SHORT REPORT

Extraocular muscle responses to high dose intravenous methylprednisolone in myasthenia gravis

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Abstract

Three patients with generalised myasthenia gravis and three with ocular myasthenia gravis received two to five courses of high dose intravenous methylprednisolone because of the failure of standard immunomodulating therapies. Changes in myasthenic signs were assessed using a four step system for grading muscle weakness and fatigability in 10 test items. Although a brief and modest amelioration was found from day 1 to day 2 after the initial infusion in two patients with generalised myasthenia gravis, all three experienced a prolonged phase of worsening followed by improvement before the next course. Conversely, for two of the patients with ocular myasthenia gravis, a transient but dramatic improvement of ptosis and ocular immobility was noted from 90 minutes to 5 hours after initiating the first infusion, followed by mild or no exacerbation. This 3 hour improvement may be related not only to possible differences in the neuromuscular junction, but also to corticosteroids unmasking the central adaptation for the peripheral ocular muscle weakness by increasing the acetylcholine release.

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In myasthenia gravis, initial exacerbation of symptoms after treatment with corticosteroids is a well known, frequent complication,¹⁻³ the mechanisms of which are not fully understood. Generally, this steroid induced exacerbation has been attributed to the direct inhibitory effect of corticosteroids on the impaired neuromuscular junction.⁴⁻⁶ All of our knowledge, however, is based on information obtained from non-ocular skeletal muscles, and the extraocular muscles have many distinctions that separate them from limb and diaphragm muscles, including a specific subgroup of neuromuscular junctions and the antigenic properties of the acetylcholine receptor (AChR).⁷ To elucidate any differences in the direct responses to corticosteroids between extraocular and other skeletal muscles, we quantitatively assessed changes in myasthenic signs after treatment with high dose intravenous methylprednisolone.

Patients and methods

PATIENTS

Three patients with generalised myasthenia gravis and three with ocular myasthenia gravis received high dose intravenous methylprednisolone because of the failure of standard therapies (table 1). Informed consent was obtained from the patients or their parents. The diagnosis of myasthenia gravis was based on accepted clinical findings, positive responses to edrophonium chloride, and raised

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Table 1 Responses to treatment with high dose IV methylprednisolone

Patient No/ Age (y)/sex	Duration of disease	Preinfusion MG score*	No of infusion courses	Early responses†		Responses after the last infusion	
				Transient improvement	Initial worsening	1 week	1 month
Generalised myasthenia gravis:							
1/29/F	10 months	13	5	11 (1–2 days)	19 (3–8 days)	7	3
2/48/M	10 months	15	5	14 (1–2 days)	18 (3–5 days)	8	5
3/14/F	2 y 2 months	9	3	ND	12 (2–5 days)	8	5
Ocular myasthenia gravis:							
4/4/F	7 months	4	2	1 (1.5–5 h)	5 (3 days)	1	0
5/11/F	6 y	4	2	ND	ND	1	1
6/57/F	2 months	5	3	3 (2–5 h)	ND	1	0

*For calculation of clinical score, grades of 10 items with four-point score are added in generalised patients and those of two items in ocular patients.

†The best or worst clinical score is shown. Parentheses indicate when clinical changes occurred. ND=not detected.

Table 2 Listing of clinical score for patients with myasthenia gravis

Weakness grade	None	Mild	Moderate	Severe
	0	1	2	3
Test items:				
(A) Muscles of limbs and trunk:				
Test items				
(1) Arms outstretched (90°, sitting) (s)	>240	90–240	10–90	<10
(2) Leg outstretched (45°, supine) (s)	>100	30–100	0–30	0
(3) Head lifted (45°, supine) (s)	>120	30–120	0–30	0
(4) Grip strength (dynamometer)	<15	15–30	30–75	>75
(Decrement after 10 maximal closure) (%)				
(5) Vital capacity (l)	3.5 (men) 2.5 (women)	2.5–3.5 1.2–2.5	1.5–2.5 1.2–1.8	<1.5 <1.2
(B) Oropharyngeal muscles:				
(6) Facial muscles	Normal	Mild weakness on lid closure, snarl	Incomplete lid closure	No mimic expressions
(7) Chewing	Normal	Fatigue on chewing solid foods	Only soft foods	Gastric tube
(8) Swallowing	Normal	Fatigue on normal foods	Incomplete palatal closure nasal speech	Gastric tube
(C) Extraocular muscles:				
(9) Palpebral muscles	Normal	Mild ptosis	Apparent ptosis with fatigability	Complete ptosis
(10) Rectus/oblique muscles	Normal	Diplopia without detectable limitation	Apparent limitation	Fixed eyes

