NEUROMUSCULAR EFFECTS OF HALOTHANE, SUXAMETHONIUM AND TUBOCURARINE IN A MYASTHENIC UNDERGOING THYMECTOMY

BY

ANIS BARAKA, ADEL AFIFI, MUSA MUALLEM, TALAL KACHACHI AND FUAD FRAYHA

SUMMARY

The neuromuscular effects of halothane, suxamethonium, and tubocurarine were observed in a female patient undergoing thymectomy because of myasthenia clinically localized to extraocular muscles. The twitch response was compared with that obtained in a control group of five non-myasthenic patients. In the control non-myasthenic group, halothane 2 per cent increased the twitch response, suxamethonium 20 mg produced complete neuromuscular block, whilst tubocurarine 3 mg produced partial block which rapidly recovered. On the other hand, in the myasthenic patient, halothane did not affect the twitch response, suxamethonium only produced partial neuromuscular block, whilst tubocurarine produced severe block associated with marked tetanic fade and post-tetanic facilitation. This altered response to halothane, resistance to depolarizing agents, and sensitivity to antidepolarizing agents were demonstrated in muscles of the body that did not show clinical weakness.

Controlled ventilation with halothane has been recommended as the most satisfactory technique for general anaesthesia in a myasthenic patient undergoing thymectomy (Wylie and Churchill-Davidson, 1966). The neuromuscular effects of halothane have, however, never been reported in myasthenia gravis. Baraka (1968) has shown, in normal man, that controlled ventilation with halothane did not depress the twitch response to ulnar nerve stimulation; actually, a slight increase in the response was observed.

The purpose of the present report is to show the neuromuscular effects of halothane, suxamethonium and tubocurarine in a myasthenic patient undergoing thymectomy, and to compare such effects with those obtained in a control group of non-myasthenic patients.

METHOD

Case history.

The patient was a 36-year-old female. Her main symptoms were drooping of eyelids and diplopia of 1 year duration. There were no other neurological symptoms and signs. The response to the edrophonium test (Osserman and Jenkins, 1966) was positive on two occasions.

Electromyography.

Needle electromyography was done in the right flexor pollicis and right first dorsal interosseous muscles. The insertion pattern (pattern of action potential during insertion of the e.m.g. needle) was normal. There were no fibrillations or fasciculations at rest. The interference pattern (summation of action potentials at maximum effort) was good with biphasic action potentials ranging between 600–1000 μV. Repetitive median nerve stimulation at frequencies of 10–100 Hz and 0.1–0.2 msec duration produced a slight decrement in amplitude of response at higher frequencies only.

Muscle biopsy.

Study of a piece from the quadriceps femoris muscle by conventional light microscopy and high resolution light microscopy did not reveal any significant abnormality. In some fibres, the intermyofibrillar space, in 1-micron sections, was widened. The myofibrillar architecture, the sarcolemma and nuclei were otherwise intact.

ANIS BARAKA,* M.B., B.CH., M.D.; ADEL AFIFI,† M.D.; MUSA MUALLEM,* M.D.; TALAL KACHACHI,* M.D.; FUAD FRAYHA,‡ M.D.; Departments of *Anesthesiology, †Neuroanatomy and ‡Surgery, American University of Beirut, Beirut, Lebanon.
Treatment with pyridostigmine 60 mg q.i.d. resulted in symptomatic improvement. Pyridostigmine was discontinued 24 hours before thymectomy. The patient was premedicated with pethidine 100 mg and atropine 0.6 mg, injected intramuscularly 30 minutes before operation. Sleep was induced with thiopentone 250 mg and maintained with nitrous oxide and oxygen (3 l./min:1 l./min) delivered via a Boyle Mark III circuit. This was supplemented with pethidine 100 mg. Ventilation was controlled throughout the procedure at a minute volume of about 10 l./min as checked by a Wright respirometer.

Studies of neuromuscular transmission.

