

Treatment with an Anabolic Agent Is Associated with Improvement in Respiratory Function in Persons with Tetraplegia: A Pilot Study

ANN M. SPUNGEN, ED.D.^{1,2,3}, DAVID R. GRIMM, ED.D.², MARIANNA STRAKHAN, B.S.¹, PIA M. PIZZOLATO, M.S., R.D.⁴,
AND WILLIAM A. BAUMAN, M.D.^{1,5,6}

Abstract

Background: Pulmonary complications are a major cause of morbidity and mortality among individuals with cervical spinal cord lesions. Strengthening of the respiratory musculature may reduce these complications. Anabolic steroids have been used to increase muscle mass and improve muscle performance. Oxandrolone, an anabolic steroid, may have beneficial effects on breathing in persons with tetraplegia.

Methods: The effect of one-month treatment with oxandrolone on weight gain and pulmonary function was studied in ten subjects with complete motor tetraplegia. Spirometry, maximal inspiratory and expiratory pressures, and resting self-rating of dyspnea (Borg Scale) were measured at baseline and repeated again at the end of one month of oxandrolone therapy (20 mg/day). Serum lipid profiles and liver function tests were performed before and after treatment. A paired t-test was used to determine pre- and post-treatment differences on the dependent variables. Percent change from baseline was calculated for each variable and tested using a one-sample t-test.

Results: On average, the subjects gained 1.4 ± 1.5 kg, a $2 \pm 2\%$ increase in weight ($p=0.01$). A significant, $9 \pm 2\%$ improvement was found in the combined measures of spirometry ($p<0.005$). Maximal inspiratory pressure improved an average of $10 \pm 7\%$ ($p<0.001$). Maximal expiratory pressure improved $9 \pm 13\%$ (non-significant). Subjective self-rating of dyspnea decreased an average of $37 \pm 28\%$ ($p<0.01$).

Conclusions: In healthy subjects with tetraplegia, the use of oxandrolone was associated with significant improvements in weight and pulmonary function, and a subjective reduction in breathlessness. Therefore, oxandrolone may be indicated to strengthen respiratory musculature in individuals who have tetraplegia and ventilatory insufficiency aggravated by superimposition of pneumonia or other such conditions. However, long-term use of oxandrolone may not be indicated, due to the adverse complications associated with this class of agents. **Key Words:** Anabolic agent, oxandrolone, breathing, pulmonary function, tetraplegia, spinal cord injury.

Background

There are approximately 200,000 individuals with spinal cord injury (SCI) in the United States

From the ¹Spinal Cord Damage Research Center, ²Assistant Professor of Medicine and ³Rehabilitation Medicine, Mount Sinai School of Medicine, New York, NY; ⁴Nutrition and Food Program, Veterans Affairs Medical Center, Bronx, NY; ⁵Professor of Medicine and Rehabilitation Medicine, Mount Sinai School of Medicine, New York, NY; and ⁶Department of Medicine, Veterans Affairs Medical Center, Bronx, NY.

Work originated at Spinal Cord Damage Research Center, Mount Sinai School of Medicine, New York, NY; and Medicine and Spinal Cord Injury Services, Veterans Affairs Medical Center, Room 1E-02, 130 West Kingsbridge Road, Bronx, NY 10468.

Address correspondence to Dr. Ann M. Spungen, Spinal Cord Damage Research Center, Room 1E-02, Veterans Affairs Medical Center, 130 West Kingsbridge Road, Bronx, NY 10468.

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today, with 7–10,000 new cases of traumatic SCI occurring each year (1). Slightly more than half of these injuries occur at the cervical level of the spine (2). Cervical paralysis and immobilization can have catastrophic impact on the respiratory muscles, which receive segmental innervation from C₁ through T₁₂. Complete transection of the spinal cord above C₃ causes paralysis of all muscles of respiration, thereby necessitating breathing support from mechanical ventilation. Injury below C₃ partially spares inspiratory muscles, including diaphragm, scalenes, and sternomastoids, but disrupts all muscles of expiration, which are innervated by nerves originating in the thoracic and lumbar spine. As a result of respiratory muscle weakness, ineffective cough and retention of airway secretions frequently lead to atelectasis and pneumonia, the two most frequent causes of morbidity and mortality in the acute period of injury (3–5), as well as in those surviving more than 6 months (6). This respiratory muscle weakness has been well documented to cause mild to severe restriction and a restrictive-

like pattern of spirometry in individuals with tetraplegia (7–11). Individuals with tetraplegia have been found to report a high prevalence of breathlessness (12).

