Pharmacology of testosterone pellet implants

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1 Introduction

The main indication for androgen therapy is the treatment of androgen deficiency in hypogonadal men. Since such androgen replacement therapy usually

E. Nieschlag et al. (eds.), *Testosterone*

involves life-long administration of testosterone, it is desirable that testosterone formulations be long-acting. The primary goal of androgen replacement therapy is to replicate the physiological actions of endogenous testosterone. This requires not just rectification of deficient androgen levels but also avoiding either supranormal or excessively fluctuating testosterone levels. Thus the practical intent of androgen replacement therapy is to maintain stable, physiological testosterone levels for prolonged periods. The pharmacological properties of testosterone, notably its rapid metabolic inactivation by the liver, have dictated that the achievement of such prolonged androgenic effects requires the development of depot, sustained-release testosterone formulations (Wilson 1980). Nevertheless, even 50 years after the entry of testosterone into the clinical armamentarium (Hamilton 1937; Foss 1939) the quest for a safe, effective, inexpensive, convenient, long-acting androgen preparation with reproducible, zero-order release profile remains an important challenge not yet met. One of the oldest testosterone formulations is the subdermal implant of testosterone pellets which provide stable testosterone levels for at least 4 months after a single implantation (Cantrill et al. 1984; Conway et al. 1988). Curiously this cheap and effective treatment modality has been neglected for decades despite its many advantages for androgen replacement therapy.

2 History

Within 2 years of its identification and synthesis in 1935, testosterone had entered clinical usage (Hamilton 1937) and within the next few years experience had been reported with a wide variety of formulations of testosterone and its derivatives. During the original purification it was recognized that testosterone, administered parenterally as the free steroid, had a severely curtailed pharmacological activity which was presumed to be due to rapid inactivation (Parkes 1938). Furthermore, the earliest clinical reports also recognized that testosterone was virtually ineffective orally (Foss 1939). Due to the poor bioavailability of oral or parenteral free testosterone, later shown to be due to its rapid metabolism (Hellman et al. 1956; Nieschlag et al. 1975, 1977; Frey et al. 1979), the need for long-acting parenteral formulations of testosterone was recognized in the late 1930's (Parkes 1938; Foss 1939).

Subdermal implants were among the earliest alternative modalities employed for testosterone administration (Deansley and Parkes 1937, 1938; Vest and Howards 1939; Howards and Vest 1939). The experimental observation that subdermal implants showed the most potent, lasting effects of any steroid formulation (Deansley and Parkes 1937, 1938; Hamilton and Dorfman 1939) were quickly applied by clinical investigators (Vest and Howards 1939; Howards and Vest 1939; Foss 1939) and testosterone implants became an established form of androgen replacement therapy. Similar effects were observed for most biologically active steroids and their esters including androgens, estrogens and progestagens (Loeser 1940; Eidelsberg and Ornstein 1940; Emmens 1941; Forbes 1941; Biskind et al. 1941; Dorfman and Hamilton 1941; Foss 1942) and very long acting

depot formulations of desoxycorticosterone acetate (DOCA) lasting up to 1 year were developed for treatment of Addisons disease (Thorn and Firor 1940).

Despite their long availability for clinical usage, there were no controlled clinical trials (Swyer 1953; Reiter 1963) and only a single pharmacological study (reporting work performed in the early 1940's [Bishop and Folley 1951]), published in the 45 years of the post-World War II era. Recently an open study including reference to testosterone pellet implants (Cantrill et al. 1984) rekindled interest in the use of this modality (Conway et al, 1988). Thus subdermal implants of testosterone, already established before 1940 as a highly effective form of androgen replacement, have remained available but with few clinical applications or pharmacological development for over 40 years. This curious neglect may be due to the perception of limited commercial value of a non-patent product. In recent years, however, the lack of convincing clinical pharmacological data has continued to impede their acceptance by clinicians.

3 Formulation and physical features

The original testosterone implants were fabricated as tablets by the high pressure compression of crystalline steroid with an excipient (usually cholesterol) into discoid or cylindrical form with convex ends (Bishop and Folley 1951). Such compressed implants proved difficult to standardize or sterilize and were excessively brittle. Implant fragmentation as well as the variability in surface hardness and smoothness (Emmens 1941) which caused pitting during erosion, both increased unpredictably the pellet surface area which accelerates absorption rate. Conversely foreign body tissue reaction on the other hand provoked encapsulation and reduced release rate. These effects led to excessive variability in release profile, especially late in the life span of the compressed implants (Bishop and Folley 1951).

