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Pharmacokinetics and Pharmacodynamics of Testosterone Pellets in Man

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ABSTRACT. We studied the pharmacokinetics and pharmacodynamics of six implanted pellets of fused crystalline testosterone. Three different regimens (6×100 mg, 6×200 mg, and 3×200 mg) were compared in a prospective, cross-over clinical trial in which androgen deficient men were administered the three-dose combinations in a randomized starting order at intervals of at least 6 months. Plasma free and total testosterone, sex hormone-binding globulin, LH, and FSH were measured before and at monthly intervals for at least 6 months after 111 pellet implantation in 43 men with hypogonadotropic ($n = 22$) or hypogonadotrophic ($n = 21$) hypogonadism. Total and free testosterone levels peaked at the first month and were maintained at physiological levels for 4 to 5 (600 mg doses) or 6 (1200 mg dose) months after a single implantation. Absorption of testosterone from 100 mg and 200 mg pellets closely approximated zero-order throughout the effective life of the pellets and exhibited a half-duration of 2.5 months. The estimated rate of release of testosterone was 1.5 (95% confidence limits $1.3-1.6$) mg/day. 200 mg pellet as determined from direct measurement

of residue in pellets recovered after extrusion and confirmed independently from percent absorbed-time plots. The bioavailability of testosterone was virtually complete and the time course was predictable from the total implant dose and, to a lesser extent, total initial surface area of pellets. Despite wide fluctuations in testosterone, SHBG levels were not changed during 6 months. In men with hypogonadotropic hypogonadism, both LH and FSH levels were uniformly and markedly suppressed by increased testosterone after pellet implantation. LH and FSH were highly correlated with each other ($r = 0.87$) and inversely with total ($r = 0.47$ and 0.45 , respectively) and free ($r = 0.46$ and 0.47) testosterone levels. Nadir LH levels occurred at 1-3 months (600 mg) and 1-4 months (1200 mg) reaching levels comparable with eugonadal controls. In contrast nadir FSH levels occurred at similar times but remained elevated compared with eugonadal controls. We conclude that fused pellets of crystalline testosterone provides very satisfactory depot androgen replacement exhibiting many desirable features for androgen replacement. (*J Clin Endocrinol Metab* 71:216-222, 1990)

TESTOSTERONE has been used for androgen replacement therapy since the 1930s in a wide variety of pharmaceutical formulations (1). The poor oral bioavailability (2) and short duration of action after parenteral administration (3) have dictated the need for a depot formulation of testosterone for androgen replacement therapy. Among the first such depot formulations was the subdermal implants of crystalline testosterone (4) however their clinical application in androgen replacement therapy has been neglected (5, 6) and detailed pharmacological studies of this modality of testosterone administration are almost totally lacking. The aim of this study was therefore to define the pharmacodynamics and pharmacokinetics of subcutaneous pellets of fused crystalline testosterone in androgen-deficient men. Specific

Received October 23, 1989.

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This study was supported by the Wellcome Trust (to D.J.H.) and Organon, Sydney, Australia Pty Ltd. This work has been presented in part at the 4th International Congress of Andrology, Florence, May 1989 and 32nd Annual Scientific Meeting of the Endocrine Society of Australia, Melbourne, September 1989.

Materials and Methods

Study design

Hypogonadal men attending the Andrology Unit, Royal Prince Alfred Hospital previously treated with parenteral testosterone esters for androgen replacement therapy and having no other chronic medical illness were enrolled in the study. The study design was a cross-over clinical trial with 3 treatment phases separated by intervening washout periods. The 3 treatment regimens used the two available pellet sizes (100 mg, 200 mg) in combinations of either 6×100 mg, 3×200 mg, or 6×200 mg. This compared the total pellet doses of 600 mg and 1200 mg while also providing contrasts that controlled the total dose (6×100 mg vs. 3×200 mg) or the total number of pellets (last injection of testosterone esters, hypogonadal men were assigned to 1 of the 3 testosterone pellet doses at random. Subsequently at intervals of not less than 6 months when the testosterone levels had returned to hypogonadal levels, men

critically we studied variations in the time course of total and free T, LH, FSH, and SHBG levels achieved by variations in pellet testosterone dose where the total dose and number of pellets are controlled.

by analyzing the increments from the subjects own baseline testosterone. The time course of hormonal data was analyzed as a factorial design with treatment (pellet dose) and time being main effects. This analytic approach was necessary due to incompleteness of data and the lack of a fully crossed design making a repeated measures analysis of variation analysis impracticable. The magnitude and highly consistent time course of hormone levels made the within-subject variance so much greater than the between-subject variance that neglecting the serial dependence over time would have a negligible effect on the analysis. Results were also analyzed by suitable linear contrasts, correlation, linear regression, unpaired *t* test, and analysis of covariance as required. Exact *P* values of hypotheses tests are provided and results are expressed as mean and its SE.

