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Pharmacology of testosterone preparations

H.M. Behre, C. Wang, D.J. Handelsman and E. Nieschlag

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14.1 Historical development of testosterone therapy

The first experimental proof that the testes produce a substance responsible for virility was provided by Berthold (1849). He transplanted testes from roosters into

the abdomen of capons and recognized that the animals with the transplanted testes behaved like normal roosters: “They crowed quite considerably, often fought among themselves and with other young roosters and showed a normal inclination toward hens”. Berthold concluded that the virilizing effects were exerted by testicular secretions reaching the target organs via the bloodstream. Berthold’s investigation is generally considered the origin of experimental endocrinology (Simmer and Simmer 1961). Following his observation various attempts were made to use testicular preparations for therapeutic purposes. The best known experiments are those by Brown-Séguard (1889), who tried testis extracts on himself which can at best have had placebo effects (Cussons *et al.* 2002). In the 1920s Voronoff transplanted testes from animals to humans for the purpose of rejuvenation (Voronoff 1920), but the effectiveness of his methods was disproven by a committee of the Royal Society London. The first testicular extracts with demonstrable biological activity were prepared by Loewe and Voss (1930) using the seminal vesicle as a test organ. Finally, the groundstone for modern androgen therapy was laid when steroidal androgens were first isolated from urine by Butenandt (1931), testosterone was obtained in crystalline form from bull testes by David *et al.* (1935) and testosterone was chemically synthesized by Butenandt and Hanisch (1935) and Ruzicka and Wettstein (1935).

Immediately after its chemical isolation and synthesis, testosterone was introduced into clinical medicine (unthinkable had it happened today) and used for the treatment of hypogonadism. Since testosterone was ineffective orally it was either compressed into pellets and applied subcutaneously or was used in the form of 17α -methyltestosterone. In the 1950s longer-acting injectable testosterone esters (Junkmann 1957) became the preferred therapeutic modality. In the 1950s and 1960s chemists and pharmacologists concentrated on the chemical modification of androgens in order to emphasize their erythropoetic (Gardner and Besa 1983) or anabolic effects (Kopera 1985). These preparations never played an important role in the treatment of hypogonadism and were abandoned for purposes of clinical medicine. In the late 1970s the orally effective testosterone undecanoate was added to the spectrum of testosterone preparations used clinically (Coert *et al.* 1975; Nieschlag *et al.* 1975). In the mid 1990s, transdermal testosterone patches applied either to scrotal skin (Bals-Pratsch *et al.* 1986) or non-scrotal skin (Mazer *et al.* 1992) were introduced into clinical practice. In 2000, a transdermal testosterone gel became available for treatment of male hypogonadism, first in the US and subsequently in other countries as well (Wang *et al.* 2000).

14.2 General considerations

Although testosterone has been in clinical use for almost 70 years, it has only slowly attracted interest from clinical researchers. This is partly due to the fact that hypogonadal men requiring testosterone treatment constitute only a minority of all

patients and hypogonadism is not a life-threatening disease. Since development of new preparations is mainly a task of the pharmaceutical industry and hypogonadal patients did not promise to contribute a substantial economic profit, development of testosterone preparations was slow. Only recently has the question of testosterone treatment of senescent men (see Chapter 16) and, to a certain extent also the search for a hormonal male contraceptive (see Chapter 23) spurred interest in the pharmacology and application of testosterone.

Today oral, buccal, injectable, implantable and transdermal testosterone preparations are available for clinical use. There are only a few studies available comparing the various preparations with the goal of identifying the optimal preparation for substitution purposes (Conway *et al.* 1988). While the older injectable preparations, which are still the predominant form for substitution, produce supraphysiological serum testosterone levels, newer preparations achieve levels closer to the physiological range. We are only beginning to understand which serum levels are required to achieve the various biological effects of testosterone and to avoid adverse side-effects. In particular, very little is known about long-term effects of testosterone therapy inherent to different preparations. Similarly, the role of the androgen receptor polymorphism in modifying testosterone action individually is becoming understood only slowly, but may lead to a pharmacogenetic concept for the therapeutic application of testosterone (e.g. Zitzmann *et al.* 2003). Under these circumstances it appears that the consensus reached by a Workshop Conference on Androgen Therapy organised jointly by WHO, NIH and FDA in 1990 still provides the best therapeutic guidelines: "The consensus view was that the major goal of therapy is to replace testosterone levels at as close to physiologic concentrations as is possible" (WHO 1992). Until other evidence is provided, all testosterone preparations will best be judged by this principle.

An important question is which androgen preparation should be used for clinical purposes. Numerous androgenic steroids have been synthesized and used clinically in the past. The synthetic androgens were produced with the aim to enhance selectively certain aspects of testosterone activity e.g. the anabolic effect on muscles or the hematopoietic effect. Some of these molecules proved to have toxic side-effects, in particular upon long-term use (as required for substitution of hypogonadism) or the desired efficacy and safety were inadequate in controlled clinical trials (as advocated by evidence-based medicine). In addition, some of these steroids cannot be converted to 5α -DHT or estrogen, as is testosterone, and therefore cannot develop the full spectrum of activities of testosterone. The important biological significance of these conversions is described in Chapters 1 to 3 of this volume. For these reasons, synthetic preparations have almost disappeared from the market and testosterone as produced naturally is the prevailing androgen used in clinical medicine. In its various preparations testosterone has been available for over six decades and, as one of the oldest "drugs" in clinical use, has demonstrated its high safety.

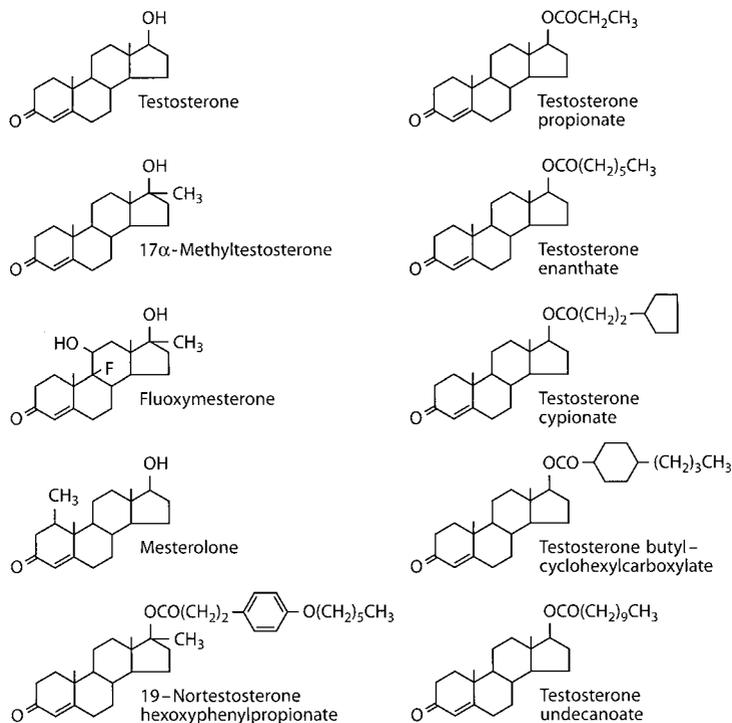


Fig. 14.1 Molecular structure of testosterone and clinically used testosterone esters and derivatives.

However, new insights into the molecular mechanisms of androgen action may lead to the development of steroids suited for specific purposes (see Chapter 20). 7 α -methyl-19-nortestosterone serves as an example, as it is experiencing a renaissance due to its high androgenicity combined with low prostatic effects shown in hypogonadal patients (Anderson *et al.* 2003). Whether such steroids may become useful and safe for clinical use remains to be seen.

This chapter provides an overview of the various conventional and new testosterone preparations used in clinical medicine.

14.3 Pharmacology of testosterone preparations

As all other androgens, testosterone derives from the basic structure of androstane. This molecule consists of three cyclohexane and one cyclopentane ring (perhydrocyclopentanephenthrane ring) and a methyl group each in position 10 and 13. Androstane itself is biologically inactive and gains activity through oxygroups in position 3 and 17. Testosterone, the quantitatively most important androgen synthesized in the organism, is characterized by an oxy group in position 3, a hydroxy group in position 17 and a double bond in position 4 (Fig. 14.1).

Table 14.1 Mode of application and dosage of various testosterone preparations

Preparation	Route of application	Full substitution dose
<i>In clinical use</i>		
Testosterone undecanoate	oral	2–4 capsules à 40 mg per day
Testosterone tablets	buccal	30 mg / twice daily
Testosterone enanthate	intramuscular injection	200–250 mg every 2–3 weeks
Testosterone cypionate	intramuscular injection	200 mg every 2 weeks
Testosterone undecanoate	intramuscular injection	1000 mg every 10–12 weeks
Testosterone implants	implantation under the abdominal skin	4 implants à 200 mg every 5–6 months
Transdermal testosterone patch	scrotal skin	1 patch per day
Transdermal testosterone patch	non-scrotal skin	1 or 2 systems per day
Transdermal testosterone gel	non-scrotal skin	5 to 10 g gel per day
<i>Under development</i>		
Testosterone cyclodextrin	sublingual	not yet determined
Testosterone buclate	intramuscular injection	not yet determined
Testosterone microcapsules	subcutaneous injection	not yet determined
<i>Obsolete</i>		
17 α -Methyltestosterone	oral	
Fluoxymesterone	sublingual/oral	

To make testosterone therapeutically effective three approaches have been used:

- 1) different routes of administration,
- 2) esterification in position 17, and
- 3) chemical modification of the molecule.

In addition, these approaches have been combined. Since of practical clinical relevance, the route of administration is used here for categorizing the various testosterone preparations (overview in Table 14.1).

14.3.1 Oral administration

14.3.1.1 Unmodified testosterone

Unmodified testosterone as physiologically secreted by the testes would appear to be the first choice when considering substitution therapy. When ingested orally in its unmodified form testosterone is absorbed well from the gut but is effectively metabolized and inactivated in the liver before it reaches the target organs (“first-pass-effect”). Only when a dose of 200 mg is ingested which exceeds 30fold the amount of testosterone produced daily by a normal man, is the metabolizing capacity of the liver overcome. With such doses an increase in peripheral testosterone blood levels becomes measurable and clinical effects can be observed (Daggett

et al. 1978; Johnsen *et al.* 1974; Nieschlag *et al.* 1975; 1977). The testosterone-metabolizing capacity of the liver, however, is age- and sex-dependent. An oral dose of 60 mg unmodified testosterone does not affect peripheral testosterone levels in normal adult men, but produces a significant rise in prepubertal boys and women (Nieschlag *et al.* 1977). This demonstrates that testosterone induces liver enzymes responsible for its own metabolism (Johnsen *et al.* 1976). When the liver is severely damaged its metabolizing capacity decreases. Thus, in patients with liver cirrhosis a dose of 60 mg testosterone (ineffective in normal men) produces high serum levels (Nieschlag *et al.* 1977).

