Comparative effects of plasma exchange and pyridostigmine on respiratory muscle strength and breathing pattern in patients with myasthenia gravis

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Abstract

Background—Pyridostigmine, an acetylcholinesterase antagonist, is useful in improving respiratory function in patients with myasthenia gravis. More recently, plasma exchange has been employed in myasthenia gravis because it acts presumably by removal of circulating antibodies against acetylcholine receptors. Surprisingly, comparative data on the effects of pyridostigmine and plasma exchange on lung volumes, respiratory muscle strength, and ventilatory control system in patients with myasthenia gravis are lacking.

Methods—Nine consecutive patients with grade IIb myasthenia gravis were studied under control conditions and after a therapeutic dose of pyridostigmine. In a second study the patients were re-evaluated a few days after a cycle of plasma exchange, before taking pyridostigmine. In each subject pulmonary volumes, inspiratory (MIP) and expiratory (MEP) muscle force, and respiratory muscle strength, calculated as average MIP and MEP as percentages of their predicted values, were measured. The ventilatory control system was evaluated in terms of volume (tidal volume, V_T) and time (inspiratory time, T_I , and total time, $TTOT$) components of the respiratory cycle. Mean inspiratory flow (V_T/T_I)—that is, the “driving”—and $T_I/TTOT$ —that is, the “timing”—components of ventilation were also measured. **Results**—In each patient treatment relieved weakness and tiredness, and dyspnoea grade was reduced with plasma exchange. Following treatment, vital capacity (VC) increased on average by 9.7% with pyridostigmine and by 14% with plasma exchange, and MIP increased by 18% and 26%, respectively. In addition, with plasma exchange but not with pyridostigmine forced expiratory volume in one second (FEV_1) increased by 16% and MEP increased by 24.5%, while functional residual capacity (FRC) decreased a little (6.8%). The change in respiratory muscle strength was related to change in VC ($r^2 = 0.48$). With plasma exchange, V_T increased by 18.6% and V_T/T_I increased by 13.5%, while neither T_I nor $T_I/TTOT$ changed.

Conclusions—Plasma exchange can be used in patients with myasthenia gravis when symptoms are not adequately controlled by anticholinesterase agents. Plasma exchange increases respiratory muscle force and tidal volume due to changes in “driving” but not “timing” of the respiratory cycle.

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Keywords: pyridostigmine, plasma exchange, myasthenia gravis, respiratory muscle strength.

Plasma exchange is regarded as an established method for treating patients with myasthenia gravis when other treatments have been ineffective.¹⁻³ It can also be used to reduce surgical complications of thymectomy. Under these circumstances plasma exchange is thought to act by reducing circulating antibodies against the acetylcholine receptor (AChR),¹ the plasma factor directly concerned in producing the disorders of neuromuscular transmission in the acquired form of the disease.^{4,5}

Several studies have reported the effects of pyridostigmine, a cholinesterase inhibitor, on respiratory muscle function in patients with myasthenia gravis.⁶⁻⁸ Whilst hypoventilation and CO_2 retention are recognised consequences from respiratory muscle weakness, there are few studies which evaluate the control of breathing in patients with chronically stable myasthenia gravis.⁸⁻¹¹ Furthermore, there are no comparative data on the effects of pyridostigmine and plasma exchange on respiratory muscle strength and ventilatory control in patients with myasthenia gravis. We have therefore undertaken an uncontrolled study to provide an insight into these aspects of treatment of myasthenia gravis

Methods

SUBJECTS

Nine consecutive patients (three men) aged 22-68 years with moderate generalised myasthenia gravis were studied. Informed consent was given by each patient and the study was approved by the local ethics committee. Diagnosis of myasthenia gravis was defined on the basis of a clinical history of tiredness, weakness of the skeletal muscles, a decremental response to repetitive motor nerve stimulation test, and

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Table 1 Anthropometric and clinical data of patients with grade IIb myasthenia gravis