Results

Clinical features

The clinical features of the hypogonadal men and eugonadal controls are listed in Table 1. Hypogonadal men had smaller testis size, lower testosterone, and increased gonadotropin levels compared with eugonadal controls. Since age, anthropometric measures [height, weight, body surface area (BSA), standardized body weight (SBW)], total and free testosterone, and sex hormone binding globulin (SHBG) were comparable in men with primary and secondary hypogonadism, their results were pooled for all analyses of testosterone and SHBG. The time course of suppression of elevated LH and FSH levels was only analysed in the men with primary (hypergonadotropic) hypogonadism. The men entering each of the three treatment regimens were comparable in all hormonal and anthropometric measures (data not shown).

Forty three men with primary (hypergonadotropic, *n* = 22) or secondary (hypogonadotropic, *n* = 21) hypogonadism were studied over a total of 111 pellet implantations (6×100 mg—28 implants; 6×200 mg—32 implants; 3×200 mg—51 implants). The proportions of men with

TABLE 1. Clinical features of hypogonadal men

No.	Age (yr)	Ht (cm)	Wt (kg)	SBW (% ideal)	Body surface area (m ²)	Mean testis volume (ml)	Total testosterone (nm)	Free testosterone (pm)	SHBG (nm)	LH (IU/L)	FSH (IU/L)	All data expressed as mean and SEM.		* Controls were normal healthy men screened as potential sperm donors. † Exact P values for the comparison by unpaired t test of men with primary		† Exact P values for the comparison by unpaired t test of men with primary
336	32 ± 0.5	177 ± 0.4	75.6 ± 0.6	106.3 ± 0.8	1.92 ± 0.01	24.6 ± 0.2	22.8 ± 0.4	612 ± 21	25.7 ± 1.1	5.7 ± 0.1	4.5 ± 0.1	336	22	21	0.574	0.566
	35 ± 3	177 ± 2	77.8 ± 4.2	109 ± 4	1.94 ± 0.06	9.7 ± 1.0	265 ± 32	265 ± 32	29.0 ± 3.0	21.5 ± 2.2	36.2 ± 3.2	Primary			0.498	0.337
	37 ± 3	175 ± 2	81.5 ± 2.4	118 ± 3	1.97 ± 0.04	6 ± 2	221 ± 32	221 ± 32	26.2 ± 2.7	24.4 ± 0.3	2.6 ± 0.3	Secondary			0	0
Type of hypogonadism																
P																

^a Controls were normal healthy men screened as potential sperm donors. ^b Exact *P* values for the comparison by unpaired *t* test of men with primary vs. secondary hypogonadism.

crossed-over to another regimens until they had completed the 3 different doses. At the time of data analysis not all men had completed each of the 3 pellet regimens. If they became symptomatic of androgen deficiency before 6 months after implantation, they were treated with testosterone ester injections until at least 6 months had elapsed before they underwent the next pellet implant procedure. Blood samples were obtained immediately before pellet implantation and at 4-week intervals thereafter. Eugonadal controls were 335 healthy age-matched men undergoing screening as potential sperm donors (7).

Pellets

The testosterone pellets (Organon (Sydney, Australia) Pty Ltd.) are formed by fusion of crystalline testosterone at elevated temperature. The two sizes 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 mm² (100 mg) and 202 mm² (200 mg) per pellet. Pellets are implanted into the lower abdominal wall in the periumbilical region under routine sterile conditions for minor surgery. After 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 about the level of the umbilicus to permit entry of the trocar (7.5 French gauge, 5 mm ID, 7 cm length). Pellets are distributed in individual, angled tracks which fan out from the single 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 completion of insertion, 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 were not prescribed routinely after implantations.

