

# 11 Comparative pharmacokinetics of testosterone esters

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## 11.1 Introduction

In replacing an endogenous hormone a safe general principle appears to be to mimic, as closely as possible, the normal concentrations of that hormone or its active metabolites. Following this principle testosterone treatment of male hypogonadism should avoid unphysiologically high testosterone serum concentrations to prevent possible side-effects or low concentrations to prevent androgen deficiency.

This chapter compares the pharmacokinetics of different testosterone esters widely used for substitution therapy and reevaluates them using computer analysis and simulation. For pharmacokinetics of special testosterone preparations the reader is referred to separate chapters: Chapter 12 for Testosterone Implants and Chapters 13 and 14 for Transdermal Testosterone.

## 11.2 Principles of pharmacokinetic evaluation

### 11.2.1 Polyexponential functions

The analysis of pharmacokinetics of different testosterone esters for clinical substitution therapy is based on the testosterone serum concentrations measured in the general circulation. Applying non-linear least squares regression analysis it is possible to obtain the best fitting  $n$ -term polyexponential function describing the pharmacokinetic profile of the drug according to the data actually measured. The use of polyexponential functions does not require a particular compartmental model to be used, which is fortunate since often there is no firm basis for choosing one such model over another. Different commercially accessible computer programs are available for calculating the parameters of the best-fitting polyexponential functions. The parameters of the polyexponential functions can be used to calculate pharmacokinetic parameters such as area-under-the-concentration-versus-time-curve (AUC), time to reach maximum serum levels ( $t_{\max}$ ), maximum serum concentration ( $c_{\max}$ ) and terminal elimination half-life ( $t_{1/2}$ ) (Wagner 1975). The pharmacokinetic single-dose analysis presented in this chapter was performed applying the computer program RSTRIP (RSTRIP Ver. 5.0, MicroMath Scientific Software, Salt Lake City, Utah, USA).

### 11.2.2 Mean residence time (MRT)

In recent years more and more noncompartmental methods have been used for pharmacokinetic analysis. Twenty years ago statistical moment theory was introduced to pharmacokinetic analysis (Yamaoka et al. 1978). The times for the individual molecules to be eliminated can be described in terms of a statistical distribution function, i.e. the individual molecules can be eliminated just by chance within the first minutes or might still reside in the body weeks later. The mean residence time is a characteristic of this collective behaviour and is the mean of the residence times of individual molecules (Cutler 1987). The mean residence time can be regarded as the statistical moment analogy to half-life ( $t_{1/2}$ ) (Gibaldi and Perrier 1982).

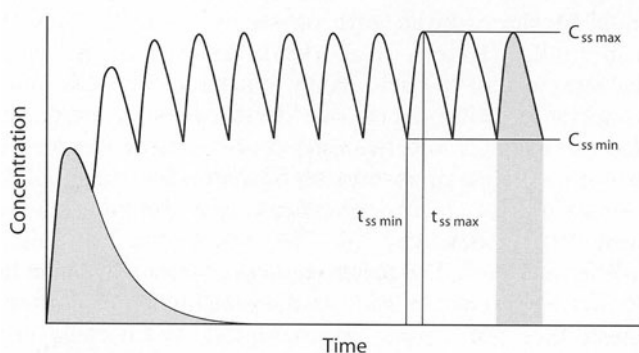
Assuming linear pharmacokinetics, the mean residence time (MRT) is characteristic for a special drug, independent of the administered dose. However, mean residence time is a function of how a drug is administered. The

MRT of a drug after non-instantaneous administration, e.g. intramuscular injection, will always be greater than the MRT after intravenous administration and can be regarded as approximately the sum of the MRT of the drug at the intramuscular depot and the MRT in the general circulation (Collier 1989; Mayer and Brazzell 1988; Yamaoka et al. 1978).

