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A safety study of administration of parenteral testosterone undecanoate to elderly men over minimally 24 months

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Summary

This study investigated the safety of administration of long-acting parenteral testosterone undecanoate (TU) to 122 hypogonadal, mainly elderly men, aged 59.6 ± 8.0 years (range 18–83 years old), with baseline testosterone levels between 5.8 and 12.1 nmol l^{-1} (mean ± SD = 9.3 ± 1.7). Patients were followed for 24 months. Plasma testosterone rose from 9.3 ± 1.7 to 14.9 ± 4.5 nmol l^{-1} ($P < 0.01$) at 3 months, then stabilised at 19.2 ± 4.6 nmol l^{-1} after 6 months. International Prostate Symptoms Scores and Residual Bladder Volumes decreased significantly ($P < 0.01$) over the study period. Prostate volume and prostate-specific antigen levels fluctuated over the study period but had not increased significantly after 24 month. Haemoglobin concentrations increased significantly ($P < 0.001$) over the 24 months while the haematocrit increased significantly ($P < 0.001$) during the first 15 months and then levelled off. Statistical analysis with expressing values as means ± SD masks excesses above reference values of individual patients. These excesses were noted in low numbers, were permanently present in some but not in other individuals, and did not increase in number over the 24 month study period. Over 24 months treatment with TU appeared acceptably safe, but longer and larger scale studies are needed.

Introduction

The progressive decline of testosterone in ageing men is supported by scientific evidence (Kaufman & Vermeulen, 2005). With age, a significant percentage of men over the age of 60 years have serum testosterone levels below the lower limits of normal for young adult men (ageing, 20–30 years) (Araujo *et al.*, 2004; Liu *et al.*, 2007). Whether older hypogonadal men will benefit from testosterone treatment and what will be the risks associated with such intervention can only be resolved by sufficiently powered studies. In the past decade evidence has been produced of the benefit of androgen treatment on multiple target organs of hypogonadal men, and recent studies show short-term beneficial effects of testosterone in older men that are similar to those in younger men (Swerdloff & Wang, 2003; Bhasin *et al.*, 2005; Page *et al.*, 2005; Allan *et al.*, 2008).

Data on the risks of testosterone administration are needed, particularly on its safety in elderly men (Bhasin *et al.*, 2006; Wang *et al.*, 2009). It is unlikely that rigorous scientific data with regard to safety of testosterone administration to elderly men will become available soon. Such studies would include 5000–7000 men. So, for the time being, smaller scale studies will have to be utilised to garner information on safety.

Main side effects of testosterone administration

polycythaemia

There is curvilinear relationship in men (not receiving testosterone administration) between plasma testosterone

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levels and haemoglobin (Zitzmann *et al.*, 2006). Testosterone exerts its effect on erythropoiesis through a number of mechanisms. Testosterone has an effect on erythropoietin production in the kidney (Cui *et al.*, 2003) but it has also a direct effect on colony formation of progenitor cells of erythrocytes (Kozlov *et al.*, 1979). In a study by Wang *et al.* (2000) a dose dependent effect of testosterone could be established on haemoglobin and the haematocrit values. This dose dependency was also apparent from another study (Dobs *et al.*, 1999), which compared the effects of transdermal versus intramuscular testosterone; the latter achieved higher plasma levels of testosterone and raised the haematocrit more than transdermal testosterone. In a recent study it could, indeed, be demonstrated that testosterone has a dose-dependent stimulatory effect on haematopoiesis in men. Remarkably, this effect was more pronounced in older men (Coviello *et al.*, 2008). Another study confirmed the relevance of the dose of testosterone and of age as factors in the stimulation of haematopoiesis (Zitzmann & Nieschlag, 2007). In addition, obesity and shorter CAG repeats appeared to be factors.

A higher value of the haematocrit is associated with stroke (Kiyohara *et al.*, 1986; Lee *et al.*, 2001), and coronary heart disease (Brown *et al.*, 2001). However, a relation between increased haematocrit as a result of androgen supplementation as such and an increased risk for stroke or any cardiovascular event in general has not been demonstrated by a large meta-analysis of placebo-controlled trials of testosterone administration to (elderly) men (Calof *et al.*, 2005).