Patients	Age (yrs)	Sex	Antibodies				Duration of both disease and treatment (yrs)	STD (mg × 10 ³)	Thymectomy
			AChR		SM				
			C	PE	C	PE			
1	68	M	20	8	1:160	<1:80	6	21.6	Yes*
2	63	M	54	42	1:160	<1:80	8	28.8	Yes*
3	65	F	85	52	—	—	4	21.6	No
4	57	M	44	25	1:160	<1:80	1	10.8	Yes*
5	22	F	35	15	—	—	1	10.8	Yes
6	30	F	18	7	—	—	2	14.4	Yes
7	33	F	15	10	—	—	4	21.6	Yes
8	38	F	28	13	—	—	1	10.8	Yes
9	30	F	64	29	—	—	5	27.0	Yes

AchR = acetylcholine receptor; SM = skeletal muscle; C = control; PE = plasma exchange; STD = steroid total dose (daily dose × 180 days × years).
* Thymoma.

a positive edrophonium chloride (Tensilon) test.¹² Acetylcholine receptor antibodies were available in all patients and skeletal muscle antibodies in three; all patients belonged to the IIb grade of myasthenia gravis according to Osserman's classification^{12,13}: I, ocular myasthenia; IIa, mild generalised myasthenia; IIb, moderate generalised myasthenia; III, acute severe myasthenia; IV, late severe myasthenia. Patients had normal routine chest radiographs. All but one (patient no. 3) had undergone a thymectomy which, in three cases (nos 1, 2, and 4), was due to thymoma. Patients were being treated with oral anticholinesterase therapy (pyridostigmine, 60 mg three or four times daily) and alternate day prednisone (20–60 mg), which was insufficient to control symptoms. No patients fulfilled the diagnostic criteria for asthma, chronic bronchitis or emphysema as suggested by the American Thoracic Society.¹⁴ All but three patients (nos 2, 8, and 9) were non-smokers.

At the time of the study they were dyspnoeic with grade II (walking at ordinary pace on the level) to III (walking at their own pace on the level) dyspnoea.¹⁵ No patient was considered to be undernourished and mean (SD) body weight, expressed as percentage of ideal weight,¹⁶ was 95(8)%. The clinical data of the patients are summarised in table 1.

MEASUREMENTS

Routine spirometric tests were performed when seated as previously described.¹⁷ The normal values for lung volumes were those proposed by the European Community for Coal and Steel.¹⁸ Maximal static inspiratory (MIP) and expiratory (MEP) pressures were measured using a differential pressure transducer (Statham SC 1001; Hato Rey, Puerto Rico). The subject, comfortably seated and wearing a noseclip, performed maximal respiratory efforts at residual volume (RV) (for MIP) and at total lung capacity (TLC) (for MEP) against an obstructed mouthpiece with a small leak (internal diameter 0.6 mm) to minimise oral pressure artefacts. The manoeuvres were repeated until three measurements sustained for at least one second and with less than 5% variability were recorded. The highest value obtained was used for analysis. MIP and MEP were expressed both in cm H₂O and as percentage of predicted value (%pred). The predicted values for MIP and MEP were those proposed by Black and Hyatt.¹⁹

After baseline routine testing while breathing room air the ventilatory pattern was evaluated. The subjects, wearing a noseclip, were put in a comfortable supine position breathing through a mouthpiece on a circuit where the inspiratory and expiratory lines were separated by a one-way valve (Hans-Rudolph, Kansas City, Missouri, USA). Airflow was measured with a Fleisch type 3 pneumotachograph and the flow signal was integrated into the volume. From the spirogram the following breath-by-breath time and volume components of the respiratory cycle were derived: inspiratory time (Ti), expiratory time (Te), total time of the respiratory cycle (T_{TOT}), and tidal volume (V_T). Mean inspiratory flow (V_T/Ti) "driving", duty cycle (Ti/T_{TOT}) "timing", respiratory frequency (Rf = 1/T_{TOT} × 60), and instantaneous ventilation (V_E = V_T × Rf) were also calculated. Expired CO₂ (P_{CO₂}) was sampled continuously at the mouth by an infrared CO₂ meter. The values for dead space and resistance of the system up to a flow of 4 l/s were 178 ml and 0.92 cm H₂O/l/s, respectively. Details of the methods have been described previously.^{8,20}

The output of the CO₂ meter, the flow signal, and the integrated flow signal were recorded continuously on a multichannel chart recorder. After a 10 minute adaptation period the baseline evaluation was started.