In hypogonadal men with normal liver function, 400–600 mg testosterone must be administered daily if the patient is to be substituted by oral testosterone (Johnsen 1978; Johnsen *et al.* 1974), a dose exceeding the testosterone production of a normal man almost 100fold. Aside from being uneconomical, the possibility of adverse effects of such huge testosterone doses cannot be excluded, especially when given over long periods of time as required for substitution therapy. However, in a small group of patients treated for as long as seven years with oral testosterone no serious side-effects were observed (Johnson 1978). Nevertheless, oral administration of unmodified testosterone has not become a generally accepted method for therapeutic purposes.

As a relict of experiments performed last century (see 14.1), preparations containing animal testis or plant extracts or dried organ powder are still being manufactured and are available on the market. Although synthesized in the testis, the testosterone content of these preparations is negligible since the testis, in contrast to other endocrine glands (such as the thyroid), does not store its hormonal products (Cussons *et al.* 2002). Moreover, the testosterone in these orally consumed products cannot become effective for the reasons described above. Such preparations may at best exert placebo effects and do not belong to a rational therapeutic repertoire. Similarly, there is no evidence that ingestion of animal testes as food has endocrine effects.

14.3.1.2 17 α -methyltestosterone

Several attempts have been made to modify the testosterone molecule by chemical means in order to render it orally effective, i.e. to delay metabolism in the liver. In this regard, the longest known testosterone derivative is 17 α -methyltestosterone (Ruzicka *et al.* 1935) which is a fully effective oral androgen preparation. 17 α -methyltestosterone is quickly absorbed and maximal blood levels are observed 90 to 120 minutes after ingestion. The half-life in blood amounts to approximately 150 minutes (Alkalay *et al.* 1973).

Ever since this steroid was introduced for clinical use, hepatotoxic side-effects such as an increase in serum liver enzymes (Carbone *et al.* 1959), cholestasis of the liver (de Lorimer *et al.* 1965; Werner *et al.* 1950), and peliosis of the liver (Westaby *et al.* 1977) have been reported repeatedly. It is of interest that humans are more

susceptible to the hepatotoxic effects of nethyltestosterone than rats (Heywood *et al.* 1977a) or dogs (Heywood *et al.* 1977b). Later, an association between long-term methyltestosterone treatment and liver tumors was found (Bird *et al.* 1979; Boyd and Mark 1977; Coombes *et al.* 1978; Falk *et al.* 1979; Farrell *et al.* 1975; Goodman and Laden 1977; McCaughan *et al.* 1985; Paradinas *et al.* 1977). While these side-effects appear to be clearly related to methyltestosterone administration, the isolated observation of a seminoma in a 36-year old man on high-dose methyltestosterone seems incidental (Vogelzang *et al.* 1986).

The hepatotoxic side-effects are due to the alkyl group in the 17α position and have also been reported for other steroids with this configuration (Krüskemper and Noell 1967). Because of the side-effects methyltestosterone should no longer be used therapeutically for hypogonadism, in particular since effective alternatives are available (Nieschlag 1981). The German Endocrine Society declared methyltestosterone obsolete in 1981 and the German Federal Health Authority ruled that methyltestosterone should be withdrawn from the market (Methyltestosterone 1988). In other countries, however, methyltestosterone is still in use, a practice which should be terminated.

14.3.1.3 Fluoxymesterone

The androgenic activity of fluoxymesterone was enhanced over that of testosterone by the introduction of fluorine and the addition of a hydroxy group into the steroid skeleton of testosterone. This substance also contains a 17α -methyl group and accordingly there is a risk of hepatotoxicity with long-term use. Therefore, this androgen has disappeared from the market.

14.3.1.4 Mesterolone

Mesterolone can be considered a derivative of the 5α -reduced testosterone metabolite 5α -dihydrotestosterone (DHT) which is protected from rapid metabolism in the liver by a methyl group in position 1 (Gerhards *et al.* 1966) and thus becomes orally active. It is free of liver toxicity. Unlike testosterone, mesterolone cannot be metabolized to estrogens (Breuer and Gütgemann 1966) and at a molecular level acts like DHT. Because of its limited effectiveness in suppressing pituitary gonadotropin secretion (Aakvaag and Stromme 1974; Gordon *et al.* 1975) it can only be considered an incomplete androgen. Altogether, mesterolone is not suited for the substitution of hypogonadism. Nevertheless, in 2001 it still represented 12% of all androgen sales in Germany.

14.3.1.5 Testosterone undecanoate

When testosterone is esterified in the 17β -position with a long fatty acid side chain such as undecanoic acid and given orally, its route of absorption from the gastrointestinal tract is slightly shifted from the vena portae to the lymph and

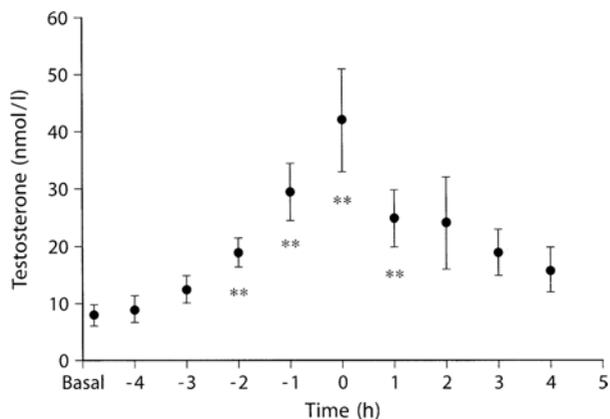


Fig. 14.2 Single-dose pharmacokinetics of testosterone undecanoate after oral administration of 120 mg of the ester to 8 hypogonadal patients. Because of high interindividual variability of testosterone serum concentrations after administration of testosterone undecanoate, individual curves were all centralized about the time of maximal serum concentrations (time 0). Asterisks indicate significantly higher testosterone serum concentrations compared to pretreatment values (basal) (mean \pm SEM).

reaches the circulation via the thoracic duct (Coert *et al.* 1975; Horst *et al.* 1976; Shackelford *et al.* 2003). Absorption is improved if the ester is taken in arachis oil (Nieschlag *et al.* 1975) and with a meal (Frey *et al.* 1979; Bagchus *et al.* 2003). After oral ingestion of a 40 mg capsule, of which 63% i.e. 25 mg is testosterone, maximum serum levels are reached two to six hours later (Nieschlag *et al.* 1975). Thus, with 2 to 4 capsules (80 to 160 mg) per day substitution of hypogonadism can be achieved.

Testosterone undecanoate pharmacokinetics after single-dose administration were tested in eight hypogonadal patients and twelve normal men (Schürmeyer *et al.* 1983). Directly before and at hourly intervals after oral application of three times 40 mg of testosterone undecanoate in arachis oil taken together with a standardized breakfast, matched saliva samples, as a parameter for free testosterone at the tissue level, and blood samples were collected hourly for up to 8 h. After administration of testosterone undecanoate, serum and saliva testosterone always showed a parallel rise and fall, as demonstrated by a constant saliva/serum testosterone ratio. On average maximum levels could be observed five hours after testosterone undecanoate administration. However, the serum testosterone profile showed high interindividual variability of the time when maximum concentrations were reached, as well as of the maximum levels themselves that ranged from 17 to 96 nmol/l. When the individual serum concentration versus time curves were centralized about the time of maximal serum concentrations, serum concentrations significantly different from basal values were seen only two hours before and one hour after the time of maximal serum concentrations in hypogonadal patients (Fig. 14.2) (Schürmeyer

et al. 1983). Based on this observation it can be deduced that even with administration of testosterone undecanoate 3 times daily, only short-lived testosterone peaks resulting in high fluctuations can be obtained.

This judgment is in agreement with the data of a two-month multiple-dose study with testosterone undecanoate for replacement therapy in hypogonadal men (Skakkebaek *et al.* 1981). Applying a double blind cross-over design, serum testosterone levels were studied in 12 hypogonadal patients to whom 80 mg of testosterone undecanoate had been administered twice per day 12 hours apart. Whereas four hours after administration of testosterone undecanoate a significant increase of testosterone serum levels was observed compared to the placebo group, twelve hours after administration no significant difference in testosterone serum levels between treatment and placebo control group was seen. Even four hours after administration, in four of twelve patients testosterone levels were still below the lower level of the normal range after both one month and two months of treatment. A significant marked variability between subjects as well as within the same subjects has also been observed in other clinical studies (Cantrill *et al.* 1984; Conway *et al.* 1988).

The original preparation of oral testosterone undecanoate had to be refrigerated (2–8°C) in the pharmacy for reasons of stability, whereas patients must store it at room temperature to ensure optimal absorption. The shelf-life at room temperature is only three months. Therefore, a new, more stable pharmaceutical formulation of testosterone undecanoate was developed in which the oleic acid solvent was replaced by castor oil and propylene glycol laurate. This new formulation can be stored at room temperature (15–30°C) for three years (Bagchus *et al.* 2003). According to an unpublished randomized multicenter study in 49 hypogonadal men, oral administration of 2 × 80 mg or 3 × 80 mg of the reformulated testosterone undecanoate might result in more physiological and stable serum testosterone levels.

