World J Urol (2003) 21: 306–310
DOI 10.1007/s00345-003-0364-x

TOPIC PAPER

Louis J. Gooren

New long-acting androgens

Received: 16 September 2003 / Accepted: 17 September 2003 / Published online: 9 October 2003

Abstract Testosterone substitution treatment aims to replace physiological actions of endogenous testosterone by steadily maintaining physiological blood levels of testosterone. The underlying conditions rendering androgen replacement necessary are usually irreversible. The consequence is that almost life-long androgen replacement is required. Patient compliance with life-long androgen replacement depends on convenient pharmaceutical formulations ensuring continuity of androgen replacement. Therefore, they must be convenient in usage with a relative independence of medical services. In elderly man, safety of androgen replacement therapy is a concern but in younger subjects (below the age of 50 years) side effects of androgens are usually minimal. For them, long-acting testosterone preparations are well suited. Testosterone implants generate, depending on the dose of implants, 3–6 months of normal plasma testosterone. This method requires minor surgery. Injectable testosterone undecanoate maintains plasma testosterone in the normal range for 12 weeks.

Keywords Testosterone · Replacement therapy · Parenteral androgen · Testosterone implant · Aging male

In cases of androgen deficiency, testosterone replacement therapy aims to replace physiological actions of endogenous testosterone by steadily maintaining physiological blood levels of testosterone [18]. The underlying conditions rendering androgen replacement necessary are usually irreversible. The consequence is that life-long androgen replacement is required. Patient compliance with life-long androgen replacement depends on convenient pharmaceutical formulations ensuring continuity of androgen replacement. The benefits of androgen replacement therapy are clear, but the delivery of testosterone to hypogonadal men in a way that approximates normal levels and patterns still poses a therapeutic challenge. Among experts, there is consensus that the major goal of testosterone substitution is "to replace testosterone levels at as close to physiological concentrations as is possible" [18]. General agreements about such an androgen replacement therapy are (1) a delivery of the physiological amount of testosterone (3-10 mg/d); (2) consistent levels of testosterone, 5α-dihydrotestosterone (DHT) and 17β-oestradiol (E_2) within normal physiological ranges; (3) a good safety profile without adverse effects on the prostate, serum lipids, liver or respiratory function; and (4) convenience in usage, patient-friendly, with a relative independence of medical services.

It is also generally accepted that testosterone, naturally produced by the testis, is viewed as the best androgen for substitution in hypogonadal men. The reason behind the selection is that testosterone can be converted to DHT and E_2, thus developing the full spectrum of testosterone activities in long-term substitution.

Quantitative aspects of androgen action

One of the pharmaceutical problems of androgen therapy is the vast amount of androgen molecules to be administered for replacement. The daily testosterone production in the eugonadal adult man lies in the range of 4–7 mg, as opposed to daily production of E_2 which lies at its peak in the late follicular phase of the menstrual cycle and amounts to 0.5–1.0 mg/day. The challenge in androgen replacement treatment has been to deliver a sufficiently large amount of androgen

L. J. Gooren
Department of Endocrinology,
Section of Andrology, VU University Medical Center,
P.O. Box 7057, 1007 MB Amsterdam, The Netherlands
E-mail: ljg.gooren@vumc.nl
Fax: +31-20-4440502

molecules to the circulation. This difficulty can be demonstrated by comparing transdermal delivery of testosterone with that of E_2. The latter has been relatively easy (two patches per week containing 50–100 μg E_2), while with transdermal testosterone treatment this is relatively difficult (daily scrotal or large nonscrotal patch containing 8–14 mg of testosterone). The large quantities of testosterone needed for their biological actions as compared with E_2 may be explained by the properties of the androgen receptor. It is conceivable that an androgen can be designed that retains (most of) its properties, but which has a hormone-receptor interaction in a way comparable to oestrogen action, where relatively few oestrogen molecules achieve powerful biological effects.