Assays

Hormones (LH, FSH, total testosterone) were measured by RIA and free testosterone by centrifugal ultrafiltration (Amicon, Melbourne, Australia) as described previously (7–9). SHBG was measured by a solid phase commercial RIA (Farmos Diagnostica, 90460, Oulunsalo, Finland). LH and FSH levels were expressed in terms of international units per L of the World Health Organization standards (LH 68/40; FSH 69/104). Within and between assay coefficients of variation were less than 10% for all assays.

Rate of testosterone absorption

The rate of absorption of testosterone from the implanted pellets was calculated from percent absorbed-time plots for total and free testosterone. In addition whenever possible extruded pellets were collected from patients noting the date of extrusion.

Data analysis

All data was stored in a customized SIR/DBMS database (10) and analyzed using appropriate BMDP statistical programs (11) on a VAX computer network. Between-subject variations in baseline endogenous testosterone were removed

primary and secondary hypogonadism were similar in all three pellet regimens. Maintenance of libido, potency, and well being was very consistent on all three androgen replacement regimens for 4–5 months on the 600 mg doses and for 6 months on the 1200-mg dose combination. Most men (30/43) expressed a preference to continue using testosterone pellets for androgen replacement. They regarded the lack of wide swings in androgen effects and the wider spacing between treatments as most desirable compared with other available testosterone formulations (6). The remainder expressed preferences for parenteral testosterone ester injections or no preferences.

Pharmacokinetics—total and free testosterone

All three pellet regimens gave highly predictable time-courses for total and free testosterone levels with a clear dose-response relationship between pellet dose and plasma testosterone levels (Fig. 1). Plasma testosterone levels peaked at the first month and gradually declined to return to baseline by 6 months after the two 600 mg dose regimens but remained significantly elevated after

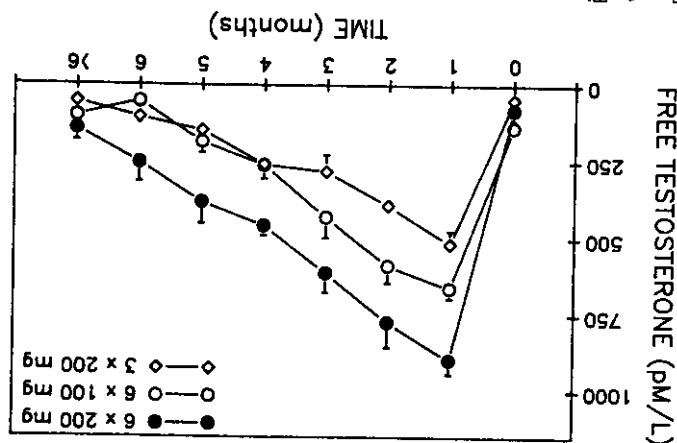
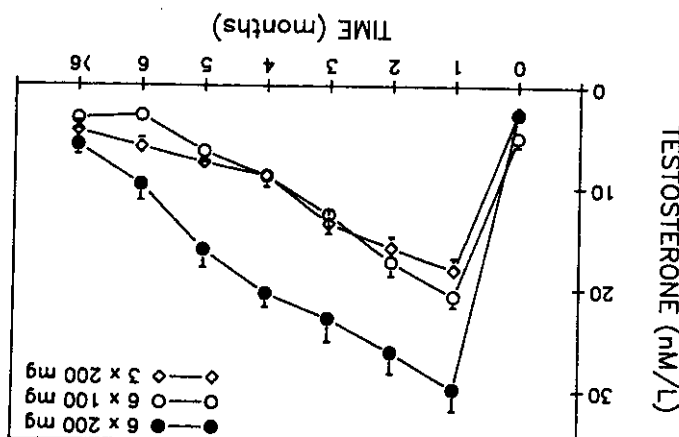


FIG. 1. Time course of total (upper panel) and free (lower panel) testosterone levels after implantation of the 3 pellet regimens in 43 hypogonadal men. Data are expressed as mean and SE of mean above the subjects own baseline testosterone level.

Plasma SHBG (Fig. 2) did not vary significantly between pellet regimens ($P = 0.87$) or over time ($P = 0.18$). SHBG was moderately correlated with both age ($r = 0.44$), BSA ($r = 0.40$), and SBW ($r = 0.25$, all $P < 0.001$).