### 11.2.3 Pharmacokinetic simulation

Assuming linear pharmacokinetics, the parameters of the  $n$ -term polyexponential function describing single-dose pharmacokinetics of a drug can be used for prediction of drug concentrations applying multiple dosing (Wagner 1975). Maximal, minimal and average serum concentrations and the time to reach maximal serum concentrations at steady state can be predicted by computer simulation (Fig. 11.1). Area from zero to infinity under the single dose concentration-versus-time-curve is equal to the area within a dosage interval at the steady state (Gibaldi and Perrier 1982).

Computer simulation can also be applied to calculate an appropriate loading dose to shorten the period of time required to attain steady state plasma concentrations and to calculate expected serum concentrations for different loading doses, maintenance doses and injection intervals (Gibaldi and Perrier 1982; Gladtko and von Hattingberg 1977; Wagner 1975). Projections of multiple dose serum concentrations have the advantage that the design of a clinical study or therapy can be simulated and it is not necessary to perform multiple experiments for varying doses and injection intervals in humans. Even when a multiple dose study is performed, peak concentrations are often missed because of the blood sampling scheme used (Wagner 1975). Usually, drug serum concentrations are measured just before the next administration, but the serum concentration at this time point is just the minimal concentra-



**Fig. 11.1.** Application of computer simulation based on pharmacokinetic parameters of single dose kinetics for prediction of multiple dose serum concentrations.  $C_{ss \max}$  maximal serum concentration at steady state;  $C_{ss \min}$  minimal serum concentration at steady state;  $t_{ss \max}$  time to reach maximal serum concentration at steady state;  $t_{ss \min}$  time to reach minimal serum concentration at steady state

tion at steady state and does not reflect the true drug concentration time course during the administration interval. To obtain the proper pharmacokinetic information, very frequent blood sampling would be necessary which is often neither feasible nor acceptable for patients or study volunteers. In this chapter some examples of dosage regimen calculations and prediction of multiple dose kinetics will be compared to the values of actually performed studies.

### 11.3 Pharmacokinetics of testosterone esters

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). Studies applying gas chromatography-mass spectrometry that allow discrimination between endogenous testosterone and exogenously administered deuterium-labelled testosterone propionate-19,19,19-d<sub>3</sub> and its metabolite testosterone-19,19,19-d<sub>3</sub> 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 time 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). The ester is then 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). Similarly, the duration of action of the orally effective ester testosterone undecanoate seems to be dependent on the time of absorption of the uncleaved lipophilic testosterone undecanoate via the ductus thoracicus from the gut (Maisey et al. 1981; Schürmeyer et al. 1983).

The unesterified testosterone is the active substance for substitution therapy of male hypogonadism. As the metabolism of the testosterone ester to the unesterified testosterone occurs rapidly, and it could be shown that e.g. after intravenous injection of testosterone enanthate or testosterone these compounds have parallel pharmacokinetics (Sokol and Swerdloff 1986), the unesterified testosterone molecule determined by specific assay is regarded as the parameter suitable for evaluating the pharmacokinetics of different testoster-

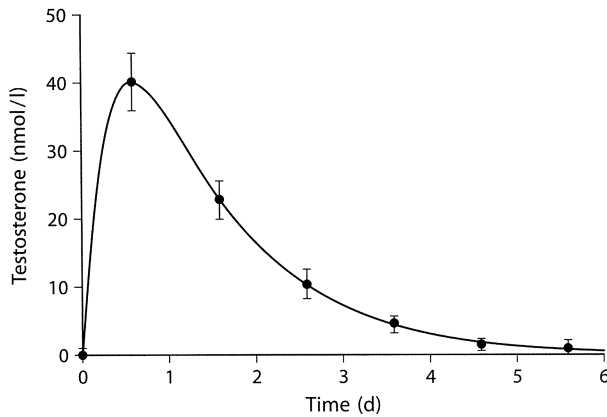
one esters for substitution therapy of male hypogonadism (Cantrill et al. 1984; Conway et al. 1988; Sokol et al. 1982; Sokol and Swerdloff 1986; Snyder and Lawrence 1980).

