

An analysis of testosterone implants for androgen replacement therapy

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Summary

OBJECTIVE To review 13 years of experience using fused crystalline testosterone implants for androgen replacement therapy in order to identify pattern of usage (including continuation rates) and adverse events emerging during therapy and factors associated with adverse events including implant extrusions.

DESIGN Retrospective review of prospectively collected data on characteristics of patients and implant procedures performed as well as adverse events reported during routine follow-up.

PATIENTS Over 13 years 973 implant procedures using fused crystalline testosterone implants were performed in 221 men.

MEASUREMENTS Continuation rates and adverse events such as extrusions, bleeding, infection or others were recorded and analysed in relationship to characteristics of the patient and the implant procedure performed.

RESULTS Overall rate of adverse events (108/973, 11.1%) was significantly related to increased numbers of implants (4.2 ± 0.1 vs 4.0 ± 0.03 , $P=0.031$) and higher levels of physical activity at work ($P=0.030$). The most common adverse effect was extrusion (83/973, 8.5%) which was related to occupational classification ($P=0.033$) and increasing work activity ($P=0.044$) and occurred more frequently than by chance in multiple (16 vs 3.3 expected) rather than single (65 vs 76.1 expected) episodes. Bleeding (22/973, 2.3%) was significantly associated with an increased number of implants (4.5 ± 0.2 vs 4.0 ± 0.03 ,

$P=0.020$) but even in the worst cases (3/22) it was of minor clinical importance. Infection was rare (6/973, 0.6%) but occurred more among thinner men. The overall continuation rate was 92.7% increasing from 86% after the first implantation to >99% after the tenth implant.

CONCLUSIONS This study demonstrates the very satisfactory clinical acceptability of testosterone pellet implants for androgen replacement therapy within a single unit with experienced operators. The only regular adverse effect is extrusion, which may be related to mechanical factors such as habitual work activity but also possibly procedural factors. Other adverse effects such as bleeding, infection and fibrosis were rare. An improved method of implant delivery would enhance this old but durable technology.

Testosterone has been administered by a very wide variety of modalities over the 6 decades since its introduction to clinical usage for androgen replacement therapy (Hamilton, 1937). From its inception, the clinical applications of testosterone have been governed by the limitation that testosterone has negligible oral bioavailability and a very short half-life when administered parenterally (Foss, 1939; Parkes, 1938). Orally active synthetic androgens, most based on the 17- α alkyl substituents, are required at high doses, multiple times daily which is unsatisfactory for life-long androgen therapy and are now considered obsolete due to their hepatotoxicity. Thus, the central problem in the clinical pharmacology of androgen replacement therapy has been the development of effective depot formulations of testosterone. Consequently, numerous alternative routes of administration were reported within the first few years after testosterone became available for clinical application. Few of these modalities have continued in use although some (e.g. sublingual/buccal) are periodically reinvented (Lisser *et al.*, 1942; Stuenkel *et al.*, 1991). In recent years testosterone ester injections in oil vehicle have been regarded as the standard form of androgen replacement therapy (Nieschlag & Behre, 1990); however, this form of treatment requires painful, deep intramuscular injections (Mackey *et al.*, 1995) at regular intervals usually not exceeding 2 weeks (Snyder & Lawrence, 1980) and exhibiting very prominent fluctuations in mood and blood testosterone concentrations (Behre *et al.*, 1990) making this regimen far from ideal for life-long androgen replacement therapy.

