Pharmacokinetic parameters of nandrolone (19-nortestosterone) after intramuscular administration of nandrolone decanoate (Deca-Durabolin®) to healthy volunteers

Herman P. Wijnand, Anneke M. G. Bosch
and Catharina W. Donker

Organon Scientific Development Group, P.O. Box 20, 5340 BH Oss, The Netherlands

Abstract. Nandrolone decanoate (Deca-Durabolin®) was injected intramuscularly into healthy volunteers. One group of females received one injection of 100 mg and three groups of males received one injection of 200 mg, two repeat injections of 100 mg or four repeat injections of 50 mg respectively. The serum levels of nandrolone (19-nortestosterone) were determined by radioimmunoassay and used to estimate pharmacokinetic parameters. The following pharmacokinetic parameters were found:
– a mean half-life of 6 days for the release of the ester from the muscular injection depot into the general circulation;
– a mean half-life of 4.3 h for the combined processes of hydrolysis of nandrolone decanoate and of distribution and elimination of nandrolone;
– a mean nandrolone serum clearance of 1.55 $l \cdot h^{-1} \cdot kg^{-1}$.
The half-life of hydrolysis of nandrolone decanoate in serum was of the order of one hour or less.
The data are consistent with linear kinetics.

Deca-Durabolin®, the decanoate ester of nandrolone (19-nortestosterone) has been used since 1962. In conditions where a sustained protein-anabolic effect is necessary relatively low dosages are required: 25–50 mg intramuscularly per 2–3 weeks. In patients with anaemias of various origin, doses up to 200 mg weekly are required. Thus far, no pharmacokinetic parameters for nandrolone decanoate in man have been reported. The aim of the present study was to estimate pharmacokinetic parameters of nandrolone following intramuscular administration of different doses of nandrolone decanoate to healthy male and female volunteers.

The clinical part of the study was performed in the 'Prinsengracht Ziekenhuis' (Vereniging voor Ziekenverpleging), Prinsengracht 769, Amsterdam, The Netherlands, by Dr. R. G. A. van Wayjen and Dr. A. van den Ende; the clinical aspects will be reported separately.

Methods

Volunteers (Table 1)

Twelve healthy male and four healthy female volunteers, 20–32 years old, participated in the study. They were divided in three groups of four men and one group of four women. In order to reduce the risk of unwanted androgenic effects in the female volunteers, their dosing was limited to one injection of 100 mg. No other drug, hormonal contraception or selfmedication was permitted for two months before and during the study.

Written informed consent was obtained from all volunteers.

Design of experiment

Volunteers in the female group (Group I) and in one male group (Group II) were injected with a single dose of nandrolone decanoate, 100 and 200 mg respectively at the first day. Before the injection of nandrolone decanoate was given, the first blood sample was taken at 8.00 a.m. On this day another seven samples were taken at the following times: 09.00, 10.00, 12.00, 14.00, 16.00, 18.00 and 20.00,

Table 1.
Individual data on volunteers.

Group number	Volunteer number	Age (year)	Height (cm)	Weight (kg)
I	1	21	165	53.5
(females)	2	21	154	50
	4	26	169	57
	8	29	160	57
II	5	20	179	74
(males)	6	25	185	70
	7	29	184	77
	9	22	178	68
III	10	21	189	64
(males)	11	27	185	76
	12	32	187	73
	13	23	182	74
IV	14	31	179	71
(males)	15	29	183	73
	16	24	185	72.5
	17	21	191	71

respectively. Thereafter the blood sampling was restricted to a sampling at 08.00 a.m. on the following days: 2, 4, 6, 8, 10, 12, 14 and 16. Volunteers in Group III (male) received injections of 100 mg on day 1 and day 5, respectively. In this group blood was sampled on the first 10 days at 08.00 a.m., starting on day 1. On the days on which nandrolone decanoate was injected (1 and 5), a blood sample was taken before the injection. Volunteers in Group IV (male) received injections of 50 mg on day 1, day 3, day 5 and day 7, respectively. In this group blood was sampled on the first 9 days at 08.00 a.m., starting on day 1. On the days on which nandrolone decanoate was injected (1, 3, 5 and 7), a blood sample was taken before the injection. The nandrolone levels in the serum were measured by radioimmunoassay. The nandrolone levels were subsequently used to calculate the pharmacokinetic parameters.