It is known from clinical studies for male contraception that testosterone esters suppress the endogenous LH and testosterone secretion (Nieschlag and Behre 1997). If pharmacokinetics of testosterone esters are studied in normal male volunteers, the testosterone concentration measurable in the serum is the sum concentration resulting from the endogenous testosterone and the serum concentration of the exogenous testosterone hydrolysed from the ester (Anderson et al. 1997). Because the endogenous testosterone is suppressed to hypogonadal values during the first days after administration of the testosterone ester, the changes in testosterone serum concentrations after administration represent the combined pharmacokinetics of the endogenous and exogenous testosterone. Hypogonadal patients are characterised 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 the 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.

### 11.3.1 Testosterone propionate

#### 11.3.1.1 Single dose pharmacokinetics

Single dose pharmacokinetics of testosterone propionate were studied in seven patients with secondary hypogonadism due to chromophobe adenomas of the pituitary, aged 19–58 years (Nieschlag et al. 1976). Five patients were investigated prior to, two patients six months after surgical removal of the adenoma. No patients had received testosterone treatment previously. 50 mg of testosterone propionate were injected at 18.00 h on the control day. Blood samples were obtained at 8.00 h on the following test days. Basal testosterone levels, measured at 8.00 h on the control day, were subtracted from the testosterone concentrations measured on the test days to evaluate the pharmacokinetics of the exogenously administered testosterone. Measured testosterone concentrations  $\pm$  SEM and the best-fitted pharmacokinetic profile of testosterone propionate kinetics are shown in Fig. 11.2. 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  $\times$  h/l, for MRT 1.5 d and 0.8 d for terminal half-life (Table 11.1).



**Fig. 11.2.** 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

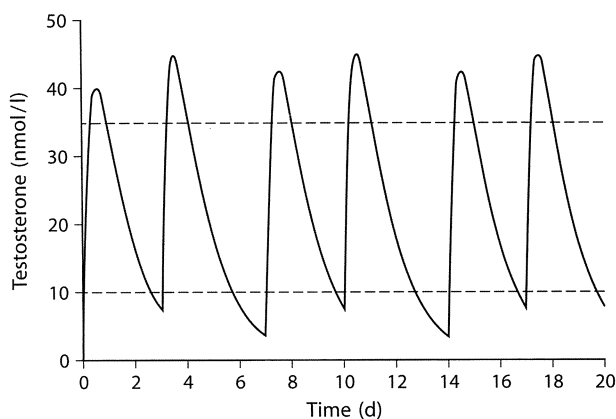
**Table 11.1** Comparative pharmacokinetics of different testosterone esters after intramuscular injection to hypogonadal patients. (MRT=mean residence time)

Testosterone ester	Terminal half-life (d)	MRT (d)
Testosterone propionate	0.8	1.5
Testosterone enanthate	4.5	8.5
Testosterone undecanoate	20.9	34.9
Testosterone buciclate	29.5	65.0

11.3.1.2 Multiple dose pharmacokinetics

Based on the single dose pharmacokinetic parameters, a multiple dose pharmacokinetic simulation was performed. Expected testosterone serum concentrations after multiple dosing of 2 times 50 mg testosterone propionate twice per week (e.g. injections Mondays and Thursdays, 8.00 h) are shown in Fig. 11.3. Shortly after injection high supraphysiological testosterone serum concentrations up to 45 nmol/l are observed. At the end of the injection interval (three and four days, respectively) 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 resulting wide fluctuations of testosterone serum concentrations and maximal injection intervals of three days for the 50 mg dose.



