Original Articles

Neuromuscular Transmission in the Newborn Infant

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The rapid development of pediatric anesthesia over the past few years has outstripped our knowledge of the basic mechanism of neuromuscular transmission in the newborn. Many clinicians have noted that during the first few weeks of life these infants tolerate relatively large doses of the depolarizing relaxant succinylcholine, yet they are believed to be particularly sensitive to the nondepolarizing relaxant d-tubocurarine. Such observations have given rise to the suggestion that the newborn infant behaves like a myasthenic patient in its response to the muscle relaxants.1

The finding that two principal types of neuromuscular block, namely, depolarization (succinylcholine) and nondepolarization (d-tubocurarine), could easily be differentiated in man2 has made it possible to test the validity of this hypothesis. The principal features of this method of differentiation can be summarized as follows: Electromyographically, a depolarization block has three consistent features: (1) A train of nerve stimuli—both fast (tetanus) or slow (twitch)—leads to a well-maintained response of the muscle fibers provided the degree of paralysis is not complete. (2) Following a period of fast (tetanic) nerve stimulation there is no obvious improvement in neuromuscular transmission (i.e., post-tetanic facilitation). (3) After an injection of an anticholinesterase drug (neostigmine or edrophonium) there is either no change or an increase in the degree of neuromuscular block.

In direct contrast, the features of a nondepolarization block are as follows: (1) A train of nerve stimuli—both fast (tetanus) or slow (twitch)—leads to a “fade” of successive responses of the muscle fibers in a manner which is very characteristic of this type of block. (2) Following a period of fast (tet-

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Method

Neuromuscular transmission was studied in five newborn infants (four female, one male) using a modification of the technique of Harvey and Masland3 as previously described by Churchill-Davidson and Richardson.4 5 The ulnar nerve at the elbow was stimulated supramaximally with needle electrodes at rates varying from 2.5 to 50 per second. The resulting contraction of the hypothenar muscles was recorded by needle electrodes and displayed on a cathode-ray oscilloscope. A simultaneous photographic record on 35 mm. film was made. Subsequently each action potential was viewed under an enlarger and the height of the various potentials was expressed as a percentage of the height of the first twitch of the control series.

The following studies were made: (1) The height of the single twitch potential (measured in millivolts). (2) The pattern of neuromuscular-transmission response to both twitch (2.5/second) and tetanic (50/second) rates of stimulation. (3) The influence of a depolarizing drug (decamethonium) upon neuromuscular transmission. (4) The effect of an anticholinesterase drug (neostigmine) upon neuromuscular transmission and also upon the neuromuscular block produced by decamethonium.

In order to prevent any volitional movement
## Table 1. Neuromuscular Transmission in Newborn Infant

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (weeks)</th>
<th>Weight (kg.)</th>
<th>Control</th>
<th>Total Dose of C. 10 (μg.)</th>
<th>Time of Admin. (minutes)</th>
<th>C. 10 Test</th>
<th>Dose of Neostigmine or Edrophonium (mg.)</th>
<th>Neostigmine or Edrophonium Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>3.2</td>
<td>7.4 (97)</td>
<td>102 (52)</td>
<td>350 (126)</td>
<td>6</td>
<td>8 (5)</td>
<td>0.125 (N)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3.6</td>
<td>6.2 (99)</td>
<td>100 (92)</td>
<td>450 (144)</td>
<td>28</td>
<td>36 (32)</td>
<td>29 (14)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3.3</td>
<td>4.7 (100)</td>
<td>100 (100)</td>
<td>300 (128)</td>
<td>10</td>
<td>44 (13)</td>
<td>43 (15)</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>3.1</td>
<td>3.1 (100)</td>
<td>100 (101)</td>
<td>360 (117)</td>
<td>27</td>
<td>25 (25)</td>
<td>26 (25)</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>3.9</td>
<td>6.3 (103)</td>
<td>108 (107)</td>
<td>400 (153)</td>
<td>13</td>
<td>67 (67)</td>
<td>70 (65)</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>7.1</td>
<td>4.5 (100)</td>
<td>96 (87)</td>
<td>400 (279)</td>
<td>8</td>
<td>24 (24)</td>
<td>24 (20)</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>2.1</td>
<td>7.0 (89)</td>
<td>98 (88)</td>
<td>200 (81)</td>
<td>18</td>
<td>55 (33)</td>
<td>47 (15)</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>3.9</td>
<td>5.1 (103)</td>
<td>103 (100)</td>
<td>250 (153)</td>
<td>10</td>
<td>59 (59)</td>
<td>64 (58)</td>
</tr>
<tr>
<td>D.R.</td>
<td>Normal Adult</td>
<td>51 yrs.</td>
<td>66</td>
<td>12.5 (100)</td>
<td>105 (107)</td>
<td>8</td>
<td>22 (22)</td>
<td>23 (20)</td>
</tr>
</tbody>
</table>