Available preparation for testosterone replacement

Three approaches are used to make testosterone therapeutically effective: routes of administration, esterification in the 17β position and chemical modification of the molecule, or a combination of approaches. This contribution will focus on the long-acting forms of testosterone replacement.

Parenteral testosterone esters

Parenteral testosterone preparations have for a long time been the mainstay of testosterone treatment and they are the most cost-effective methods. The most commonly used forms include 17β-hydroxyl esters of testosterone, which are administered with slow-release, oil-based vehicles. Commonly used intramuscular injectable testosterone esters are short-acting testosterone propionate and longer-acting testosterone enanthate and cypionate.

Testosterone enanthate is one of the most commonly used intramuscular testosterone esters. After a single injection of 250 mg, maximal testosterone concentrations are reached after 10 h; the terminal half life is 4.5 days [17]. At a dose of 200 –250 mg, the optimal injection interval is 2–3 weeks but peak and through values are clearly above and below the normal range, so that only 45–55% of the injection interval plasma testosterone levels are in the normal range. Other testosterone esters are testosterone cypionate and testosterone cyclohexanocarboxylate. The pharmacokinetics of these testosterone esters are very similar to those of testosterone enanthate [21, 22]. Administration of 200 mg every 2 weeks provides an acceptable form of testosterone replacement. With most of the latter testosterone esters, a maximum concentration follows approximately 72 h after injection. Testosterone levels slowly diminish during the following 10–14 days, showing an exponential decline of serum testosterone levels reaching baseline at approximately day 21 [25]. As a result, the testosterone levels before the next injection are low [20, 24]. The normal pattern of circadian rhythm of testosterone is not provided and the injections are painful [14]. A vast number of patients experience these strongly fluctuating levels as unpleasant ('roller coaster effect').

Thus, most intramuscular presentations of testosterone are associated with a number of disadvantages. The profile of testosterone levels may be accompanied by disturbing fluctuations in sexual function, energy level, and mood [15]. Although levels of DHT are normal, androgen metabolites are frequently not physiological and E_2 concentrations may become excessive in some men. High post-injection levels of testosterone predispose the patient to acne and polycythaemia, and E_2 causing gynaecomastia. In some patients, injections may be associated with bleeding or bruising [14].

Therefore, there is a clear need for testosterone preparations which are longer-acting with more stable plasma testosterone levels and which require less frequent administration.

Parenteral testosterone undecanoate

Oral testosterone undecanoate dissolved in oil and encapsulated has been available since the early 1970s. A study from China [28] revealed that that this compound administered parenterally had a significantly longer half-life than the conventional parenteral testosterone esters. After experimentation comparing different concentrations and solutions, 1000 mg testosterone undecanoate in 4 ml castor oil proved to deliver an attactive pharmacokinetic profile: the terminal half life was 33.9 ± 4.9 days, with maximal levels of 19.3 ± 2.1 nmol/L reached after 11.4 ± 1.5 days [3]. Later studies with four injections of 1000 mg testosterone undecanoate in 4 ml castor oil at 6-week intervals in hypogonadal men showed that intervals between two injections may be as long as 13 weeks. Serum testosterone levels were never found to lie below the lower limit of normal, while only short-lived peaks above normal (40.8 ± 3.8 nmol/L) were observed after the third and fourth injection interval [19]. In a study of testosterone undecanoate given to seven hypogonadal men with intervals of 12 weeks, serum testosterone, DHT and E_2 were mostly within the normal range and showed a tendency to decrease with longer intervals. Safety parameters such as body weight, hemoglobin, serum lipids and PSA and prostate volume did not change significantly during 3.2 years of observation. Maximum testosterone levels during steady state were measured after 1 week and amounted to 32 ± 11.7 nmol/L. The investigators concluded that this preparation had significant advantages over the conventional parenteral testosterone esters such as considerably longer intervals between injections and significantly less severe and frequent supraphysiological plasma testosterone levels [23, 27].

