

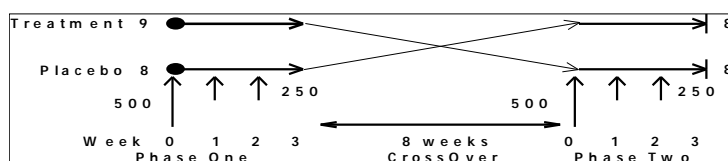
The acute effects of high dose testosterone on sleep in ageing men

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Introduction

Obstructive sleep apnea is a disease characterised by multiple apneas (episodes where breathing ceases) which typically occur 400-500 times each night and results in hypoxia and recurrent arousals from sleep. The sleep disturbance and hypoxia leads to cardiovascular, endocrine, psychological and mental morbidity and traffic accidents. No placebo-controlled studies have reported that testosterone worsens breathing during sleep in older men, although worsening sleep apnea is often cited as an idiosyncratic risk of testosterone therapy based on limited data. Since testosterone (male hormone) replacement therapy is increasingly being evaluated in older men and age is associated with worsening sleep, we evaluated the safety of acute high dose intramuscular testosterone on sleep in a balanced randomised order placebo-controlled cross-over study.

Methods



Seventeen ambulatory men over 60 years of age without significant co-morbidities were randomised to receive 3 injections of mixed testosterone esters (500, 250, 250 mg at weekly intervals) or matching oil-based placebo. After a washout period of 8 weeks, subjects crossed-over to the other treatment. Sleep, physical and mental performance, physical activity, body composition and upper airway calibre were assessed at entry and at the end of each treatment period. Sleep was assessed by overnight laboratory sleep study with the key polysomnographic variable being the total Respiratory Disturbance Index (RDI) which is the number of apnoeic events per hour of sleep. Physical and mental performance was assessed by quality of life questionnaires (SF36 and FOSQ), driving simulation testing and by the neurobehavioural assessment battery which measures sleep-sensitive psychomotor variables including reaction time, sleepiness, mood and vigilance. Variables which might explain potential sleep changes were also measured including body composition (by bioimpedance using the Lukaski formula), upper airway calibre (acoustic reflectometry) and hormone concentrations (using standard commercially available radioimmunoassays).

Results

At baseline, mean (SE) age was 69 (1) years, Body Mass Index (BMI) was 27 (1) kg/m² and total RDI was 15 (3) events/hour. Data was analysed by standard crossover (Grizzle) techniques: period and carryover effects were not detected. Testosterone therapy resulted in a marked increase in serum testosterone (~50 nmol/L) and estradiol (~120 pmol/L) to high supraphysiological concentrations and a feedback suppression of gonadotropins to the limit of detection of the assay (all P<0.001). Testosterone therapy worsened breathing during sleep: total RDI (~7 events/hour, P=0.05) and non-REM RDI (~7 events/hour, P=0.02) were significantly increased, but no effect on REM RDI (P=0.80) was seen. Testosterone treatment reduced the time slept in total (57 minutes), non REM (41 min) and REM (16 min) sleep (all P<0.05). Sleep efficiency (time asleep/time in bed) was also significantly reduced (13%, P<0.05). A small but significant increase in BMI of 0.8 kg/m² occurred in association with an increase in weight (~2 kg, P<0.05) and lean body mass (~3 kg, P<0.05, P<0.05) and a reduction on fat mass (~1 kg, P<0.05); however, upper airway calibre was not significantly changed. Physical activity assessed objectively (accelerometry) and by self-report (PASE questionnaire), driving ability, physical and mental performance and quality-of-life were not changed by treatment.

Discussion

We conclude that testosterone treatment in elderly men results in expected hormonal changes, particularly marked increases in testosterone and estradiol to high supraphysiological concentrations and is associated with a reduction in total sleep time and sleep efficiency as well as an increase in sleep disordered breathing. In addition, body composition was significantly improved. This study shows that short-term supraphysiological testosterone supplementation can worsen sleep, particularly non-REM sleep, but that these changes did not acutely impair physical or mental function, and were not explained by narrowing in upper airway calibre. It raises concern regarding the recreational use of high dose testosterone in young men, but does not exclude the possibility that lower dose steady state supplementation in older men may still be safe.

In a randomised, placebo controlled clinical study, we have shown for the first time that high dose short term testosterone treatment can acutely worsen sleep and breathing in older men. Further longer term studies in young men, or in older men using lower doses are required to establish risk or safety.