14.3.2 Sublingual application

17 α -methyltestosterone was found to be more effective when applied sublingually than when ingested orally (Escamilla 1949). This type of substitution should, however, not be practised because of the liver toxicity of methyltestosterone summarized above. The solubility of the hydrophobic testosterone molecule can be enhanced by incorporation into hydroxypropyl- β -cyclodextrins (Pitha *et al.* 1986) which are macro-ring structures consisting of cyclic oligosaccharides. When testosterone incorporated into such cyclodextrins is administered sublingually steep increases in serum testosterone occur lasting for one or two hours (Stuenkel *et al.* 1991). Hypogonadal men treated with three daily doses for 60 days showed improvement of their condition (Salehian *et al.* 1995; Wang *et al.* 1996). This is an interesting approach to testosterone substitution, but unless more constant serum levels can

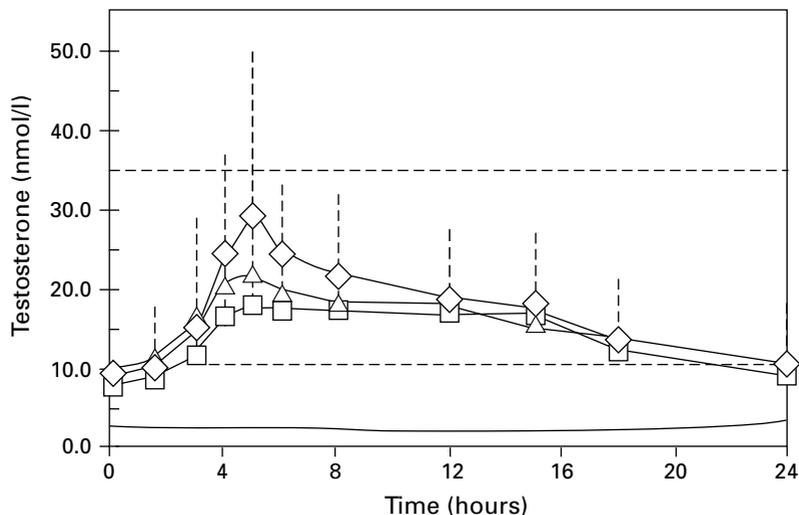


Fig. 14.3 Mean (\pm SD), baseline-adjusted serum concentrations of testosterone after application of placebo (solid line), 10 mg (squares), 20 mg (triangles) and 30 mg (diamonds) of buccal testosterone at steady state (day 10 of dosing). Broken lines indicate normal range of testosterone (adapted from Baisley *et al.* 2002, reproduced by permission of the Society of Endocrinology).

be achieved this therapy would require repeated daily applications and would have the same disadvantages as conventional oral testosterone undecanoate therapy.

14.3.3 Buccal application

Administration of testosterone via the buccal mucosa bypasses the liver and avoids first-pass clearance by delivering the drug directly into systemic circulation. Compared to sublingual administration, buccal mucosa is less permeable and potentially better suited for sustained delivery systems. An initial randomized, double-blind, placebo-controlled study in hypogonadal patients receiving 10 mg testosterone or placebo buccal tablets showed unfavourable pharmacokinetics with serum levels of testosterone far above the upper normal range and returning to baseline as soon as four to six hours after administration (Dobs *et al.* 1998).

Significantly improved pharmacokinetics were obtained with newly formulated buccal tablets. In a randomized, double-blind, crossover design 24 healthy men received a GnRH agonist for suppression of endogenous testosterone (Baisley *et al.* 2002). Buccal tablets containing 10, 20 or 30 mg testosterone were taken daily at 8.00 h for 10 days. Steady state was reached by day 5. Peak total and free testosterone were reached eight to nine hours after tablet application (Fig. 14.3). Hormone concentrations increased with the testosterone dose of the tablets, but this increase was less than dose-proportional. Whereas the average concentration of testosterone did

not exceed the normal range, some individual blood samples still showed supraphysiological testosterone concentrations. About half of the volunteers reported local discomfort at the buccal application site, in most subjects during the first treatment period. The advantage of this buccal testosterone preparation seems to be the mimicking of the physiological circadian testosterone rhythm, however, long-term studies in hypogonadal patients including evaluation of acceptability are awaited.

A new testosterone bioadhesive buccal system was designed to adhere rapidly to the buccal mucosa and gellify for delivering testosterone steadily into the circulation. The pharmacokinetics were evaluated in 82 hypogonadal men. The tablet (30 mg testosterone) was applied twice daily to the upper gums for three months. 73% of the patients reached an average testosterone concentration over 24 hours within the physiological range. Local problems associated with tablet use were transient and minimal. This bioadhesive buccal system is approved for use in hypogonadal men in the U.S.A. and approval in Europe is expected.

14.3.4 Nasal application

The first-pass effect of the liver can also be avoided by applying testosterone to the nasal mucosa (Danner and Frick 1980). However, unreliable absorption patterns and short-lived serum peaks prevent this form of application from becoming a desirable option for long-term substitution therapy and it has never passed the experimental state.

14.3.5 Rectal application

In order to avoid the first-pass effect of the liver, testosterone can be applied rectally in suppositories (Hamburger 1958). Administration of a suppository containing 40 mg testosterone results in an immediate and steep rise of serum testosterone lasting for about four hours. Effective serum levels can be achieved by repeated applications (Nieschlag *et al.* 1976). This therapy, however, never gained much popularity probably because the patients find it unacceptable to use suppositories three times daily on a long-term routine basis.

14.3.6 Intramuscular application

The most widely-used testosterone substitution therapy is the intramuscular injection of testosterone esters. Unmodified testosterone has a half-life of only ten minutes and would have to be injected very frequently. Esterification of the testosterone molecule at position 17, e.g., with propionic or enanthic acid, prolongs the activity of testosterone in proportion to the length of the side chain when administered intramuscularly (Junkmann 1952; 1957). The deep intramuscular injection of testosterone esters in oily vehicle is generally safe and well tolerated, but can cause minor side-effects such as local pain (Mackey *et al.* 1995).

Studies applying gas chromatography-mass spectrometry that allow discrimination between endogenous testosterone and exogenously administered deuterium-labelled testosterone propionate-19,19,19-d₃ and its metabolite testosterone-19,19,19-d₃ were able to show that after intramuscular administration, the testosterone ester is slowly absorbed into the general circulation and then rapidly converted to the active unesterified metabolite (Fujioka *et al.* 1986). The observation that the duration at the injection site is the major factor determining the residence time of the drug in the body agrees with pharmacokinetic studies in rats showing that the androgen ester 19-nortestosterone decanoate, when injected into the musculus gastrocnemius of the rat *in vivo*, is absorbed unchanged from the injection depot in the muscle into the general circulation according to first-order kinetics with a long half-life of 130 h (van der Vies 1965). Comparisons of the absorption kinetics of different testosterone esters clearly show that the half-lives of the absorption of the esters increase when the esterified fatty acids have a longer chain (van der Vies 1985). In addition, pharmacokinetics are influenced by the oily vehicle, the injection site and the injection volume (Minto *et al.* 1997).

After absorption from the intramuscular depot, the testosterone ester is rapidly hydrolysed in plasma, as could be shown by *in vitro* rat studies (van der Vies 1970) and *in vivo* human studies (Fujioka *et al.* 1986). The rate of hydrolysis again depends on the structure of the acid chain, but this process is much faster than release from the injection depot (van der Vies 1985). The metabolism of the testosterone ester to the unesterified testosterone occurs rapidly so that testosterone enanthate or testosterone have nearly identical intravenous pharmacokinetics (Sokol and Swerdloff 1986). Similarly, the duration of action of the orally effective ester testosterone undecanoate seems to be dependent on the duration of absorption of the uncleaved lipophilic testosterone undecanoate via the ductus thoracicus from the gut (Maisey *et al.* 1981; Schürmeyer *et al.* 1983).

In men treated with testosterone, the testosterone concentration measurable in the serum is the sum of endogenous testosterone and exogenous testosterone hydrolysed from the injected ester. Hypogonadal patients are characterized by impaired or absent endogenous testosterone secretion; exogenous testosterone administration can further suppress endogenous testosterone secretion only to a limited degree, if at all. Accordingly, in hypogonadal patients the serum concentration versus time profile is mainly a reflection of the pharmacokinetics of exogenously administered testosterone ester alone. In this chapter the evaluation of pharmacokinetic parameters for different testosterone esters is based on the increases of testosterone serum concentrations over basal levels in hypogonadal patients.

Table 14.2 Comparative pharmacokinetics of different testosterone esters after intramuscular injection to hypogonadal patients

Testosterone ester	Terminal elimination half-life (d)
Testosterone propionate	0.8
Testosterone enanthate	4.5
Testosterone buciclate	29.5
Testosterone undecanoate	33.9

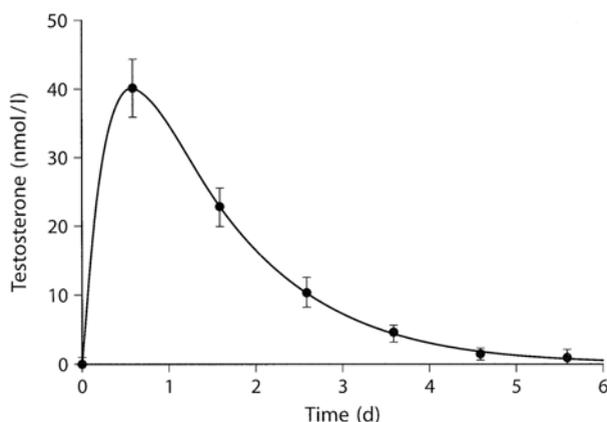


Fig. 14.4 Single-dose pharmacokinetics of testosterone propionate in seven hypogonadal patients. Closed circles, mean \pm SEM of testosterone serum concentrations actually measured; curve, best-fitted pharmacokinetic profile.

14.3.6.1 Testosterone propionate

Single-dose pharmacokinetics of 50 mg testosterone propionate after intramuscular injection to seven hypogonadal patients and the best-fitted pharmacokinetic profile are shown in Fig. 14.4 (Nieschlag *et al.* 1976). Maximal testosterone levels in the supraphysiological range were seen shortly after injection (40.2 nmol/l, t_{\max} = 14 h). Testosterone levels below the normal range were observed following day 2 (57 h) after injection. The calculated values for AUC were 1843 nmol * h/l, for MRT 1.5 d and 0.8 d for terminal half-life (Table 14.2).