Ventilatory parameters were calculated from the data averaged from the breaths recorded over 10 minutes.

PLASMAPHERESIS

Plasma exchange was performed using a discontinuous flux cellular separator (Dideco model Progress BT 790A) and by mono-use cell apheresis (Dideco model BT 225). Perfusion of plasma substitutes consisted of: (a) 750–1000 ml saline, (b) 500 ml 10% colloidal solution of low molecular weight dextran in saline, (c) three Baxter electrolytic rehydrating Solution (300 ml) plus 5000 IU heparin, and (d) four 50 ml vials of 20% human albumin added to 750 ml saline. According to the American Society for Apheresis²¹ plasma volume removal was 5% body weight. Each patient had 5–9 courses of plasma exchange.

DATA ANALYSIS

Statistical analysis was performed by two way analysis of the variance and intergroup com-

Table 2 Mean (SD) baseline pulmonary function data under control conditions (C), after pyridostigmine administration (P), and plasma exchange (PE) in patients with myasthenia gravis

	VC (SR)	FRC (SR)	RV (SR)	TLC (SR)	FEV ₁ (SR)	FEV ₁ /VC (%)	MIP (%pred)	MEP (%pred)
C	-1.46 (1.88)	1.21 (1.26)	1.74 (1.96)	-0.14 (1.17)	-1.52 (1.65)	77.7 (16.3)	56.2 (19.5)	38.2 (18.8)
P	-0.80 (1.72)	1.23 (1.46)	1.14 (2.03)	-0.25 (1.18)	-0.96 (1.54)	76.8 (12.7)	68.5 (21.2)	45.2 (16.2)
PE	-0.35 (1.56)	0.775 (1.26)	0.77 (1.79)	0.10 (1.22)	-0.47 (1.43)	78.4 (13.6)	75.8 (21.3)	50.6 (16.5)
Analysis of variance								
F	12.71	6.99	4.79	2.21	10.43	0.28	30.35	4.013
p	0.0005	0.01	0.025	NS	0.002	0.76	0.0001	0.05
Bonferroni test (p values)								
P v C	<0.05	NS	NS	NS	NS	NS	<0.05	NS
PE v C	<0.05	<0.05	<0.05	NS	<0.05	NS	<0.05	<0.05
PE v P	NS	<0.05	NS	NS	NS	NS	<0.05	NS

SR=standardised residuals; VC=vital capacity; FRC=functional residual capacity; RV=residual volume; TLC=total lung capacity; FEV₁=forced expiratory volume in one second; MIP=maximal inspiratory pressure; MEP=maximal expiratory pressure.

parisons by the Bonferroni test. Spirometric values have been reported as standardised residuals²² obtained by dividing the absolute residuals by the residual standard deviations taken from the regression equation.¹⁸ A p value of <0.05 was considered to be significant.

PROTOCOL

All treatment was withdrawn from the patients at least 12 hours before the study. Baseline lung function, MIP, MEP, and ventilatory pattern were measured at approximately 09.00 hours. Patients were allowed to rest between tests to avoid the effect of fatigue.

Study I: The patient was fasted and a single oral dose (120 mg) of pyridostigmine was given. Functional evaluation was repeated when patients felt better (less difficulty with chewing and swallowing, decrease in facial and limb muscle weakness), approximately 30 minutes after administration of the drug.

Study II: One to two days after the first study patients underwent the first of 5–9 courses of plasma exchange. Treatment was performed over 18–27 days, and 2–4 days after completion of the plasma exchange cycle dyspnoea grade, spirometry, respiratory muscle strength, and the pattern of breathing were re-evaluated at the same time in the morning as in the first study.

Study III: Four patients who carried out the first study on an off-steroid day were re-

evaluated on either the on-steroid or off-steroid day 30 minutes and two hours after a dose of 120 mg pyridostigmine.