The ulnar nerve was supramaximally stimulated by a Block-Aid monitor (Burroughs Wellcome & Co. (Canada) Ltd.) at intervals of 4 sec. The resultant adduction of thumb was measured by a modified Grass model FT-03 force displacement transducer (fig. 1) recording on a Grass polygraph at a speed of 0.5 mm/sec. When a steady twitch response was obtained, 2–4 per cent halothane was added to the inhaled anaesthetic mixture from a Fluotec vaporizer placed outside the circuit. The effect of halothane on the twitch response was observed. Suxamethonium 20 mg was then injected intravenously and the trachea was intubated at the time of maximum block. After complete recovery of the twitch response, 1-mg increments of tubocurarine were injected and their effect on the muscle twitch observed.

The same technique of anaesthesia and neuromuscular investigation was repeated on a control group of five non-myasthenic adult patients undergoing herniorrhaphy.

FIG. 1
Grass force displacement transducer FT-03 which can be secured to the hand of patient by a modification of the method suggested by Walts, Lebowitz and Dillon (1968). The transducer can be secured to the hand by few strips of 1-inch adhesive tape.

FIG. 2
Tracing of twitch response to ulnar nerve stimulation at intervals of 4 seconds, showing the effect of inhalation of halothane in a non-myasthenic patient. An increase in the twitch response is observed throughout the period of inhalation.

FIG. 3
Continuous tracings of twitch response in myasthenic patient showing that halothane has no effect. Upper tracing shows the effect when halothane 2 per cent was added to the inhaled anaesthetic mixture from a Fluotec vaporizer placed outside the circuit. Lower tracing shows the effect when the concentration of halothane was increased to 4 per cent. (Same scale as fig. 2.)
**Fig. 4**
Tracing of the twitch response in a non-myasthenic patient showing the blocking effect of suxamethonium 20 mg. Complete neuromuscular block is observed.

**Fig. 5**
Tracing of the twitch response in myasthenic patient showing the blocking effect of suxamethonium 20 mg. Partial block is observed. (Same scale as fig. 4.)

**Fig. 6**
Tracing of the twitch response in non-myasthenic patient. Tubocurarine 1 mg does not produce any effect. Tubocurarine 3 mg produces partial block which is followed by rapid recovery.

**Fig. 7**
Continuous tracings of the twitch response in the myasthenic patient.

A. Tubocurarine 1 mg produces about 50 per cent neuromuscular block associated with fade on tetanic stimulation (T), and post-tetanic facilitation (PTF). Tubocurarine 3 mg produces marked block associated with complete tetanic fade.

B. Cessation of halothane enhances recovery from tubocurarine block.

C. Reversal of tubocurarine block by neostigmine.
RESULTS

Effect of halothane.
In non-myasthenic patients, inhalation of 2–4 per cent halothane always increased the twitch response by 10–25 per cent. The stimulant effect was maintained throughout the whole period of inhalation (fig. 2). In the myasthenic patient, halothane did not produce any change in the twitch response (fig. 3).

Effect of suxamethonium.
In non-myasthenic patients, the intravenous injection of suxamethonium 20 mg produced complete block of the twitch response in every case (fig. 4). In the myasthenic patient, injection of the same dose only produced partial block (fig. 5).

Effect of tubocurarine.
In non-myasthenic patients, the intravenous injection of tubocurarine 1 mg did not produce any change in the twitch response. Tubocurarine 3 mg produced 0–50 per cent depression which showed rapid recovery (fig. 6). In the myasthenic patient, tubocurarine 1 mg produced about 50 per cent block of neuromuscular transmission, associated with tetanic fade and post-tetanic facilitation. Tubocurarine 3 mg produced about 90 per cent block with a marked tetanic fade (fig. 7A). Neuromuscular block following tubocurarine 3 mg did not show recovery except after cessation of halothane inhalation (fig. 7B). Reversal with neostigmine was required (fig. 7C).

