A study of sensitivity to curare in myasthenic disorders using a regional technique

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SYNOPSIS A study of curare sensitivity has been made in ocular myasthenia, myasthenia gravis, and the myasthenic syndrome sometimes associated with carcinoma, using a regional technique. Sensitivity is greater than in normal subjects. The injection of 0.125 mg d-tubocurarine resulted in a neuromuscular transmission block in all but a few of those cases with ocular myasthenia and in all cases of generalized myasthenia. Furthermore, the block persisted for longer than in normal subjects after the release of the tourniquet. This sensitivity to curare was not directly related to myasthenic weakness. The reasons for this are discussed and an explanation for such curare sensitivity is suggested.

Undue sensitivity to curare is a recognized feature of myasthenic disorders and has been used as a diagnostic tool in myasthenia gravis (Bennett and Cash, 1943; Pelikan *et al.*, 1953; Grob *et al.*, 1956). The survey of Rowland *et al.* (1961) showed that excessive sensitivity was always found in generalized myasthenia gravis and occurred also in a proportion of patients with ocular myasthenia. It is of interest that the weakest muscles were not always the most sensitive and undue sensitivity was sometimes found in latent myasthenia with no weakness at the time of study.

In such studies, interpretation relied upon clinical observation so that 'faulty observations, malingering and suggestion may lead to falsely positive results' (Rowland *et al.*, 1961).

A regional method for measuring curare sensitivity, described in a previous paper (Brown *et al.*, 1975) was therefore undertaken in patients with myasthenic disorders. A much smaller dose of d-tubocurarine could be given and, since neuromuscular stimulation is used, there is no need for voluntary muscle contraction, a possible source of error. Furthermore, the recording of muscle action potentials (MAP) evoked by trains of stimuli yields more detailed information

about changes in neuromuscular transmission in this situation.

METHODS

The subjects were 11 patients with generalized myasthenia gravis, 10 patients with ocular myasthenia, and two patients with the myasthenic syndrome sometimes associated with carcinoma (Eaton-Lambert syndrome). The patients with myasthenia gravis took their usual dose of anticholinesterase drugs on the day of investigation. The clinical details are outlined in Table 1.

The methods used and precautions taken were identical to those described in the study of normal subjects (Brown *et al.*, 1975) but as the dosage of d-tubocurarine used in normal subjects (0.5 mg) would cause so great a block in neuromuscular transmission in myasthenic subjects that in most instances the evoked MAP would be no longer recordable, a dosage of 0.125 mg was used. This enabled differences in sensitivity to be discerned amongst the myasthenic subjects.

RESULTS

These are summarized in the Table and in Figs 1 and 2. Among the patients with ocular myasthenia, two were resistant to the dose given, three showed only a slight response, while five developed a significant persisting block of neuro-

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TABLE
'REGIONAL' CURARE SENSITIVITY IN MYASTHENIC DISORDERS (MUSCLE ACTION POTENTIAL EXPRESSED AS % OF PRE-CURARE AMPLITUDE)

Patient	Age (yr)	Duration (yr)	Severity	Fade of evoked MAP in hand	Pyridostigmine dosage 4 hrly (mg)	Response to stimulus train at								
						1 minute			11 minutes			21 minutes		
						First response	Last response	Fade ratio	First response	Last response	Fade ratio	First response	Last response	Fade ratio
Ocular myasthenia														
I.T.	40	2	++		90	100	100	100	100	100	100	100		
W.K.	72	1½	+		120	100	100	100	100	100	100	100		
W.H.	66	2½	++		120	96	96	100	100	100	100	100		
B.C.	35	2	++		120	94	94	100	100	100	100	100		
B.W.	29	15	++		60	90	90	100	100	100	100	100		
E.L.	38	6	++		180	92	92	100	100	100	100	100		
R.M.	29	1	+		15	86	86	100	88	88	86	86		
					(neostigmine)			90	90	84	84	100		
B.F.	30	3½	+		—	82	62	86	80	88	88	100		
J.T.	44	6	—		—	76	48	80	80	84	84	100		
A.B.	33	1	+		90	64	26	84	52	84	60	140		
Mean	42					88	79.4	92.8	89	94.3	90.2	104		
Standard deviation						11.4	25.4	8.01	15.4	7.95	12.9	0.12		
Myasthenia gravis														
M.P.	69	1	—	—	120	82	60	98	92	100	100	100		
J.W.	56	1	—	—	120	83	72	86	78	78	72	108		
T.M.	38	1½	++	+	150	79	50	83	56	86	58	149		
L.S.	48	9	+	+	180	64	64	81	81	81	81	100		
								1.37	1.15	1.07	1.00	100		
								1.57	1.48	1.10	1.08	100		
								0.47	0.18	0.18	0.12	100		