Lower urinary tract symptoms and prostate disease

Several follow-up studies of men receiving testosterone treatment (Morales, 2004; Schultheiss *et al.*, 2004; Calof *et al.*, 2005) have failed to demonstrate an exacerbation of voiding symptoms due to benign prostatic hyperplasia. Complications such as urinary retention in therapy group did not occur at higher rates than in controls receiving placebo. The occurrence of prostate cancer after testosterone administration to (elderly) men has been reported (Ebling *et al.*, 1997; Loughlin & Richie, 1997; Curran & Bihrle, 1999; Rhoden & Morgentaler, 2004; Sengupta *et al.*, 2005). By contrast, a variety of studies using various designs and testosterone formulations over periods between several months and 15 years, in men with a wide range of ages, have not revealed an increased risk of prostate cancer (Tenover, 1992; Chamberlain *et al.*, 1994; Carter *et al.*, 1995; Morgentaler *et al.*, 1996; Giovannucci *et al.*, 1997; Heikkila *et al.*, 1999; Hsing, 2001; Thompson *et al.*, 2003; Andriole *et al.*, 2004a,b; Clark *et al.*, 2004; Marks *et al.*, 2006; Morgentaler, 2007; Yassin & Saad, 2007, 2008; Coward *et al.*, 2008). A meta-analysis found that testosterone treatment in older men compared to placebo was not associated with a significantly higher risk of detection of prostate cancer (Calof *et al.*, 2005), although the frequency of prostate biopsies was much higher in the testosterone-treated group than in the placebo group (Calof *et al.*, 2005).

There is a consensus now that administration of testosterone to elderly men is a responsible practice provided certain guidelines of professional bodies are followed with regard to testosterone administration to elderly men (Bhasin *et al.*, 2006; Wang *et al.*, 2009). In this study, we analysed risks of testosterone administration to a large cohort of mainly elderly men.

Subjects and methods

A cohort of 122 mainly elderly men, aged 59.6 ± 8.0 years (SD) years (range 18–83 years old), with baseline testosterone between 5.8 and 12.1 nmol l^{-1} (mean ± SD = 9.3 ± 1.7) were studied. The aetiology of their hypogonadism was late onset hypogonadism (Kaufman & Vermeulen, 2005) except for three subjects. They had sought urological consultation for a number of reasons: erectile dysfunction, questions about their testosterone status or a variety of urological complaints. They received treatment with parenteral testosterone undecanoate (TU) (administration at 0 and 6 weeks and thereafter every 12 weeks) whereupon the plasma testosterone returned to the physiological range.

They were followed for at least 24 months after the beginning of the treatment.

All men had given their consent to be included in this study monitoring the safety of testosterone administration to elderly men. The study protocol had been approved by the institute's ethical review board for studies in humans.

At intervals of 3 months, after an overnight fast, blood samples were collected between 8 and 11 a.m. Haemoglobin (Hb) and haematocrit (Hct) were measured using standardised routine laboratory methods. Post-void residual bladder volume (RBV), and prostate volume (PV) were measured using Sonoace SA 8000 SE with three ultrasound probes; for abdominal measurement of residual bladder urine volume a probe with 3–7 MHz and for PV a transrectal probe of 5–12 MHz were used. The International Prostate Symptoms Score (IPSS) was assessed.

All analysis was performed using STATA (Stata Corp, College Station, TX, USA). The significance of mean difference over time was determined using linear mixed model (West *et al.*, 2007). Patients were categorised into two groups based upon their measured values of exceeding the upper limit of reference values: PSA > 4 ng ml^{-1}, haemoglobin > 10.98 mmol l^{-1}, (for conversion to g l^{-1}

divide by 0.6206) and haematocrit > 52%. According to these criteria, patients were also categorised into four age groups using quartiles. Significant levels of association between PSA, IPSS score, haemoglobin concentration, haematocrit and age group were determined using Fisher's exact test. Significant level of trend of association was determined by Mantel–Haenszel test (Dowdy *et al.*, 2004). The cumulative incidence of having a haematocrit or haemoglobin concentration increased beyond the upper limit of reference values was calculated by dividing the number of patients who did not exceed the upper limit at previous time points by the number of patients exceeding the upper limit of reference values (Gerstman, 2003).