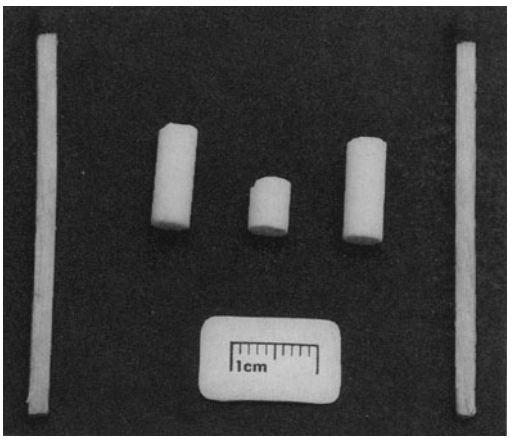

Fig. 1. Testosterone pellet implants illustrated are made by melting crystalline steroid without excipient and moulding into a cylindrical shape with a diameter of 4.5 mm. Lengths of 6 mm (100 mg) or 12 mm (200 mg) are then cut. The two 200 mg implants (*left* and *right*) and a 100 mg implant *(centre)* are shown against a 1 cm scale and flanked by two match sticks for size comparison

The limitations of the original testosterone tablet-like implants led, by the 1950's, to a switch in manufacture from high pressure compression to high temperature moulding. The fused pellets are made without excipients by raising testosterone above its melting point (154–155 C) and casting the steroid in a cylindrical mould. This process produces implants with more uniform composition and release pattern, a longer life-span and greater robustness during handling (e.g. at implantation). The reduced tissue reaction, however, increased the liability to extrusion due to reduced fibrous tethering. In addition to high temperature exposure during fabrication, the pellets are also gamma-irradiated for sterilization. The testosterone pellet implants (Organon (Aust) Pty Ltd, Sydney, Australia) currently are available in two sizes, 100 mg and 200 mg (Fig. 1). These have a common cylindrical shape with a diameter of 4.5 mm and lengths of 6 mm (100 mg) and 12 mm (200 mg) with total initial surface areas of 117 sq mm (100 mg) and 202 sq mm (200 mg) per pellet.

4 Implantation procedure

Pellets are implanted under sterile conditions for routine minor surgery. The preferred site is the lower abdominal wall in the periumbilical region but other possible sites used include the deltoid, gluteal, and upper thigh. Following injection of local anesthetic (5–10 ml 2% xylocaine), 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). Pellets are distributed in individual tracks fanning out from the puncture site and the pellets are discharged from the trocar by an obturator at a distance of 5–10 cm from the puncture site. After insertion of all pellets, the puncture wound is closed without suture by using adhesive strips and covered with a simple dressing which is changed daily for a week. Due to the rarity of infections, antibiotics are not required routinely after implantations although in patients with poor hygiene, predisposition to infection or early signs of an infection after implantation, antibiotics may be advisable.

5 Absorption

5.1 Mechanism of absorption

Absorption of testosterone from the pellets occurs via an uniform erosion of the pellet's surface. Empirical evidence for this includes the observation that pellets recovered up to 3 months after implantation retain their cylindrical shape (Fig. 2). A mathematical model incorporating a uniform rate of surface erosion (Forbes 1941) fits data available from direct measurements of release rate well (Bishop and Folley 1951). Direct testing of the importance of pellet surface area for absorption is difficult since in the two pellet sizes available, surface area and dose are mostly confounded due to the common cylindrical shape and diameter. In

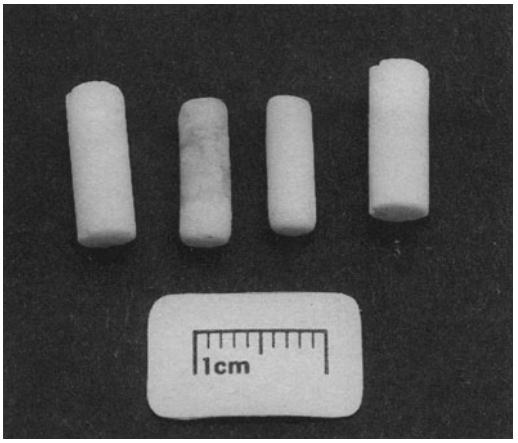

Fig. 2. Testosterone pellet implants are absorbed by an uniform surface erosion mechanism that preserves their original cylindrical shape. The two unimplanted 200 mg pellets (*far left* and *right*) are shown in comparison with two 200 mg pellets which were extruded 43 *(left)* and 62 *(right)* days after implantation

order to examine for evidence of an effect of pellet surface area independent of dose, we compared the effects of 3×200 mg with 6×100 mg pellet implants which controlled for total dose (600 mg) while allowing for a 16% difference in initial surface area. The regimen with greater initial surface area produced higher free testosterone levels and greater gonadotropin suppression in the first (but not the second) 3 months. This evidence supports the surface area-limited release mechanism. Deviations from the surface erosion model can be expected if the absorbing area enlarges unpredictably due to surface irregularities, pitting or fragmentation of the pellet or if absorption via matrix-controlled diffusion supervenes as the pellet size decreases. While pellet geometry (especially surface area) appears the rate-limiting factor in testosterone absorption from subdermal pellets (Emmens 1941), additional factors are also important. These include (i) the chemistry of the steroid especially its hydrophobicity, (ii) pellet hardness, smoothness and size, (iii) the site of implantation, its local blood flow and trauma and (iv) the tissue reaction and encasing of the pellet (Foss 1939; Emmens 1941; Forbes 1941; Bishop and Folley 1951). Circulating sex steroid levels, however, appear not to be important (Emmens, 1941). Few of these factors have been systematically tested in humans and the importance of pellet geometry and site of implantation in regulating testosterone release rate warrant further evaluation.