Results

Baseline pulmonary function data and maximal inspiratory and expiratory pressures for patients are summarised in table 2 and fig 1. Some patients exhibited a low vital capacity (VC) (nos 1–3, 5, 6), while functional residual capacity (FRC) (nos 1, 3, 9) and residual volume (RV) (nos 1, 3, 5, 6) were mild to moderately increased in some patients. The ratio of the forced expiratory volume in one second (FEV₁) to VC was low in the three patients with a smoking history (nos 1, 2, 4). MEP was slightly to moderately reduced in all patients and MIP in all but two (nos 7 and 8).

The characteristics of the breathing pattern in the patients were compared with those of a group of 11 age-matched normal subjects (nine women of mean (SD) age 42.1 (16.1) years (range 20–67)) as shown in table 3 and fig 2. As a group the patients exhibited a more rapid and shallow breathing pattern: smaller V_T, T_I and greater R_f and V_T/T_I. All these differences were significant (p<0.025 to <0.005). In contrast, ventilation (V_E) was similar in the patients and controls.

As shown in table 2 and fig 1, pyridostigmine and plasma exchange both resulted in a sig-

Table 3 Breathing pattern under control conditions (C), after pyridostigmine (P) administration, and plasma exchange (PE) in patients with myasthenia gravis. Values are mean (SD)

	V _E (l/min)	V _T (l)	T _I (s)	R _f (breaths/min)	V _T /T _I (l/s)	T _I /T _{TOT}
C	9.65 (1.5)	0.57 (0.1)	1.3 (0.2)	17.63 (4.2)	0.45 (0.1)	0.37 (0.06)
P	9.94 (2.2)	0.62 (0.14)	1.34 (0.3)	16.7 (4.6)	0.47 (0.12)	0.36 (0.06)
PE	11.2 (2.7)	0.7 (0.1)	1.4 (0.3)	16.1 (3.8)	0.52 (0.1)	0.37 (0.05)
Analysis of variance						
F	3.16	10.14	1.05	1.99	8.61	0.14
p	NS	0.002	NS	NS	0.005	NS
Bonferroni test (p values)						
P v C	NS	NS	NS	NS	NS	NS
PE v C	NS	<0.05	NS	NS	<0.05	NS
PE v P	NS	<0.05	NS	NS	<0.05	NS

V_E=minute ventilation; V_T=tidal volume; T_I=inspiratory time; R_f=respiratory frequency; V_T/T_I=mean inspiratory flow; T_I/T_{TOT}=timing.

Figure 1 Individual change in vital capacity (VC), forced expiratory volume in one second (FEV₁), maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP) after pyridostigmine (P) and plasma exchange (PE) in the nine patients with myasthenia gravis. C = control.

nificant increase in VC ($p < 0.05$ for both treatments). Plasma exchange resulted in a mild but significant decrease in FRC compared with both control and pyridostigmine ($p < 0.05$ for both comparisons). RV decreased and FEV₁ increased with plasma exchange but not with pyridostigmine ($p < 0.05$ for both variables). Both treatments resulted in a significant increase in MIP ($p < 0.05$ for both), but the increase in MIP with plasma exchange was greater than that with pyridostigmine ($p < 0.05$); in contrast, MEP increased only with plasma exchange ($p < 0.05$).

Change in respiratory muscle strength, calculated as the average % predicted MIP and MEP,²³ significantly related to change in VC ($r = 0.696$, $p = 0.001$), but neither related to change in FRC nor to the duration of the disease. For each subject the calculated total dose of steroid (daily dose $\times$ 180 days $\times$ years, table 1) did not relate to baseline MIP or respiratory muscle strength, nor to improvement in MIP or respiratory muscle strength with pyridostigmine or plasma exchange.

In terms of breathing pattern (table 3 and fig 2) V_T and V_T/T_I increased with plasma exchange compared with both the control and pyridostigmine groups ($p < 0.05$ for all comparisons). In contrast, T_I/T_{ROT} did not change with either treatment.