Anabolic steroids have been used to increase muscle mass and thereby improve performance and function. Clinical trials have demonstrated that oxandrolone, an anabolic steroid, is a safe and effective oral adjunct to promote weight gain, predominantly lean tissue, in a variety of pathophysiological conditions, and that it has low potential for androgenic effects (13, 14). Unlike many other anabolic steroids, oxandrolone undergoes little overall metabolic transformation in the liver, and it is well tolerated in men and women (13). Oxandrolone offers potent anabolic activity, which is estimated as 6.3 times greater than that of methyltestosterone (14). Because oxandrolone may have an anabolic effect on the muscles of respiration, our group investigated the potential of this agent to improve measures of breathing in individuals with tetraplegia.

Methods

Subjects

Subjects were recruited for the study based on the inclusion and exclusion criteria. The inclusion criteria consisted of: (1) cervical spinal cord injury more than one year and (2) ability to follow instructions to participate in the study. The exclusion criteria consisted of: (1) pre-injury history of pulmonary disease or respiratory symptoms; (2) active pulmonary infection; (3) receiving medications known to alter airway tone; (4) current smokers who smoke more than $1/2$ pack/day; (5) diabetes mellitus; (6) abnormal liver function tests (LFTs); and (7) serum albumin <3.5 g/dL. Ten male subjects with complete motor tetraplegia were enrolled in this study. Four subjects had complete sensory and 6 had incomplete sensory SCI. Three subjects had lesions beginning at C4; seven subjects had lesions beginning at C5. One subject was a current smoker of less than $1/2$ pack/day; the other 9 subjects were non-smokers. All subjects were currently healthy with no pulmonary complications. However, the restrictive-like pulmonary defect commonly seen in those with cervical spinal cord lesion (6–11) was demonstrated in our subjects. Institutional Review Board approval was obtained from the Veterans Affairs Medical Center, Bronx, NY, and informed consent was given by all subjects prior to enrollment in the study.

Study Design and Statistical Analyses

A one-way within-subjects-design was used to perform the study. Two separate baseline measurements were performed one week apart and averaged prior to oxandrolone administration (20 mg/day). Repeat measurements were performed after one month of treatment. Pre- and post-treatment values were compared by a matched sample t-test. The percent change from baseline was calculated and compared to the null hypothesis using a one-sample t-test. A probability of less than 0.05 was considered to be significant. The results are reported as mean \pm SD.

Pulmonary Function (Spirometry and Maximal Pressures)

Pulmonary function measurements were obtained from subjects while seated in their wheelchairs, using a computerized pulmonary function lab (System 2200, SensorMedics Inc., Yorba Linda, CA). A minimum of three flow-volume loop trials that included the full inspiratory portion of the loop were performed according to the recommendations of the American Thoracic Society (15–17). Spirometry results were expressed as absolute values and the percent was predicted based upon the standards of Morris et al. (18). Forced vital capacity (FVC), forced expired volume in one second (FEV_1), the ratio of FEV_1/FVC , peak expiratory flow rate (PEF), forced inspiratory vital capacity (FIVC) and forced inspiratory vital capacity in one second ($FIVC_1$) were chosen to be analyzed and reported. Respiratory muscle strength was obtained by measurement of maximal inspiratory (PI_{max}) and expiratory (PE_{max}) pressures, using an electronic portable mouth pressure meter (Vacu-Med, Ventura, CA). Three maximum inspiratory efforts at functional residual capacity and three maximum expiratory efforts at total lung capacity were performed. The best effort for each of the three maximal inspiratory and expiratory pressures were recorded.

Symptoms of Dyspnea

Resting breathlessness was determined by use of the modified Borg dyspnea scale and was self-reported by the subjects before each testing session.

Nutritional Intake

The subjects were instructed by a registered dietitian to eat a minimum of 1 g/kg/day of protein during the course of the treatment month.

Serum Lipid Profile and Liver Function Tests

Blood samples were drawn and analyzed for the serum lipid profile and liver function tests by personnel of the clinical laboratory, Veterans Affairs Medical Center, Bronx, NY. Determinations were performed for total cholesterol, triglycerides, and high density lipoprotein cholesterol (HDL-c), and calculated for low-density lipoprotein cholesterol (LDL-c) [LDL-c = total cholesterol - HDL-c - (triglycerides/5)]. Liver function tests (LFTs) were determined for serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), and lactic dehydrogenase (LDH).