**Fig. 11.3.** 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

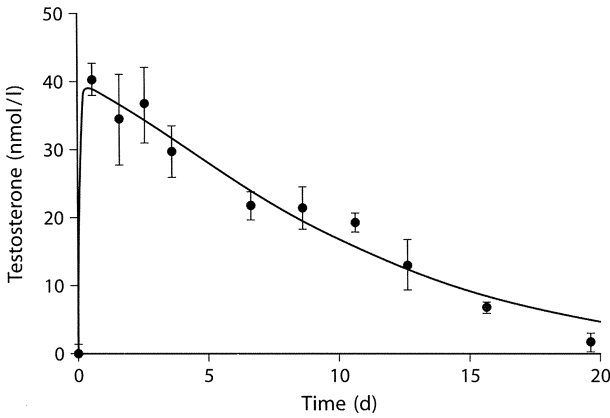
## 11.3.2 Testosterone enanthate

### 11.3.2.1 Single dose pharmacokinetics

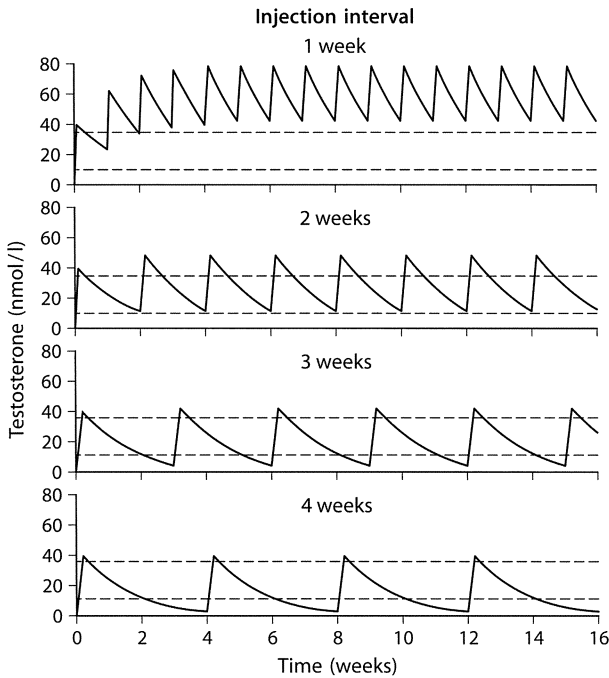
Single dose pharmacokinetics of testosterone enanthate were studied in seven patients with primary hypogonadism, three castrates and four patients with Klinefelter syndrome, aged 20–58 years (Nieschlag et al. 1976). The usual testosterone substitution therapy in these patients was discontinued at least six weeks before the investigation. 250 mg of testosterone enanthate were injected at 18.00 h on the control day. Blood samples were obtained at 8.00 h on the following test days. Increases of testosterone serum concentrations (mean  $\pm$  SEM) over basal values (measured on control day) and the best fitted pharmacokinetic profile of testosterone enanthate kinetics are shown in Fig. 11.4. 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  $\times$  h/l for AUC, 8.5 d for MRT and 4.5 d for terminal half-life (Table 11.1).

### 11.3.2.2 Multiple dose pharmacokinetics

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. 11.5). Injecting 250 mg of testosterone enanthate every two weeks results in maximal supraphysiological testosterone serum concentrations up to 51 nmol/l shortly after injection and testosterone serum levels at the lower range for normal



**Fig. 11.4.** 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. 11.5.** 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

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. 11.5).



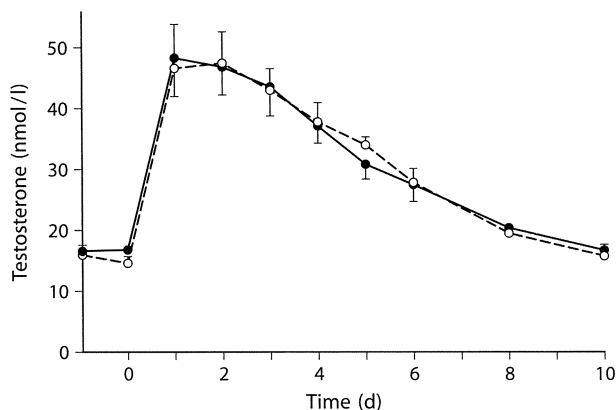
The calculated testosterone serum concentrations at steady state obtained by computer simulation correspond well to the results of published studies describing multiple dose testosterone enanthate pharmacokinetics. In a clinical trial for male contraception 20 healthy men were injected with 200 mg/wk 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 injection of 200 mg testosterone enanthate. Very similar data were obtained in recent 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 of 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 injections 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 of 300 mg every 3 weeks to guarantee an effective substitution therapy.

