THE RESPONSE OF THE NEWBORN INFANT TO MUSCLE RELAXANTS*

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FOR SOME YEARS PAST the response of the neonate to relaxant drugs has been regarded as being different from that of the average adult patient. This clinical observation has led to the suggestion that the neonate responds to muscle relaxants in a manner similar to that of patients with myasthenia gravis¹. In other words, the newborn would appear to be resistant to depolarizing drugs and extremely sensitive to non-depolarizing drugs. Bush and Stead² observed the dose of *d*-tubocurarine required to produce "adequate control of ventilation and satisfactory operating conditions" in a large series of newborn infants undergoing surgery. They concluded that only during the first ten days of life did the neonate show some "sensitivity" to *d*-tubocurarine.

An attempt has been made to verify this hypothesis. The response of the neonate to depolarizing drugs has already been reported³. It only remained, therefore, to study the effect of non-depolarizing drugs in this group of patients.

METHOD

Neuromuscular transmission was studied in three newborn infants (two female, one male) using a modification of the technique of Harvey and Masland (1941) 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 with a duration of 0.1 millisecond. The action potentials of the contracting hypothenar muscles were recorded with needle electrodes and displayed on a cathode-ray oscilloscope. A simultaneous photographic record on 35-mm film was made and subsequently each action potential was examined under an enlarger and the height of the various potentials expressed as a percentage of the first twitch control of the series.

The following studies were made: (*a*) the effect of a dose of *d*-tubocurarine upon neuromuscular transmission, (*b*) the effect of a dose of an anticholinesterase drug—neostigmine or edrophonium (Tensilon)—upon the neuromuscular block produced by *d*-tubocurarine.

In order to prevent volitional activity each infant was anaesthetized with nitrous oxide and oxygen (4 l./minute) to which 5 per cent (250 ml/min) of cyclopropane was occasionally added in order to maintain the lightest possible level of anaesthesia. The gases were administered via a T-piece after endotracheal intubation, which was performed without anaesthesia. Respiration was assisted when the ventilatory volume was judged to be inadequate. Body temperature was maintained by the use of an incubator and a radiant-heat lamp.

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All drugs were administered into a scalp vein on a body-weight basis, as calculated from the clinical dose required for an average adult patient of 64 kg (140 lb), viz

<i>D-tubocurarine chloride</i>	Dose required to produce paralysis of hypothenar muscles in an adult patient (64 kg) = 12 mg, i.e. 187 μ g/kg
<i>Neostigmine methylsulphate</i>	Effective dose in adults is 2.5–5.0 mg for full anticholinesterase activity (preceded by 1 mg atropine sulphate)
<i>Edrophonium (Tensilon)</i>	Effective dose in adults is 5–10 mg for full anticholinesterase activity

RESULTS

Full details of the findings are given in Table I, and a typical response is shown in Figure 1. Certain aspects of these results, however, require further emphasis

TABLE I
CONTROL

	Case no	Age in weeks	Weight in kg	Height of twitch in Mv (%)*	Height of tetanus (%)	Height of twitch (%)
S E	1	1	3.0	5.5 (115)	115 (112)	115 (115)
M U	2	3	3.25	5.7 (100)	100 (110)	98 (100)
A K	3	2	3.1	3.3 (100)	108 (122)	110 (115)

AFTER *d*-TUBOCURARINE

	Case no	Total dose D T C in μ g	Time of admin (from start) in min	Height of twitch (%)	Height of tetanus (%)	Height of twitch (%)
S E	1	450 [560]	4	12 (12)	15 (11)	12 (12)
M U	2	600 [610]	7	30 (15)	40 (17)	52 (25)
A K	3	500 [580]	13	65 (35)	72 (45)	105 (80)

AFTER NEOSTIGMINE OR EDROPHONIUM

	Case no	Total dose neostig or edrophonium in mg	Time of admin (from start) in min	Height of twitch (%)	Height of tetanus (%)	Height of twitch (%)
S E	1	0.150 (N)	13	110 (112)	130 (95)	110 (102)
M U	2	0.148 (N)	10	90 (60)	92 (35)	95 (70)
A K	3	1.0 (E)	20	100 (100)	105 (112)	115 (100)

*The height of the first action potential (twitch) of the control series (expressed here in millivolts) is taken to equal 100

The height of the fourth action potential of the series is represented as ()

The equivalent dose in μ g/kg B W in adults required for paresis is expressed as []

FIGURE 1 Effect of *d* tubocurarine and neostigmine in a neonate (M U) A Control showing the effect of twitch rates of nerve stimulation (2.5/sec) before and after tetanic stimulation (50/sec) B Same after administration of 600 μ g *d* tubocurarine picture taken at 9th minute C Same four minutes after administration of 0.148 mg neostigmine methyl sulphate picture taken at 14th minute Time base = 0.01 second

(a) *Sensitivity of the Hypothenar Muscles to d-Tubocurarine Chloride*

The dose of *d*-tubocurarine required to produce paralysis of the hand muscles in an average adult patient is about the same as that required for the neonate on a purely body-weight calculation (based on an average adult body-weight of 64 kg or 140 lb)

During this examination a clinical observation was made that the respiratory tidal volume diminished *pari passu* with the paresis in the hand muscles, whereas in the adult patient paralysis of the hand muscles can be produced without apparent reduction in the tidal volume