The height of the fourth action potential of the series is represented as [   ]. The height of the smallest action potential of the series is represented as [   ]. The equivalent dose (μg/kg) required for paralyzis in adults (calculated on a body weight basis) is expressed in [   ]. N = neostigmine sulphate. E = edrophonium (Tension).
each infant was anesthetized with nitrous oxide and oxygen (4:1 liters) to which 5 per cent (250 ml./minute) of cyclopropane was added only intermittently so as to maintain the lightest possible level of anesthesia. The gases were administered via a T-piece after endotracheal intubation, which was carried out without anesthesia. Respiration was assisted at all times in an attempt to maintain adequate ventilation and reduce the risk of a high carbon dioxide level influencing the results. Body temperature was maintained either by the use of an incubator or by a radiant heat lamp. All drugs were administered into a scalp vein on a body weight basis as calculated from the equivalent clinical doses required for an average adult patient of 64 kg. (140 pounds):

Decamethonium Iodide. Dose required to produce paralysis of hypotension muscles in adult patient (64 kg.) = 2.5 mg., i.e., 39 μg./kg. body weight.

Neostigmine Sulphate. Effective dose in adults is 2.5–5.0 mg. for full anticholinesterase activity.

Edrophonium (Tensilon). Effective dose in adults is 5–10 mg. for full anticholinesterase activity.

**Results**

The full details of the findings are presented in table 1. Certain aspects of these results, however, require further emphasis:

The Height of the Single Twitch Potential (Millivolts) in Newborn. In adult patients the height of the action potential ranges between 5.6 and 20.8 millivolts. In this series the height of the action potential varied from 3.1 to 7.4 with an average of 5.5 millivolts. This finding may be due to a difference in the total number of end-plates and muscle fibers within the recording area of an infant and an adult patient.

The Pattern of Response to Both Twitch (2.5/Second) and Tetanic Rates of Stimulation. In almost every infant the twitch rate of nerve stimulation was well maintained. Tetanic stimulation, however, was remarkably poorly sustained in comparison with the normal adult patient, and after 20 seconds the height of the action potential had often dropped to less than half the control value. In three infants post-tetanic facilitation was observed for a brief period, but only lasted for a few seconds. Again, in contrast to the normal adult patient, the presence of post-tetanic exhaustion was observed in four out of seven studies, and this persisted for 5–15 minutes after the end of the period of tetanic stimulation.

The Influence of a Depolarizing Drug (Decamethonium). The motor end-plate of the newborn shows "tolerance" to a depolarizing drug, since to produce paresis of its limb muscles two to three times the equivalent dose of decamethonium required for an adult is necessary. This resistance is even greater when it is realized that weight for weight the newborn possesses less bulk of muscle than does the adult patient.

In normal adult patients the administration of 2.5 mg. decamethonium results in a neuromuscular block showing all the classical signs of a depolarization block. An example of this is shown in figure 1, and it should be noted how the decamethonium produces a severe degree of paresis, the tetanic stimulation (though reduced) is well sustained, and there is no post-tetanic facilitation.

In direct contrast, in the premature and newborn infant tetanic stimulation was not well sustained and there was some evidence of post-tetanic facilitation in this series after a comparable dose of decamethonium (fig. 2, table 1).

The Effect of Anticholinesterase Drugs. In adult patients the administration of a dose of anticholinesterase drug in the presence of a depolarization block leads either to no alteration in the block or to an increase in the degree of paresis (fig. 1). Again, in direct contrast, there was always some degree of improvement in neuromuscular transmission following the administration of an anticholinesterase drug in the newborn (table 1). This was best seen in the premature infant (−4 weeks, weight 2.1 kg.) as illustrated in figure 2 and also in a newborn infant aged 1½ weeks and weighing 3.3 kg. as shown in figure 3.

**Discussion**

These results indicate that neuromuscular transmission in the premature and newborn infant differs radically from that observed in the normal adult patient. There are several
Fig. 1. Effect of decamethonium and neostigmine in normal adult patient. (A) Control showing the effect of twitch rates of stimulation (2.5/second) before and after tetanic stimulation (50/second). (B) Same after 2.5 mg, decamethonium. Picture taken at twelfth minute. (C) Same four minutes after 2.5 mg, neostigmine. Picture taken at sixteenth minute. Time base (□□□) = 0.01 second. 1 millivolt represented as height of \( \frac{1}{2} \).
points that require special emphasis. First, tetanic stimulation (50 per second) was poorly tolerated. Secondly, in some cases a brief period of post-tetanic facilitation was soon followed by a prolonged interval of post-tetanic exhaustion lasting from five to fifteen minutes.

Fig. 2. Effect of decamethonium and neostigmine in premature infant (2.1 kg.). (A) Control showing the effect of twitch rates of stimulation (2.5/second) before and after tetanic stimulation (50/second). (B) Same after 200 µg. of decamethonium. Picture taken at twentieth minute. (C) Same four minutes after 0.01 mg. neostigmine. Picture taken at twenty-fourth minute. Time base (—) = 0.01 second. 1 millivolt represented as height of .
Fig. 3. Effect of decamethonium and edrophonium on neonate (3.3 kg.). (A) Control showing the effect of twitch rates of stimulation (2.5/second) before and after tetanic stimulation (50/second). (B) Same after 300 µg. of decamethonium. Picture taken at twelfth minute. (C) Same four minutes after 1.0 mg. edrophonium. Picture taken at sixteenth minute. Time base (-----) = 0.01 second. 1 millivolt represented as height of ]].