5.2 Kinetics of absorption

Absorption rate of testosterone from pellets appears to be limited by the exposed pellet surface area from which the steroid leeches out into the extracellular fluid. Empirical calculation of the effective testosterone release rate can be made both directly from measurement of residue in extruded pellets and indirectly from the percent absorbed-time plots and these independent estimates are in reasonable agreement. A direct estimate of absorption rate of 1.5 (95% C.L. 1.4–1.7) mg/day/200 mg pellet was derived from remnants of six 200 mg pellets which exhibited linear rate of release with time up to 92 days (Fig. 3). An indirect, cor-

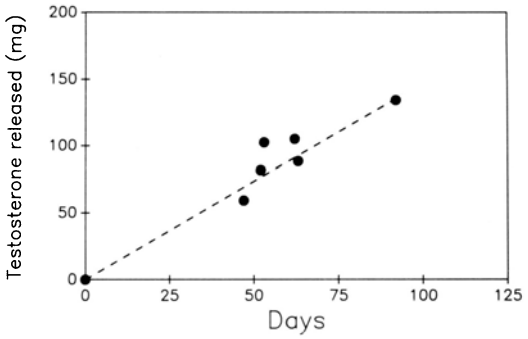

Fig. 3. Direct estimates of testosterone release rate. The weights of six 200 mg pellets that were extruded at various times after implantation are plotted against time carried in the body. The extruded pellets were cleaned, dried and weighed to determine the mass of testosterone released by comparison with unimplanted 200 mg pellets. The amount of testosterone released was a linear function of time up to 92 days and the estimate of testosterone release rate provided by the slope of the regression was 1.5 mg/day/200 mg pellet

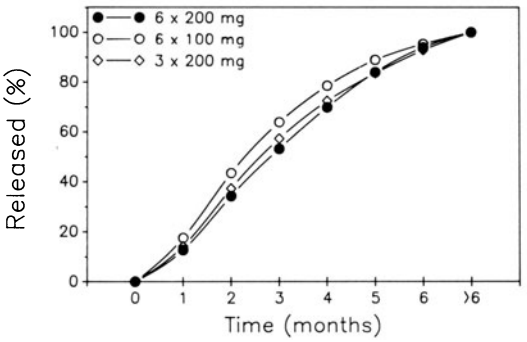

Fig. 4. Percent absorbed-time plots of testosterone release over 6 months in 43 hypogonadal men on one of the 3 pellet regimens 6 × 200 mg (*closed circles*, n = 32), 6 × 100 mg (*open circles*, n = 28) and 3 × 200 mg (*open diamonds*, n = 51). The near linear plots indicate a virtual zero-order release rate and the similarity of the 3 curves indicate that the release rates for the 100 mg and 200 mg pellets are similar

roborative estimate was obtained independently from the percent absorbed-time plots which, being nearly linear (Fig. 4), provided evidence of a very good approximation to ideal zero-order release for either total or free testosterone. These curves provided an estimate of 2.5 months for the effective half-time of absorption and calculated testosterone release rate of 0.65 mg/day/100 mg pellet. Neither the size nor number of pellets influenced the rate of testosterone absorption. These calculations are comparable with the only other available estimate of 1.1 mg/day/100 mg pellet from fused testosterone pellets removed at intervals after implantation in the antecubital or subscapular region (Bishop and Folley 1951). The 41% lower release rate of fused pellets implanted in the anterior ab-

dominal wall (our study) despite a 66% greater initial surface area suggest important site-specific release characteristics.

The present estimates of testosterone release rate are also consistent with indirect estimates that can be calculated (much less accurately) from increments in circulating testosterone produced by implantation of single 100 mg and 200 mg pellets in women (Thom et al. 1981; Dewis et al. 1986) after correcting for gender differences in testosterone clearance rates (Southren et al. 1968; Gandy 1977).

6 Bioavailability

The bioavailability of testosterone from subdermal pellets is virtually complete as calculated from the net appearance of testosterone in the bloodstream. The net release of testosterone in the circulation can be calculated from the time-course of testosterone levels if the whole body testosterone metabolic clearance rate is known and remains constant throughout the study. Since SHBG levels, which are the major determinant of testosterone metabolic clearance rate (Vermeulen et al. 1969), remain unaltered following pellet implantation it is reasonable to assume a constant testosterone clearance rate (mean 540 l/sq m/day [Southren et al. 1968; Gandy 1977]) throughout the life-span of a pellet implant. Such a calculation indicates that by 6 months virtually all the testosterone from the 600 mg pellet and about 90% of that in the 1200 mg pellets was absorbed. Consistent with the near complete bioavailability, net testosterone release is closely correlated with pellet dose ($r = 0.999$) so that a 6×200 mg dose regimen gives twice that of either 6x100 mg or 3×200 mg regimen, the latter two of which gave very similar net release of testosterone. This high bioavailability is not unexpected for a steroid administered parenterally and absorbed into the systemic circulation avoiding first-pass hepatic inactivation.