Based on single-dose pharmacokinetic parameters, a multiple-dose pharmacokinetic simulation was performed. Expected testosterone serum concentrations after multiple dosing of 50 mg testosterone propionate twice per week (e.g. injections Mondays and Thursdays, 8.00 h) are shown in Fig. 14.5. Shortly after injection high supraphysiological testosterone serum concentrations of up to 45 nmol/l are observed. At the end of the injection interval (three and four days, respectively)

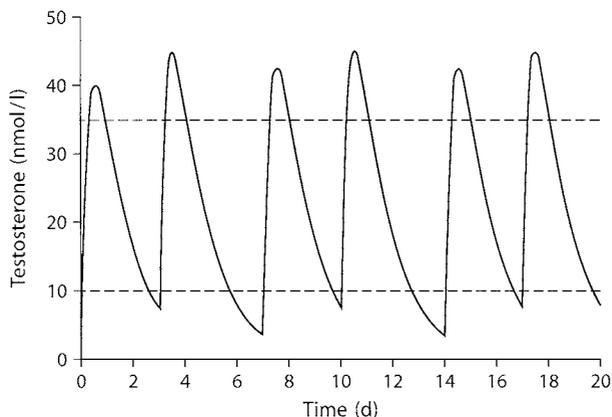


Fig. 14.5 Multiple-dose pharmacokinetics of testosterone propionate after injection of 50 mg testosterone propionate twice per week (e.g. Mondays and Thursdays). *Solid curve*, pharmacokinetic simulation; *broken lines*, range of normal testosterone values.

testosterone serum concentrations below the lower range of normal testosterone values are projected (7 nmol/l and 3 nmol/l, respectively).

Judged by the data from pharmacokinetic analysis and simulation, administration of testosterone propionate is not suitable for substitution therapy of male hypogonadism because of its short-term kinetics resulting in wide fluctuations of testosterone serum concentrations and maximal injection intervals of three days for the 50 mg dose.

14.3.6.2 Testosterone enanthate

Single-dose pharmacokinetics of testosterone enanthate after intramuscular administration of 250 mg testosterone enanthate to seven hypogonadal patients and the best-fitted pharmacokinetic profile are shown in Fig. 14.6 (Nieschlag *et al.* 1976). Maximal testosterone levels in the supraphysiological range were seen shortly after injection (39.4 nmol/l, $t_{\max} = 10$ h). Testosterone levels below the normal range were observed following day 12 after injection. The calculated values were 9911 nmol * h/l for AUC, 8.5 d for MRT and 4.5 d for terminal half-life (Table 14.2).

Based on the pharmacokinetic parameters of single-dose pharmacokinetics multiple-dose pharmacokinetic simulations for equal doses of 250 mg testosterone enanthate and injection intervals of one to four weeks were performed. With weekly injection intervals supraphysiological maximal testosterone serum concentrations up to 78 nmol/l are observed at steady state shortly after injection and supraphysiological minimal testosterone serum concentrations up to 40 nmol/l just before the next injection (Fig. 14.7). Injecting 250 mg of testosterone enanthate every two

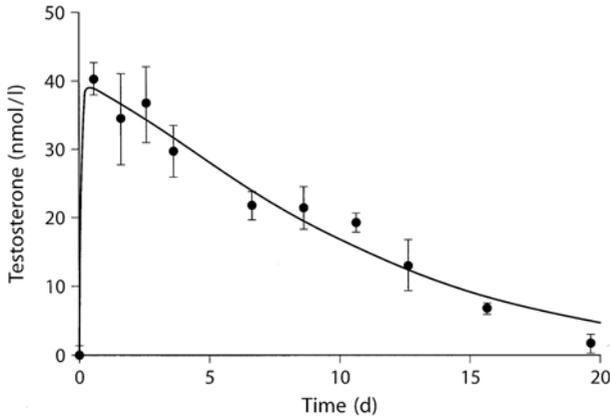


Fig. 14.6 Single-dose pharmacokinetics of testosterone enanthate in seven hypogonadal patients. *Closed circles*, mean \pm SEM of testosterone serum concentrations actually measured; *curve*, best-fitted pharmacokinetic profile.

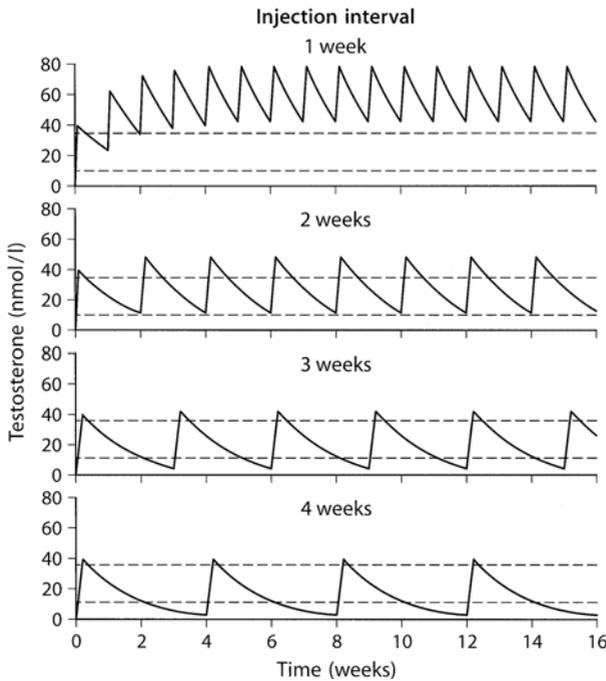


Fig. 14.7 Multiple-dose pharmacokinetics of testosterone enanthate after injection of 250 mg testosterone enanthate every week (*upper panel*), every second week (*upper middle panel*), every three weeks (*lower middle panel*) and every four weeks (*lower panel*). *Solid curves*, pharmacokinetic simulations; *broken lines*, range of normal testosterone values.

weeks results in maximal supraphysiological testosterone serum concentrations of up to 51 nmol/l shortly after injection and testosterone serum levels at the lower range for normal testosterone serum concentration shortly before the next injection. If the injection interval is extended to three weeks, testosterone serum concentrations below the normal range are observed 14 days after injection. With injection intervals of four weeks, testosterone serum concentrations are in the subnormal range at week three and four and effective testosterone substitution is not guaranteed (Fig. 14.7).

The calculated testosterone serum concentrations at steady state obtained by computer simulation correspond well to the results of published studies describing multiple-dose testosterone enanthate pharmacokinetics. In a clinical trial for male contraception 20 healthy men were injected with 200 mg/wk of testosterone enanthate for 12 weeks (Cunningham *et al.* 1978). Minimal serum concentrations of testosterone at steady state, i.e. the testosterone serum concentration just before the next injection, were measured at 31.2 nmol/l to 39.5 nmol/l after weekly injections of 200 mg testosterone enanthate. Very similar data were obtained in further contraceptive studies when normal men received 200 mg/wk testosterone enanthate injections for 18 months (Anderson and Wu 1996; Wu *et al.* 1996). The data of these studies fit well with the computer-calculated minimal testosterone serum concentrations of 40 nmol/l and maximal testosterone levels 78 nmol/l after multiple injections of testosterone enanthate at a dosage of 250 mg/wk.

Snyder and Lawrence (1980) administered 100 mg/wk ($n = 12$), 200 mg/2 wks ($n = 10$), 300 mg/3 wks ($n = 9$) and 400 mg/4 wks ($n = 6$) testosterone enanthate to hypogonadal patients during a study period of three months. Blood was drawn during the last injection period, when steady state had been reached, every day (100 mg/wk) up to every fourth day (400 mg/4 wks). Similar to the computer simulation described above for 250 mg testosterone enanthate and injection intervals of one to four weeks, initial supraphysiological testosterone serum levels were seen shortly after injection. In the 100 mg/wk treatment group, where daily blood sampling was performed, mean peak serum concentrations were seen 24 h after injection. Comparable to the results of the computer simulation, after injection of 200 mg/2 wks testosterone enanthate, following initial supraphysiological testosterone serum levels, values fell to progressively lower values before the next injection, eventually reaching the lower normal limit (Snyder and Lawrence 1980). Similar results were described after injection of 300 mg/3 wks or 400 mg/4 wks testosterone enanthate. The authors conclude that the testosterone enanthate doses of 200 mg have to be injected every two weeks or doses of 300 mg every 3 weeks to guarantee effective substitution therapy.

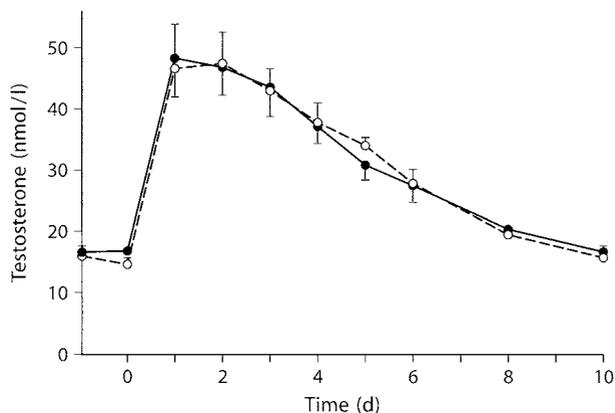


Fig. 14.8 Comparative pharmacokinetics of 194 mg of testosterone enanthate and 200 mg of testosterone cypionate after intramuscular injection to 6 normal volunteers. *Closed circles*, mean \pm SEM of testosterone enanthate kinetics; *open circles*, mean \pm SEM of testosterone cypionate kinetics.

14.3.6.3 Testosterone cypionate and testosterone cyclohexanecarboxylate

Testosterone cypionate (cyclopentylpropionate) pharmacokinetics were compared with those of testosterone enanthate in a cross-over study involving six healthy men aged 20–29 years. Three subjects received 194 mg of testosterone enanthate, followed seven weeks later by 200 mg of testosterone cypionate and vice versa (amount of unesterified testosterone 140 mg in both preparations). The serum testosterone profiles were identical after injection of both preparations in equivalent doses, both in terms of maximal concentrations and in terms of duration of elevation above basal levels (Fig. 14.8) (Schulte-Beerbühl and Nieschlag 1980).

In a subsequent clinical study the pharmacokinetics of testosterone cyclohexanecarboxylate were compared to the pharmacokinetics of testosterone enanthate in a single-blind cross-over study in seven healthy young men (Schürmeyer and Nieschlag 1984). After injection of either testosterone enanthate or testosterone cyclohexanecarboxylate, testosterone concentrations in serum increased sharply and reached maximum levels, 4–5 times above basal, 8–24 h after injection. During following days a parallel decay of testosterone levels occurred after injection of either ester preparations, with testosterone serum concentrations slightly, but significantly lower after testosterone cyclohexanecarboxylate injection compared to testosterone enanthate injection two, three and seven days after administration. Basal serum levels were reached seven days after testosterone cyclohexanecarboxylate administration and nine days after injection of testosterone enanthate.