Testosterone buciclate

Testosterone buciclate is long-acting, slow-release preparation. The half life is about 30 days and maximum concentrations of 13.1 ± 1.8 nmol/L. An injection of 1000 mg testosterone buciclate maintained serum testosterone levels within the normal range for approximately 16 weeks [2]. With a 600-mg testosterone buciclate injection, this was about 12 weeks [1, 26]. In spite of the merits of testosterone buciclate as a long-acting preparation, there has been no active follow-up of the above studies and no attempts are being made to make the preparation available for clinical use.

Testosterone microspheres

Biodegradable microspheres containing testosterone may be a method for slow release of testosterone [5]. An injection of 630 mg of microencapsulated testosterone in hypogonadal men maintained serum testosterone levels in the eugonadal range for approximately 75 days [4]. Testosterone release from the microcapsule formulation over the first 10 weeks approximated zero order kinetics. Serum DHT levels were in the normal range with a normal T/DHT ratio. Serum LH and FSH declined significantly, which was also the case with SHBG. There have been no follow-up studies since 1992.

Testosterone implants

Subdermal pellet implantation was among the earliest effective treatment modalities for clinical use of testosterone and became an established form of androgen replacement by 1940 (for review see Handelsman et al. [8]). Several reports have outlined its desirable pharmacological properties [6, 7, 8, 10, 16, 29] but its use and merits and its complications have been best documented by the group of Handelsman [8, 9, 11, 12, 13].

The original implants were not very well standardized, resulting in uneven release, but this problem has been overcome. There are now pellet implants available in two sizes: 100 (length: 6 mm, diameter 4.5 mm) and 200 mm (length 12 mm, diameter 4.5 mm).

Pellets are implanted under sterile conditions, usually under the skin of the lower abdominal wall. Implantation at the hip has a higher extrusion rate, but 'track geometry' (two versus four tracks) had no influence [12]. Antibiotic impregnation of the pellets did not decrease the extrusion rate [13].

Absorption of testosterone from the subdermal pellets occurs via uniform erosion of the pellet's surface, from which testosterone leeches out according to the solubility of testosterone in the extracellular fluid. Deviations from the simple surface erosion model may occur late in the time course of absorption if the surface area becomes irregular. Other factors are pellet smoothness/hardness, the site of implantation with its local blood flow and reaction of the surrounding tissue, which may lead to encasing of the pellet.

The effective testosterone release rate from a 200-mg pellet is 1.3 mg/day (95% confidence interval 1.22–0.137). The number of pellets has no effect on the testosterone absorption rate. With treatment with pellets, it is possible to replicate the daily testosterone production rate of 3–9 mg in eugonadal men. A single implant of three to six pellets of 200 mg will provide the patient with a physiological daily dose of testosterone for 4–6 months. Pellets constitute a flexible dosage form by using various combinations of pellets of 100 and 200 mg with a delivery of testosterone between 0.65 and 7.8 mg/day in increments of 0.65 mg. Based on clinical pharmacology and clinical experience, the routine dose is 4×200 mg implants. The time course of plasma testosterone levels is predictable and it is usually sufficient to review a patient after the third month of an uncomplicated implant. It can be calculated that virtually all testosterone will be absorbed from a 200-mg pellet within 6 months.

Like other depot testosterone formulations, testosterone implants demonstrate a minor and transient accelerated initial release. This lasts for 1–2 days and involves only 1.5% of total testosterone. The mean plasma testosterone levels reached during these 'bursts' are < 50 nmol/L (upper levels of reference values is 35 nmol/L). This compares favourably with injectable testosterone esters, which peak to levels between 40–80 nmol/L, with every administration once per 2–4 weeks.

The bioavailability of testosterone (defined by appearance in blood stream) from testosterone pellets is virtually complete. There is no first pass hepatic inactivation effect and virtually all released testosterone is absorbed into the systemic circulation.