Thirdly, the muscles of these infants demonstrated a remarkable "resistance" or "tolerance" to the paretic effect of decamethonium.

Furthermore, this depolarizing drug produced a neuromuscular block in the newborn infant that showed many of the features of
nondepolarization. After decamethonium both twitch and tetanic rates of nerve stimulation produced a distinct "fade" in successive action potentials. Following this, the injection of an anticholinesterase drug (neostigmine) led to a marked improvement in neuromuscular transmission. Some features of this type of block closely resembled a "dual" type of response previously described for patients with myasthenia gravis and also after the prolonged infusion of large doses of this type of drug in normal adult patients.

Although a wide species variation in animals has been demonstrated very little experimental work has been done on neuromuscular transmission in the newborn infant. Clinical experience, however, has shown that these infants tolerate the depolarizing muscle relaxant succinylcholine extremely well and they often require a total dose that would paralyze an adult patient. Moreover, fasciculations—a prominent feature in adults—are not observed on the injection of succinylcholine in the newborn. These are also absent in cases of myasthenia gravis.

Much of the evidence presented points to the similarity in neuromuscular transmission between that of the premature or newborn infant and patients with myasthenia gravis, as has previously been pointed out by Jackson Rees.

The present evidence available on the causation of myasthenia gravis is conflicting. Dahlback and his colleagues have measured the muscle end-plate potentials of biopsy specimens of the intercostal muscles in myasthenic patients. They concluded that "there exists in myasthenia gravis a prejunctional deficiency affecting either transmitter formation or the transmitter release mechanism." Desmedt reached a similar conclusion based on an electromyographic study of the post-tetanic effects in myasthenic patients. On the other hand, there is the view that myasthenia could be related to an abnormal behavior of the motor end-plates. This concept is based essentially on electromyographic studies of the pharmacologic effects of decamethonium and of choline and acetylcholine.

Dillon and his colleagues using a muscle biopsy technique, have confirmed that myasthenic muscle is resistant to the depolarizing activity of decamethonium.

Since there is no evidence to suggest that decamethonium acts at any site other than the motor end-plate, some involvement of the end-plate must be assumed to be present in myasthenia gravis, and the whole condition cannot be explained solely on the basis of a prejunctional deficiency.

The finding that all the motor end-plates throughout the entire body of the myasthenic patient are resistant to the depolarizing action of decamethonium reveals that the condition is a generalized and not a localized one. Furthermore, this abnormality of response to decamethonium remains at all times—even when the patient is in an apparent "complete clinical remission" with no detectable muscle weakness. This resistance to the depolarizing action of decamethonium (combined with the presence of a dual block) can now also be demonstrated in premature and newborn infants. However, during the first few weeks of life the neuromuscular transmission of infants undergoes a change, so that by the time they reach the age of six months the adult pattern of neuromuscular transmission has been attained.

It could be postulated, therefore, that in some rare instances the fetal type of neuromuscular transmission persists into adult life and that these patients may ultimately develop myasthenia gravis. The reason why some muscles should suddenly become "clinically weak" whilst others remain apparently unaffected, and also why spontaneous remissions should occur, still remains obscure. On this basis, myasthenia gravis could well be a congenital defect of the motor nerve-ending which only rarely reveals itself in later life.

These findings should also be considered in relation to "neonatal" myasthenia gravis. This condition was first described by Strickroot and others in 1942 as a transient disease of infants (appearing at birth or soon after) born to mothers with myasthenia gravis. Nearly thirty cases have been described in the world literature. All these cases required anticholinesterase drugs soon after birth but nearly every one of them had ceased to need treatment four weeks later.

The fact that neonatal myasthenia gravis is commonly associated with a similar condition in the mother lends support to the theory that myasthenia gravis is an inherited failure of
development of the motor end-plates. Furthermore, it raises the whole question of the possible value of the wider use of small doses of anticholinesterase drugs in neonates exhibiting weak muscle-power at birth.

From a purely clinical aspect, these findings are mainly of interest in the treatment of the infant who (after receiving a dose of succinylcholine) breathes inadequately at the end of a long operation. If the presence of a full dual block can be demonstrated, then a small dose of an anticholinesterase drug will improve neuromuscular transmission.

Summary

Neuromuscular transmission has been studied electromyographically in five newborn infants, and the influence of decamethonium iodide, neostigmine sulphate and edrophonium chloride has been noted.

The results suggest that neuromuscular transmission in the first few weeks of life differs from that seen in adult patients in that the characteristics of the block obtained after decamethonium strongly resemble many of the features seen in patients with myasthenia gravis.

On the basis of these findings it is suggested that myasthenia gravis could be interpreted as a congenital defect which persists into adult life. At some stage in the patient's career—for reasons unknown—the desensitization of the motor end-plate to acetylcholine becomes increased and the patient exhibits the signs of clinical weakness.

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References