Because testosterone cypionate, testosterone cyclohexanecarboxylate and testosterone enanthate had comparable suppressing effects on LH and consequently on endogenous testosterone secretion, it can be concluded from these studies in normal volunteers that all three esters with similar molecular structure possess comparable pharmacokinetics of exogenous testosterone serum concentrations. Testosterone cypionate or testosterone cyclohexanecarboxylate do not provide a more advantageous pharmacokinetic profile than testosterone enanthate. This observation is in agreement with a clinical study of replacement therapy with single-dose administration of 200 mg of testosterone cypionate in 11 hypogonadal patients (Nankin 1987).

14.3.6.4 Testosterone ester combinations

Testosterone ester mixtures have been widely used for substitution therapy of male hypogonadism (e.g. *Testoviron^R Depot 50*: 20 mg testosterone propionate and 55 mg testosterone enanthate; *Testoviron^R Depot 100*: 25 mg testosterone propionate and 100 mg testosterone enanthate; *Sustanon^R 250*: 30 mg testosterone propionate, 60 mg testosterone phenylpropionate, 60 mg testosterone isocaproate and 100 mg testosterone decanoate). These combinations are used following the postulate that the so-called short-acting testosterone ester (e.g. testosterone propionate) is the effective testosterone for substitution during the first days of treatment and the so-called long-acting testosterone (e.g. testosterone enanthate) warrants effective substitution for the end of injection interval. However, this assumption is not supported by the pharmacokinetic parameters of the individual testosterone esters. Both testosterone propionate and testosterone enanthate cause highest testosterone serum concentrations shortly after injection (Fig. 14.4 and Fig. 14.6). Accordingly, addition of testosterone propionate to testosterone enanthate only increases the initial undesired testosterone peak and worsens the pharmacokinetic profile that ideally should follow zero-order kinetics (Fig. 14.9). The computer simulation agrees well with the limited published single-dose testosterone values that have been measured in hypogonadal patients treated with the combination of testosterone propionate and testosterone enanthate. Maximal increases of approximately 40 nmol/l testosterone over basal values are described one day after intramuscular administration of a testosterone ester combination of 115.7 mg testosterone enanthate and 20 mg testosterone propionate to three hypogonadal patients (Fukutani *et al.* 1974).

A comparison of computer-simulated testosterone serum concentrations after multiple-dose injections of *Testoviron^R Depot 100* (110 mg testosterone enanthate and 25 mg testosterone propionate = 100 mg unesterified testosterone) every 10 d and 139 mg testosterone enanthate (= 100 mg unesterified testosterone) every 10 d is shown in Fig. 14.10. As can be expected by the single-dose kinetics of the

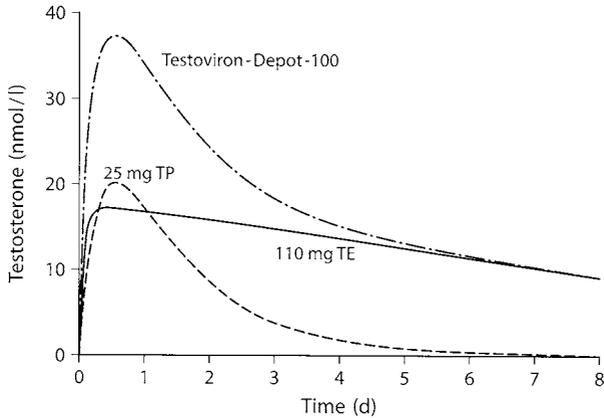


Fig. 14.9 Pharmacokinetic profile of Testoviron^R Depot 100 (110 mg testosterone enanthate and 25 mg testosterone propionate) in comparison to the pharmacokinetics of the individual testosterone esters of the mixture. *Curves*, pharmacokinetic simulations.

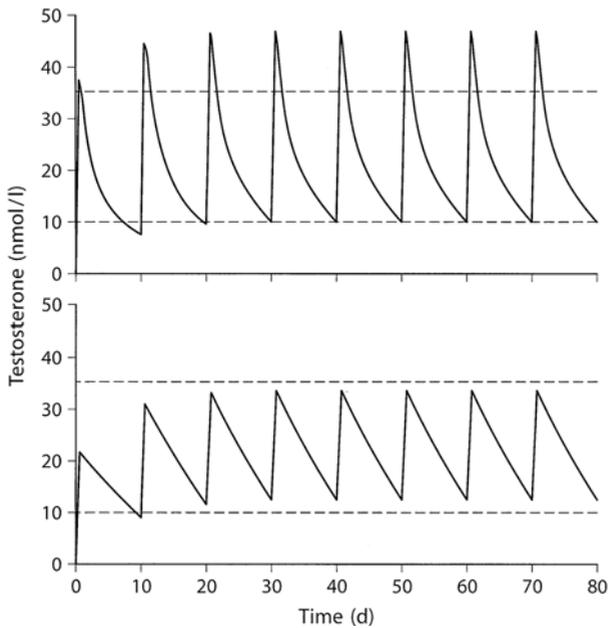


Fig. 14.10 Multiple-dose pharmacokinetics of the testosterone ester mixture Testoviron^R Depot 100 (110 mg testosterone enanthate and 25 mg testosterone propionate = 100 mg unesterified testosterone, upper panel) every 10 d in comparison to 139 mg testosterone enanthate (= 100 mg unesterified testosterone, lower panel) every 10 d. *Solid curves*, pharmacokinetic simulations; *broken lines*, range of normal testosterone values.

individual esters, injection of the testosterone ester mixture (upper panel) produces a much wider fluctuation of testosterone serum concentrations relative to injection of testosterone enanthate alone (lower panel). This simulation shows that injections of testosterone enanthate alone produce a more favourable pharmacokinetic profile in comparison to injections of testosterone propionate and testosterone enanthate ester mixtures in comparable doses. For treatment of male hypogonadism there is no advantage in combining the available short- and long-acting testosterone esters.

14.3.6.5 Testosterone buciclate

The disadvantage of all esters described so far is that they produce initially supra-physiological testosterone levels which may exceed normal levels severalfold and then slowly decline, so that before the next injection pathologically low levels may be reached. Some patients recognize these ups and downs of testosterone levels in parallel variations of general well-being, sexual activity and emotional stability. Despite these disadvantages testosterone enanthate and cypionate are still the standard therapy for male hypogonadism.

Because of these shortcomings of the available esters the World Health Organization (WHO) initiated a steroid synthesis programme (Crabbé *et al.* 1980) out of which a series of new testosterone esters was developed. When tested in laboratory rodents a specific ester was identified that showed greatly prolonged activity, namely *testosterone-trans-4-n-butylcyclohexyl-carboxylate*, generic name *testosterone buciclate*. This preparation is injected intramuscularly in an aqueous solution, in contrast to the other testosterone esters which are dissolved in oily solution.

A first study on the pharmacokinetics of the new WHO/NIH androgen ester testosterone buciclate was performed in two groups of orchietomized cynomolgus monkeys (Weinbauer *et al.* 1986). Intramuscular injections of testosterone enanthate resulted in supraphysiological serum levels of testosterone for eight days, followed by a rapid decline with levels lower than the physiological limit after three weeks. In contrast, testosterone buciclate produced a moderate increase of serum testosterone levels into the physiological range, and serum levels remained in this range for a period of four months. These favourable results on the pharmacokinetics of testosterone buciclate were confirmed in castrated rhesus monkeys (Rajalakshmi and Ramakrishnan 1989).

To assess the pharmacokinetics of testosterone buciclate in men the first clinical study was performed in eight men with primary hypogonadism (Behre and Nieschlag 1992). The men were randomly assigned to two study groups and were given either 200 (group I) or 600 mg (group II) testosterone buciclate intramuscularly. Whereas in group I serum androgen levels did not rise to normal values, in group II androgens increased significantly and were maintained in the normal range up to 12 weeks with maximal serum levels (c_{\max}) of 13.1 ± 0.9 nmol/l

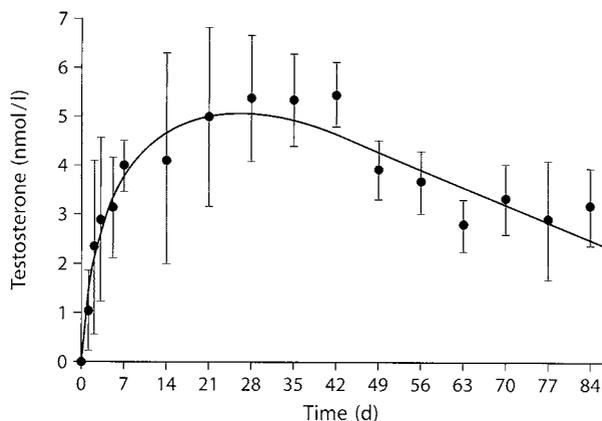


Fig. 14.11 Single-dose pharmacokinetics of testosterone buciclate after intramuscular injection of 600 mg of the ester to four hypogonadal patients. Closed circles, mean \pm SEM of testosterone serum concentrations actually measured; curve, best-fitted pharmacokinetic profile.

(mean \pm SEM) in study week 6 (t_{\max}). No initial burst release of testosterone was observed in either study group. Pharmacokinetic analysis revealed a terminal elimination half-life of 29.5 ± 3.9 days (Fig. 14.11) (Table 14.2).

Because of the promising results of the first clinical study with testosterone buciclate, a follow-up study was initiated. After complete wash-out from previous therapy all hypogonadal men received a single intramuscular injection of 1000 mg testosterone buciclate. As in the previous study with lower doses, no initial burst release of testosterone was observed. Maximal testosterone serum levels were observed nine weeks (t_{\max}) after injection with a mean value of 13.1 ± 1.8 nmol/l (c_{\max}). Following peak concentrations, testosterone serum levels gradually declined and remained within the normal range up to week 16. This study demonstrated that an increase of the injected dose of testosterone buciclate from 600 to 1000 mg prolongs the duration of action significantly, but does not lead to significantly higher maximal serum levels of testosterone.

The long duration of action of testosterone buciclate was also demonstrated in a contraceptive study with this new testosterone ester. After a single intramuscular injection of 1200 mg testosterone buciclate at a concentration of 400 mg/ml to eight normal men, serum levels of testosterone remained within the normal range, whereas gonadotropins and spermatogenesis was significantly suppressed for at least 18 weeks (Behre *et al.* 1995). These studies demonstrate that the long-acting testosterone buciclate is well suited for substitution therapy of male hypogonadism as well as for male contraception. However, this compound has not been developed into a marketable product and is currently not available.