In each patient treatment relieved weakness and tiredness. In particular, with plasma exchange the improvement began within a few days of initiating exchange and continued for some days after the cycle ceased; dyspnoea grade lessened from III to II in some patients and from II to I (hurrying on a level or walking up a slight hill) in the others. Autoantibody levels always changed after plasma exchange (table 1).

In the third study the two hour increases in respiratory muscle strength (fig 3), VC, FEV₁, and breathing pattern did not consistently differ compared with 30 minute increases recorded either on the on-steroid or off-steroid day.

Discussion

We have shown that both pyridostigmine and plasma exchange improve symptoms and respiratory function in a group of patients with grade IIb myasthenia gravis. There were increases in static and dynamic lung volumes and respiratory muscle strength for both agents, but only plasma exchange led to changes in tidal volume and mean inspiratory flow, suggesting that this modality of treatment affects the "driving" and not the "timing" of the respiratory cycle.

We have found low values for VC and high values for RV in our patients with myasthenia

Figure 2 Individual change in minute ventilation ($\dot{V}_E$), tidal volume (V_T), mean inspiratory flow (V_T/T_I), and inspiratory time (T_I) after pyridostigmine (P) and plasma exchange (PE) in the nine patients with myasthenia gravis. C = control.

Figure 3 Individual change in maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) 30 minutes and 120 minutes after the administration of 120 mg pyridostigmine.

gravis which has been reported before,^{6-8,24} and may be a reflection of decreased muscle strength.^{9,24} However, we found that the increase in respiratory muscle strength with treatment accounted for about 50% of the variability in the increase in VC. This finding, together with previous data from patients with miscellaneous myopathies,^{23,25} suggests that abnormal muscle mechanics is not the sole reason for reduced VC in patients with myasthenia gravis. In our study FRC decreased with plasma exchange but was unchanged by pyridostigmine. It has been shown that FRC was not changed by orally administered pyridostigmine,⁸ but did increase with injected drug.⁶

FRC is determined by the balance between lung and chest wall forces, so the observed fall in FRC by plasma exchange could have resulted from an increased elastic recoil of the lung, a decrease in the outward recoil of the chest wall, or a combination of the two.²⁵ We do not have data on elastic recoil of the lung to allow us to establish which factor was dominant in lowering FRC in our subjects. The fall in FRC with plasma exchange would facilitate an increase in MIP, but in our data we did not find any significant relationship between change in FRC and change in MIP.

It could be argued that examination of respiratory mechanics only 30 minutes after

pyridostigmine administration is too early to permit maximal absorption from the gastrointestinal tract and action at the neuromuscular junction. Furthermore, the criteria for assessing benefit from oral pyridostigmine in patients with myasthenia gravis often relies solely on a patient's subjective response with improvement in chewing, swallowing, or less ocular, facial or limb weakness. We have found that two hours after oral administration of 120 mg pyridostigmine the changes in lung volumes did not substantially differ from the changes after 30 minutes, whether recorded on the day when on or off corticosteroids. This finding agrees with the data of Shale *et al.*²⁶ In terms of respiratory muscle strength, after the initial increase of 22% and 35% from control in MIP and MEP, respectively, these parameters did not increase any further, consistent with the observations of Rindqvist and Rindqvist,²⁴ in whose study the maximum increase in MIP and MEP after neostigmine injection was 17% and 15% predicted respectively. Similarly, in the study by Mier-Jedrzejowicz *et al.*⁷ MIP increased by a mean of 37% and MEP by a mean of 28% after administration of intravenous edrophonium.