Plasma free testosterone was highly correlated with total testosterone ($r = 0.90$) and therefore free testosterone levels exhibited a very similar time course to 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 x 100-mg regimen compared with the 3 x 200-mg regimen. Plasma total testosterone was not correlated with either age or physique ($P > 0.15$) but plasma free T was inversely correlated weakly with BSA ($r = -0.09$, $P = 0.06$), and SBW ($r = -0.13$, $P = 0.004$) but not age ($P > 0.5$).

Plasma free testosterone was highly correlated with total testosterone ($r = 0.95$). The 1200-mg regimen produced higher total testosterone levels than the two 600-mg regimens ($F = 137.8$, $P < 0.0001$ for contrast on dose) while the two 600-mg regimens gave similar time course for plasma total testosterone ($F = 0.4$, $P = 0.95$).

Pharmacokinetics—absorption kinetics

Net testosterone release (area-under-curve of testosterone vs. time plot) was highly correlated with pellet dose ($r = 0.999$) with the 1200 mg dose (130.1 arbitrary units) giving very close to twice that of either 600 mg combination (6 x 100 mg—73.5 U; 3 x 200 mg—73.9 U). Net testosterone release also correlated with total initial surface area of the pellets ($r = 0.988$). The net bioavailable free testosterone was also highly correlated with both total pellet T dose (6 x 200 mg—3493 U; 6 x 100 mg—2305 U; 3 x 200 mg—1757 U; $r = 0.951$) however the correlation with initial pellet surface area ($r = 0.986$) was stronger. Assuming a constant testosterone MCR of 540 $l/m^2 \cdot day$ (12) and using the AUC data and mean body

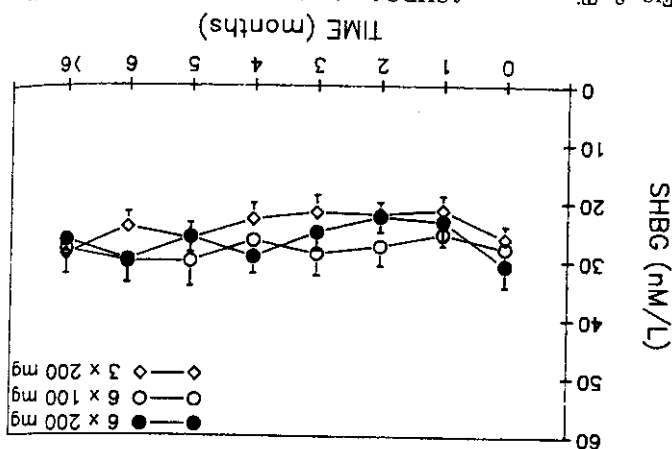


FIG. 2. Time course of SHBG levels after implantation of the 3 pellet regimens in 43 hypogonadal men. Data are expressed as mean and SE of mean.

surface area of our subjects, the average net release of testosterone was calculated to be 1100 mg from the 1200-mg dose and 645 mg from the 600-mg doses after 6 months.

Rates of absorption of testosterone from the pellets were estimated from percent absorbed-time plots (Fig. 3). These indicated a nearly linear (zero-order) release of testosterone over months that was not influenced by the size or number of pellets. An almost identical pattern was also observed for free testosterone (data not shown). The estimated half-time of absorption was approximately 2.5 months and the rate of testosterone release was 1.3 mg/day for the 200 mg pellet and 0.65 mg/day for the 100 mg pellet.

An independent estimate of rate of absorption was obtained from pellets recovered after extrusion. The remnants of six 200 mg pellets were recovered after extrusion at different times after implantation and the net release of testosterone was calculated by comparison with nonimplanted 200-mg pellets (Fig. 4). The estimated rate of release was linear with time up to 92 days

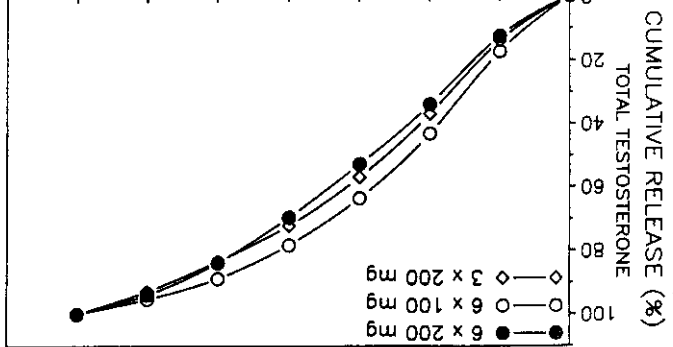


Fig. 3. Percent absorbed-time plot for testosterone from the three combinations of pellets. Note the nearly linear rate of release consistent with 0 order release.