concentrations of anti-AChR antibody.⁸ Diagnosis of ocular myasthenia gravis in seronegative patients 4 and 5 also was supported by their positive responses to a cold test⁹ and an “enhanced ptosis” manoeuvre.¹⁰ Thymoma was present in patients 1, 2, and 6. All patients with generalised myasthenia gravis had experienced a myasthenic crisis over the previous several months, and had undergone extended thymectomy and plasmapheresis. Despite receiving oral prednisolone (30 to 100 mg/alternate days) and azathioprine (75 to 100 mg/day), their persistent, moderate clinical symptoms continued. However, their ocular signs were minimal to mild. The three patients with ocular myasthenia gravis had been placed on oral prednisolone (30 to 60 mg/alternate days) with or without pyridostigmine but failed to recover from severe ptosis and ocular immobility. In all but patient 1, pyridostigmine had been discontinued due to crisis (patients 2 and 3) or lack of benefit (patient 6).

TREATMENT PROTOCOL

Methylprednisolone sodium succinate (30 mg/kg/day (maximal dose at 1 g/day)) was infused intravenously in 500 ml normal saline solution over 3 hours for 3 consecutive days, followed by a 4 day infusion free period. This course was repeated three to five times in patients with generalised myasthenia gravis and two to three times in patients with ocular myasthenia gravis. To avoid any possible symptomatic alterations, previous medications were continued in all patients.

CLINICAL MUSCLE TESTING (MYASTHENIA GRAVIS SCORE)

Muscle weakness and fatigability were graded on a four point scale modified from the report by Besinger *et al* (table 2).¹¹ For calculation, the scores of all 10 items were totalled in patients with generalised myasthenia gravis, and two items in patients with ocular myasthenia gravis. All the patients were assessed by the one observer (AK). All muscle tests were carried out around 800 am, before morning medication, except for changes in ocular signs that appeared shortly after starting the initial infusion.

Results

Before the infusion, no obvious fluctuations in clinical severity were detected. From day 1 to day 2 after the initial infusion, two of the three patients with generalised myasthenia gravis (patients 1 and 2) experienced a slight improvement, which was reflected in a minimal reduction in the myasthenia gravis scores of palpebral muscles and vital capacity (table 1). However, from day 3 a marked weakness requiring artificial ventilation developed (table 1, figure A), whereas only mild ptosis recurred. Despite initial worsening, however, titres of anti-AChR antibody decreased (figure A). As the second course began, the exacerbated symptoms tended to improve; patient 1 was weaned from ventilator support. Thereafter, a similar but less severe worsening occurred as the treatment course advanced. Patient 2 recovered from supported ventilation after completion of his third course. Patient 3 did not experience any transient improvement; her symptoms worsened 3 or 4 days after each treatment, but the degree of worsening became less severe. Their symptoms began to alleviate 5 or 6 days after the last infusion and this improvement continued for 5 to 22 months after treatment. Along with the clinical alleviation, titres of anti-AChR antibody decreased in patients 1 and 2.

By contrast, two of the three patients with ocular myasthenia gravis (patients 4 and 6) exhibited immediate but short lived amelioration of ptosis and ophthalmoparesis that began 90 minutes to 2 hours after initiation of the first infusion (table 1, figure B). This steroid induced alleviation of ocular signs lasted about 3 hours, followed by a gradual return to the original condition (patient 6) or mild worsening at day 3 (patient 4). Ptosis and ocular immobility responded similarly to intravenous methylprednisolone. After treatment with methylprednisolone, their ocular symptoms gradually improved; however, they did not experience similar immediate improvement with subsequent infusions. Patient 5 gradually recovered. After completion of the treatment, the eye signs of patients 4 and 6 became normal; a slight limitation of ocular movement

(A) Sequential changes in the clinical severity (myasthenia gravis score) and anti-AChR antibody titres in a patient with generalised myasthenia gravis (patient 1) treated with high dose intravenous methylprednisolone. Alt days=alternate days. (B) Transient improvement of ptosis in a patient with ocular myasthenia gravis (patient 4) treated with high dose intravenous methylprednisolone. Upper row; before infusion. Middle row; 3 hours after the initiation of infusion. Lower row; 1 day after the initial infusion.

remained in patient 5. Patient 6 with a thymoma underwent thymectomy. All three patients remained stable for 7 to 24 months after treatment. Patient 6 had a detectable anti-AChR antibody concentration, which gradually declined as she recovered clinically. No serious adverse events except the poststeroid exacerbation were noted in this series.