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Subdermal implants, originally developed by Deansley and Parkes (Deansley & Parkes, 1937, 1938), were the first true depot formulations of testosterone and were rapidly applied to clinical practice (Biskind *et al.*, 1941; Hamilton & Dorfman, 1939; Howard & Vest, 1939; Vest & Howard, 1939). The original testosterone pellets were formulated by high pressure compression of testosterone mixed with cholesterol, but in the early 1950s an alternative method of manufacture was developed whereby the steroid alone without excipient was melted and cast into a solid cylindrical shape on cooling (Handelsman, 1990, 1991). Fused crystalline implants have been available for over 4 decades but declined in popularity so that by 1980 they had fallen largely into disuse. Over the last decade as their pharmacology has been defined clearly for the first time (Cantrill *et al.*, 1984; Conway *et al.*, 1988; Handelsman, 1990; Handelsman *et al.*, 1990; Jockenhovel *et al.*, 1996) revealing near-ideal depot properties, their usage has again increased markedly. Despite their long history of availability and the recent revival of usage, there are no reports of systematic experience with use of such implants. We therefore reviewed 13 years of experience using fused crystalline testosterone implants for androgen replacement therapy utilizing prospectively collected data in order to characterize the pattern of usage and adverse events emerging as well as to identify possible factors associated with adverse events, especially implant extrusions.

Materials and methods

Testosterone implant procedure

Since the mid 1980s, testosterone pellet implants have been the mainstay of androgen replacement therapy in the Andrology Unit, Royal Prince Alfred Hospital. The implant procedure has remained unchanged apart from minor details throughout the period surveyed (Handelsman, 1990, 1991). Apart from the absolute contraindications of hormone-sensitive (prostate, breast) cancer, all men requiring androgen replacement therapy are offered testosterone implants as an alternative to conventional testosterone esters in oil or oral testosterone undecanoate. At the end of each course, patients have the option to undergo another implantation or to switch to another form of androgen replacement therapy.

Implants are administered under sterile conditions for routine minor office surgery using a stainless steel, wide-bore trocar, cannula and obturator set. One assistant is required and the procedure is usually completed within 10–15 minutes. The implants are placed subdermally in the lower abdominal wall lateral to, and about level with or just below, the umbilicus. None were placed in other possible sites such as buttocks, deltoid, gluteal or proximal thigh. During the implantation

procedure the patient lies on a comfortable bed, the shaved skin site is sterilized with alcohol with or without an iodine-based antiseptic solution and draped to leave access to the incision site. Following injection of local anesthetic (10 ml 2% xylocaine without adrenaline injected into the incision site and along the direction of proposed implant tracks), a small incision (0.5–1.0 cm) is made with a scalpel at least 5 cm from the mid-line at the level of the umbilicus to allow introduction of the trocar (7.5 French gauge, 5 mm ID, 7 cm length). Once an entry site has been created, implants are removed under sterile conditions from the glass vial and either gently grasped with forceps or tapped onto a sterile gauze or container. Implants are then inserted into individual tracks fanning out radially from the single puncture site and the implants are expelled from the trocar by an obturator at a distance of 5–10 cm from the puncture site. After insertion of all implants, the puncture wound is closed without suture by using adhesive sterile strips and covered with a sterile, clear plastic, waterproof adhesive dressing which is left in place for 5–7 days and then removed by the patient. Sutures have been used only rarely either where there was suspicion of allergy to sterile strips or at the patients request. Rarely, topical pressure over the puncture site for 1–2 minutes is needed to stop blood oozing from the implant insertion site. Antibiotics are not prescribed routinely. Patients are advised to avoid vigorous exertion and bending for a few days but are able to return to work the same or next day.

Follow-up

Following the first implantation, patients are followed monthly by evaluation of symptoms and blood samples for hormone assay. Implantations are scheduled at intervals of not less than 6 months when the patients' own characteristic androgen-deficient symptoms have returned and testosterone concentrations have returned to baseline levels. After subsequent implantations, follow-up is less intensive with blood samples scheduled after the fourth month when symptoms have returned. At each visit any side-effects (including extrusions) since the last visit are recorded. Patients are instructed to notify the clinic if extrusion seems likely or has occurred and after any extrusion, the date is recorded and the extruded implants collected for examination and analysis.

