THE ROLE OF THE ANAESTHETIST IN A DIAGNOSTIC MYASTHENIA GRAVIS CLINIC

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I INTRODUCTION

THE RESULTS OF modern research have led to a general acceptance of the theory that the abnormality in myasthenia gravis is at the neuromuscular junction

Churchill-Davidson and Richardson,¹ using a combination of drugs and electromyographic technique, in patients with myasthenia gravis, found evidence of a general alteration in the response of their motor end-plates throughout the body, even in clinically unaffected muscles. They suggested that although acetylcholine was produced in a normal manner in myasthenic patients, the end-plate responded to it, or one of its breakdown products, in a different manner than in normal muscle. Since then Grob,² using intra-arterial injections of acetylcholine, found that the end-plate of myasthenic patients also responded differently to choline, a normal breakdown product of acetylcholine, compared with normal muscle. It was found that there was first a paralysis due to this injected acetylcholine, followed by recovery. This was then followed rapidly by a secondary phase of prolonged paralysis thought to be due to choline. In the myasthenia gravis patient this second phase of paralysis was reversible by neostigmine, whereas in normal muscle, administration of neostigmine in the second phase produces a further decrease in muscle strength and a further drop in electromyographic potential.

The present concept of myasthenia gravis is therefore an alteration in the response of the motor end-plate, so that acetylcholine no longer only produces a short-lived depolarization but also leads to a competitive block.

Mild cases of myasthenia gravis present a difficult problem of diagnosis. It is hardly surprising, therefore, that many drugs have been used at one time or another as tests for the presence of this condition.

Both neostigmine and edrophonium have been widely used in tests for the presence of myasthenia gravis. Both drugs act by inhibiting the action of cholinesterase and by direct depolarization at the motor end-plate. In myasthenia gravis the action of both these drugs is to improve muscle power. Edrophonium, by virtue of its short duration of action (one to two minutes) and minimal muscarinic side-effects, can be given intravenously (10 mg) and has now largely replaced neostigmine as a diagnostic agent.

Bennett and Cash³ were among the first to suggest the use of *d*-tubocurarine as a test for the presence of myasthenia gravis. They pointed out that myasthenic

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patients show an increased sensitivity to this drug so that doses varying from $\frac{1}{5}$ th to $\frac{1}{100}$ th of the normal are capable of producing profound weakness. The "curare test" for the presence of myasthenia gravis has now become widely accepted, but it has limitations. For instance, only the clinically affected muscles of a patient with myasthenia gravis show this sensitivity. The most sensitive muscles are those that already give evidence of clinical weakness. In contrast to the decamethonium test, which demonstrates a generalized change in the mild case of myasthenia gravis, the curare test may fail, and in the severe case may prove hazardous.

Whereas the neostigmine and edrophonium tests are often equivocal, the decamethonium test has consistently demonstrated its definitive diagnostic value.

II METHOD

These studies have been conducted by physicians representing three disciplines: neurology, physical medicine, and anaesthesiology. The anaesthetist is an essential member of this team by virtue of his knowledge of the pharmacology and physiology of the myoneural junction and his ability to manage possible ventilatory inadequacy, which may develop in these patients during the test. In addition, he is able to provide a continuity of care when a patient from the clinic is referred for thymectomy or other surgical procedures.

This method of electromyographic diagnosis for myasthenia gravis is a modification of the one used by Churchill-Davidson and Richardson^{1,4}. The patient is placed supine on a table with an intravenous infusion running in his forearm. A dilute solution of decamethonium (30 mg in 12 ml) is prepared for injection. Surface recording electrodes are placed over the thenar muscles whether clinically affected or not and the median nerve is then stimulated at the wrist with a supramaximal square-wave stimulus of 0.1-msec duration. Stimuli are spaced at between 1 and 60 seconds apart. The height (voltage) of the evoked action potential is observed on the oscilloscope and recorded on film. The volitional power is studied by the measurement of the grip strength in the opposite hand using a rolled sphygmomanometer cuff initially inflated at 50 mm Hg, straight leg raising, and the range of extraocular muscle movements. After the control readings are recorded, 10 mg decamethonium (40 ml) is injected intravenously followed by a further 0.5 mg (20 ml) at the end of the second minute. The action potentials and volitional power are measured periodically and recorded before and after each injection. At the end of the fourth minute a further 0.5 mg of decamethonium is injected if the grip strength is only slightly reduced. Every two minutes the above procedures are repeated until the grip strength is decreased significantly from the original reading. This usually precedes reduction of the action potential. A total dose of 2.5 to 3.5 mg decamethonium is given if there is only a slight decrease in volitional power. If at any time there is any difficulty in respiration, the administration of decamethonium is not repeated.