Demisch and Nickelsen (1983) deduce from their studies with testosterone enanthate for testosterone replacement therapy that if a dose of 250 mg testosterone enanthate once every three weeks is used, the concentration of both total and "free" testosterone are sufficiently high in the first and second week. In the third week, however, total testosterone moves to the lower limit of the male range and erectile disturbances were reported by the patients.

### 11.3.3 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 cypio-



**Fig. 11.6.** 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

nate 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. 11.6, 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, aged 22–31 years. Four volunteers chosen at random first received 200 mg testosterone cyclohexanecarboxylate, followed five weeks later by a 200 mg testosterone enanthate injection. The other three volunteers received testosterone enanthate first and testosterone cyclohexanecarboxylate five weeks later (Schürmeyer and Nieschlag 1984).

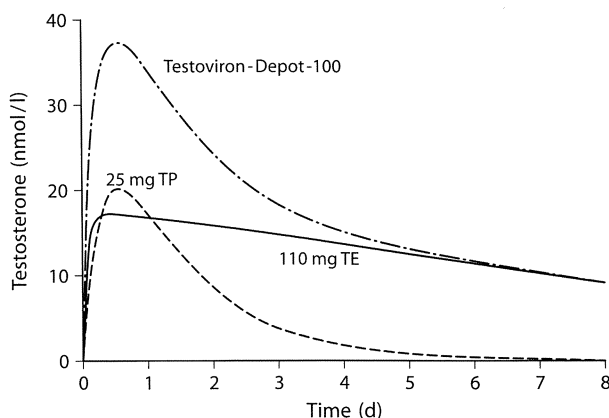
After injection of either testosterone enanthate or testosterone cyclohexanecarboxylate, testosterone concentrations in serum increased sharply and reached maximum levels, 4–5 times above basal, 8–24 h after injection. During following days a parallel decay of testosterone levels occurred after injection of both 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.

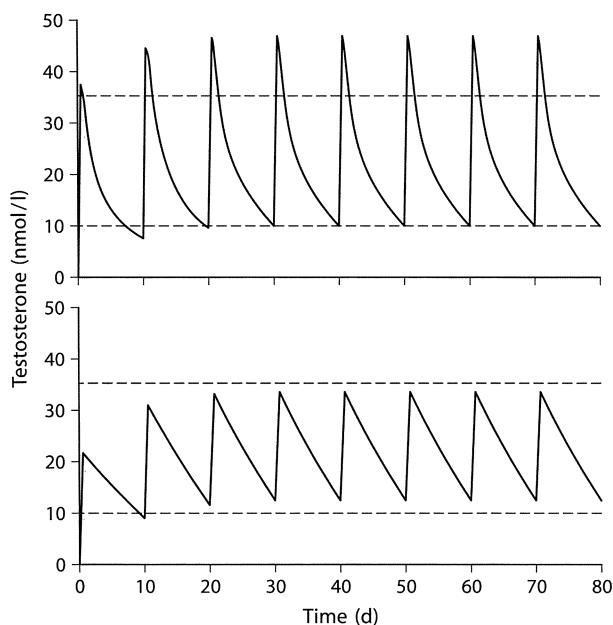
This observation is in agreement with a clinical study of replacement therapy with single dose administration of 200 mg of testosterone cypionate in 11 hypogonadal patients (Nankin 1987). Pharmacokinetics of testosterone cypionate were very similar to the pharmacokinetics of testosterone enanthate described above, with peak testosterone serum concentrations shortly occurring after injection and decay to baseline values by day 13 to 14 after injection.