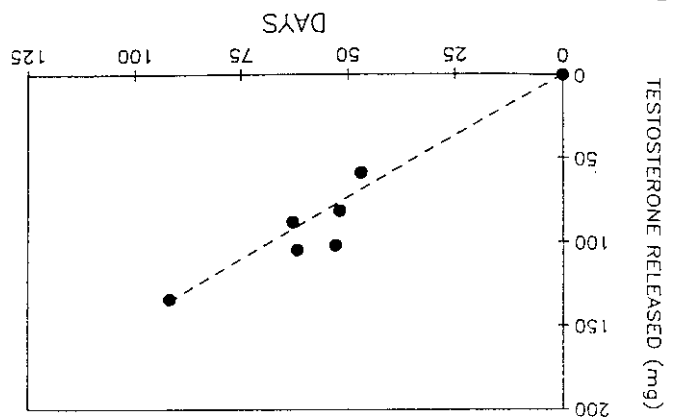


Fig. 4. Amount of testosterone released from 200-mg pellets which were extruded at various times after implantation. Estimated release rate of testosterone is 1.5 mg/day-pellet. For further details see text.

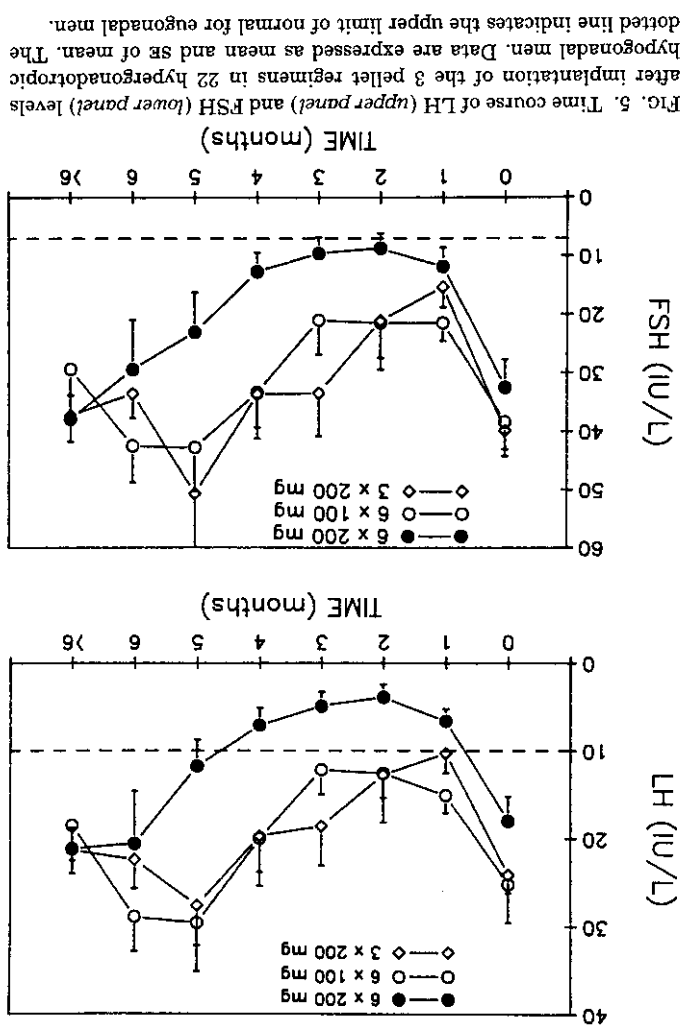


Fig. 5. Time course of LH (upper panel) and FSH (lower panel) levels after implantation of the 3 pellet regimens in 22 hypogonadotropic hypogonadal men. Data are expressed as mean and SE of mean. The dotted line indicates the upper limit of normal for eugonadal men. ($r = 0.993$) and provided an estimate of 1.5 (95% confidence limits 1.4-1.7) mg/day-200 mg pellet. The extruded pellets retained the original cylindrical shape although the one longest *in situ* (92 days) disintegrated into fragments on handling.

