

# Effects of alternate-day prednisone therapy on respiratory function in myasthenia gravis<sup>1</sup>

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**Newball, H. H. and Brahim, S. A. (1976). *Thorax*, 31, 410–413. Effects of alternate-day prednisone therapy on respiratory function in myasthenia gravis.** To determine the effects of alternate-day prednisone therapy on respiratory function in myasthenia gravis, eight patients were evaluated during 'days on' and 'days off' prednisone. The patients were treated with long-term (up to three years), high-single-dose, alternate-day oral prednisone. After patients had been controlled with alternate-day prednisone they had no episodes of acute respiratory insufficiency or myasthenic crises. Although a small reduction in respiratory function during the day off prednisone was seen in some patients, the change was not statistically significant for the group and was probably physiologically unimportant in most patients. The data indicate that in myasthenic patients who have no underlying lung disease respiratory function is not significantly compromised by administering the prednisone on alternate days.

The most feared complication of myasthenia gravis is the development of a 'crisis'. This term is applied to a myasthenic patient whenever respiratory distress and ventilatory inadequacy occur. One problem of therapy is that the disease affects different muscles to different degrees. The dose of anticholinesterase which relieves ophthalmoplegia, for example, may paralyse the respiratory muscles. When this is seen, the most important endpoint, namely respiratory function, should be used to determine the optimum dosage of therapy.

Recently a new mode of therapy was introduced for patients with myasthenia gravis. It consisted of long-term, high-single-dosage (100 mg), alternate-day oral prednisone (Warmolts and Engel, 1972). Because there are significantly fewer side effects of alternate-day versus daily prednisone therapy (Harter, Reddy, and Thorn, 1963), the former is preferable.

The object of the present study is to determine whether alternate-day prednisone therapy is associated with significant fluctuations of respiratory function in myasthenic patients.

## MATERIAL AND METHODS

**PATIENTS** Eight patients being followed regularly by the Medical Neurology Service (Table I) were

admitted to the pulmonary ward for these studies. The diagnosis of myasthenia gravis was established by a characteristic medical history and electromyogram and a positive Tensilon test. The patients were started on at least 100 mg of oral prednisone on alternate days, and the dose was slowly tapered as the disease was controlled (Warmolts *et al.*, 1972). All anticholinergic drugs were withdrawn. At the time of respiratory function evaluation the disease was considered well controlled in all subjects. Seven had no history of pulmonary disease except for previous episodes of acute respiratory insufficiency associated with myasthenic crises. Patient 8 was unaware of his obstructive lung disease until the onset of myasthenia gravis.

**METHODS** Respiratory function was determined at least four times during the day. These times were usually at 8.00 am, 11.00 am, 2.00 pm, and 5.00 pm. The patients received their prednisone as a single dose at 7.00 am of the 'day on', which allowed at least one hour for the absorption of the drug before the studies were begun.

Functional residual capacity (FRC), total lung capacity (TLC), and airway resistance (Raw) were determined by the technique of DuBois *et al.* (1956a) and DuBois, Botelho, and Comroe

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TABLE I  
ALTERNATE-DAY PREDNISONE THERAPY OF PATIENTS WITH MYASTHENIA GRAVIS

Patient	Age	Sex	Wt(kg)	Ht(cm)	Date of First Symptoms	Date Prednisone Started	Present Therapy Prednisone (mg)	Date Studied
1	34	M	92	175	July 1970	September 1972	100	September 1973
2	57	M	81	178	April 1972	September 1972	110	October 1973
3	70	M	81	169	January 1972	September 1972	70	October 1973
4	39	F	60	160	July 1961	June 1971	45	October 1973
5	52	F	95	163	February 1967	October 1971	100	October 1973
6	58	F	54	160	May 1963	September 1970	70	November 1973
7	16	F	55	165	October 1972	September 1973	50	November 1973
8	49	M	99	176	October 1971	January 1972	100	March 1973

TABLE II  
EFFECTS ON RESPIRATORY FUNCTION OF ALTERNATE-DAY PREDNISONE IN MYASTHENIA GRAVIS

Patient	FVC(l.)	FEV <sub>1</sub> (l.)	MMF(l/s)	PF(l/min)	MVV(l/min)	Dt <sub>co</sub> (ml min <sup>-1</sup> torr <sup>-1</sup> )
1	3.12(3.37)	2.25(2.50)	1.65(2.05)	363(422)	93(116)	22.8(25.3)
2	4.61(4.74)	3.49(3.61)	3.38(3.44)	672(666)	171(172)	22.0(21.9)
3	2.92(2.89)	2.25(2.20)	2.22(2.34)	322(318)	94(106)	21.0(21.5)
4	3.27(3.29)	2.81(2.81)	3.95(3.80)	382(412)	106(111)	22.4(21.6)
5	2.90(3.02)	2.35(2.40)	2.70(2.56)	307(310)	85(90)	18.6(19.5)
6	2.71(2.69)	2.02(2.00)	2.00(2.16)	221(210)	89(90)	23.7(24.1)
7	3.04(2.82)	2.91(2.79)	4.00(4.66)	355(348)	100(87)	27.3(26.9)
8	3.02(3.50)	1.67(1.91)	0.85(0.86)	165(195)	49(47)	28.8(24.9)
Mean % change <sup>1</sup> SE P	0.43 1.64 NS	0.83 1.75 NS	9.95 4.84 NS	3.55 2.71 NS	5.90 3.92 NS	3.29 1.94 NS