14.3.6.6 Testosterone undecanoate

While testosterone undecanoate has been available for oral substitution for more than two decades, it was first demonstrated in China that intramuscular administration of testosterone undecanoate in tea seed oil (125 mg/ml) has a prolonged duration of action (Wang *et al.* 1991). Therefore the pharmacokinetics of testosterone undecanoate in comparison to testosterone enanthate were tested in two groups of orchietomized cynomolgus monkeys (Partsch *et al.* 1995). After injection of 10 mg/kg body weight of the respective esters serum levels of testosterone remained above the lower limit of normal for 108 days, compared to 31 days after testosterone enanthate injection. Pharmacokinetic analysis revealed a terminal half-life of 25.7 ± 4.0 days for testosterone undecanoate, compared to 10.3 ± 1.1 days for testosterone enanthate. The maximal testosterone concentration of 72.6 ± 11.7 nmol/l after testosterone undecanoate injection was significantly lower than 177.0 ± 21.3 nmol/l after testosterone enanthate injection.

In a recent monkey study it was demonstrated that biological effects of testosterone esters are determined by the pharmacokinetics and degree of aromatization rather than the total dose administered (Weinbauer *et al.* 2003). Twenty adult male cynomolgus monkeys were randomly assigned to treatment for 28 weeks with either testosterone enanthate every four weeks, testosterone buciclate every seven weeks, or testosterone undecanoate every ten weeks. Each injection delivered 20 mg pure testosterone per kilogram body weight. Despite a smaller total dose of testosterone, increase in body weight or lowering effects on serum lipids were significantly stronger with the long-acting testosterone undecanoate or buciclate compared to testosterone enanthate.

In a clinical study in Asian hypogonadal men, eight patients received one intramuscular injection of 500 mg and 7 of the initial 8 hypogonadal patients one injection of 1000 mg testosterone undecanoate (in eight milliliters tea seed oil) in a cross-over design (Zhang *et al.* 1998). Follow-up blood samples were obtained weekly up to week 9 after injection. In both study groups, mean serum levels of testosterone were above the upper limit of normal during the first two weeks after injection. Thereafter, mean serum concentration remained in the normal range up to week 7 after injection in the 500 mg-dose group and at least up to week 9 in the 1000 mg-dose group. The terminal elimination half-lives were 18.3 ± 2.3 and 23.7 ± 2.7 days for the 500 mg-dose and 1000 mg-dose groups, respectively. Administration of 500 mg of this testosterone preparation every four weeks, after an initial loading dose of 1000 mg, for up to 12 months to 308 healthy men for male contraception maintained serum levels of testosterone in the normal range when measured directly before the next injection (Gu *et al.* 2003).

In the first study in Caucasian men, intramuscular injections of 250 mg or 1000 mg testosterone undecanoate in tea seed oil were given to 14 hypogonadal

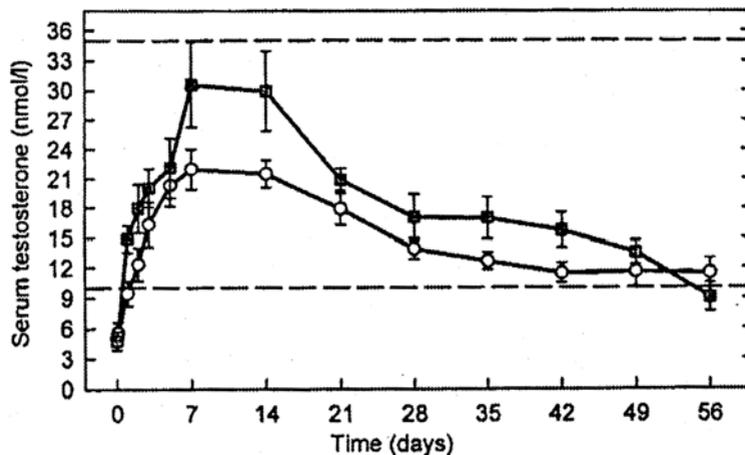


Fig. 14.12 Serum concentrations (mean \pm SEM) of testosterone after single-dose intramuscular injections of 1000 mg testosterone undecanoate in tea seed oil in 7 hypogonadal men (squares) or castor oil in 14 hypogonadal men (circles). Broken lines indicate normal range of testosterone (adapted from Behre *et al.* 1999a, reproduced by permission of the European Journal of Endocrinology).

patients (Behre *et al.* 1999a). Follow-up examinations were performed 1, 2, 3, 5 and 7 days after injection and then weekly up to study week 8. Whereas no prolonged increase of testosterone was observed in the 250 mg-group, serum levels of testosterone in the higher dose group increased from 4.8 ± 0.9 nmol/l (mean \pm SEM) to maximum levels of 30.5 ± 4.3 nmol/l at day 7 (t_{\max}). Testosterone levels remained within the normal range up to week 7 (13.5 ± 1.2 nmol/l). Non-linear regression analysis revealed a terminal elimination half-life for intramuscular testosterone undecanoate of 20.9 ± 6.0 days (Fig. 14.12).

Similar to the preclinical study in monkeys, the clinical study in hypogonadal men demonstrated favourable pharmacokinetics of intramuscular testosterone undecanoate. Because of the relatively low concentration of 125 mg testosterone undecanoate per milliliter tea seed oil, however, administration of the 1000 mg dose requires an injection volume of 8 ml which renders intramuscular administration impracticable. Therefore, the preparation was reformulated and testosterone undecanoate dissolved in castor oil at a higher concentration of 250 mg/ml. 14 hypogonadal patients received one intramuscular injection of 1000 mg of the reformulated testosterone undecanoate preparation (Behre *et al.* 1999a). Maximal serum levels with the reformulated preparation were lower than with the Chinese preparation and remained within the mid-normal range (Fig. 14.12). Pharmacokinetic analysis revealed a long terminal elimination half-life of 33.9 ± 4.9 days (Table 14.2).

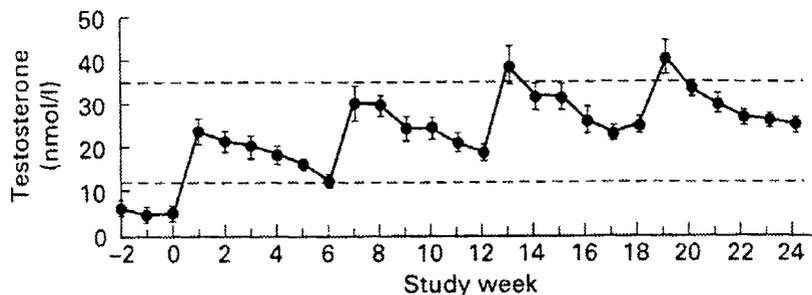


Fig. 14.13 Serum concentrations (mean \pm SEM) of testosterone after multiple intramuscular injections of 1000 mg testosterone undecanoate in castor oil in 13 hypogonadal men. Broken lines indicate normal range of testosterone (adapted with permission from Nieschlag *et al.* 1999, copyright 1999, Blackwell Publishing).

Due to these favourable pharmacokinetics a first, prospective, open-label study with repeated intramuscular injection was initiated (Nieschlag *et al.* 1999). 13 hypogonadal men received four intramuscular injections of 1000 mg testosterone undecanoate in castor oil at six-week intervals. Following the first injection, mean serum levels of testosterone were never found below the lower limit of normal (Fig. 14.13). However, peak and trough serum concentrations of testosterone increased during the six-month treatment, with testosterone levels above the upper normal limit after the third and fourth injection. Therefore, in seven of the 13 hypogonadal men injections were given at gradually increasing intervals between the fifth and tenth injection, and from then on every 12 weeks (von Eckardstein and Nieschlag 2002). During steady state, serum levels of testosterone remained in the normal range with maximal concentrations of 32.0 ± 11.7 nmol/l (mean \pm SD) one week after injection and nadir levels before the next injection of 12.6 ± 3.7 nmol/l (Fig. 14.14). As this preparation has been approved for clinical use in Europe, intramuscular testosterone undecanoate in castor oil will become a significantly improved testosterone preparation for treatment of male hypogonadism as well as for male contraception (see Chapter 23).

14.3.6.7 Testosterone decanoate

Testosterone decanoate differs from testosterone undecanoate by one carbon atom in the ester side chain. It has been widely administered for many years as part of a mixture with shorter-action testosterone esters, however, it has not been available as a single preparation. To date there are no detailed studies published on the pharmacokinetics of administration of testosterone decanoate to hypogonadal men. Recently, intramuscular injections of 400 mg of testosterone decanoate were given four times every four weeks to normal men in a contraceptive study (Anderson *et al.* 2002). Endogenous testosterone was suppressed by concomitant administration

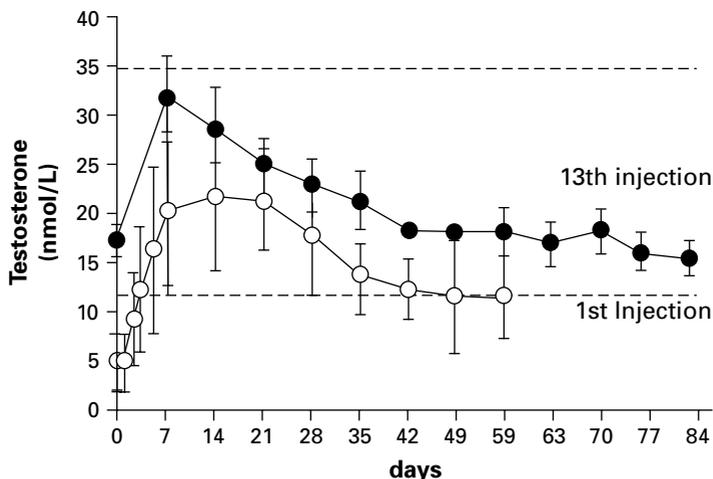


Fig. 14.14 Serum concentrations (mean \pm SD) of testosterone after single injection of 1000 mg testosterone undecanoate in castor oil in 14 hypogonadal men (open circles) and during multiple injections with the same dose every 12 weeks. Broken lines indicate normal range of testosterone (adapted with permission from von Eckardstein and Nieschlag, 2002).

of etonogestrel implants. Nadir testosterone levels before the next injection were in the lower normal range, whereas serum levels were at the upper normal limit one week after injection. From these limited data it can be concluded that testosterone decanoate seems to have an improved pharmacokinetic profile over testosterone enanthate, but does not allow similar prolonged injection intervals of about 12 weeks, as demonstrated for testosterone undecanoate in hypogonadal men.