Pharmacodynamics-LH and FSH

Both plasma LH and FSH (Fig. 5) levels were markedly suppressed by all three regimens in men with primary (hypogonadotropic) hypogonadism with a marked dose dependency as the 1200-mg regimen produced significantly greater and more sustained suppression of LH and FSH than the two 600-mg regimens (linear contrast $F = 16.1$, $P < 0.001$ (LH); $F = 12.1$, $P < 0.001$ (FSH)). The two 600-mg regimens produced similar time courses for plasma LH ($F = 1.0$, $P = 0.32$) and FSH ($F = 0.01$, $P = 0.93$) levels. 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

hypogonadal men. Despite the clinical use of testosterone pellets for 50 yr (4), pharmacological data has been remarkably sparse (5, 6) and the dose and duration characteristics of this formulation has not been described systematically. Authoritative reviews of androgen replacement therapy have described implants as having "virtually no clinical utility" (13) or have omitted or barely mentioned this modality (1, 14, 15). The dearth of pharmacological information may explain the relatively limited clinical use of a highly effective depot form of testosterone replacement therapy.

The rate of absorption of testosterone from the pellets appears to provide a very good approximation to zero-order release. This is supported by the near-linear percent absorbed-time plots and, independently, by direct measurements of absorption from pellets retrieved after extrusion which gave linear absorption for up to 92 days after implantation. This remarkably good approximation to zero-order release obtained with the simply formulated fused crystalline steroid pellets appears to be characteristic of a variety of crystalline steroid depots (16-18). The rate of testosterone release calculated by two independent methods gave estimates in close agreement. The direct estimate of the testosterone release rate was 1.5 mg/day for the 200-mg pellet (0.75%/day) and, in view of the identical percent absorbed-time plots, half that for the 100-mg pellets. The only comparable direct estimate of testosterone release rates from fused pellets (16) was 1.1 mg/day. 100-mg pellet when implanted in the antecubital or subscapular regions. The pellets in the present study implanted in the anterior abdominal wall gave a 41% lower release rate despite a 66% greater initial surface area. This discrepancy may reflect an important site-specific difference in testosterone absorption rates. The mechanism of steroid absorption from fused pellets appears to be a uniform-erosion mechanism involving the gradual dissolution of a crystalline steroid of sparing solubility into the extracellular fluid (16-18). Our observation of higher free testosterone and more sustained gonadotropin suppression levels during the first (but not the second) 3 months after the 600-mg regimen with the greater initial surface area (6×100 mg) does support the importance of pellet geometry in limiting the testosterone release rate. The potential effects of the site of implantation and variations in its blood flow remain speculative at present.

It should be noted that these fused pellets are quite different from the original subdermal implants made by high pressure compression into a tablet-like form of testosterone with excipient (usually cholesterol) which undergo much greater encapsulation and fibrosis than is observed with the fused pellets (16). The lesser degree of fibrosis produced by the fused pellets compared with the older compressed pellets may be responsible for the lower

LH levels between 1 and 4 months with return to baseline only at 6 months. Nadir LH levels achieved were comparable with eugonadal control on the 1200-mg dose but remained elevated with both 600-mg dose combinations. Similar effects were also observed for suppression of FSH levels. Both 600-mg dose regimens produced nadir FSH levels between 1 and 2 months but after 3 months the effects of the 6×100 -mg combination (with the higher initial surface area) were sustained longer than the 3×200 -mg dose which had returned to baseline by 3 months. In contrast the 1200-mg dose induced sustained FSH suppression with return to baseline levels only after 6 months. Nadir FSH levels remained elevated in all three treatment regimens compared with eugonadal controls. The generally parallel suppression of LH and FSH was consistent with their overall high correlation ($r = 0.87$ for quadratic regression) with each other. Plasma LH and FSH were also each inversely correlated with total [$r = 0.47$ (LH), 0.45 (FSH)] and free [$r = 0.46$ (LH), 0.47 (FSH)] testosterone.