The clinical pharmacology of testosterone implants has been reported in several studies [7, 8, 10]. The most comprehensive study involved a random sequence crossover design clinical study of 43 androgen-deficient men [8]. These men were treated sequentially with three regimens: six 100-mg, three 200-mg and six 200-mg testosterone pellets at intervals of 6 months when blood testosterone levels returned to baseline. Implantation of testosterone pellets provided highly reproducible dose-dependent time course related plasma levels of total and free testosterone. Plasma testosterone on the 1200-mg dose were higher but no differences were observed between the six 100-mg and the three 200-mg pellet implantations producing similar plasma testosterone levels and a similar time course. Plasma testosterone levels peaked at the first month and gradually declined to return to baseline by 6 months after either six 100-mg or the three 200-mg pellet implantations. But the plasma levels remained significantly higher following the six 200-mg pellet implantation.

Maintenance of libido, potency and well-being appeared to be very consistent with the 600-mg testoster-

one implants for 4–5 months and 6 months with the 1200-mg implant.

In the studies of Handelsman et al., Jockenhővel et al., and Zacharin and Warne, using a cross-over design of testosterone implants and injectable testosterone esters, most men preferred testosterone pellets rather than injectable testosterone esters [8, 10, 29]. The latter were disliked because of the wide swings in plasma testosterone levels experienced subjectively as swings in mood and energy and the frequent administrations as compared with the implantation of pellets. Pellet implants are particularly suitable for androgen-deficient men who dislike or are unable to have regular injections. It is best used in men in whom the beneficial effects of testosterone replacement and tolerance for androgens have already been established with treatment of shorter-acting testosterone preparations. In the rare event that rapid discontinuation of androgen administration is necessary (such as in case of a prostate carcinoma), minor surgery to remove the implants may be necessary.

Suppression of LH and FSH in hypergonadotropic hypogonadal men occurred in a dose-dependent fashion by all three implant regimens. The 1200-mg implants produced a significantly greater suppression than the two regimens of 600 mg. With the 1200 mg, the suppression of LH showed nadir levels between 1 and 4 months with return to baseline only at 6 months. With the 600-mg regimens, nadir levels of LH were observed between 1 and 3 months with an increase beginning by 4 months and return to baseline by 5 months. Interestingly, the suppression of elevated gonadotropin levels in men with primary hypogonadism mirrored closely the time course of clinical androgen effects and the maintenance of physiologic testosterone levels. This suggests that the adequacy of testosterone replacement can be monitored by measuring not only plasma testosterone levels but also the degree of suppression of gonadotropins.

Plasma SHBG levels were not altered by implantation of pellets amounting to 400–1200 mg in the study of Conway et al. [7] but a small decrease was seen in the study of Jockenhővel et al. [10]. This contrasts with the marked decrease of plasma SHBG after administration of injectable testosterone esters or oral testosterone undecanoate [7]. In the view of Conway et al. [7], a decline of plasma SHBG with testosterone replacements is an indication of an overload of replaced androgen on liver metabolism.

During the first 4 months after implantation of six 100-mg pellets in androgen-deficient men, hemoglobulin levels rose. There were no other significant changes in other biochemical variables.

In experienced hands, pellet implantation has few side effects and is generally well tolerated. In a review of 973 consecutive implantations prospectively studied in 221 men over 13 years, the continuation rate was 93% overall. One or more adverse effects were observed after 11% of the implantations, consisting of extrusions (8.5%), bleeding (2.3%) and infections (0.6%) [9].

In spite of the well-documented merits, testosterone pellets are only available in Australia, South Africa and the UK.

For properties of different testosterone preparations, see Table 1.

Conclusion

Most medical conditions requiring androgen replacement therapy are irreversible. As a consequence, androgen replacement therapy extends often over many decades. Therefore, patient compliance is of utmost importance. Non-compliance does not only impair sexual functioning but is also associated with reductions in muscle and bone mass and with negative effects on mood and vitality. In other words, chronic testosterone deficiency affects quality of life negatively.

Among experts there is consensus as to the requirements of androgen replacement therapy [18]. Replacement with unmodified testosterone is preferred, with a treatment modality and in a dose which maintains plasma testosterone in the physiological range over 24 h of the day. For some of its functions, testosterone is a prohormone to be further metabolized to E_2 and DHT. Ideally, plasma levels of E_2 and DHT generated by administration of testosterone should also lie in the physiological range. Adverse effects of androgen replacement therapy should be minimal.