14.3.6.8 Testosterone microspheres

Drugs can be incorporated into biodegradable microspheres. When injected intramuscularly, such drug-loaded microspheres provide controlled release of the substance for several weeks or even months. As an example, microencapsulated GnRH agonists have become a valuable modality in the treatment of prostatic carcinoma. Testosterone has been incorporated into poly(DL-lactide-co-glycolide) microspheres. When first tested in castrated monkeys single injections resulted in an elevation of serum levels above the lower limit of normal for several months (Asch *et al.* 1986). When similar microsphere injections containing 315 mg of testosterone were given to eight hypogonadal men, serum testosterone levels slowly increased to peak levels at about eight weeks and fell thereafter to reach pathological levels again by 11 weeks (Burris *et al.* 1988). In a later study the size-range and the testosterone loading of the microspheres were adjusted so that in hypogonadal men single intramuscular injections resulted in relatively constant serum levels within the normal range for about 70 days (Bhasin *et al.* 1992). These two clinical studies demonstrated

that the microspheres can be adapted to the required needs and the results were encouraging. However, this formulation of microspheres is technically difficult to manufacture consistently and requires two painful, large-volume intramuscular injections that limits its appeal for long-term therapy.

14.3.7 Subdermal application

14.3.7.1 Testosterone pellets

Subdermal testosterone pellet implantation was among the earliest effective modalities employed for clinical application of testosterone which became an established form of androgen replacement therapy by 1940 (Deansley and Parks 1938; Vest and Howard 1939). With the advent of other modalities, e.g. intramuscular testosterone ester injections, they went out of general use. However, investigations in the 1990s redefined the favourable pharmacokinetic profiles and clinical pharmacology of testosterone implants (Handelsman *et al.* 1990; Jockenhövel *et al.* 1996).

The original testosterone implants were manufactured by high-pressure tableting of crystalline steroid with a cholesterol excipient. These proved brittle, hard to standardize or sterilize and exhibited surface unevenness and fragmentation during *in-vivo* absorption to produce an uneven late release rate. These limitations were overcome in the 1950s by switching to high-temperature moulding whereby molten testosterone was cast into cylindrical moulds to produce more robust implants. These have more uniform composition, resulting in a more steady and prolonged release and reduced tissue reaction. Sterilization is achieved by a combination of high-temperature exposure during manufacture together with surface sterilization or, more recently, gamma-irradiation. The testosterone implants are currently available in two sizes with a common diameter of 4.5 mm: 6 mm length for the 100 mg and 12 mm length for the 200 mg implant. Pellets are usually implanted under the skin of the lower abdominal wall under sterile conditions using a trochar and cannula.

The estimated half-life of absorption of testosterone from subdermal implants is 2.5 months. On average, approximately 1.3 mg of testosterone are released per day from the 200 mg pellet. Testosterone implants demonstrate a minor and transient accelerated initial “burst” release, which lasts for 1–2 days (Jockenhövel *et al.* 1996). The most comprehensive pharmacokinetic evaluation of testosterone implants was done in a random-sequence, cross-over clinical study of 43 androgen-deficient men with primary or secondary hypogonadism (Handelsman *et al.* 1990). Patients were treated sequentially with 3 regimens – six 100 mg, three 200 mg or six 200 mg implants – at intervals of at least six months. Implantation of testosterone pellets resulted in a highly reproducible and dose-dependent time-course for circulation of total and free testosterone. Testosterone concentrations reached baseline by six months after either of the 600 mg dose regimens but remained significantly elevated

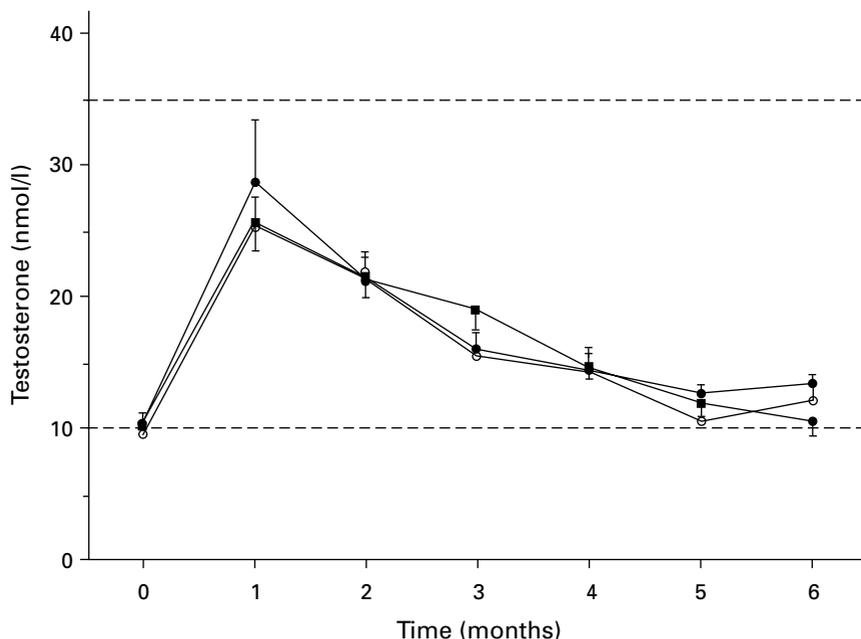


Fig. 14.15 Blood total testosterone in 43 hypogonadal men receiving four 200 mg pellets (800 mg) implanted either under the skin of the lateral abdominal wall (in 4 tracks [filled circles], $n = 9$; or in 2 tracks [open circles], $n = 16$) or in the hip region (filled squares, $n = 18$) (adapted with permission from Kelleher *et al.* 2001, copyright 2001, Blackwell Publishing).

after six months following the 1200 mg dose. The standard dose for hypogonadal men is 800 mg every six months, which can be titrated individually (Fig. 14.15).

Pellet implantation has few side-effects and is generally well tolerated. Adverse events after implantations were extrusions (8.5–12% per procedure), bruising (2.3–8.8%) and infections (0.6–4%) (Handelsman *et al.* 1997; Kelleher *et al.* 1999). Due to the long-lasting effect and the inconvenience of removal, preferably pellets 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.

14.3.7.2 Testosterone microcapsules

Testosterone can be encapsulated in a biodegradable matrix composed of lactide/glycolide copolymer which is suitable for subcutaneous injection. The pharmacokinetics and pharmacodynamics of this microcapsule formulation were tested in fourteen hypogonadal men in an open-label, prospective study (Amory *et al.* 2002). Patients received either 267 mg ($n = 7$, injection of 2.5 ml of the formulation) or 534 mg of testosterone ($n = 7$, two injections of 2.5 ml). Peak serum

concentrations were already seen at the first follow-up examination on day 1. In the higher-dose group, mean serum concentrations were at the upper limit of normal at this time-point. Thereafter, testosterone levels declined rapidly in both groups with mean serum levels below 10 nmol/l after 5 and 7 weeks, respectively. In the higher-dose group, serum levels of free testosterone, bioavailable testosterone, estradiol and DHT exceeded the normal range for at least the first week after injection. Two subjects complained of transient tenderness and fullness at the injection sites. Multiple-dose studies are still outstanding, and therefore the appropriate injection interval for long-term therapy has not yet been determined. One disadvantage of the testosterone microcapsule formulation seems to be the early burst release of testosterone, which limits the clinically acceptable dose and shortens the maximal injection interval.

14.3.8 Transdermal application

The skin easily absorbs steroids and other drugs and transdermal drug delivery has become a widely used therapeutic modality. The scrotum shows the highest rate of steroid absorption, about 40-fold higher than the forearm (Feldmann and Maibach 1967). This difference in absorption rates has been exploited for the development of a transdermal therapeutic system (TTS) to deliver testosterone. 40 and 60 cm² large polymeric membranes loaded with 10 or 15 mg testosterone when attached to the scrotal skin deliver sufficient amounts of the steroid to provide hypogonadal men with serum levels in the physiological range (Bals-Pratsch *et al.* 1986; 1988; Findlay *et al.* 1987; Korenmann *et al.* 1987). The application of the patch to scrotal skin requires hair clipping or shaving to optimize adherence. The membranes need to be renewed every day. When applied in the morning and worn until the next morning the resulting serum testosterone levels resemble the normal diurnal variations of serum testosterone in normal men without supraphysiological peaks (Bals-Pratsch *et al.* 1988). Long-term therapy up to ten years with daily administration of the scrotal patch in 11 hypogonadal men produced steady-state serum levels of testosterone and estradiol in the normal range and serum levels of DHT at or slightly above the higher limit of normal without significant adverse side-effects (Fig. 14.16) (Behre *et al.* 1999b).

While testosterone is readily absorbed by genital skin, transdermal systems for use on non-genital skin require enhancers to facilitate sufficient testosterone passage through the skin. The permeation enhanced testosterone patch delivers 2.5 mg/day testosterone when applied to non-scrotal skin. If one or two such systems are worn for 24 hours physiologic serum testosterone levels can be mimicked, as with scrotal patches (Fig. 14.17) (Brocks *et al.* 1996; Meikle *et al.* 1996). Due to the alcoholic enhancer used and the occlusive nature of the systems, the application is associated with skin irritation in up to 60% of the subjects, with most users discontinuing

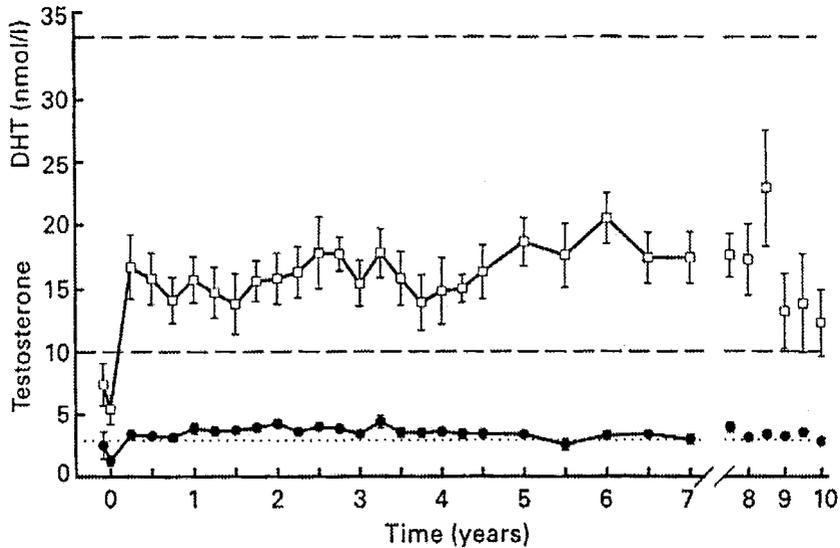


Fig. 14.16 Serum concentrations (mean \pm SEM) of testosterone (squares) and DHT (circles) in 11 hypogonadal men before and during treatment with transscrotal testosterone patches. Broken lines indicate normal range of testosterone, dotted line upper normal limit of DHT (adapted with permission from Behre *et al.* 1999b, copyright 1999, Blackwell Publishing).