Numbers outside parentheses are from 'day off' and numbers within parentheses from 'day on' prednisone. Numbers represent the mean of all observations for the day.

<sup>1</sup>Numbers represent average percentage change of 'day off' to 'day on' for eight patients.

(1956b). The FRC was also determined by helium dilution (Meneely and Kaltreider, 1949). Spirometric tests—forced vital capacity (FVC), expiratory volume in the first second (FEV<sub>1</sub>), maximal mid-expiratory flow (MMF) and peak flow (PF), and the maximal voluntary ventilation (MVV)—were determined with a Stead-Wells spirometer (Warren E. Collins); the diffusing capacity (DL<sub>co</sub>) was determined by the single-breath technique (Gaensler and Smith, 1973). The diffusing capacity, FRC, TLC, and Raw at each time interval represent the mean of three measurements. Spirometric tests at each time interval represent the best of three measurements. Arterial blood gases were measured in duplicate with standard electrodes (Radiometer Model BMS3). The data were analysed by the Student's *t* test for paired observations.

#### RESULTS

Routine pulmonary function results in the eight patients were within predicted norms (Kory *et al.*, 1961; Boren, Kory, and Syner, 1966) except those of subject 8, which showed airways obstruction. Tables II and III show the effects of alternate-day

prednisone therapy on respiratory function in the eight patients. These data of two consecutive days—a 'day on' and a 'day off' prednisone—represent the average of the respective four determinations for the 'day off' versus the 'day on'. Several studies were obtained throughout the day because preliminary data on subject 8 showed large intra-

TABLE III  
EFFECTS ON RESPIRATORY FUNCTION OF ALTERNATE-DAY PREDNISONE IN MYASTHENIA GRAVIS

Patient	TLC(l)	FRC(l)	Raw (cmH <sub>2</sub> O l <sup>-1</sup> s)
1	5.54(5.86)	2.92(3.06)	2.01(1.37)
2	7.42(7.78)	3.87(4.28)	0.70(0.74)
3	4.87(5.18)	2.60(2.64)	1.20(0.82)
4	5.05(4.97)	2.55(2.48)	1.02(1.01)
5	5.06(5.27)	2.66(2.71)	0.79(0.73)
6	5.61(5.30)	3.71(3.40)	2.02(2.02)
7	5.67(5.72)	3.72(3.71)	1.30(1.33)
8	11.67(10.16)	9.16(7.54)	4.26(3.65)
Mean % change <sup>1</sup> SE P	0.04 2.32 NS	-1.35 3.04 NS	-9.85 5.27 NS

Numbers outside parentheses are from 'day off' and numbers within parentheses from 'day on' prednisone. Numbers represent the mean of all observations for the day.

<sup>1</sup>Numbers represent average percentage change of 'day off' to 'day on' for eight patients.

day variation in lung function, which later proved to be a result of obstructive lung disease rather than a result of alternate-day prednisone therapy (Fig. 1). Except in subject 8, there were no significant intra-day changes. Patient 1 showed improvement of all parameters from the 'day off' to the 'day on' (Tables II and III). Patient 8 had a decrease of TLC, FRC, and RV from the 'day off' to the 'day on' (Fig. 1) with an increase in FVC and FEV<sub>1</sub>. Because of his obstructive lung disease with hyperinflation, this represented improved respiratory function. In patient 8, this pattern of better respiratory function during the 'day on' has now persisted for about two years. As a group, there were no significant changes of any of the parameters from the 'day off' to the 'day on' prednisone. These patients have been followed for periods of months to over two years, and repeated pulmonary function studies over that time have shown no consistent differences between

'day on' and 'day off' with the exception of subjects 1 and 8. Table IV shows that, except for a decreased Pco<sub>2</sub> in patients 4 and 6 (indicating hyperventilation), and a decreased Po<sub>2</sub> in patient 8 (probably secondary to obstructive lung disease), the arterial blood gases measured during the 'day off' prednisone (when one might expect to see abnormalities, if there were any) are within normal limits.