7 Pharmacokinetics

7.1 Pharmacological studies

Our pharmacological studies have been reported in detail elsewhere (Conway et al. 1988; Handelsman et al. 1990). Hypogonadal men ($n = 43$) with either primary (hypergonadotropic, $n = 22$) or secondary (hypogonadotropic, $n = 21$) hypogonadism previously treated with parenteral testosterone esters entered a crossover clinical trial after at least one month from the last injection of testosterone esters. They were assigned at random to one of the 3 testosterone pellet regimens, 6×100 mg, 3×200 mg or 6×200 mg, and subsequently at intervals of at least 6 months when the testosterone levels had returned to baseline, they crossed-over to another regimen until they had completed the 3 different doses. The men entering each of the 3 treatment regimens were comparable in baseline testosterone and anthropometric measures. Blood samples for testosterone and gonadotropin assay were obtained immediately prior to pellet implantation and at 4 week inter-

vals thereafter for a total of 111 pellet implantations (6 × 100 mg - 28 implants; 6 × 200 mg - 32 implants; 3 × 200 mg - 51 implants). Eugonadal controls were 335 healthy age-matched men undergoing screening as potential sperm donors (Handelsman et al. 1984).

7.2 Total and free testosterone levels

Implantation of testosterone pellets gives highly reproducible and dose-dependent time-course for circulating total and free testosterone (Fig. 5). Total testosterone levels on the 1200 mg dose are higher ($p < 0.0001$) than those of either 600 mg combinations which in turn produced similar ($p = 0.95$) circulating testosterone levels and time courses. Plasma testosterone levels peaked at the 1st month and gradually declined to return to baseline by 6 months after either 600 mg dose regimens but remained significantly elevated after 6 months following the 1200 mg dose. Plasma free testosterone was so highly correlated ($r = 0.90$) with total testosterone that free testosterone levels exhibited virtually the same time-course as that of total testosterone. The one exception was that free testosterone levels were significantly higher in the first (but not the second) 3 months after the 6 × 100 mg regimen which had a higher initial surface area compared

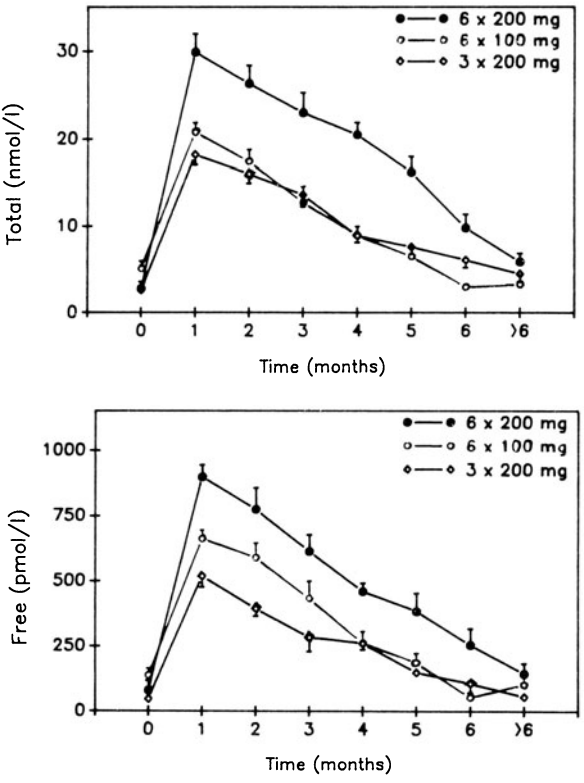

Fig. 5. Total *(upper panel)* and free *(lower panel)* testosterone levels over 6 months in 43 hypogonadal men on one of the 3 pellet regimens 6 × 200 mg (*closed circles*, n = 32), 6 × 100 mg (*open circles*, n = 28) and 3 × 200 mg (*open diamonds*, n = 51). Data is plotted as mean and standard error of mean

with the 3 × 200 mg regimen consistent with an effect of initial pellet surface area on early testosterone release rates.

Although many steroid implants (Burris et al. 1988; Diaz-Sanchez et al. 1989) demonstrate an accelerated initial (or "burst") release, this does not occur with testosterone pellet implants. Weekly blood sampling for one month after implantation of 6 × 100 mg testosterone pellets in 15 hypogonadal men (Conway et al. 1988) demonstrated a gradual rise of total and free testosterone and suppression of gonadotropins (Fig. 6). Peak testosterone levels were attained between 2 and

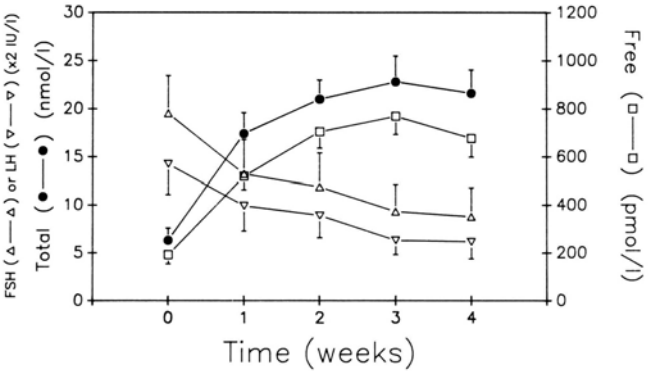

Fig. 6. Total *(closed circles)* and free *(open sqaures)* testosterone and LH *(open triangle)* and FSH *(open inverse triangle)* in 15 hypogonadal men having blood sampled at weekly intervals for the first months after undergoing implantation of 6 × 100 mg testosterone pellets. Gonadotropins are plotted only for the 9 men with primary (hypergonadotropic) hypogonadism. Note the smooth rise of testosterone and suppression of gonadotropins without evidence of initial burst release of testosterone. Data plotted as mean and standard error of the mean

