OBSTRUCTIVE SLEEP APNEA SYNDROME INDUCED BY TESTOSTERONE ADMINISTRATION

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THE obstructive sleep apnea syndrome is a recently described clinical disorder that results from repetitive episodes of upper-airway occlusion during sleep.[1] Since the syndrome occurs much more frequently in males than females,[2] it is reasonable to postulate that androgens may be important in its cause. We describe below a man in whom both the symptoms and laboratory features of the obstructive sleep apnea syndrome developed on two separate occasions in association with the administration of exogenous testosterone. The symptoms and findings remitted each time that testosterone was discontinued. These observations suggest that testosterone has a causal role in the sleep apnea syndrome.

CASE REPORT

A 36-year-old man volunteered to participate in a study of contraceptive agents for men. His medical history and physical examination were normal except for moderate obesity. The results of routine hematologic and blood-chemistry studies were normal, including a hematocrit of 48 per cent, total serum testosterone of 3.4 ng per milliliter, and free serum testosterone of 143 pg per milliliter. After a five-month control period, the subject received 200 mg of intramuscular testosterone enanthate per week for seven months. Then, while testosterone administration was continued, human chorionic gonadotropin (5000 IU given intramuscularly three times weekly) was added for the next three months.

Ten months after the beginning of the study, the subject reported progressive difficulty in sleeping, daytime somnolence, and mood depression. He denied having respiratory symptoms, but he did have a lifelong history of loud snoring. Another physician had given him amoxapine (150 mg per day) for depression and cimetidine (300 mg three times daily) for symptoms of reflux esophagitis. Physical examination revealed an obese, lethargic man with a weight of 133 kg — an increase of 24 kg since entry into the study, a height of 175 cm, and blood pressure of 140/98 mm Hg. A complete examination of the upper airway revealed no source of obstruction, and the remainder of the examination was remarkable only for pitting pedal edema.

Laboratory data included a hematocrit of 54 per cent (a hemoglobin of 18.6 g per deciliter), but arterial blood gases, serum electrolytes, the creatinine level, and liver function were normal. An electrocardiogram and chest roentgenogram were also normal. Testing of pulmonary function disclosed a reduced functional residual capacity consistent with obesity as well as a mild obstructive defect (FEV_1/FVC = 64 per cent), for which aminophylline was started (300 mg three times daily). Sleep studies and ventilatory-drive studies were conducted to evaluate the symptoms of sleep apnea. Polysomnography was performed during a single overnight study by simultaneously measuring and recording the electroencephalogram, electrocardiogram, electro-oculogram, digastric electromyogram, end-tidal carbon dioxide, airflow at nose and mouth, ear oximetry, and chest and abdominal impedance plethysmograms. Sleep stages were scored according to the criteria of Rechtschaffen and Kales,[3] and episodes of apnea by the criteria of Guilleminault.[2] The hypoxic ventilatory response was measured with the isocapnic method of Weil et al.,[4] and the hypercapnic ventilatory response by the rebreathing technique of Read.[5] Total testosterone levels were determined by radioimmunoassay,[6] and serum free testosterone was calculated as described previously.[7,8]

After these studies were completed, testosterone and human chorionic gonadotropin were discontinued, and the patient was restudied five weeks later. At this time, he described a definite improvement in the quality of his sleep and in his mood, as well as a reduction of daytime somnolence. The results of a physical examination were similar except for the absence of pedal edema and systemic hypertension. Testosterone enanthate injections of 200 mg weekly were then resumed, and after five injections the symptoms returned, as did the pedal edema. Sleep studies and ventilatory-drive studies were repeated, after which testosterone was again discontinued. After six months without exogenous testosterone all the patient's symptoms had resolved, and a final study was conducted. Special care was taken to maintain identical regimens of amoxapine, aminophylline, and cimetidine during each of the four sleep studies.

RESULTS

Testosterone administration was associated with exacerbations of clinical symptoms and laboratory features of the sleep apnea syndrome on two separate occasions. The apneic index (number of episodes of apnea lasting for more than 10 seconds per hour of sleep) was markedly increased during the periods of testosterone administration, with values of 26 and 40 (Table 1; normal ≤5). These changes were too great to be attributed to night-to-night variation in the test results.[9] Like most patients with the sleep apnea syndrome, our subject had all three types of apnea (obstructive, mixed, and central), but obstructive and mixed episodes predominated. While he was receiving testosterone, many episodes of apnea were associated with arterial oxygen desaturation (as low as 65 per cent) and bradycardia. The distribution of sleep stages was similar on each examination, although there were more frequent awakenings and less REM (rapid-eye-movement) sleep during testosterone administration.

On both occasions when testosterone was discontinued, symptoms and disordered breathing during sleep were reduced. Five weeks after testosterone was stopped, most laboratory values had improved, and after six months all values had returned to normal (Table 1). The hematocrit, which increased to a maximum of 58 per cent during testosterone, returned to 48 per cent after a prolonged period without hormone injections.