Side effects

Pellet implantation had few side effects. Three instances of mild bleeding controlled by topical pressure occurred within 2-3 h after pellet implantation and another of a hematoma causing discomfort was observed within a few days after implantation. There were 11 extrusions of at least 1 pellet and 4 episodes of infection after 111 implants. Most (6/11) extrusion episodes involved the loss of only one pellet and the greatest number of pellets extruded was 3/6 pellets. The frequency of pellet extrusion was related to operator skill since the frequency fell from an incidence of 40% of an extrusion episode after the first 15 procedures to 5% in the later 96 implants. Extrusions were significantly more frequent after implantation of 6×100 -mg pellets (25% vs. 5%, $P = 0.008$) and after implantation of 100-mg pellets (8.9% vs. 1.4%, $P = 0.0001$) but were unrelated to whether three or six pellets were implanted ($P = 0.22$). These findings probably reflected a temporal trend in operator experience since the 6×100 -mg pellets was the earliest employed. Infections followed a pellet extrusion and all abated quickly during administration of broad-spectrum antibiotics. Palpable fibrosis at the sites of past pellet implantation was observed in a few subjects but these incidental observations were unaccompanied by any complications relating to subsequent pellet implantation or absorption. In up to 5 yr of use there have been no subjects with sufficient scarring to interfere with any further implants.

Discussion

This study reports the first detailed pharmacokinetic and pharmacodynamic study of testosterone pellets in

The implantation of testosterone pellets produce reproducible and dose-dependent time course for circulating total and free testosterone lasting for 4-5 months after a single implant of the 600-mg dose combinations and 6 months for the 1200-mg dose. The pellets provide a flexible dosage form with smooth, physiological, and sustained androgenic effects as manifested by markedly lower SHBG levels (6). This is consistent with the liver rather than a physiological effect of androgens on metabolic clearance rate (21, 22), the invariance of SHBG levels following testosterone pellet implants supports the validity of the assumptions about the constancy of testosterone MCRs assumed in the calculations of bioavailability and indirect estimates of testosterone release rates.

Acknowledgments

The authors are grateful for the assistance of Mr. Paul Mutton of Organon (Australia) Pty Ltd. and the staff of the Endocrinology laboratory for their expert help in performing the assays.

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frequency of fibrosis but conversely may also be related to the higher rates of extrusion due to the weaker anchoring of pellets in their tracks. Minor palpable fibrosis, due to foreign body tissue reaction (5), observed at implant sites of some men may persist after the complete dissolution of the fused pellets and does not necessarily indicate residual unabsorbed steroid.

All three pellet regimens caused no change in immunoreactive SHBG levels in contrast with parenteral testosterone esters and oral testosterone undecanoate which markedly lower SHBG levels (6). This is consistent with the postulate (6, 19) that decreases in SHBG levels are a manifestation of excessive or toxic androgen effects on the liver rather than a physiological effect of androgens on metabolic clearance rate (21, 22), the invariance of SHBG levels following testosterone pellet implants supports the validity of the assumptions about the constancy of testosterone MCRs assumed in the calculations of bioavailability and indirect estimates of testosterone release rates.

The suppressive effects of the pellets on elevated LH and FSH levels was dose dependent and mirrored closely the time course of testosterone absorption. The strong inverse correlation of testosterone with gonadotropin suppression in men with primary hypogonadism is consistent with the observation that the duration of gonadotropin suppression after pellet implantation reflects accurately the maintenance of physiological testosterone levels. The observation that nadir LH levels were suppressed into or just above the eugonadal range whereas FSH levels remained elevated is consistent with the role of nonsteroidal gonadal factors such as inhibin in regulating FSH preferentially. Thus gonadotropin suppression in men with primary hypogonadism can augment clinical monitoring of androgenic effects after testosterone pellet implantation.

Testosterone ester injections administered in an oily vehicle remains the most widely used testosterone formulation for androgen replacement therapy in clinical practice (1, 14, 15). Comparative clinical trials have demonstrated however that the durability and stability of androgenic effects after testosterone pellet implants are much preferable by patients who have experienced the alternatives (5, 6). Given the calculated testosterone release rates it is possible with various pellet combinations to readily produce daily testosterone release rates of 0.75-9 mg/day in increments of 0.75 mg/day using the two available pellet sizes. Thus the normal testosterone production rate of 3-9 mg/day (12) can be reproduced by a single implant of two to six pellets (400-1200 mg) which will last for between 4 and 6 months. The only drawbacks of testosterone pellet implants in androgen replacement therapy are the requirement for minor sur-