Results

Patients were followed for 24 months. Plasma testosterone rose from 9.3 ± 1.7 to 14.9 ± 4.5 nmol l^{-1} ($P < 0.01$) at 3 months, then stabilised at 19.2 ± 4.6 nmol l^{-1} after the first 6 months of the study ($P < 0.05$). Figure 1 and Table 1 show the average levels of IPSS, PSA, haemoglobin concentration, haematocrit, RBV and PV over the study period. IPSS and RBV decreased significantly over the 24-month study period (Table 1). At the beginning of the study PSA levels were 1.53 ± 1.91 ng ml^{-1} and at the end of the 24 months 1.59 ± 1.1 ng ml^{-1} (n.s.). Prostate volume did not change significantly over the study period. The mean haemoglobin concentration and the mean haematocrit increased significantly over the first 15 months of the treatment, then levelled off until the end (Table 1). Table 2 provides the level of significance of changes over an interval of 3 months during the 24-month study period. It provides insight into the time table of changes induced by testosterone treatment over the 24-month study period (Table 3). This patient underwent biopsying of the prostate and there were no signs of malignancy. A total of 16 patients had haemoglobin concentrations exceeding 10.98 mmol l^{-1} (upper limit of reference values) at least once during the study period. A total of 15 patients had haematocrit levels higher than 52% (upper limit of reference values) at least once during the study period. There was no upward trend in the number of subjects with values above the upper limit of reference values over the 24 months of the study (Table 3).

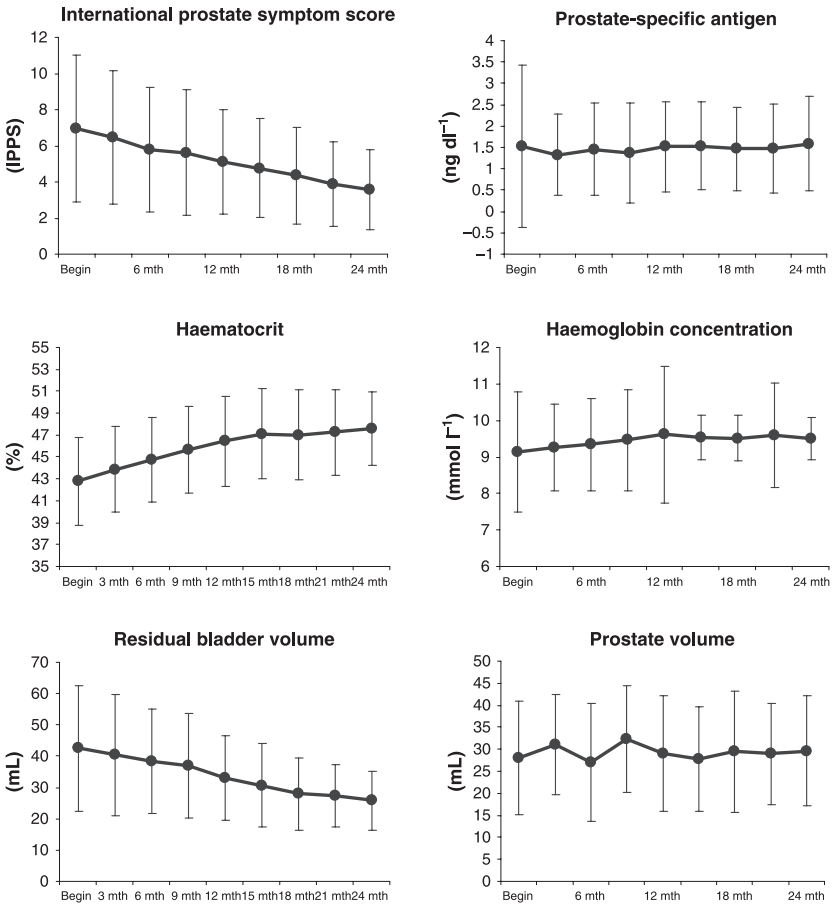

Fig. 1 Average safety parameters over the 24-month study period.