#### 11.3.4 Testosterone ester combinations

Testosterone ester mixtures have been widely used for substitution therapy of male hypogonadism (e.g. *Testoviron Depot 50*: 20 mg testosterone propionate and 55 mg testosterone enanthate; *Testoviron Depot 100*: 25 mg testosterone propionate and 110 mg testosterone enanthate; *Sustanon 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 single testosterone esters. Both testosterone propionate and testosterone enanthate cause highest testosterone serum concentrations shortly after injection (Fig. 11.2 and Fig. 11.4). 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. 11.7). 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



**Fig. 11.7.** Pharmacokinetic profile of Testoviron 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. 11.8.** Multiple dose pharmacokinetics of the testosterone ester mixture Testoviron 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

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 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. 11.8. As can be expected by the single dose kinetics of the 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 the 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 short- and long-acting testosterone esters.

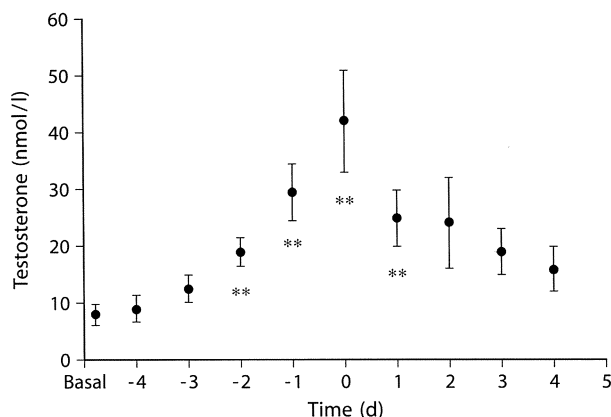
### 11.3.5 Testosterone undecanoate

#### 11.3.5.1 Oral administration

Testosterone undecanoate pharmacokinetics after single dose administration were tested in eight hypogonadal patients and twelve normal men (Schür-

meyer et al. 1983). Directly before and at hourly intervals after oral application of three times 40 mg of testosterone undecanoate in arachis oil (Andriol) taken together with a standardized breakfast, matched saliva samples, as a parameter for free testosterone at the tissue level, and blood samples were collected at hourly intervals 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 5 h after testosterone undecanoate administration. However, the serum testosterone profile showed a 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. Due to the high interindividual variability of testosterone serum levels achieved, no meaningful n-term polyexponential function describing the pharmacokinetics of testosterone undecanoate in normal men or hypogonadal patients could be calculated by computer analysis. 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. 11.9, 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,



**Fig. 11.9.** 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 significant higher testosterone serum concentrations compared to pretreatment values (basal) (mean  $\pm$  SEM)

serum testosterone levels were studied in 12 hypogonadal patients to whom 80 mg of testosterone undecanoate had been administered twice per day 12 h apart. Whereas 4 h after administration of testosterone undecanoate a significant increase of testosterone serum levels was observed compared to the placebo group, no significant difference in testosterone serum levels between treatment and placebo control group was seen 12 h after administration. Even 4 h 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). From these and our own studies on the pharmacokinetics of testosterone undecanoate it can be concluded that, because of its unpredictable pharmacokinetics due to high inter- and intraindividual variability, the marked fluctuations of testosterone serum levels and the unreliable rise of testosterone levels to the normal range, testosterone undecanoate is not a satisfactory drug for substitution therapy of male hypogonadism.