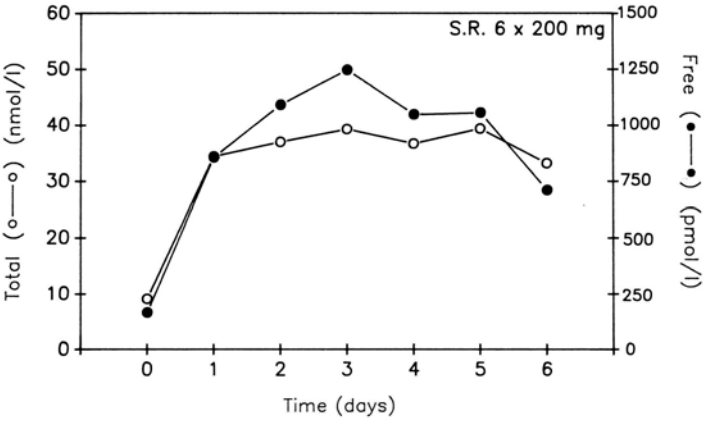

Fig. 7. Total *(closed circles)* and free *(open circles)* testosterone in one hypogonadal man undergoing daily blood sampling for a week after implantation of 6 × 200 mg pellets. Note the lack of initial burst release of testosterone with plateau levels achieved after the first day and maintained steadily throughout the week

4 weeks after implantation. Furthermore even during daily blood sampling after implantation either 6 × 200 mg (Fig. 7) or 6 × 100 mg (data not shown) pellets indicate an absence of "burst" release by the first day after implantation. Thus the early release of testosterone from pellets is gradual, lacking the "burst" release or overshoot observed with some other testosterone formulations (Burris et al. 1988; Diaz-Sanchez et al. 1989). Although "burst" release is not completely excluded by our observations, if present it would only occur for the first day at most.

8 Pharmacodynamics

8.1 Clinical effects

Maintenance of libido, potency and well-being is very consistent on all 3 androgen replacement regimens for 4–5 months on either 600 mg regimen and for 6 months on the 1200 mg dose combination. After switching from regular maintenance with testosterone ester injection, most men (30/43) expressed a preference to continue using testosterone pellets for androgen replacement. The most frequent reasons were the lack of wide swings in androgen effects and the infrequency of treatments as the desirable features of testosterone pellet implant therapy. The remainder expressed preferences for parenteral testosterone ester injections or no preferences.

8.2 LH and FSH suppression

Suppression of elevated LH and FSH levels was studied in the 22 men with hypergonadotropic hypogonadism (Fig. 8). Plasma LH and FSH were markedly suppressed by all 3 regimens and in a dose-dependent fashion. This reciprocal relationship reflects the strong inverse correlations of total and free testosterone with LH ($r = 0.47$, 0.46 respectively) and FSH ($r = 0.45$, 0.47). The parallel suppression of LH and FSH was also consistent with their high correlation ($r = 0.87$) with each other. The 1200 mg (6 × 200 mg) regimen produced significantly greater and more sustained suppression of LH and FSH (both $p < 0.001$) than the two 600 mg regimens while the two 600 mg regimens had very similar time-courses for plasma LH and FSH levels (both $p > 0.30$).

The 600 mg dose regimens produced nadir LH levels between 1 and 3 months with a significant increase by 4 months and return to baseline at 5 months. In contrast the 1200 mg dose produced nadir LH levels between 1 and 4 months with return to baseline only at 6 months. Nadir LH levels achieved were comparable with eugonadal controls on the 1200 mg dose but remained elevated with both 600 mg dose combinations. The time-course for suppression of FSH levels was similar. Both 600 mg dose regimens produced nadir FSH levels between 1 and 2 months. At 3 months the 6 × 100 mg combination maintained suppression of FSH returning to baseline levels at 4 months whereas the 3 × 200 mg dose produced shorter duration of FSH levels which had returned to baseline by 3 months. In contrast the 1200 mg dose induced sustained FSH suppression with