Data analysis

From 1984 records have been kept prospectively for each pellet implantation procedure. In addition to identifying information, these records include patient details (primary and other diagnoses, height, weight, occupation, work and leisure activity grade) and details of the implantation procedure (operator, wound dressing, site and side of insertion, number of implants,

batch number, testosterone dose) as well as serial records following each follow-up visit recording hormone concentrations (LH, FSH, total and free testosterone) and adverse events (extrusion, bleeding, infection, other). Occupation was coded according to a modified form of the Australian Standard Classification of Occupation using 13 codes (managerial/supervisor, professional, para-professional, clerical + related, sales, service, trades and other non-agricultural skilled, skilled agricultural, plant operator, processing/manufacturing, basic manual, military, other unclassified). Work activity was coded on a 4-point scale as minimal (including unemployed, student, retired, pensioner), sedentary, easy/light movement and heavy movement. Leisure activity was on a 5-level scale as mostly sitting, often walking, sports 1–3/month, sports 1/week, and sports 2–5/week. Continuation rate was defined as the probability that a patient having an implant procedure would subsequently have another one. Discontinuation was defined as a patient having no subsequent implants for at least 12 months after an implantation procedure. The data were maintained in a customized database using Paradox software. Results were expressed as mean and standard error of the mean or as proportions as appropriate and analysed by analysis of variance or *t*-test using BMDP software (Dixon, 1992) or by exact contingency methods using StaXact-3 for Windows software (Mehta & Patel, 1995). Confidence intervals were determined from the Poisson or binomial distributions as appropriate (Gardner & Altman, 1989).

Results

Over the 13-year survey period, 973 implant procedures were performed in 221 men comprising 178 hypogonadal men, among whom hypogonadism was primary (hypergonadotrophic) in 86 men (including 18 bilaterally orchidectomized), secondary (hypogonadotrophic) in 82 men and 10 having mixed hypogonadism together with 43 normal men (mostly volunteers for research studies). All procedures used 200 mg testosterone implants apart from 6 using 100 mg implants. The standard androgen replacement therapy dosage is 4 200 mg implants (800 mg) at intervals of 4–6 months (Table 1). Most implantations (900/973, 92.5%) were performed by 2 operators.

Table 1 Number of implants and procedures per patient

	Mean $\pm$ SEM	Median	Range
Age	38 $\pm$ 1	34	15–73
Implants per procedure	4.0 $\pm$ 0	4	2–6
Procedures per patient	4.7 $\pm$ 0.1	4	1–23

Continuation rate

Routinely after run-off from each implantation, patients have the choice to continue with implants or switch to another modality of androgen replacement therapy. The overall continuation rate for implants was 93% (95% confidence interval (CI) 91–95%); however, this varied with duration on treatment as continuation rate was 88% (95% CI 82–92%) after the first implant, 91% (5% CI 84–95%) after the second, 95% (95% CI 92–97%) between the third to ninth implant and 99% (95% CI 96–100%) for the tenth implant and thereafter.

Side-effects

Following the 973 implantations, there were 865 (89%) with no adverse effects and 108 (11%) followed by 1 or more adverse effects. The adverse effects recorded consisted of 83 (8.5%) extrusion, 22 (2.3%) bleeding and 6 (0.6%) infection episodes. Considering all adverse effects together, the only significant predictors were that those experiencing any adverse effects had higher levels of physical activity at work ($P = 0.030$) and received more implants (4.2 ± 0.1 vs 4.0 ± 0.03 , $P = 0.031$) than those without any adverse effects, respectively. There were no significant effects of age, height, weight, body mass index (BMI), body surface area (duBois formula) or body weight (expressed as % ideal according to Metropolitan Life Insurance tables) nor any relationship to side of implantation, wound dressing, diagnosis, occupational classification or leisure activity.