The low MIP and MEP values found in our patients are likely to reflect respiratory muscle weakness – that is, the failure to generate force. In patients with myasthenia gravis inspiratory muscle weakness might depend on the defect in neuromuscular transmission and corticosteroid myopathy which is a well known adverse effect from corticosteroid treatment.^{27,28} There is considerable evidence that abnormalities at the neuromuscular junction are the major problem in myasthenia gravis.^{29–31} In this context the removal of AChR antibodies with plasma exchange¹ could account, in part, for the increase in respiratory muscle strength. The increase in MIP with pyridostigmine will in part be due to the fact that anticholinesterase antagonists increase both the action potential and force of skeletal muscle.³⁰ With respect to the effect of corticosteroids, these may reduce respiratory muscle function in animals and man.^{20,27,28,32} In particular, they may affect striated muscles (IIB fibre atrophy) including respiratory muscle structure and function.^{27,32} However, we were not able to find any relation between the total dose of corticosteroid and baseline respiratory muscle strength, or its increase with therapy. It is therefore unlikely that long term corticosteroid treatment played a part in the decrease in respiratory muscle strength noted before and after treatment. Our finding of a greater decrease in MEP than in MIP agrees with data from patients with neuromuscular disorders.^{23,33} There are no data available which compare the histological features of the diaphragm and expiratory muscles in patients with myasthenia gravis to help to explain this observation.

Because patients with myasthenia gravis vary in the time of their optimal strength with dose regimen, each patient should be studied on either their day on or off steroid. The results from our third study showed that changes in pulmonary volumes and respiratory muscle

strength were indifferent to the corticosteroid regimen, and this argues against a possible undesirable influence on our results by the fact that our patients received alternate day corticosteroid therapy. In addition, our observation that the response to pyridostigmine did not differ between days on and off steroid supports this as a safe and satisfactory dose regimen for patients with myasthenia gravis.

Our patients had a rapid and shallow breathing pattern – that is, the respiratory central output was modulated via shorter inspiratory time (Ti) into a tachypnoeic pattern of breathing and smaller VT. This more rapid and shallow breathing is similar to that observed in patients with several neuromuscular disorders^{8–11,34,35} including myasthenic myopathy²⁹ with chronic^{9,34} or acute^{10,11} ventilatory failure. In neuromuscular disorders either afferent information from weak respiratory muscles^{36,37} and stiffened rib cage,³⁴ or vagal afferent information from the lung,^{34,35} have been thought to act on the central inspiratory controller to terminate inspiration. The observation that Ti lay unchanged with treatment suggests that neither pyridostigmine nor plasma exchange were able to modify factors which act on the central inspiratory controller to terminate inspiration. Tidal volume (VT) increased with plasma exchange but not with pyridostigmine. There is some evidence that in patients with myasthenia gravis pyridostigmine is able to increase VT during some experimental conditions which are suspected to increase tiredness and weakness of the respiratory muscles – for example, exogenous CO₂ stimulation – but not during quiet breathing.⁸ The reason why plasma exchange was able to increase VT in spontaneously breathing patients is likely to be complex. Rochester³⁸ has recently hypothesised that, in order to decrease the dyspnoea sensation, patients with muscle weakness decrease the ratio of the inspiratory pressure for a given breath (Pbr) to the maximal inspiratory pressure (MIP), thereby decreasing VT. Our data showing a lower dyspnoea grade and an increased MIP are consistent with the possibility that plasma exchange brings about a greater Pbr/MIP ratio promoting, as reported, a greater VT.

In many respiratory disorders the inspiratory drive has commonly been assessed in terms of both VT/Ti and mouth occlusion pressure,³⁹ but in patients with respiratory muscle weakness either VT/Ti or mouth occlusion pressure can underestimate the effective inspiratory drive.^{35,36} Thus, the observation in patients of a higher VT/Ti is not unlikely to reflect a normal or even increased neural drive to the inspiratory muscles. The reasons for this higher drive in patients with myasthenia gravis⁸ and other neuromuscular disorders have been provided elsewhere.^{35–37} “Driving” (VT/Ti) but not “timing” (Ti/TOT) was found to increase with plasma exchange. Based on the equation³⁹

$$\dot{V}_E = V_T \times R_f = V_T/T_i \times T_i/T_{TOT},$$

the increase in VT and VT/Ti is the mechanism whereby $\dot{V}_E$ may be maintained or may increase.

We conclude that plasma exchange can be used in patients with myasthenia gravis whose symptoms are not completely controlled by anticholinesterase agents, and that plasma exchange increases respiratory muscle force and tidal volume by a change in the "driving" but not the "timing" of the respiratory cycle.

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