Arterial oxygen saturation measured while the subject was awake remained between 96 and 97 per cent in all studies. The hypoxic and hypercapnic ventilatory

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Table 1. Clinical and Laboratory Data in a Man with Sleep Apnea during Treatment with Testosterone.

	One Year on Testosterone	Five Weeks off Testosterone	Five Weeks on Testosterone	Six Months off Testosterone
Apneic index	26	8	40	1
Percentage of type of apnea (obstructive/mixed/central)	66/13/21	36/37/27	52/13/35	43/28/29
Total sleep time (min)	131	233	329	363
Free testosterone (pg/ml)	773	79	541	111
Weight (kg)	126	125	130	125
Hypoxic ventilatory response (A) *	132	59	93	62
Hypercapnic ventilatory response (S) †	2.6	1.4	1.1	1.1
Oxygen consumption (ml/min)	387	320	383	290

*"A" denotes the shape parameter of ventilation (liters per minute) versus partial pressure of alveolar oxygen (torr).

†"S" denotes the slope of ventilation (liters per minute) versus partial pressure of alveolar carbon dioxide (torr).

responses were within normal limits for this laboratory[10] on each study but tended to be more brisk during treatment with testosterone. Oxygen consumption was also greater during administration of the hormone.

Discussion

The development of the sleep apnea syndrome in this patient was clearly related to testosterone administration and could not be attributed to other factors, such as changes in medication or body weight. His obesity and history of snoring may have been predisposing factors, but the sleep apnea syndrome occurred only while he was receiving exogenous testosterone.

A relation between sex steroids and sleep apnea has often been suggested. Males are more likely to have obstructive sleep apnea than females,[2] and disordered breathing during sleep is more common among normal males than premenopausal females.[11] These observations and the fact that progesterone is known to stimulate waking ventilatory drives[12] has led some investigators to suggest that progesterone may protect against the development of obstructive sleep apnea.[13,14] However, progesterone, even when given in pharmacologic doses, does not usually help patients with obstructive sleep apnea.[14,15] It is also of interest that loud snoring is more common in men than women, since the physiologic mechanisms responsible for snoring and for obstructive sleep apnea are similar.[16] It may be that the abnormal relaxation of the pharyngeal muscles found in both snoring and obstructive sleep apnea is affected by levels of circulating hormones, including testosterone.

Observations by other investigators are consistent with our findings. Harman et al. examined the frequency of disordered breathing in sleep in 14 subjects with morbid obesity; none of the seven female subjects had disordered breathing or oxygen desaturation, but six of the seven males had either abnormal breathing or oxygen desaturation.[17] The one male subject without episodes was clinically hypogonadal and had a low serum testosterone level. Strumpf et al. examined a patient in whom the Pickwickian syndrome developed while he was receiving testosterone.[18] Weight reduction, treatment with progesterone, and discontinuation of the hormone resulted in clinical improvement.

The effect of testosterone on ventilatory drives has received minimal attention. Koepchen demonstrated a minor increase in hypercapnic ventilatory response,[19] but the patient reported by Strumpf[18] had a reduction in this response while receiving testosterone. Our patient tended to have brisker ventilatory drives during testosterone treatment. This effect may have been related to increased oxygen consumption and therefore to increased metabolic rate. These results suggest that the apparent effect of testosterone in inducing sleep apnea in this patient was not related to a reduction in waking ventilatory drives.

Our patient's clinical course has implications for the experimental and therapeutic use of exogenous testosterone. Other studies have demonstrated that some of the findings in the sleep apnea syndrome, such as peripheral edema, erythrocytosis, and even cor pulmonale, may complicate testosterone therapy.[18,20,21] The erythrocytosis associated with testosterone is related to increased erythropoietin activity as well as a direct bone-marrow stimulatory effect.[22] Although erythrocytosis (2 to 3 percentage-point increases in hematocrit) occurs in most normal men receiving the dosage used in our subject,[23] occasionally the hematocrit increases to levels greater than 55 per cent even when the testosterone is given in replacement dosages.[20] The development of the sleep apnea syndrome with associated nocturnal oxygen desaturation may be the reason for this excessive erythrocytosis in some patients.

A controlled study of the effect of testosterone on sleep apnea is needed to verify the proposed relation. Although our subject received supraphysiologic doses of testosterone, we suggest that any patients receiving testosterone be followed for the signs and symptoms of obstructive sleep apnea. We recommend that these patients be asked about snoring, daytime somnolence, sleep, and emotional disturbances. They should be examined for systemic hypertension, excessive eryth-

rocytosis, edema, and cor pulmonale. Worsening of a patient's condition during testosterone administration should prompt a complete sleep study, and the dose should be reduced or discontinued if the obstructive sleep apnea syndrome is confirmed.

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