(b) *Reversal of the Neuromuscular Block (d-Tubocurarine) by an Anticholinesterase in the Neonate*

The block produced by *d*-tubocurarine in the neonate was readily reversed by a proportional dose of neostigmine methylsulphate and atropine sulphate (Fig 1C) or by edrophonium (Tensilon), but in the latter case the improvement was only short-lived

DISCUSSION

Although these findings can be interpreted as demonstrating that the response of the neonate to non-depolarizing relaxant drugs is very similar to what one has come to expect in the average adult patient, there is the possible exception of an increased susceptibility of the respiratory muscles. At this point it must be emphasized that this is only a clinical observation, and that no direct measurement of respiratory tidal volume was made. Nevertheless, such a state of affairs might well explain the traditional view of anaesthetists that the neonate is particularly sensitive to non-depolarizing drugs.

This intimate relationship between the paralysis of the hand and respiratory muscles in the neonate could be explained in a number of ways, but only the two principal theories will be considered here. The first theory suggests that the respiratory muscles in the neonate are genuinely more sensitive to *d*-tubocurarine because of some particular property of the motor end-plate or muscle fibre. The second hypothesis claims that the neonate possesses much less respiratory reserve than the adult. This would mean that the neonate requires almost all its respiratory muscle fibres *all* the time to produce a normal tidal volume, in other words the tidal volume of the neonate is approximately equal to its vital capacity. This is in marked contrast to the adult patient, where the tidal volume is normally about one-tenth of the vital capacity.

Before considering neonatal neuromuscular transmission as a whole, it is necessary to recapitulate the principal features of the effect of a depolarizing drug (decamethonium) on the neonate³

- 1 The neonate has a tolerance or resistance to depolarizing drugs which (on a body-weight basis) is comparable to 2-3 times the adult dose for the same degree of paresis.

- 2 In the premature and newborn infant the electromyographic features of the neuromuscular block produced by decamethonium are not those of pure de-

polarization but are of the "dual" type similar to that described for cases of myasthenia gravis. This characteristic is most easily detected in the premature infant and gradually disappears during the first few months of life.

Neonatal neuromuscular transmission, therefore, would seem to be different from that observed in adult patients. There are many similarities, however, to that found in patients with myasthenia gravis. One of the principal features of cases of myasthenia is that the muscles can broadly be classified into two groups—those that are clinically weak and give way to a "dual" type of block on the injection of a depolarizing drug, and those that are *not* clinically weak and show a *resistance* to depolarizing drugs. In very mild cases of myasthenia only a few muscles of the body—such as the eyelids—are affected, and all the remaining muscles are found to be highly resistant to depolarizing drugs. The milder the myasthenia, the greater is this resistance found to be. It is not difficult, therefore, to assume that there must be individuals who are leading perfectly normal lives, yet who have a marked resistance to depolarizing drugs. Such individuals might be described as "pre-myasthenic."

These studies in neonates suggest that the resistant phase of myasthenia may well be due to an arrest in phylogenetic development resulting in the persistence of neonatal neuromuscular transmission into adult life. Thus, at any time, as a result of some unknown factor, the full picture of myasthenia gravis with its concomitant clinical weakness may develop. This hypothesis can also be used to explain congenital myasthenia, which is a condition of severe muscle weakness developing at birth and responding to anticholinesterase therapy, yet which appears to remit spontaneously during the first few months of life.

In conclusion, these studies suggest that the clinical use of repeated doses of succinylcholine in the neonate may lead to a dual block with all the difficulties of treatment of prolonged inadequate ventilation that are sometimes encountered in the adult. It is suggested, therefore, that *d*-tubocurarine is a more suitable relaxant drug for producing prolonged relaxation in the newborn infant. It should always be used sparingly and its accurate administration requires a drastic dilution. Nevertheless, provided the motor end-plates are not excessively saturated by an overdose of *d*-tubocurarine, it appears that the neuromuscular block is readily reversible.

SUMMARY

1 The injection of a non-depolarizing relaxant drug (*d*-tubocurarine) in the neonate leads to a neuromuscular block similar to that observed in an adult patient.

2 There was no evidence of increased sensitivity of the hand muscles of the neonate to *d*-tubocurarine as compared with the adult. The possibility of increased "sensitivity" of the respiratory muscles is discussed.

3 The similarity between some aspects of neuromuscular transmission in the newborn and in patients with myasthenia gravis is described.

4 The suggestion is made that *d*-tubocurarine (well diluted) is more suitable than suxamethonium for producing muscular relaxation in the neonate.

RÉSUMÉ

L'injection d'un myorésolutif non dépolarisant (*d*-tubocurarine) produit, chez le nouveau-né un blocage neuromusculaire identique à celui qu'on observe chez l'adulte

Par comparaison avec l'adulte, le nouveau-né n'a pas présenté une plus grande sensibilité des muscles de la main à la *d*-tubocurarine. Quant à la possibilité d'une plus grande sensibilité des muscles respiratoires, elle est discutable.

On décrit la ressemblance entre certains aspects de la transmission neuromusculaire chez le nouveau-né et chez le malade atteint de myasthénie grave. Il nous semble que la *d*-tubocurarine (bien diluée) est préférable au suxaméthonium pour produire la résolution musculaire chez le nouveau-né.

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