As indicated above, patient compliance is of great importance. Therefore, the various ART modalities must be discussed with the individual patient to explore personal preferences and idiosyncracies, which, in the end, will impact on patient compliance. In younger subjects (below the age of 50 years) side effects of androgens are usually minimal. For them, long-acting testosterone preparations are well suited. Most of them try to avoid the medical circuit as much as possible and a

Table 1 Properties of different testosterone preparations

	Normal T/24 hours	Normal E_2	Normal DHT	Convenience	Dose flexibility
Injectable T esters	–	±	±	±	–
Oral TU	±	+	±	+	+
Scrotal T patch	+	+	–	–	–
Non scrotal T patch	+	+	+	±	–
T gel	+	+	+	+	+
T implants	+	+	+	+	±
Injectable TU	+	+	+	+	–

+ favourable, ± reasonable, – faulty, *T* testosterone, *E_2* 17*β*-oestradiol, *DHT* 5*α*-dehydrotestosterone, *TU* testosterone undecanoate

long-acting testosterone preparations allows a reduction in visits to the clinic. In elderly man, safety of androgen replacement therapy is more of a concern. Therefore, in elderly man short-acting testosterone preparations are preferable. In case a prostate malignancy or polyglobuly is diagnosed, plasma testosterone levels should be reduced within days.

In the years to come, with a better understanding of the biological actions of testosterone in the various target organs and of the safety aspects, particularly with regard to the prostate, the goals of androgen replacement therapy may have to be reformulated. Androgenic compounds with different degrees of tissue selectivity may find their place in androgen replacement treatment.