Extrusions. Extrusions involved a single pellet in 65 and multiple pellets in 16 (12 double, 2 triple, 2 quadruple) with 2 having insufficient detail. In no instance was additional androgen therapy required to be administered on clinical grounds. If extrusions were an isolated random event, the frequency of single and multiple occurrences would be consistent with a Poisson distribution (Gardner & Altman, 1989). Assuming a Poisson distribution and calculating the numbers of single and multiple extrusions expected from the overall extrusion rate there were, however, significantly fewer single (65 vs 76.1 expected) and more multiple (16 vs 3.3 expected) extrusions than expected by chance alone ($P = 0.011$). The mean time to first extrusion was 61 ± 4 ($n = 81$, median 54 days, range 7–196 days) days since implantation, to the second extrusion was 69 ± 8 ($n = 16$, median 66 days post-implantation, range 25–142 days post-implantation) and to the third 92 ± 22 ($n = 4$) days post-implantation. Extrusion was related to occupational classification ($P = 0.033$) and increasing work activity ($P = 0.044$) but not associated with any differences in age, number of implants, body physique, diagnosis, side of implantation, wound dressing

or leisure activity. Occupational classifications with highest apparent risk (>20%) were para-professional and service and the lowest apparent risk (<5.1%) were professional and skilled agricultural workers. Considered annually, there were no significant temporal trends in extrusion rates between 1984 and 1995 nor were there any obvious batch-specific trends. Given the baseline extrusion rate of 8.5%, the sample size required to demonstrate changes in extrusion rate ($\alpha = 0.05$, $\beta = 0.80$) is 900 per group for 25% reduction, 175 per group for a 50% reduction and 40 per group for a 75% reduction in extrusion rate.

Bleeding. Bleeding episodes were graded as mild (4), moderate (15) or severe (3). None of the bleeding episodes was associated with use of non-steroidal analgesics before or after the implantation. Considering all bleeding episodes, the only predictor of bleeding was the higher number of implants among those who experienced a bleeding episode compared with those who never experienced a bleeding episode (4.5 ± 0.2 vs 4.0 ± 0.03 , $P = 0.020$). There was no relationship between side of implantation, wound dressing, diagnosis, occupational classification, work or leisure activity, age or body physique. The 3 most significant bleeding episodes required prolonged digital pressure on the incision for 30–45 minutes with an estimated blood loss of <50 ml in 2 cases and pressure for 2 hours with ~100 ml blood loss in 1 case. No distinctive features of these cases could be identified.

Infection. Infection was rare but was more frequent in thin men (BMI 21.9 ± 1.9 vs 25.6 ± 0.2 kg/m², $P = 0.052$; SBW 96.7 ± 8.3 vs $112.9 \pm 0.7\%$ ideal, $P = 0.054$) but was unrelated to number of implants, age, height, weight or BSA.

Other. Other hypothetical adverse effects such as allergy to local anaesthetic and keloid formation were not encountered. Subdermal fibrosis, just detectable with careful palpation as small subdermal nodules at the sites of previous pellets, was common but never sufficient to prevent subsequent implantations nor were they reported as painful or otherwise symptomatic. Mild discomfort related to the minor surgery is common but rarely serious enough to prevent returning to work and/or usual daily activities the same or next day.

Discussion

This study of 13 years experience demonstrates the very satisfactory clinical tolerability of testosterone pellet implants as a modality for long-term androgen replacement therapy. Most androgen-deficient men who have been treated previously with conventional treatment, usually testosterone ester injections, strongly prefer this modality of treatment due to longer

periods free from need for regular tablet consumption, medical visits or uncomfortable injections. It is relevant that freedom from fluctuating blood testosterone concentrations and mood which are favoured by patients receiving testosterone implants are also among the features highlighted as advantages by users of transdermal testosterone (Meikle *et al.*, 1996). The high continuation rates, especially after the first 2 cycles, confirm that this modality is well accepted by men requiring androgen replacement therapy. Our definition of continuation rate that any prolonged interruption of implant administration at our unit was counted as a discontinuation was conservative as this counted as discontinuations patients who ceased all androgen therapy and those travelling away from Sydney for prolonged periods, as well as neglecting the possibility that patients may have had implants elsewhere. In fact it was rare that men stabilized on testosterone pellet implants chose to resume other conventional forms of androgen replacement therapy, such as testosterone ester in oil vehicle injections (Nieschlag & Behre, 1990).