### **11.3.5.2 Intramuscular administration**

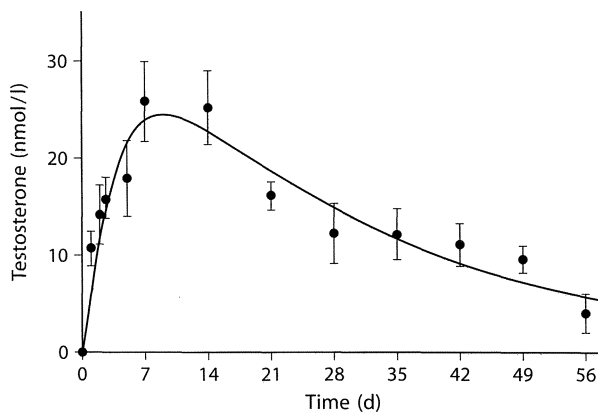
#### **11.3.5.2.1 Preclinical studies**

While testosterone undecanoate has been available for oral substitution for more than two decades, it was recently demonstrated in China that intramuscular administration of testosterone undecanoate in teaseed oil (125 mg/ml) has a prolonged duration of action (Wang 1991). We therefore tested the pharmacokinetics of testosterone undecanoate in comparison to testosterone enanthate 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  $25.7 \pm 4.0$  days and mean residence time of  $40.7 \pm 4.1$  days for testosterone undecanoate, compared to  $10.3 \pm 1.1$  days and  $11.6 \pm 1.1$  days for testosterone enanthate. The maximal testosterone concentration of  $72.6 \pm 11.7$  nmol/l after testosterone undecanoate injection was significantly lower than  $177.0 \pm 21.3$  nmol/l after testosterone enanthate injection.

#### **11.3.5.2.2 Clinical studies**

Because of the favourably long duration of action of intramuscular testosterone undecanoate in monkeys we subsequently performed a clinical phase I-study on the single dose pharmacokinetics of testosterone undecanoate in man. Hypogonadal patients were given intramuscular injections of 250 mg ( $n=7$ ) or 1000 mg testosterone undecanoate ( $n=7$ ). Follow-up examinations were performed 1, 2, 3, 5 and 7 days after injection and then weekly up to

**Fig. 11.10.** Single dose pharmacokinetics of testosterone undecanoate after intramuscular injection of 1000 mg of the ester to seven hypogonadal patients. Closed circles, mean  $\pm$  SEM of testosterone serum concentrations actually measured; curve, best-fitted pharmacokinetic profile



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  $4.8 \pm 0.9$  nmol/l (mean  $\pm$  SEM) to maximum levels of  $30.5 \pm 4.3$  nmol/l at day 7 ( $t_{\max}$ ). Testosterone levels remained within the normal range up to week 7 ( $13.5 \pm 1.2$  nmol/l). Non-linear least squares regression analysis revealed a terminal elimination half-life for intramuscular testosterone undecanoate of  $20.9 \pm 6.0$  days and a mean residence time of  $34.9 \pm 8.2$  days (Fig. 11.10) (Table 11.1).

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 teaseed oil, however, administration of the 1000 mg dose requires an injection volume of 8 ml which renders intramuscular administration impracticable. In collaboration with Jenapharm (Jena, Germany) we reformulated the intramuscular testosterone undecanoate preparation and performed a clinical study with testosterone undecanoate dissolved in castor oil at a higher concentration of 250 mg/ml. 14 hypogonadal patients received an intramuscular injection of 1000 mg of the reformulated testosterone undecanoate preparation. Maximal serum levels were lower than in the study with the Chinese preparation and did not exceed 25 nmol/l. This observation is in agreement with a elegant study on a possible influence of injection volume on the pharmacokinetics of nandrolone esters (Minto et al. 1997). As in the first study the duration of action of intramuscular testosterone undecanoate was six to eight weeks. Follow-up studies with multiple injections of 1000 mg testosterone undecanoate every six to eight weeks are currently being performed which are based on pharmacokinetic computer simulation.