References

1. Behre HM, Nieschlag E (1992) Testosterone buciclate (20 Aet-1) in hypogonadal men: pharmacokinetics and pharmacodynamics of the new long-acting androgen ester. J Clin Endocrinol Metab 75:1204–1210
2. Behre HM, Baus S, Kliesch S, Keck C, Simoni M, Nieschlag E (1995) Potential of testosterone buciclate for male contraception: endocrine differences between responders and nonresponders. J Clin Endocrinol Metab 80:2394–2403
3. Behre HM, Abshagen K, Oettel M, Hubler D, Nieschlag E (1999) Intramuscular injection of testosterone undecanoate for the treatment of male hypogonadism: phase I studies. Eur J Endocrinol 140:414–419
4. Bhasin S, Swerdloff RS, Steiner B, Peterson MA, Meridores T, Galmirini M, Pandian MR, Goldberg R, Berman N (1992) A biodegradable testosterone microcapsule formulation provides uniform eugonadal levels of testosterone for 10–11 weeks in hypogonadal men. J Clin Endocrinol Metab 74:75–83
5. Burris AS, Ewing LL, Sherins RJ (1988) Initial trial of slow-release testosterone microspheres in hypogonadal men. Fertil Steril 50:493–497
6. Cantrill JA, Dewis P, Large DM, Newman M, Anderson DC (1984) Which testosterone replacement therapy? Clin Endocrinol (Oxf) 21:97–107
7. Conway AJ, Boylan LM, Howe C, Ross G, Handelsman DJ (1988) Randomized clinical trial of testosterone replacement therapy in hypogonadal men. Int J Androl 11:247–264
8. Handelsman DJ, Conway AJ, Boylan LM (1990) Pharmacokinetics and pharmacodynamics of testosterone pellets in man. J Clin Endocrinol Metab 71:216–222
9. Handelsman DJ, Mackey MA, Howe C, Turner L, Conway AJ (1997) An analysis of testosterone implants for androgen replacement therapy. Clin Endocrinol (Oxf) 47:311–316
10. Jockenhovel F, Vogel E, Kreutzer M, Reinhardt W, Lederbogen S, Reinwein D (1996) Pharmacokinetics and pharmacodynamics of subcutaneous testosterone implants in hypogonadal men. Clin Endocrinol (Oxf) 45:61–71
11. Kelleher S, Turner L, Howe C, Conway AJ, Handelsman DJ (1999) Extrusion of testosterone pellets: a randomized controlled clinical study. Clin Endocrinol (Oxf) 51:469–471
12. Kelleher S, Conway AJ, Handelsman DJ (2001) Influence of implantation site and track geometry on the extrusion rate and pharmacology of testosterone implants. Clin Endocrinol (Oxf) 55:531–536
13. Kelleher S, Conway AJ, Handelsman DJ (2002) A randomised controlled clinical trial of antibiotic impregnation of testosterone pellet implants to reduce extrusion rate. Eur J Endocrinol 146:513–518
14. Mackey MA, Conway AJ, Handelsman DJ (1995) Tolerability of intramuscular injections of testosterone ester in oil vehicle. Hum Reprod 10:862–865
15. Matsumoto AM (1994) Hormonal therapy of male hypogonadism. Endocrinol Metab Clin North Am 23:857–875
16. Nieschlag E (1996) Testosterone replacement therapy: something old, something new. Clin Endocrinol (Oxf) 45:261–262
17. Nieschlag E, Behre HM (1998) Comparative pharmacokinetics of testosterone esters. In: Nieschlag E, Behre HM (eds) Testosterone: action, deficiency, substitution. Springer, Berlin, Heidelberg, New York, pp 294–328
18. Nieschlag E, Wang C, Handelsman DJ, Swerdloff RS, Wu FC, Einer-Jensen N, Waites G (1992) Guidelines for the use of androgens. Special Programme of Research, Development and Research Training in Human Reproduction of the World Health Organisation. World Health Organisation, Geneva
19. Nieschlag E, Buchter D, von Eckardstein S, Abshagen K, Simoni M, Behre HM (1999) Repeated intramuscular injections of testosterone undecanoate for substitution therapy in hypogonadal men. Clin Endocrinol (Oxf) 51:757–763
20. Plymate S (1994) Hypogonadism. Endocrinol Metab Clin North Am 23:749–772
21. Schulte-Beerbuhl M, Nieschlag E (1980) Comparison of testosterone, dihydrotestosterone, luteinizing hormone, and follicle-stimulating hormone in serum after injection of testosterone enanthate of testosterone cypionate. Fertil Steril 33:201–203
22. Schurmeyer T, Nieschlag E (1984) Comparative pharmacokinetics of testosterone enanthate and testosterone cyclohexanecarboxylate as assessed by serum and salivary testosterone levels in normal men. Int J Androl 7:181–187
23. Seftel A (2002) Treatment of male hypogonadism with testosterone undecanoate injected at extended intervals of 12 weeks: a phase II study. J Urol 168:2315–2316
24. Snyder PJ, Lawrence DA (1980) Treatment of male hypogonadism with testosterone enanthate. J Clin Endocrinol Metab 51:1335–1339
25. Sokol RZ, Palacios A, Campfield LA, Saul C, Swerdloff RS (1982) Comparison of the kinetics of injectable testosterone in eugonadal and hypogonadal men. Fertil Steril 37:425–430
26. Tschop M, Behre HM, Nieschlag E, Dressendorfer RA, Strasburger CJ (1998) A time-resolved fluorescence immunoassay for the measurement of testosterone in saliva: monitoring of testosterone replacement therapy with testosterone buciclate. Clin Chem Lab Med 36:223–230
27. von Eckardstein S, Nieschlag E (2002) Treatment of male hypogonadism with testosterone undecanoate injected at extended intervals of 12 weeks: a phase II study. J Androl 23:419–425
28. Wang LZ (1991) The therapeutic effect of domestically produced testosterone undecanoate in Klinefelter's syndrome. New Drugs Market 8:28–32
29. Zacharin MR, Warne GL (1997) Treatment of hypogonadal adolescent boys with long acting subcutaneous testosterone pellets. Arch Dis Child 76:495–499