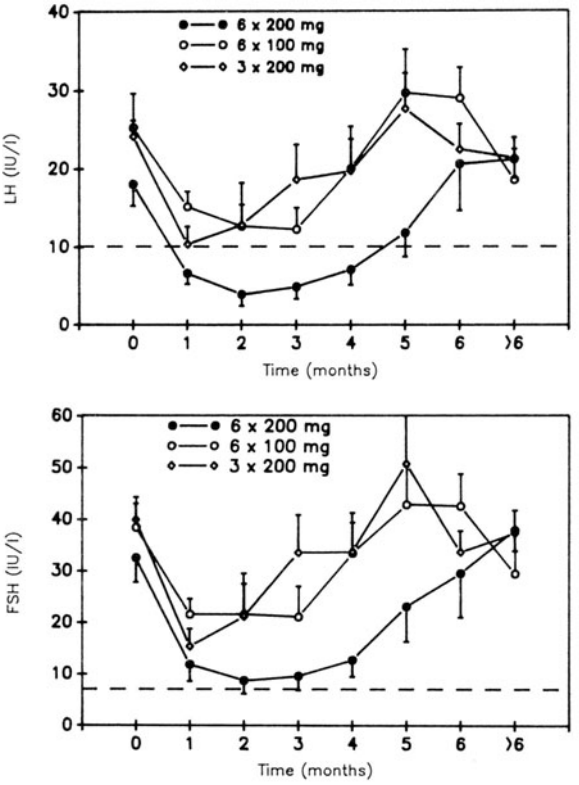

Fig. 8. LH *(upper panel)* and FSH *(lower panel)* levels over 6 months in 22 men with primary (hypergonadotropic) hypogonadism on one of the 3 pellet regimens 6 × 200 mg *(closed circles)*, 6 × 100 mg *(open circles)* and 3 × 200 mg *(open diamonds)*. Dashed line indicates the upper limit of normal eugonadal male range and mean LH levels are suppressed into or just above this range whereas mean FSH levels remain elevated. The fall and rise of LH and FSH mirrors closely the reciprocal changes in testosterone levels. Data is plotted as mean and standard error of mean

return to baseline levels only after 6 months. Nadir FSH levels remained elevated in all 3 treatment regimens compared with eugonadal controls.

The suppression of elevated gonadotropins in men with primary hypogonadism mirrored closely both the time-course of clinical androgenic effects and the maintenance of physiological testosterone levels. This provides the basis for the observation that clinical monitoring can be readily accomplished by the suppression of gonadotropins as well as the clinical effects and testosterone levels. The ability of testosterone, released from pellet implants, to suppress nadir LH levels to eugonadal levels, while FSH levels remained supra-normal, is consistent with the role of non-steroidal testicular factors, possibly including inhibin, in regulating FSH preferentially (Ying 1988).

8.3 SHBG

Plasma SHBG levels are not altered by implantation of 600–1200 mg testosterone pellets (Fig. 9). The stability of SHBG levels on all 3 pellet regimens confirms our previous findings with 6 × 100 mg pellets and contrasts with parenteral testosterone esters and oral testosterone undecanoate which do lower SHBG levels (Conway et al. 1988). In contrast to the lack of effect of testosterone, SHBG is

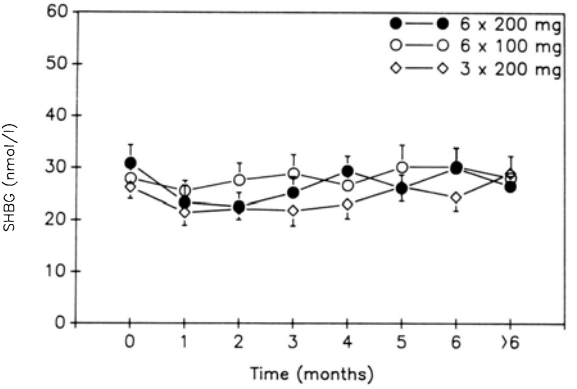

Fig. 9. Plasma SHBG levels over 6 months in 43 hypogonadal men on one of the 3 pellet regimens 6 × 200 mg (*closed circles*, n = 32), 6 × 100 mg (*open circles*, n = 28) and 3 × 200 mg (*open diamonds*, n = 51). Note the lack of significant change in SHBG levels over time or with testosterone pellet dose. Data is plotted as mean and standard error of mean

positively correlated with age and body surface area (both $r > 0.40$, $p < 0.0001$). This route-dependent difference in the effects of androgen replacement therapy on SHBG levels supports the suggestion (Conway et al. 1988) that reduced SHBG levels are a manifestation of toxic effects on the liver rather than a physiological effect of androgens (Anderson 1974). This is analogous to the effects of estrogens where parenteral administration avoids many effects of oral estrogens on circulating levels of hepatic proteins (von Schoultz and Carlstrom 1989).

Since SHBG levels are the major determinant of the testosterone metabolic clearance rate (Vermeulen et al. 1969; Petra et al. 1985), the invariance of SHBG levels following testosterone pellet implantation permits a calculation of the net amount of testosterone absorbed from the implanted pellets. On this basis virtually all the testosterone from the 600 mg pellet and about 90% of that in the 1200 mg pellets was absorbed by 6 months consistent with virtually complete bioavailability of testosterone from the fused pellets.

8.4 Biochemistry and hematology

Routine biochemical and hematological variables were examined by autoanalyzer methods at monthly intervals for 6 months after implantation of 6 × 100 mg testosterone pellets. Hemoglobin and hematocrit levels rose while plasma iron and urea fell in a reciprocal fashion to testosterone levels during the first 4 months after implantation of 6 × 100 mg testosterone pellets (Fig. 10). These changes reflect the anabolic effects of androgens on erythrocyte (Gardner and Besa 1983) and total body protein (Kochakian 1976). There were no significant or consistent changes in other biochemical (plasma sodium, potassium, chloride, bicarbonate, glucose, creatinine, calcium, phosphate, uric acid) or hematological (total and differential leukocyte and platelet counts, mean corpuscular volume and mean corpuscular hemoglobin) variables following pellet implantation. In particular there were no significant abnormalities of biochemical liver function tests (total protein, albumin, bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl tripeptidase) or non-fasting cholesterol and triglycerides.