Overall adverse effects were uncommon with extrusion, occurring at a frequency at ~8.5% per procedure (or 2.5% per pellet), being the most regular and yet generally considered an acceptable risk when balanced against the convenience of long inter-implant intervals as well as smooth symptomatic effects of this modality of androgen replacement. This estimate of extrusion rate includes the totality of our experience and consequently includes learning periods for new operators during which time higher extrusion rates are characteristic. This extrusion rate is comparable with our earlier estimate (Handelsman, 1990) and confirmed by another investigator (Jockenhovel *et al.*, 1996). The regular retention of patients in our clinical service and the regular checking for adverse events ensures that our estimates of extrusions and other adverse effect rates are likely to be reasonably accurate. The significant excess of multiple over single extrusion episodes indicates that extrusion may be initiated by factors associated with the implantation procedure such as chemical irritation or infection and further studies of this possibility are under way. Other adverse effects, such as bleeding, infection and scarring, were uncommon and had minimal impact on the acceptability of testosterone implants, especially when compared with testosterone ester injections (Mackey *et al.*, 1995). The lack of significant adverse effects is partly attributable to experience in the implantation but also to the policy of not performing implants on any time schedule but rather adequate monitoring to determine when further treatment is required. In evaluating this experience, it should be noted that implantations were performed mostly by experienced operators regularly performing an average of 2 procedures per week, since the extrusion rate may be higher for inexperienced or occasional operators. Overall, our experience is that this modality of androgen

replacement therapy is very well tolerated and popular with patients.

Among adverse effects the only significant predictors were the number of pellets implanted, habitual work activity and thinness. The impact of the number of pellets on adverse event rate was mostly due to its effect on bleeding. Most (19/22, 86%) bleeding episodes from the incision were minor involving either bruising within the first day after implantation or requiring only topical application of pressure to the incision at the end of the procedure. Implantation is technically more difficult in very thin patients whose lack of subdermal fat makes placement of the implants more troublesome, and thinness was significantly associated with post-implantation infection. Clinically these episodes resembled non-purulent cellulitis and subsided during treatment with oral, broad-spectrum antibiotics. Another significant predictor of the extrusion rate was the occupational classification and the grade of work (but not leisure) activity. This suggests that mechanical factors, related to habitual daytime physical activity patterns and the siting of implants near the belt and trouser waistline, may predispose to extrusion perhaps by causing minor movement of the implants near the site of implantation. Unfortunately, we have had no mechanism to determine the exact location (upper vs lower or lateral vs medial) of the pellets from any implant procedure extrude. Interestingly, extrusions followed a pattern most consistent with a rare, random process except that multiple extrusions occurred more often than by chance alone. As multiple extrusions occur more frequently than by chance, it is likely that there are within-subject or procedure-related factors that predispose to extrusion. There was no relationship to the side of implantation nor to the physique of the recipient. It is unclear from our analysis that this greater risk relates to individual patient idiosyncrasy (i.e. occurs disproportionately among certain individuals) or is a random event among individuals but that once a single extrusion is imminent, a further extrusion is more likely regardless of the individual. The limited data available do not support the former proposition.

Fibrosis is rarely a problem in practical usage of implants. Although a minority of androgen-deficient men using testosterone implants for androgen replacement therapy do develop palpable fibrosis at old implantation sites, this is rarely of clinical significance either symptomatically or making more difficult subsequent implants at that site. Some hypothetical adverse effects following testosterone implantation, such as allergy to local anaesthetics or keloid scar formation, have not yet been observed but must be regarded as relative contraindications to the minor surgery involved in implantation.

In future, the use of testosterone implants for androgen replacement therapy is likely to continue due to its unrivalled properties as a depot testosterone formulation. The newer, long-acting formulations such as testosterone buciclate (Behre &

Nieschlag, 1992) and microspheres (Bhasin *et al.*, 1992) are likely to be equally popular although they have a shorter duration of action (2–3 vs 6 months) and microspheres may also be more expensive. The daily costs of testosterone implants are equivalent and the acceptability to patients superior to testosterone ester injections. On the other hand, the outdated and cumbersome implantation procedure is suboptimal and an improved form of delivery would even further enhance this old but durable technology.

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