This group of hypothermic babies had a respiratory complication rate of 35 per cent as compared to a rate of 12 per cent in those infants whose temperature remained 96 F. or above. Of equal importance was the observation that those infants who received a muscle relaxant and had postoperative hypothermia had a respiratory complication rate of 48 per cent, as compared to a rate of 9 per cent in those infants who had a relaxant but did not become hypothermic, and a rate of 13 per cent in those infants who had neither a muscle relaxant nor became hypothermic.

These findings have led us to believe that the use of a muscle relaxant in the young infant may result in unexpected postoperative respiratory difficulties, not only because of the ease of overdosage of this age group, but also because it increases the normal tendency of the infant to lower his body temperature under general anesthesia. The mechanism by which this occurs is probably via the inhibition of shivering. The preoperative average temperature of both nonrelaxant and relaxant groups was 98 F. In both groups the major fall in temperature occurred during the first two hours of anesthesia. As anesthesia continued beyond the two-hour mark the nonrelaxant group remained at a level of 96 F., while the relaxant group continued to drift to lower temperatures. After 3 hours of anesthesia the nonrelaxant group had an average temperature of 95.9 F., but the relaxant group had an average temperature of 93.8 F.

If it is true that one of the mechanisms by which a muscle relaxant increases the respiratory complication rate is by causing more profound hypothermia, why was this effect quite clearly demonstrated by *d*-tubocurarine and not by succinylcholine? The explanation, we believe, lies in the fact that succinylcholine was given by intermittent injection. Under these circumstances, because of the relative short duration of action of the drug, inhibition of shivering was not continuous, as compared to the prolonged effect of *d*-tubocurarine, and falls in body temperature tended to be less profound.

Our conclusion that the association of *d*-tubocurarine and hypothermia resulted in a high incidence of postoperative respiratory depression seemed, at first glance, to conflict with the findings of Zaimis, Cannard and Price [16] who demonstrated in adult man, that a lowering of muscle temperature of 5–9 degrees F. increased the neuromuscular blocking action of succinylcholine while, to a lesser degree, decreased *d*-tubocurarine activity. According to the findings of these workers the combination of hypothermia with succinylcholine should theoretically give rise to a high rate of respiratory depression. However, they also demonstrated that during rewarming a reversal of these effects occurred, that is, succinylcholine block was reduced and *d*-tubocurarine block was potentiated. Since it was a routine policy to place our infants in warm Isolettes immediately after surgery, it is possible that *d*-tubocurarine potentiation occurred. The effect of changes of body temperature upon drug activity, however, cannot be readily separated from the effect of the temperature itself upon the body physiology in general. Nor can it be excluded that the depressant effect of hypothermia upon respiration may predominate over the attenuating effect of hypothermia on the drug itself.

It was not surprising to find that the 0–7 day old infants had a higher rate of complications that any of the other 3 groups. Their smaller size predisposed them to more rapid and pronounced falls in body temperature and made proper dosage difficult to estimate. Because it has been suggested by Stead [1] that the newborn's response to *d*-tubocurarine was similar to that in myasthenia gravis, it was believed that this youngest age group should show this abnormal response to the highest degree. Thus, if all the *d*-tubocurarine cases were eliminated from the calculations of complication-rates, the rate of the 0–7 day old group would tend to approach those of each of the other 3 groups. This did not prove to be the case. After the elimination of all the *d*-tubocurarine cases from the data the complication rates went from 33 to 26 per cent in the 0–7 day old group and from 15 to 13 per cent in each of the other age groups, indicating that in this small series, at least, the increased incidence of respiratory difficulties in the 0–7 day old group was not due to any abnormal response of these infants to *d*-tubocurarine.

Summary and Conclusions

The clinical records of 220 infants, between 0–12 weeks of age, were reviewed for evidence of postoperative respiratory depression.

Twenty-seven per cent of the infants who were given a muscle relaxant had postoperative respiratory depression, as compared to 12 per cent in those who did not receive a relaxant drug.

Any factor which increased the tendency of the anesthetized infant to lower his body temperature caused a rise in the postoperative respiratory depression rate. These factors included prolonged myoneural blockade, increased duration of anesthesia and age of the infant.

The increased incidence of respiratory depression in the immediate postoperative period following the use of a muscle relaxant was a result of overdose and/or hypothermia.

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