Results

The mean age of the group was 41 ± 9 years (range: 26–51). The subjects had a mean duration of injury of 16 ± 8 years (range: 7–31). The mean height was 1.81 ± 0.07 m (range: 1.73–1.93). Mean weight increased by $2 \pm 2\%$ after one month of oxandrolone treatment (76.9 ± 18.3 vs. 78.3 ± 18.9 kg, $p < 0.05$).

As expected in persons with cervical cord lesions, baseline pulmonary function values were significantly reduced from predicted, but measures of spirometry showed significant improvement after one month of oxandrolone treatment (Table 1). Percent change from baseline increased an average

of $9.3 \pm 2.4\%$ for the spirometry values combined (Fig. 1).

Baseline values for P_Imax and P_Emax were significantly reduced from those predicted (62 ± 19 and $15 \pm 13\%$ predicted) (Table 2). P_Imax and P_Emax significantly increased by an average of 7.3 ± 5.5 cm H₂O and 5.1 ± 7.1 cm H₂O, respectively (Table 2). The percent increase from baseline for P_Imax was significant ($10.2 \pm 6.8\%$, $p < 0.005$), although for P_Emax the increase did not reach significance ($9.2 \pm 13.2\%$) (Fig. 2). Subjective symptoms of resting dyspnea were reduced by 37 ± 28 percent, a half point reduction on the Borg scale (2.0 ± 2.0 vs. 1.5 ± 2.0 , $p < 0.05$).

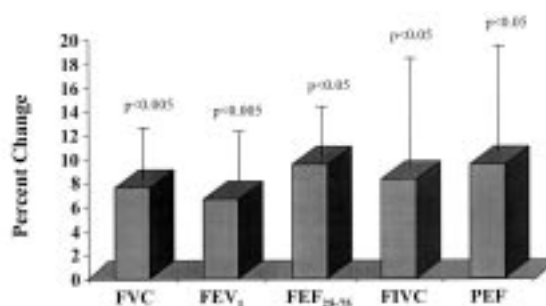


Fig. 1. Percent change in pulmonary function from baseline after one month of oxandrolone treatment.

FVC=forced vital capacity, FEV₁=forced expired volume in one second, FEF₂₅₋₇₅=forced expiratory flow between 25 and 75 percent of the FVC, FIVC=forced inspiratory vital capacity, and PEF=peak expiratory flow rate. p values represent significant change from baseline.

Table 1
Results of Pulmonary Values Before and After One Month of Oxandrolone Therapy

	Baseline L (%pred)	Post- Treatment L (%pred)	Paired Differences L
FVC	2.79±0.95 (53±18)	2.99±1.01 * (57±19) *	0.196±0.167
FEV ₁	2.23±0.73 (56±19)	2.36±0.71 * (59±18) *	0.122±0.970
FEV ₁ /FVC	(83±12)	(83±10)	(<1±5)
FEF ₂₅₋₇₅	2.39±0.96 (56±23)	2.56±0.94 (59±23)	0.170±0.260
FIVC	2.53±0.90 (47±17)	2.71±0.93 § (49±19)	0.178±0.187
PEF L/sec	4.42±1.53 (45±16)	4.72±1.42 (48±14)	0.307±0.603

Results are reported as mean±SD.

Paired differences=mean values for the post-treatment minus the baseline for each subject.

*p<0.005 and §p<0.05 for baseline versus post-treatment.

%pred=percent of predicted.

FVC=forced vital capacity; FEV₁=forced expired volume in one second;

FIVC=forced inspired vital capacity; PEF=peak expiratory flow rate

Table 2
Results of Maximal Pressures Before and After One Month of Oxandrolone Therapy

	Baseline cm H ₂ O (%pred)	Post- Treatment cm H ₂ O (%pred)	Paired Differences cm H ₂ O
PImax	74±22 62±19	81±24 * 68±20 *	7±5
PEmax	34±29 15±13	39±31 § 18±14 §	5±7

Results are reported as mean±SD.

Paired differences=mean values for the post-treatment minus the baseline for each subject.

*p<0.005 and §p<0.05 for baseline versus post-treatment.

% pred=percent of predicted.

PImax and PEmax=maximal inspiratory and expiratory pressures.