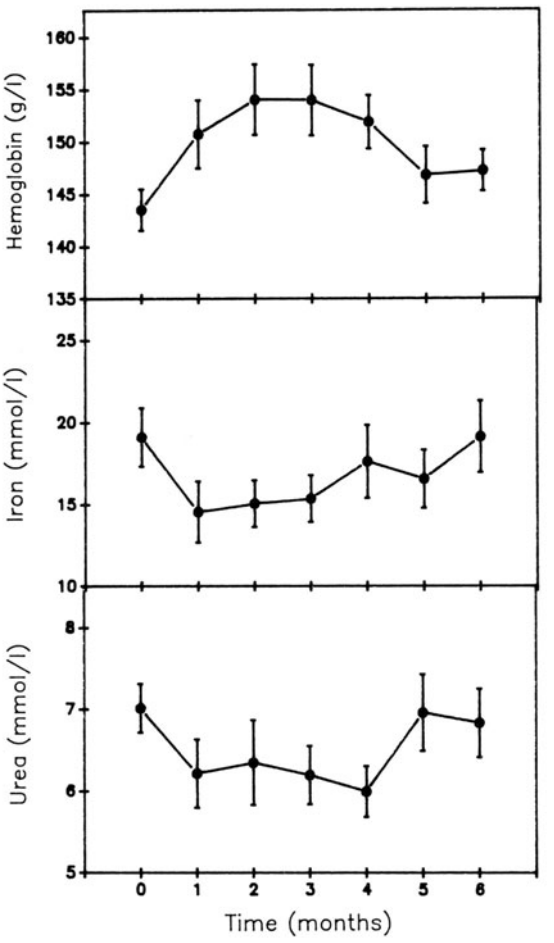

Fig. 10. Hemoglobin *(upper panel)*, plasma iron *(middle panel)* and plasma urea *(lower panel)* in 15 hypogonadal men having blood sampled at monthly intervals for 6 months after undergoing implantation of 6 × 100 mg testosterone pellets. Data plotted as mean and standard error of the mean

9 Side-effects

Pellet implantation has few side-effects. Minor discomfort at the puncture site or implant track is noted for a few hours in a few men. Immediate post-implant oozing from the incision site is uncommon and readily controlled by topical pressure. The major side-effect is pellet extrusion. While this is infrequent, the rate depends on operator skill but can be maintained at about 5% with experience. Most extrusions involve the loss of only a single pellet and do not require specific treatment or replacement of pellets. Infection occurs rarely after an extrusion and usually abates quickly during antibiotic administration. Palpable fibrosis at the sites of past pellet implantation is uncommon and when observed it does not influence subsequent pellet implantations or absorption. In some instances persistent palpable fibrosis due to a foreign body reaction may be observed after the complete dissolution of the pellet and does not necessarily indicate residual unabsorbed steroid. Fibrosis with the fused pellets is less frequent

than reported with the use of older style compressed, cholesterol-containing implants (Bishop and Folley 1951) such as are available in the USA. The lower incidence of fibrosis and the higher extrusion rates observed with the fused pellets compared with the older compressed implants may be due to the implant-induced fibrosis causing firmer anchoring and better retention of the pellet in the implant track.

10 Clinical use of testosterone pellet implants

10.1 Indications, contra-indications and limitations

Androgen deficiency of any type sufficient to warrant testosterone therapy is an indication for testosterone pellet implant therapy. There is no evidence of any differential responses according to the type or cause of the hypogonadism, the clinical features or the patient's age. Pellet implants are particularly suitable for androgen-deficient men who dislike or are unable to have regular injections (e.g. adolescents, frequent travelers). Due to their long-lasting effects and the inconvenience of removal, pellets preferably should be used by men in whom the beneficial effects and tolerance for androgen replacement therapy have already been established by treatment with shorter-acting testosterone preparations. Similarly in the rare event that rapid interruption of testosterone therapy is necessary (e.g. the diagnosis of prostate cancer), it is a limitation of pellet implants that immediate cessation of androgen action requires minor surgery to remove pellets. The only contra-indications are those relating to androgen therapy itself (e.g. prostate cancer) and those relating to the minor surgery of implantation (e.g. bleeding disorders, allergy to local anesthetics). Caution is advised for keloid-prone individuals and implantation in the usual abdominal wall site may be difficult in men with very little subcutaneous fat.

10.2 Dose and monitoring

Since the pellet testosterone release rate is known (1.5 mg/day/200 mg pellet), it is possible to replicate the daily testosterone production rate of 3–9 mg in eugonadal men (Southren et al. 1968; Gandy 1977) by a single implant of two to six 200 mg pellets (400–1200 mg) which will last for between 4 and 6 months. Indeed pellets constitute a highly flexible dosage form since by using various combinations of 100 mg and 200 mg pellets it is possible to administer testosterone at release rates of 0.75 to 9 mg per day in increments of 0.75 mg/day. Individual monitoring of androgenic effects can be readily performed by the observation of clinical effects, testosterone levels and, in men with primary hypogonadism, suppression of gonadotropin levels as for other testosterone preparations. In the light of the pharmacological studies and previous experience the routine dose is 3×200 mg implants. Due to the predictability of the time-course, it is usually sufficient after an uncomplicated implant to review the patients at monthly intervals

after the 3rd month until additional testosterone therapy is clinically and/or biochemically indicated.