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C.McG.	75	7	—	90	62	54	1.15	86	82	1.05	92	92	1.00
H.T.	59	2½	—	150	—	36	1.72	82	78	1.05	92	86	1.07
R.C.	65	2½	+	150	56	34	1.64	74	48	1.54	82	58	1.42
C.K.	58	8	—	90	47	36	1.3	54	38	1.42	57	40	1.42
T.R.	58	6	+	150	30	22	1.36	40	32	1.25	46	36	1.28
T.R.	58	6	+++	150	12	4	30.0	34	22	1.54	47	36	1.31
J.B.	29	1½	++	150	20	8	2.5	30	12	2.5	40	15	2.65
T.F.	55	20	+	—	4	0	(4)	8	2	4.0	15	3	5.0
Mean	55		—		50.1	36.7	1.81	63.0	51.8	1.58	68.0	56.4	1.64
Standard deviation					27.5	24.2	0.90	28.7	30.6	0.86	26.3	31.0	1.14
Mean (normal subjects)					61.8	43.4	1.76	82.6	70.1	1.29	89.4	84.3	1.09
t test against normal subjects to 0.5 mg dTC					1.348	0.798	0.313	2.469	1.92	1.408	3.139	3.234	2.152
P (%)					> 10	> 10	> 10	< 5	> 10	> 10	< 1	< 1	< 5
Ocular and generalized myasthenia													
Mean					67.3	56.1	1.56	76.5	68.7	1.35	79.9	71.8	1.37
Standard deviation					28.7	32.5	0.79	26.2	30.9	0.69	23.8	29.5	0.89
Mean (normal subjects)					61.8	43.4	1.76	82.6	70.1	1.29	89.4	84.3	1.09
t test against normal subjects to 0.5 mg dTC					0.716	1.703	0.703	0.895	0.173	0.367	1.618	1.669	1.377
(P = 10%)													
Myasthenic syndrome													
J.R.	55	½		—	11	11	1.00	17	13	1.3	17	14	1.2
F.P.	68	25		—	43	15	1.88	35	12	2.9	47	21	2.24
F.P.	68	25			45	13	3.5	44	17	2.69	49	19	2.58
Guanidine 22 mg per kg b.w./day

FIG. 1. Effect of the 'regional' injection of 0.125 mg d-tubocurarine in myasthenic disorders (see text).

FIG. 2. Examples of curare sensitivity in different myasthenic disorders. Recordings of superimposed muscle action potentials evoked by the stimulus train. In each: on the left, before injection; on the right, after 0.125 mg d-tubocurarine. A: B.F., ocular myasthenia. B: R.C., generalized myasthenia. C: F.P., myasthenic syndrome. D: T.F., latent myasthenia. Vertical divisions: A, B, and D, 2 mV. C: 1 mV. Horizontal divisions: 2 ms.

muscular transmission which in some instances was comparable with that seen in the subjects with generalized myasthenia gravis.

Among the patients with generalized myasthenia, there was some effect upon neuromuscular transmission in all cases to the dose of 0.125 mg, a quarter of that required to cause a significant reproducible response in the majority of normal subjects. In the combined series of ocular and generalized myasthenia, this dose caused changes not significantly different from those caused by 0.5 mg in normal subjects (Table). In the generalized myasthenia series, the MAP at 11 minutes remained smaller than in normal subjects ($t=2.47$, $P<0.05$), this difference being even more significant at 21 minutes ($t=3.14$, $P<0.05$).

FIG. 3. Patient T.F.: muscle action potential evoked by a 10 second train of nerve stimulation at a frequency of 10 per second. A: superimposed responses, 2 ms per horizontal division. B: Sequential responses, 1 s per horizontal division, 4 mV per vertical division.

In one patient with the Eaton-Lambert syndrome, the study was repeated after she had commenced treatment with guanidine, 22 mg per kg body weight per day, which drug increases the amount of acetylcholine released by each nerve impulse (Otsuka and Endo, 1960). This did not significantly affect the curare sensitivity.

In one patient with generalized myasthenia gravis the study was performed both during a clinical remission and in a relapse. There was very little difference in curare sensitivity on each occasion.

DISCUSSION

In that the dosage of d-tubocurarine differs from that used in normal subjects, a direct comparison of the responses cannot be made. Nevertheless, the fact that the changes induced in myasthenic disorders using a quarter of the

dose for normal subjects were in fact greater than the changes induced in such normal subjects is significant. Undue curare sensitivity was found in every case of generalized myasthenia by Rowland *et al.* (1961). That we have been able to show this in each case in this series shows that this technique is reliable.

Since there will be variations from case to case in perfusion of d-tubocurarine to the neuromuscular junction after its injection, significance cannot be attached to small differences in the MAP immediately after the injection. However, the differences here are great enough to show that neuromuscular transmission is abnormal in myasthenic disorders. There is also extremely slow recovery in patients with marked sensitivity. Binding of the curare at the receptor site (Paton, 1961) might delay recovery, yet, when the concentration of curare falls below a critical level at this site, some improvement in neuromuscular transmission should occur. The release of the tourniquet in our studies must lead to such a fall in concentration due to perfusion with blood containing no curare, yet no such rapid improvement occurs—indeed, the limb may remain weak for some hours.