In the second part of the test edrophonium 10 mg is administered intravenously. The edrophonium is injected when the action potential is stabilized, preferably

at about 50 per cent of its original value. Edrophonium rapidly relieves the decamethonium-induced paresis in the patients with myasthenia gravis, without further drop or with improvement in the action potential, whereas it increases the paresis in normal subjects, with a corresponding further drop in their evoked muscle action potential.

III RESULTS

The following results were obtained from observations on 23 patients suspected of having myasthenia gravis and 14 normal (control) subjects. Of the 23 suspected patients, 14 patients were confirmed as having myasthenia gravis.

Following an intravenous injection (10 mg) of decamethonium, normal conscious subjects (controls) demonstrated an early, progressive decrease in extraocular muscle strength, then in hand-grip strength, and finally a corresponding drop in their evoked muscle action potential (Fig 1). All these values decreased further, following administration of edrophonium 10 mg (Fig 1). When the two clinical measurements of hand-grip strength and extraocular muscle weakness were objectively considered to have returned to pre-test performance, the action potential remained subnormal (Fig 1), reflecting the patients' subjective feeling of weakness.

FIGURE 1 The course of electromyographic action potential and hand-grip strength in a normal subject (J A H) following decamethonium and edrophonium administration. Note the lack of resistance in electromyographic action potential drop, and further decrease in the action potential following edrophonium administration.

PATIENT (P.P.)

FIGURE 2 Course of electromyographic action potential, hand-grip strength, and eye signs in myasthenia gravis (ocular form) following decamethonium and edrophonium administration. Note the marked resistance to change in electromyographic action potential following decamethonium administration. In contrast to the normal subject's response (Fig. 1), there is an increase in the hand-grip strength and extraocular muscle response following edrophonium administration.

In contrast, myasthenia gravis patients demonstrated resistance to decamethonium, as measured by extraocular muscle strength, hand-grip strength, and evoked muscle action potential. In fact, in the ocular forms of this disease the evoked muscle action potential may never alter, in spite of large doses of decamethonium, from the pre-test base-line reading (Fig. 2). With larger doses of decamethonium in the generalized forms of myasthenia gravis, the evoked muscle action potential eventually decreased (Fig. 3). In both forms (ocular and generalized) there was improvement in evoked muscle action potential, hand-grip strength, and extraocular muscle strength following the administration of edrophonium (Figs. 2 and 3).

IV DISCUSSION

Decamethonium is believed to act in a manner similar to acetylcholine but has the advantage that it is not destroyed by cholinesterase.⁵ Its use in a patient with myasthenia gravis is, therefore, of particular importance and has been described fully by Churchill-Davidson and Richardson.⁴ In normal subjects the injection

FIGURE 3 Course of electromyographic action potential, eye signs, and hand-grip strength in myasthenia gravis (generalized form, post-thymectomy). Note that there is not only resistance to drop in electromyographic action potential, following decamethonium administration, but also there is an actual initial increase in hand-grip strength. Again, there is improvement in electromyographic action potential, hand-grip strength, and extraocular muscle activity following edrophonium administration.

of decamethonium produces a neuromuscular block with all the signs and symptoms of depolarization. In cases of myasthenia gravis it shows evidence of a dual block (depolarization block followed by a competitive block). In the clinically unaffected muscles in the myasthenia gravis patient there is marked resistance to decamethonium-induced muscle weakness and reduction of the corresponding evoked muscle action potential.

The combination of electromyographic techniques with decamethonium and edrophonium has enabled the identification of three stages in the progression of myasthenia gravis muscle. These three stages may coexist in different muscles in the same patient.

1 Stage of Resistance

In this stage the muscle shows no evidence of clinical weakness but the motor end-plate shows a remarkable tolerance to the depolarizing action of decamethonium. Whereas in normal subjects a dose of 25 to 30 mg is capable of producing profound paralysis, myasthenic muscle in the stage of resistance can tolerate doses three to four times as great before showing evidence of any weakness.⁶ The fact that this resistance is so clearly shown in very mild cases of myasthenia gravis gives decamethonium superiority over "curare" as a test in the diagnosis of myasthenia gravis. We have commonly seen this stage in patients with the ocular forms of myasthenia gravis (Fig 2).

2 *Stage of Dual Block*

The onset of this stage in a muscle is manifested by the appearance of clinical weakness. Decamethonium, acting like a large dose of acetylcholine, eventually produces a competitive block, which is reversible by the injection of an anticholinesterase substance (edrophonium). There may also be present some muscle fibres in a state of depolarizing block. The simultaneous presence of muscle fibres in each type of block constitutes the dual block phenomenon⁶. In contrast, decamethonium in small doses in normal subjects leads to a depolarization type of neuromuscular block. In larger or repeated doses a competitive block may be produced. This would lend support to the theory that there is a more sensitive decamethonium competitive block effect in the patient with myasthenia gravis than in the normal subject. If, now, an anticholinesterase drug is given to normal subjects, it produces summation of depolarization with increased weakness and a corresponding drop in the evoked muscle action potential.