Discussion

The direct effect of corticosteroids on neuromuscular function may be most apparent when a massive intravenous dose of corticosteroids is pulsed in patients with myasthenia gravis who have a severe neuromuscular transmission defect. A brief and modest amelioration of generalised symptoms was detected from day 1 to day 2 during the first course. This was followed by a marked exacerbation of generalised weakness with a gradual return to the previous condition by the second course. During subsequent courses, a similar but less severe worsening occurred as treatment advanced. Finally, a marked improvement of the myasthenia began to occur from several days after completion of the treatment. By contrast, two of the three patients with only ocular symptoms exhibited a transient but dramatic improvement of their ocular manifestations shortly after initiating the first infusion, followed by mild or no exacerbation.

In patients with myasthenia gravis who received single doses of prednisone orally, Miller *et al* found acute inhibition of neuromuscular function manifested by increased decremental responses, reduced twitch tension, and lowered maximum contraction strength.⁶ They suggested a direct inhibitory

effect of oral prednisone on neuromuscular function as an explanation for this inhibition.⁶ Recent evidence suggests that myopathy with selective loss of thick (myosin) filaments can be associated with large corticosteroid doses in patients who were receiving non-depolarising neuromuscular blocking agents¹² and in patients with severe generalised myasthenia gravis.¹³ However, because strength improves over a few months in myopathy,¹² transient weakness in our patients is unlikely due to an effect on the muscle fibres.

Direct steroid effects have been studied in normal and myasthenic animals with conflicting results,^{4,5} presumably because of different effects of various drugs in different species. Corticosteroids may exert two opposing direct actions on neuromuscular transmission.^{4,5} Corticosteroids facilitate spontaneous release of ACh as shown by an increasing frequency of miniature end plate potentials (MEPPs), whereas they decrease MEPP amplitude.^{4,5} Grossie and Albuquerque found that MEPP amplitude in the limb muscle increased slightly on day 1 of treatment, but decreased to close to control values by day 2.¹⁴ Our clinical study confirmed these findings in part, and showed that marked inhibitory effects were prolonged in non-ocular muscles despite only a subtle facilitation at the beginning. Suppression of the immune system by corticosteroids gradually improves neuromuscular function, accounting for a less severe decline with subsequent courses or a rapid recovery after the discontinuation of methylprednisolone.

Conversely, a marked facilitatory effect was evident on the extraocular muscles. Precise mechanisms for these different responses to

corticosteroids are uncertain. The neuromuscular junctions of the rectus and oblique extraocular muscles may differ from those of the non-ocular muscles in that they contain multiterminal neuromuscular junctions and fetal-type AChR⁷; however, another group showed that expression of fetal-type AChR in the extraocular muscles was comparable with that in the other muscles.¹⁵ Although the fibre type composition of the levator muscle generally resembles that of the global layer of the rectus and oblique extraocular muscles, it differs in that the levator muscle conspicuously lacks the multiply innervated fibre-type and fetal-type AChR.^{7, 16} Common histological findings between the rectus and oblique and levator extraocular muscles are: (1) some end plates possess shallow postjunctional folds; and (2) a high density capillary network is present.^{16, 17} These common findings may be related to the direct facilitatory effect of corticosteroids on myasthenic ocular signs.

The CNS compensates for peripheral weakness of the extraocular muscles.^{10, 18} Edrophonium administration unmasks this central adaptation, occasionally resulting in lid retraction and saccadic hypermetria or macrosaccadic oscillations.¹⁸ The acute effect of corticosteroids may be due to an increase of ACh, which causes dramatic but transient alleviation of ocular myasthenia by unmasking the central adaptation. This transient alleviation may be more apparent when the central adaptation is large due to profound ptosis and ophthalmoplegia, but the myasthenic lesion is not permanent. Central adaptation may be lost after gradual recovery, which could explain the absence of a similar dramatic response with the initial infusion of subsequent courses.

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