DISCUSSION

In myasthenia gravis a large proportion of the endplate potentials are subthreshold, i.e. they do not trigger an action potential, while the remainder are barely threshold. Repetitive nerve stimuli evoke successively smaller muscle action potentials indicating an increasing block of neuromuscular transmission (Elmqvist et al., 1964).

The present investigation has shown that in patients with localized myasthenic manifestations, other muscles might be affected even in the absence of clinical weakness or electromyographic abnormalities. This latent myasthenia is manifested by the abnormal response to drugs acting on the neuromuscular junction. A marked neuromuscular block, associated with tetanic fade and post-tetanic facilitation can be precipitated by a very small dose of antidepolarizing agent such as 0.016 mg/kg tubocurarine.

In contrast with the increased sensitivity to antidepolarizing agents, the muscles of the myasthenic patient show resistance to suxamethonium. The phenomenon has been observed with other depolarizing agents such as decamethonium by Churchill-Davidson and Richardson (1953), who emphasized that resistance is most obvious in the uninvolved muscles of patients with localized myasthenia.

The increased sensitivity to antidepolarizing agents can be attributed to a presynaptic reduction in the amount of acetylcholine released (Desmedt, 1966), and/or postsynaptic alteration of the endplate chemoreceptors’ response to the chemical transmitter (Grob, Johns and Harvey, 1955). The resistance to depolarizing agents, however, favours a postsynaptic effect.

The response of myasthenic patients to muscle relaxants is different from that in carcinomatous neuropathy (Rooke et al., 1970). The latter patients are sensitive to both antidepolarizing and depolarizing relaxants. The neuromuscular defect in carcinomatous neuropathy seems best explained by decreased transmitter release, while in myasthenia, it is probably a deranged effect (Grob, Namba and Feldman, 1960).

In non-myasthenic patients, halothane increased the twitch response to nerve stimulation. This has been attributed to a direct positive inotropic effect on the muscle (Sabawalla and Dillon, 1958; Baraka, 1968). In the myasthenic patient, however, this increased response is not observed. It is therefore probable that the neuromuscular defect of myasthenia gravis is not limited to one component of the neuromuscular junction, but rather involves the nerve terminals, the endplate and even the muscle itself. In a disease considered to be a disorder of the neuromuscular junction it should not be surprising to find evidence of both pre- and post-synaptic lesions reflected in the skeletal muscle (Fenichel, 1966).

REFERENCES
ES WURDEN DIE NEUROMUSKULÄREN WIRKUNGEN VON HALOTHAN, SUXAMETHONIUM UND TUBOCURARIN BEI EINEM MYASTHENIKER WAHREND EINES OPERATIVEN EINGRIFFES ZUSAMMENFASSUNG


EFECTOS NEUROMUSCULARES DEL HALOTANO, SUXAMETONIUM Y TUBOCURARINA EN UNA MYASTENICIO DURANTE LA OPERACION RESUMEN

Fueron observados los efectos neuromusculares del halotano, suxametoniurn y tubocurarina en una paciente femenina sometida a thymectomy a causa de una miastenia localizada clinicamente en los músculos extraoculares. La respuesta de contracción fue comparada con la obtenida en un grupo control de cinco pacientes no miasténculos. En el grupo de control no miasténico, el halotano al 2 por ciento aumentó la respuesta de contracción, 20 mg de suxametoniurn produjeron bloqueo neuromuscular completo, y 3 mg de tubocurarina produjeron bloqueo parcial con rápido restablecimiento. Por otra parte, en la paciente miasténica, el halotano no influyó sobre la respuesta de contracción, el suxametoniurn produjo un severo bloqueo asociado con marcada debilitación tetánica y facilitación posttetánica. Esta respuesta modificada al halotano, resistencia a agentes depolarizantes, y sensibilidad a agentes antidespolarizantes fueron demostradas en músculos del cuerpo que no mostraban una debilidad clínica.