If 'binding' of curare to the receptor substance preventing access of acetylcholine (Feldman and Tyrell, 1970) alone was responsible for the perpetuation of the block, then a similar rate of recovery might be expected in normal and myasthenic subjects. That this is not the case suggests that the availability of acetylcholine during recovery must be a significant factor. The altered curare sensitivity in myasthenia gravis could therefore be explained on the basis of a prejunctional defect.

The anticholinesterase medication being taken by the patients at the time of their study should affect the response to curare. It was not thought justified to stop this on clinical grounds and the results show that it did not, in fact, mask the undue sensitivity in such patients. Furthermore, there is no correlation between anticholinesterase dosage and the degree of curare sensitivity, though edrophonium (Tensilon) does affect the rate of recovery from the curare-induced block in normal subjects (Brown *et al.*, 1975). Thus, the effect of such medication appears to play little part in the response to curare with this technique.

The investigation has the following advantages in the study of myasthenic patients: medication need not be stopped; the total dosage of d-tubocurarine is small and does not have to be repeated; finally, should a severe block of neuromuscular transmission occur on this dose, the decline in evoked MAP in the hand will give ample warning before the tourniquet is released and the remaining d-tubocurarine enters the systemic circulation.

The dosage used still necessitates precautions against possible respiratory failure. One of our patients, T.F., a very strong man, whose myasthenia had been 'latent' for 15 years, developed an almost complete block of neuromuscular transmission in the hand after the injection and after release of the tourniquet he had transient ptosis, diplopia, and slight breathing difficulty, though not enough to require assisted ventilation.

The latter patient illustrates one of the most interesting aspects of curare sensitivity in myasthenic disorders. A situation may exist where the neuromuscular junction is capable of transmitting impulses to the limit of physiological requirement, yet it is unable to combat the competitive blocking action of curare. Contrariwise, impaired neuromuscular transmission in myasthenia, enough to cause significant weakness and fatigue, is compatible with only slight impairment in the ability to combat the effect of curare.

Extreme sensitivity to curare may exist without symptoms in other disorders. In patients studied with the Eaton-Lambert syndrome, excessive sensitivity was unaccompanied by any weakness or fatigue at the site studied. The neuromuscular transmission findings in patient T.F., who exhibited such marked curare sensitivity with latent myasthenia gravis, are also pertinent. Repetitive nerve stimulation at slow rates resulted in a slight decline in MAP amplitude, but at rapid rates facilitation of up to 140% occurred (Fig. 3). This phenomenon is seen in patients with myasthenia gravis only when there is an associated defect in the acetylcholine release mechanism (Brown and Johns, 1969; Takamore, 1971).

What is the explanation for curare sensitivity in these disorders? The defect of neuromuscular transmission in myasthenia gravis is complex.

The diminished size of acetylcholine quanta is thought to be due to a defect in their packaging or formation (Elmqvist *et al.*, 1964) and, in addition, there is altered end plate sensitivity to acetylcholine (Grob *et al.*, 1966).

Excessive curare-sensitivity has been reported in the myasthenic syndrome sometimes associated with carcinoma (Lambert *et al.*, 1961). In our series the greatest degree of curare sensitivity seems to be associated with defective acetylcholine release, either in the Eaton-Lambert syndrome or in the occasional case of myasthenia gravis exhibiting evoked muscle action potential facilitation at rapid rates of nerve stimulation. While quanta can be released by a nerve impulse (so that loss of strength in the limb may not be evident), the undue curare sensitivity might be due to a lower than normal concentration of acetylcholine within the neuromuscular junction between periods of active neuromuscular transmission when the arrival of the nerve impulse results in acetylcholine release. Indeed, microelectrode studies in the Eaton-Lambert syndrome reveal a reduction in spontaneous acetylcholine quanta release (Elmqvist and Lambert, 1968). This could be the counterpart to the resistance to curare which can be induced in normal subjects by raising the acetylcholine concentration through repetitive nerve stimulation during its injection.

Such an explanation for curare sensitivity can be applied to the more complex block of myasthenia gravis: while inadequate jets of acetylcholine, released by nerve impulse, might result in the weakness, acetylcholine concentration within the synaptic space between impulses of neuromuscular transmission may be too low to compete with the curare. Thus, if ocular myasthenia with generalized curare sensitivity be considered, there could be asymptomatic widespread reduction in acetylcholine released spontaneously within the neuromuscular spaces with deficient transmission of acetylcholine in the active state confined to the extraocular muscles.

The possibility that the altered curare sensitivity in myasthenic disorders is due to post-junctional changes must also be considered. Since the integrity of the post-junctional membrane is dependent upon acetylcholine release, it is equally possible that the binding of curare is

altered or that the structural changes in the post-junctional membrane in myasthenic disorders are in some way responsible for the altered sensitivity.

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