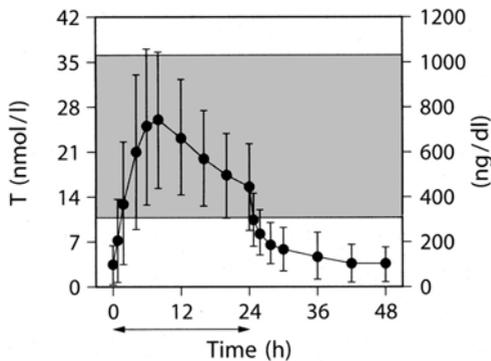


Fig. 14.17 Serum concentrations (mean \pm SD) of testosterone during and after nighttime application of two non-scrotal testosterone systems to the backs of 34 hypogonadal men. Shaded area indicates normal range of testosterone (adapted with permission from Meikle *et al.* 1996, copyright 1996, The Endocrine Society).

application because of the skin irritation (Jordan 1997; Parker and Armitage 1999). Preapplication of corticosteroid cream to the skin has been reported to decrease the severity of skin irritation, although the effects on pharmacokinetics of testosterone are unclear. Another larger non-scrotal patch causes less skin irritation (about 12% itching and 3% erythema) but may create adherence problems (Jordan *et al.* 1998).

Nevertheless, both transdermal modalities through either scrotal or non-genital skin provide physiologic serum testosterone levels and have been shown to reverse the signs and symptoms of male hypogonadism with only minor systemic side-effects (Behre *et al.* 1999b; Dobs *et al.* 1999).

In 2000, a 1% colourless hydroalcoholic gel containing 25 or 50 mg testosterone in 2.5 or 5 g gel was approved for clinical use in hypogonadism. The gel dries in less than 5 min without leaving a visible residue on the skin. About 9 to 14% of the testosterone in the gel is bioavailable. Application of the testosterone gel increased serum testosterone levels into the normal range within one hour after application (Wang *et al.* 2000). Steady-state serum levels are achieved 48–72 hours after initiation of therapy, whereas pre-treatment serum testosterone levels are seen four days after stopping application. The application of the testosterone gel at four sites (application skin areas approximately four times that of one site) resulted in an area under the curve of testosterone which was 23% higher compared to application of the same amount of gel on one site. However, this difference did not achieve statistical significance in the nine hypogonadal men tested (Wang *et al.* 2000).

Long-term pharmacokinetics of the transdermal testosterone gel were evaluated in 227 hypogonadal men (Swerdlhoff *et al.* 2000). Patients were randomly assigned to application of 5 or 10 g of the testosterone gel or two patches of a non-scrotal testosterone system. After 90 days of testosterone gel treatment, the dose was titrated up (5 to 7.5 g) or down (10 to 7.5 g) if the preapplication serum testosterone levels were outside the normal adult male range. During long-term treatment mean serum levels of testosterone were maintained in the mid normal range with 5 g of gel and in the upper normal range with 10 g of gel (Fig. 14.18). Testosterone gel application resulted in dose-proportionate increases in serum DHT and E₂ as well as dose-proportionate decreases of gonadotropins.

The advantages of the testosterone gel over the testosterone patch are a lower incidence of skin irritation, the ease of application, the invisibility of the dried gel, and the ability to deliver testosterone dose-dependently to the low, mid or upper normal range. A potential adverse side-effect of testosterone gel application is the transfer of testosterone to women or children upon close contact with the skin. Transfer of transdermal testosterone from the skin can be avoided by applying gel to skin covered by clothing or showering after application. This preparation has gained a significant market share of androgen formulations in Europe and the United States, although it is marketed at a slightly higher price than the patches and at a much higher price than injectable testosterone.

Currently, a number of other testosterone gels and creams are being developed. Two recent randomized controlled studies demonstrated a dose-dependent increase

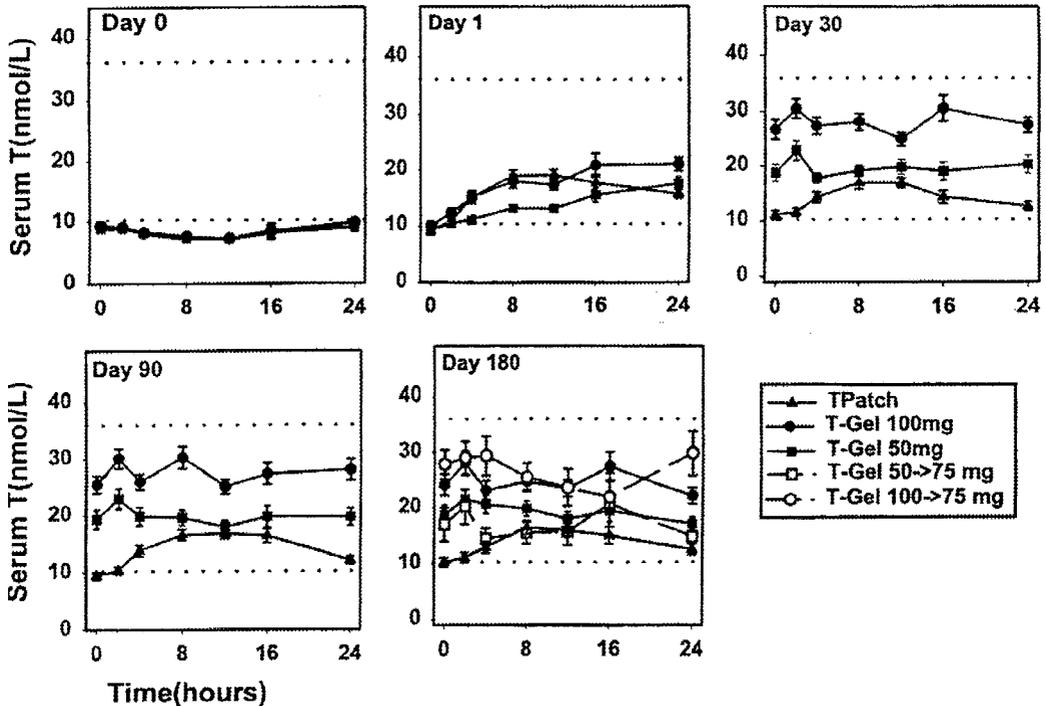


Fig. 14.18 Serum concentrations (mean \pm SEM) of testosterone before (day 0) and after transdermal testosterone applications on days 1, 30, 90, and 180. Time 0 was 0800 h, when blood sampling usually began. On day 90, the dose in the subjects applying testosterone gel 50 or 100 mg was up- or down-titrated if their preapplication serum testosterone levels were below or above the normal adult male range, respectively. Dotted lines denote the adult normal range (adapted with permission from Swerdloff *et al.* 2000, copyright 2000, The Endocrine Society).

of testosterone serum levels to the normal range in hypogonadal men after 90 days of application of 5 g/d or 10 g/d of another hydroalcoholic topical gel containing 1% testosterone compared to non-scrotal testosterone patches ($n = 208$, McNicholas *et al.* 2003) or compared to non-scrotal testosterone patches and placebo gel ($n = 406$, Steidle *et al.* 2003). Application of 5 g/d of a 2.5% hydroalcoholic gel increased serum levels of testosterone to the normal range in 14 gonadotropin-suppressed normal men (Rolf *et al.* 2002a). Washing of the skin after 10 min. did not influence the pharmacokinetic profile. No interpersonal testosterone transfer could be detected after evaporation of the alcohol vehicle of this testosterone gel (Rolf *et al.* 2002b). This gel preparation can also be administered at a dose of 1 g/d to the scrotal skin. Ongoing randomized controlled studies in hypogonadal patients indicate the efficacy and practicability of administration of this gel to normal or scrotal skin.

14.4 Key messages

- Oral, buccal, injectable, subdermal implantable and transdermal testosterone preparations are available for clinical use. The best preparation is the one that replaces testosterone serum levels at as close to physiologic concentrations as possible.
- Oral administration of the currently available testosterone undecanoate preparation results in high interindividual and intraindividual variability of serum testosterone values.
- Daily or twice daily buccal administration of testosterone tablets increases serum testosterone to the normal range. Acceptability of this application form has yet to be determined.
- The available testosterone esters for intramuscular injection (testosterone propionate, testosterone enanthate, testosterone cypionate, testosterone cyclohexanecarboxylate) are still widely used but suboptimal for the treatment of male hypogonadism. Doses and injection intervals most frequently used in the clinic lead to initial supraphysiological testosterone levels and subnormal values before the next injection. To obtain testosterone serum concentrations continuously in the normal range, unacceptably frequent small doses would have to be injected.
- Intramuscular injection of 1000 mg testosterone undecanoate to hypogonadal men maintains serum levels of testosterone within the normal range for up to 12 weeks. Recently approved for clinical use, intramuscular testosterone undecanoate will become a valuable preparation for depot substitution therapy of male hypogonadism and for male contraception.
- A single implantation procedure of testosterone pellets provides serum levels of testosterone in the normal range for up to six months. Pellet extrusion occurs in about 10% of the implantation procedures. Due to the long-lasting effect and the inconvenience of removal, preferably pellets should be used by men in whom the beneficial effects and tolerance for androgen replacement therapy have already been established.
- Subcutaneous injection of testosterone microcapsules in hypogonadal men increases serum testosterone levels to the normal range for five to seven weeks. One disadvantage of the testosterone microcapsules formulation seems to be the early burst release of testosterone.
- Transdermal application of testosterone by scrotal or non-scrotal patches increases serum levels of testosterone to the normal range and even mimics the physiological circadian testosterone rhythm. Non-scrotal testosterone patches cause skin irritations in up to 60% of patients, or might have adherence problems.
- Daily administration of testosterone gel increases serum levels of testosterone in hypogonadal patients dose-dependently to the normal range. Acceptability of the gel is high and it has become a standard replacement therapy within the first years following its approval.

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