This is the most common form of myasthenia gravis, where anticholinesterase therapy is effective in controlling the condition.

3 *Stage of Myopathy (or Refractoriness)*

After prolonged periods in which the muscle fibre has not contracted, the muscle atrophies, and clinical wasting is evident. This stage is seen clinically where increasing doses of anticholinesterases result in no further improvement in muscle strength.

The evidence available⁷ suggests that the natural history of the development of myasthenia gravis often goes through the stages in the order in which they have been discussed. The severity of the disease depends on the number of muscle fibres blocked competitively. If most of the fibres are merely in the resistant phase, then the condition is mild.

Decamethonium, therefore, may be used advantageously as a test for the presence of myasthenia gravis.

V SUMMARY

A modified method of electromyographic diagnosis for myasthenia gravis using decamethonium is described. The role of the anaesthetist in association with a neurologist and physiatrist in this myasthenia gravis diagnostic clinic is outlined.

The combination of electromyographic techniques with decamethonium and edrophonium has enabled the identification of three stages in the progression of myasthenia gravis muscle: (1) stage of resistance, (2) stage of dual block, (3) stage of myopathy (refractoriness).

In contrast to the decamethonium test, which enables the demonstration of a generalized change of neuromuscular transmission in the mild case of myasthenia gravis (the group of cases which present a difficult problem of diagnosis), the "curare" test may fail. In the severe case the curare test may prove hazardous. In addition, whereas the neostigmine and edrophonium tests are often equivocal,

the decamethonium test has consistently demonstrated its definite diagnostic value. Decamethonium, therefore, may be used advantageously as a test for the presence of myasthenia gravis.

RÉSUMÉ

Nous avons décrit une méthode modifiée de diagnostic électromyographique de la myasthénie grave en employant le décaméthonium. Nous avons tracé le rôle de l'anesthésiste qui se joint au neurologue et au psychiatre pour établir le diagnostic clinique de la myasthénie grave.

L'association des techniques électromyographiques avec l'administration du décaméthonium et de l'édrophonium a rendu possible l'identification de trois différents degrés dans l'évolution de la myasthénie musculaire: (1) degré de résistance, (2) degré de blocage double, (3) degré de myopathie.

Par contraste avec le test du décaméthonium qui rend possible une illustration d'un changement généralisé de la transmission neuromusculaire dans les cas bénins de myasthénie grave (c'est ce groupe de malades qui présentent un problème difficile de diagnostic), le test au curare peut faillir à la tâche. Dans les cas sérieux ou graves, le test au curare peut s'avérer risqué. De plus, étant donné que les tests à la néostigmine et à l'édrophonium sont souvent identiques, le test au décaméthonium a constamment démontré sa valeur diagnostique précise. En conséquence, on peut se servir avec avantage du décaméthonium pour dépister la présence d'une myasthénie grave.

REFERENCES

- 1 CHURCHILL-DAVIDSON, H. C. & RICHARDSON, A. T. The Action of Decamethonium Iodide (C10) in Myasthenia Gravis. *J. Neurol. Psychiat.* 15: 129 (1952).
- 2 GROB, D., JOHNS, R. J., & HARVEY, A. M. Alterations in Neuromuscular Transmissions in Myasthenia Gravis as Determined by Studies of Drug Action. *Am. J. Med.* 19: 684 (1955).
- 3 BENNETT, A. E. & CASH, P. T. Myasthenia Gravis: Curare Sensitivity. New Diagnostic Test and Approach to Causation. *Arch. Neurol. Psychiat.* 49: 537 (1943).
- 4 CHURCHILL-DAVIDSON, H. C. & RICHARDSON, A. T. Decamethonium Iodide (C10): Some Observations on Its Action using Electromyography. *Proc. Roy. Soc. Med.* 45: 179 (1952).
- 5 ZAIMIS, E. J. The Action of Decamethonium on Normal and Denervated Mammalian Muscle. *J. Physiol. (Lond.)* 112: 176 (1951).
- 6 CHURCHILL-DAVIDSON, H. C. & RICHARDSON, A. T. Neuromuscular Transmission in Myasthenia Gravis. *J. Physiol. (Lond.)* 122: 252 (1953).
- 7 FOLDES, F. F. & McNALL, P. G. Myasthenia Gravis. A Guide for Anaesthesiologists. *Anesthesiology* 23: 837-872 (1962).