Table 1 Safety data of 122 men 122 hypogonadal, mainly elderly men, aged 59.6 ± 8.0 years, receiving treatment with testosterone undecanaoate. Data are presented as mean ± SD (for conversion of haemoglobin mmol l^{-1} to g l^{-1} divide by 0.6202)

	IPS score		Bladder residual volume (ml)		Prostate volume (ml)		PSA (ng ml^{-1})		Haemoglobin (mmol l^{-1})		Haematocrit (%)	
Time	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Begin	6.95	4.05	42.58	20.12	27.98	12.90	1.53	1.91	8.4	1.0	42.80	4.03
3 months	6.46	3.68	40.40	19.34	31.05	11.38	1.32	0.95	8.5	0.9	43.88	3.92
6 months	5.80	3.45	38.45	16.79	27.00	13.41	1.46	1.08	8.7	0.9	44.76	3.84
9 months	5.62	3.49	36.96	16.81	32.23	12.14	1.37	1.17	9.4	1.0	45.71	3.96
12 months	5.12	2.90	33.05	13.63	28.92	13.13	1.51	1.05	9.5	1.1	46.44	4.14
15 months	4.76	2.75	30.60	13.33	27.72	11.93	1.53	1.03	9.6	1.0	47.12	4.15
18 months	4.35	2.67	27.94	11.67	29.46	13.74	1.46	0.98	9.5	0.9	47.02	4.12
21 months	3.88	2.33	27.34	9.80	28.92	11.52	1.48	1.04	9.6	0.9	47.25	3.91
24 months	3.57	2.24	25.76	9.33	29.66	12.59	1.59	1.11	9.7	0.8	47.62	3.37

Table 2 Significance of change in study parameter over the period of treatment of 24 months

	IPS score	PSA (ng ml^{-1})	Haematocrit (%)	Haematocrit (mmol l^{-1})	Bladder residual volume (ml)	Prostate volume (ml)
TT	0.966	0.047	0.000	0.000	0.437	0.006
Time	0.000	0.486	0.000	0.000	0.000	0.001
0–3 months	0.025	0.084	0.000	0.562	0.035	0.755
3–6 months	0.002	0.848	0.000	0.408	0.295	0.004
6–9 months	0.164	0.590	0.000	0.109	0.172	0.917
9–12 months	0.019	0.798	0.000	0.064	0.000	0.176
12–15 months	0.017	0.550	0.000	0.931	0.045	0.400
15–18 months	0.090	0.953	0.304	0.866	0.103	0.082
18–21 months	0.003	0.859	0.685	0.214	0.709	0.691
21–24 months	0.164	0.367	0.343	0.408	0.084	0.368
0–24 months	0.000	0.509	0.000	0.000	0.000	0.000

Table 4 shows the relationship between age and the cumulative incidence of excesses above upper limits of reference values over the 24-month study period. In this study, age appeared not significantly associated with any excesses above the upper limit of reference values. There was no significant trend of increasing or decreasing cumulative incidence associated with ageing. The cumulative incidence or risk of having a haematocrit or haemoglobin concentration increased beyond the upper limit of reference values ranged between 0% and 2.7% and 0.4% and 1.7%, respectively.