### 11.3.6 Testosterone buciclate

#### 11.3.6.1 Preclinical studies

A first study on the pharmacokinetics of the new WHO/NIH androgen ester testosterone buciclate was performed in two groups of four long-term orchietomized cynomolgus monkeys, *Macaca fascicularis*, weighing 2.8–4.6 kg (Weinbauer et al. 1986). One group received a single intramuscular injection of 40 mg testosterone buciclate in aqueous suspension or 32.8 mg testosterone enanthate dissolved in sesame oil. Both preparations contained equal amounts of testosterone, namely 23.6 mg. Testosterone enanthate injections 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 with a peak level ( $c_{\max}$ ) of  $29.9 \pm 5.9$  nmol/l on day 14. Serum levels of testosterone remained in the physiological range for a period of four months. The levels never exceeded the physiological range of testosterone.

These favourable results on the pharmacokinetics of testosterone buciclate were confirmed in castrated rhesus monkeys. After a single intramuscular injection of 40 mg testosterone buciclate in 1 ml to nine monkeys, serum levels of testosterone remained in the normal physiological range for 80–136 days (Rajalakshmi and Ramakrishnan 1989). In addition, it could be demonstrated in castrated rhesus monkeys that significantly higher testosterone levels can be achieved when the intramuscular injection of 80 mg testosterone buciclate is given as four injections of 0.5 ml at four different sites compared to a single injection of 2 ml (Rajalakshmi and Ramakrishnan 1989).

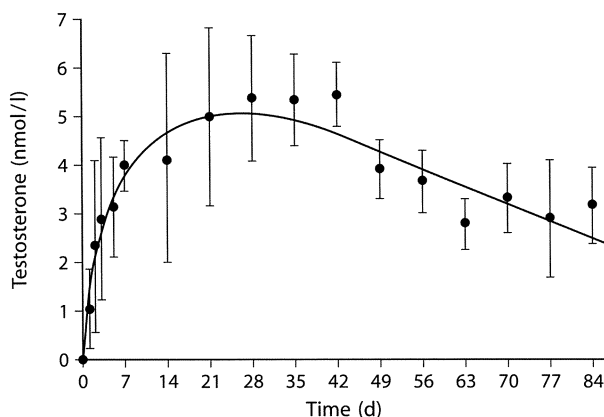
#### 11.3.6.2 Clinical studies

To assess the pharmacokinetics of testosterone buciclate in men the first clinical study was performed in eight men with primary hypogonadism under the auspices of the WHO Male Task Force on Methods for the Regulation of Male Fertility (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  $13.1 \pm 0.9$  nmol/l (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  $29.5 \pm 3.9$  days and a mean residence time of  $65.0 \pm 9.9$  days (Fig. 11.11) (Table 11.1).

Because of the promising results of the first clinical study with testosterone buciclate, a follow-up study was initiated in six patients with primary hypogonadism. After complete wash-out from previous therapy all men re-



**Fig. 11.11.** 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



ceived 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  $13.1 \pm 1.8$  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 recently also demonstrated in the first contraceptive study with this new testosterone ester. After a single 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.

#### 11.4. Key messages

- Results of clinical studies demonstrate that computerized pharmacokinetic analysis and simulation can be applied with advantage to predict multiple-dose serum concentrations from single dose kinetics and are valuable tools for planning clinical therapy.
- The available testosterone esters for intramuscular injection (testosterone propionate, testosterone enanthate, testosterone cypionate, testosterone cyclohexanecarboxylate) are not satisfactory 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.

- Oral administration of testosterone undecanoate results in high interindividual and intraindividual variability of serum testosterone values. The testosterone elevations, only short-lived, result in wide fluctuations of serum concentrations.
- Intramuscular injection of 1000 mg testosterone undecanoate to hypogonadal men maintains serum levels of testosterone within the normal range for six to eight weeks. If multiple dose studies currently performed confirm these initial results, intramuscular testosterone undecanoate could become a valuable preparation for substitution therapy of male hypogonadism and for male contraception.
- The longest duration of action can be achieved with testosterone buciclate. A single intramuscular injection of 1000 mg maintains serum testosterone in the physiological range for 16 weeks. Unfortunately, testosterone buciclate is not yet available for clinical therapy.

## 11.5. References

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