10.3 Comparison with other testosterone formulations

In a randomized, cross-over comparative study of the 3 most widely used testosterone formulations (oral, IM esters, pellets), pellets demonstrated superior durability and stability of clinical effects (Cantrill et al. 1984; Conway et al. 1988). The long duration of effect permits infrequent applications which in turn minimizes compliance problems and facilitates long-term treatment. Immediately after having completed the 3 phases of the comparative study, patients expressed a preference for remaining on pellets (43%), returning to testosterone ester injections (43%) and very few wished to use oral medication (14%). After a further year nearly all (86%) had switched to pellet implants and none remained on the oral androgen. The principal reasons for choosing implants were the dislike of fluctuating androgen levels and the frequency of medications experienced with other preparations.

10.4 Costs

The daily costs of androgen replacement therapy (average retail costs in Australian pharmacy) with the pellet implants ($US 1.25) is higher than that of testosterone esters ($US 0.75) but much lower than testosterone undecanoate ($US 4.00) although these relativities differ in England where pellets are the least expensive androgen replacement therapy (Cantrill et al. 1984). These retail costs can be compared with the daily cost of the steroid ingredients (from a fine chemical catalog) which are 1.3 cents (pellet), 22 cents (testosterone enanthate) and $ 3.65 (testosterone undecanoate). Thus while the ingredient cost is only a small fraction of the retail pharmaceutical price for such a simple formulation, the testosterone pellets still represent an economical formulation costing little more than testosterone esters which require much more frequent administration.

11 Future

11.1 Development of pellet implants

Despite its simplicity and effectiveness, the pellet implant modality would benefit substantially from further technical improvement. The major defect is the cumbersome implantation procedure involving both unwieldy instruments and bulky pellets. Refinement of the procedure might be envisaged to improve the trocar and cannula insertion technique and to the simplification of the implanted material from several bulky pellets to a single smaller pellet by substituting more potent androgens (or esters). Systematic study of various implant sites would be valuable in increasing the number of implant sites and defining the site-specific

variations in release rate and duration of action of pellets which are suspected (Bishop and Folley 1951; Handelsman et al. 1990).

11.2 New applications

Androgens are used for both specific indications such as androgen replacement therapy and for non-specific indications. The long-acting features and convenience of testosterone pellets make them suitable for further applications of androgen replacement therapy. These include testosterone as an adjunct in hormonal male contraceptive regimens and in ageing men.

A variety of hormonal regimens including androgens with or without progestagens or GnRH analogs have been tested for their ability to suppress spermatogenesis sufficiently to act an an effective male contraceptive (Knuth and Nieschlag 1987). The failure of hormonal regimens to induce azoospermia uniformly despite marked gonadotropin suppression has raised the possibility that testosterone may reverse the effects of gonadotropin withdrawal on spermatogenesis (Weinbauer et al. 1989). The recent downward revision of estimates of physiological testosterone concentraions in the testis (Rommerts 1988) indicate a possible mechanism whereby excessive fluctuations in circulating testosterone levels produced by the conventional testosterone ester injections could contribute to the failure of spermatogenic suppression during androgen administration. These observations prompted the hypothesis that steady-state testosterone preparations might be more effective in suppressing spermatogenesis. Preliminary results in a study to test this hypothesis indicate that testosterone pellets, by producing steady and physiological testosterone levels, suppress spermatogenesis in normal men at least as effectively as testosterone ester injections while causing virtually no acne unlike the ester injections (Handelsman, unpublished data).

Another application of testosterone pellets is in testing the effects of androgen therapy in reversing the potentially deleterious effects of declining testosterone levels in aged men especially those with chronic medical illnesses (Nieschlag et al. 1981; Deslypere and Vermeulen 1984; Handelsman and Staraj 1985). Such studies have been limited by the lack of suitable long-acting, convenient and effective androgen preparations (Mooradian et al. 1987) and testosterone pellets may be valuable in facilitating the critical testing of this hypothesis.

Non-specific indications for the pharmacological applications of androgens in the absence of androgen deficiency include anemia due to marrow or renal failure, osteoporosis, breast cancer and hereditary angioedema. Such empirical applications are eventually rendered obsolete by clinical advances that provide more specific treatments. This was recently illustrated by the advent of recombinant human erythropoeitin (Groopman et al, 1989) which makes redundant the use of androgens for anemia (Neff et al. 1985).

12 Summary and conclusions

The ideal androgen preparation for long-term androgen replacement therapy would be safe, effective, inexpensive, already marketed, long-acting due to depot properties and exhibit zero-order release. Such an androgen formulation is not available but the testosterone pellets fulfill many of these criteria and in our opinion are superior to any presently available testosterone preparations.

The testosterone pellets are highly effective, economical, already marketed, have very long-acting properties and stability of effects with zero-order release pattern. A single implant of 600–1200 mg can provide stable, effective and well-tolerated androgen replacement for 4–6 or more months. Total and free testosterone levels rise gradually to peak at 1 month and gradually decline over several months before returning to baseline. SHBG levels are unaffected and, in men with primary hypogonadism, gonadotropin levels are markedly suppressed in a mirror-image of the testosterone levels. Clinical monitoring of the androgenic effects of the pellets can be achieved by clinical, hormonal or both methods as for other testosterone preparations. Drawbacks include the requirement for limited minor surgical skill for the implantation procedure. The only significant side-effect is pellet extrusion which will occur following implant procedures in about 5% of cases with the acquisition of some experience.

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