Discussion

In a cohort of 122 hypogonadal, mainly elderly men, aged 59.6 ± 8.0 years treated with parenteral TU for at least 24 months, there were no adverse effects on lower urinary tract symptoms, There was a decline in scores of the IPSS. Also the RBV decreased. No case of prostate cancer was observed in this cohort over the study period of 24 months. A span of time of 24–30 months of testosterone treatment obviously does not allow conclusions as to the long-term safety of testosterone administration with regard to prostate cancer. Longer and larger scale studies are required to answer those questions. Over the observation period there was no indication of an increase in PV. PSA levels stabilised at 1.59 ± 1.1 ng ml^{-1}, a value not significantly higher than baseline values. Progressive ageing in itself is associated with an increase in PSA values (Snyder *et al.*, 1999). Further, administration of testosterone to hypogonadal men leads to an increase of PSA levels (Calof *et al.*, 2005).

There was an increase in haemoglobin and haematocrit values which, on an average, were not above the upper limit of normal over the treatment period. Statistical analysis with calculations of mean values and SD masks individual excesses above the upper limit of reference values. To report individual excesses, patients were categorised into two groups based on their measured values of whether or not exceeding the upper limit of reference values. There were indeed small numbers of patients with values of safety parameters exceeding the upper limit of reference values but the number of patients did not rise over the study period and the elevated levels were not

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Table 3 Number of patients with safety parameter exceeding upper limit of reference values at each study period

	Haemoglobin (mmol l^{-1})	Haematocrit (%)	PSA (ng ml^{-1})
	>10.98	>52%	>4
Begin	2	4	3
3 months	5	6	1
6 months	4	5	3
9 months	6	7	2
12 months	1	7	2
15 months	6	4	1
18 months	2	4	1
21 months	2	5	1
24 months	4	4	1

Table 4 Number of patients with safety parameter increased exceeding upper limit of reference values during the treatment

	Haematocrit (%)	Haemoglobin (mmol l^{-1})	PSA (ng ml^{-1})
	>52	>10.98	>4
Age (years)			
18–42	2	3	0
43–55	4	2	1
56–62	3	1	2
>63	0	1	1
P-value[a]	0.089	0.240	1.000
Trend[b]	0.060	0.072	1.000

[a]Fisher's exact test.
[b]Mantel–Haenzel test.

necessarily encountered in the same individuals. No relationship with age could be established, which has been reported for effects of testosterone administration on haemoglobin and haematocrit values (Zitzmann *et al.*, 2006; Coviello *et al.*, 2008). A relationship between testosterone levels following testosterone administration and resulting values of haemoglobin and haematocrit (Dobs *et al.*, 1999; Wang *et al.*, 2000; Zitzmann *et al.*, 2006) has been reported but was not apparent from the results of this study. Also, a relationship with plasma estradiol has been reported (Zitzmann *et al.*, 2006; Coviello *et al.*, 2008). Plasma oestradiol levels were not measured in this study but they usually are related to circulating testosterone (Coviello *et al.*, 2008). The rise of haemoglobin and haematocrit levels above the reference range is clinically relevant. A higher value of the haematocrit is associated with stroke (Kiyohara *et al.*, 1986; Lee *et al.*, 2001), and coronary heart disease (Brown *et al.*, 2001). From this study it appeared that, with a testosterone preparation like parenteral TU generating stable levels of plasma testosterone, haemoglobin and haematocrit levels have reached a plateau after 12–15 months. This might imply that, similar to the follow-up of serum PSA, after a first uneventful year of testosterone administration, levels of haematocrit and haemoglobin should be checked once a year.

The safety of TU with regard to erythropoiesis observed in this study is probably to be ascribed to the fact that achieved values of plasma testosterone were constantly in the reference range.

In summary, testosterone deficiency is a common but not an obligatory condition in elderly men. There are numerous indications that a supplementation therapy has beneficial effects. Our data indicate that the short-term risks for the prostate and erythropoiesis are acceptable, confirming results from earlier studies of TU in elderly men (Yassin & Saad, 2007, 2008). Following the guidelines as specified by a number of professional organisations, testosterone-deficient elderly men can be responsibly treated with testosterone (Bhasin *et al.*, 2006; Wang *et al.*, 2009). Needless to say that studies with much larger numbers of men and for a longer period of time are needed to resolve the question of safety of testosterone administration to elderly men.

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