DISCUSSION

Tables II and III show that even though there are large individual changes of respiratory function, for the patients as a group there were no significant differences between 'day off' and 'day on'. Our studies indicate that patients without underlying lung disease do not have large changes in pulmonary function from the 'day on' to the 'day off' prednisone. Even though the reported data are only from two consecutive days, repeated pulmonary function tests obtained over periods of months to over two years, during follow-up visits of the patients, show that with the exception of subject 8 (who shows progressive obstructive lung disease as a result of smoking two packs of cigarettes per day), there have been only minor variations in lung function from 'days on' to 'days off'.

In our experience, when patients start prednisone therapy they show obvious differences in respiratory strength from the 'day on' to the 'day off'. During these early stages of therapy patients can remain off the mechanical ventilator for longer periods of time and have greater vital capacities during the 'day on'. Electromyographic evaluation of neuromuscular synaptic efficiency confirms that during the early stages of prednisone therapy muscle strength is greater during the 'day on' (Warmolts and Engel, 1972). The mechanism by which prednisone increases muscle strength in these patients is not well understood (Engel and Warmolts, 1971). Later on these differences of 'day on' versus 'day off' become smaller and may disappear in some patients.

Subject 1 has consistently shown a minor improvement in all pulmonary function parameters during his day on prednisone (Tables II and III). However, because he has no major underlying lung disease, these changes are probably physiologically unimportant for him. In contrast to subject 8, he has no major diurnal variation of lung function (Fig. 2). Subject 8 shows major diurnal, as well as 'day on' to 'day off' changes in lung function (Tables II and III; Fig. 1).

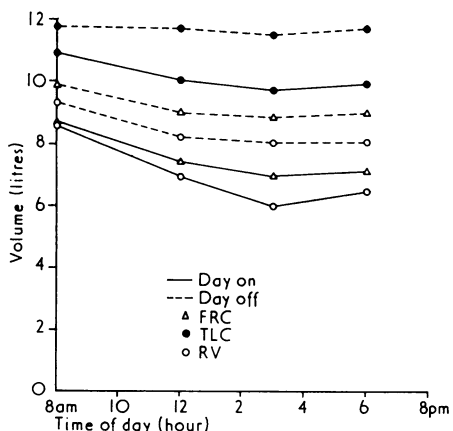


FIG. 1. Patient 8. Lung volumes determined plethysmographically. Volumes show intra- and inter-day fluctuation.

TABLE IV  
ARTERIAL BLOOD GASES OF PATIENTS WITH MYASTHENIA GRAVIS ON ALTERNATE-DAY PREDNISONE

Patient	pH	Pco <sub>2</sub>	Po <sub>2</sub>
1	7.42	38.0	77.0
2	7.37	38.1	77.1
3	7.40	40.8	85.3
4	7.41	31.8	95.6
5	7.46	34.2	81.0
6	7.46	32.0	101.2
7	—	—	—
8	7.42	45.0	71.0

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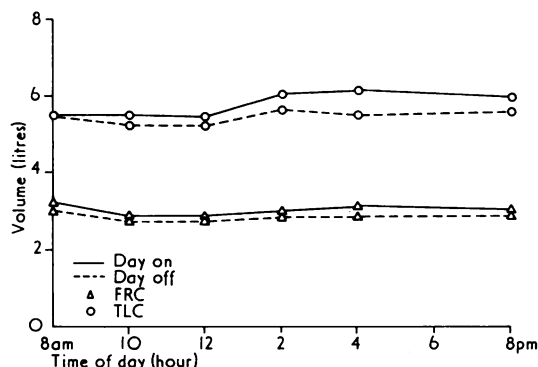


FIG. 2. Patient 1. Lung volumes measured plethysmographically. Volumes show little intra- or inter-day fluctuation.

Patients with myasthenia gravis develop a 'crisis' whenever severe respiratory distress and ventilatory inadequacy occur. A crisis may result from undertreatment or overtreatment with anticholinesterases, or decreased responsiveness to those drugs. All our patients except patient 8 were placed on prednisone therapy because of decreased responsiveness to anticholinesterase drugs leading to myasthenic crises. During the year preceding prednisone therapy, while being treated with anticholinesterase drugs, patients 1 to 7 had one or more episodes of acute respiratory insufficiency associated with generalized weakness, all requiring tracheostomy. Since being treated with prednisone alone, for periods up to three years (Table I), none of the patients has had a myasthenic crisis or any episodes of acute respiratory insufficiency, and respiratory function has in general remained stable during the day. This contrasts with patients on anticholinesterase therapy in whom the FVC may fall substantially several times a day just before the administration of anticholinesterase drugs (Osserman and Jenkins, 1971). Thus alternate-day prednisone therapy not only decreases the frequency of myasthenic crises but also provides a smoother course of therapy when compared to previous treatment with anticholinesterase drugs.

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