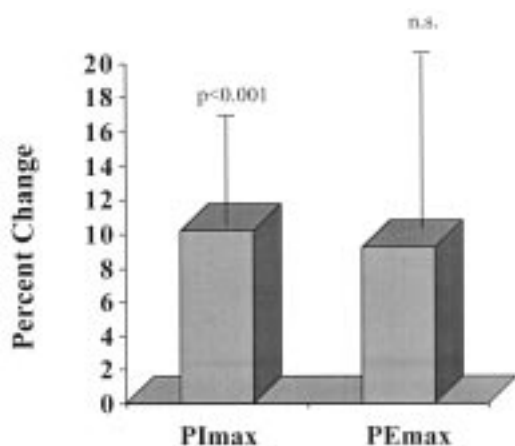


Fig. 2. Percent change in maximal pressures from baseline after one month of oxandrolone treatment.

n.s.=non-significant, PImax=maximal inspiratory pressure, PEmax=maximal expiratory pressure.

p value represents significant change from baseline.

After one month of oxandrolone treatment, liver function enzymes increased slightly from baseline, but remained in the normal range except for ALT, which increased by 2-fold above the upper limit of normal ($p<0.05$). Total cholesterol, triglycerides and LDL-c increased slightly from baseline, but remained within the normal clinical range (150 ± 17 vs. 156 ± 28 , 97 ± 47 vs. 81 ± 31 , and 89 ± 14 vs. 117 ± 29 mg/dL, respectively). Serum HDL-c decreased significantly by an average of 47% (43 ± 9 vs. 23 ± 5 mg/dL, $p<0.0001$).

The normal values for liver function tests are: ALT < 45 U/L, AST < 41 U/L, total cholesterol < 200 mg/dL, LDL < 130 mg/dL, and HDL > 35 mg/dL.

Discussion

Improvements were noted in both the inspiratory (FIVC and FIV₁) and expiratory (FVC,

FEV₁, FEF_{25-75%}, and PEF) portions of the spirometric maneuver. The diaphragm is innervated at C₃ to C₅ and is predominantly used for resting breathing. The intercostals (innervated T₁ to T₁₂) and abdominal wall muscle group (innervated T₇ to L₄) provide respiratory muscle strength for maximal inspiratory and expiratory efforts. With denervation of the intercostal and abdominal wall muscles of respiration, the diaphragm can be recruited for maximal inspiratory and expiratory efforts. Although diaphragmatic size was not measured, the positive changes in pulmonary function are probably explained by an increase in diaphragmatic mass.

Improvements in the maximal inspiratory pressures are consistent with the findings of Annemie et al. (13), in which the effect of an anabolic agent (nandrolone decanoate) combined with nutritional supplementation, and nutritional supplementation alone, and placebo were compared. After 4 weeks of treatment, the nandrolone decanoate combined with nutritional supplementation group and the nutritional supplementation alone group demonstrated significant improvement in PImax compared with the placebo group. However, after 8 weeks of treatment, only the nandrolone decanoate combined with nutritional supplementation group was significantly different from the placebo group. The nandrolone decanoate combined with nutritional supplementation group also demonstrated concurrent improvement in weight gain and fat-free mass (measured by bioelectrical impedance plethysmography). Subjects in our study gained an average of 1.4 kg of weight, albeit body composition was not determined. Oxandrolone has some advantages over nandrolone decanoate. Nandrolone decanoate is administered by intramuscular injection; oxandrolone is an oral preparation. Additionally, nandrolone decanoate has an

androgenic-to-anabolic activity ratio of 1:2.5–1:4, whereas oxandrolone has much higher anabolic potency (1:3–1:13) (19).

Use of the anabolic agent oxandrolone was associated with significant improvement in pulmonary function and subjective rating of dyspnea at rest in subjects with tetraplegia. This improvement is likely the result of increased respiratory muscle mass due to the anabolic function of oxandrolone. Further studies are planned using a double-blind placebo trial to determine the efficacy of therapy. Follow-up after discontinuing treatment, to determine the length of time of a potential beneficial residual effect in pulmonary function, should be considered, as well as the rapidity of return to baseline values of HDL-c levels and LFTs. Chronic use of oxandrolone may not be indicated, due to the adverse changes in serum HDL-c levels. However, the significance of the serum HDL-c change is not clear, given the known suppressant effects of anabolic steroids on lipoprotein a [Lp(a)] levels (20, 21). If HDL-c levels are reduced concurrently with Lp(a) levels, then the net effect for cardiovascular risk may be negligible. If an anabolic agent without the adverse HDL-c complications becomes available in the future, its chronic use in reducing pulmonary complications in persons with tetraplegia may be determined.

In conclusion, oxandrolone may be indicated for individuals with tetraplegia who are nutritionally depleted and have compromised pulmonary function due to pneumonia, atelectasis, bronchial spasms or other such conditions, and who are in need of respiratory muscle strengthening to assist with breathing.

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