Administration

Nandrolone decanoate was administered by deep injection into the musculus quadriceps femoris. The injections were given at 08.00 h after blood sampling.

Pharmaceutical formulation

The doses of 100 and 200 mg nandrolone decanoate were administered as Deca-Durabolin® '100' (100 mg nandrolone decanoate per ml, dissolved in arachis oil), while the dose of 50 mg was administered as Deca-Durabolin® (50 mg nandrolone decanoate per ml, dissolved in arachis oil).

Handling of the samples

Blood samples for serum production were taken from an antecubital vein according to the above mentioned schedule (see: Design of experiment). For the production of serum samples, blood was left for at least one h at 4°C and then centrifuged. Serum samples were stored at −20°C. The samples were randomized and blindly determined.

Analysis

Nandrolone levels in serum were determined by radioimmunoassay (Bosch 1983), at the Biochemical Research and Development Laboratories, Organon Scientific Development Group, Oss, The Netherlands. After extraction and chromatography the samples were assayed undiluted or after 1 in 10 or 1 in 100 dilution. All determinations were performed in triplicate.

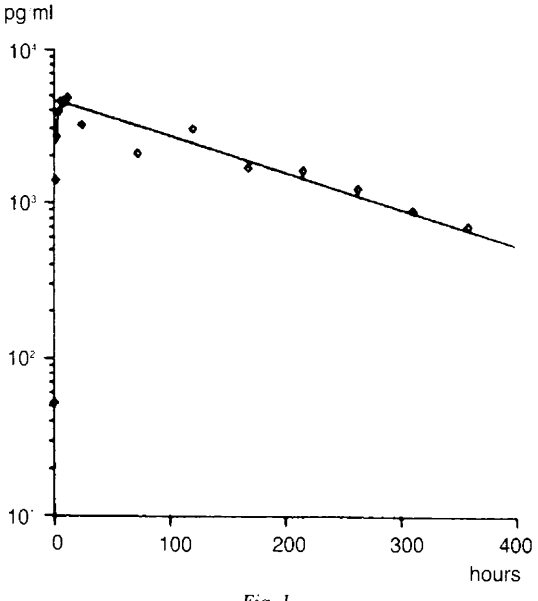


Fig. 1.
Nandrolone levels in serum after intramuscular injection of 100 mg of nandrolone decanoate. Group I, Volunteer 2 (female).

Results and Discussion

Nandrolone serum levels

The results of the determinations of nandrolone levels in the serum samples are shown in Table 2 and Table 3. For Groups I and II, representing the single-dose administrations, the peak times and peak levels of nandrolone in serum are given in Table 4.

Choice of a pharmacokinetic model

Van der Vies (1965) reported that nandrolone 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, with a half-life of the order of 130 h. It was also reported (Van der Vies 1970) that nandrolone esters are rapidly hydrolyzed in rat plasma in vitro, exhibiting a half-life which becomes smaller as the concentration of nandrolone ester decreases. For example, for nandrolone phenylpropionate this author reported a half-life of hydrolysis of 88 min at a concentration of 1000 $\mu g \cdot ml^{-1}$, 24 min at 100 $\mu g \cdot ml^{-1}$, 15 min at 20 $\mu g \cdot ml^{-1}$ and 4 min at 1 $\mu g \cdot ml^{-1}$. Although no data on nandrolone decanoate were reported, it was found that various other anabolic steroid esters in rat plasma also showed hydrolysis in vitro; under the conditions of these studies (16 h at 37°C) all steroid esters hydrolyzed to some extent (5–99%). Given the serum levels of nandrolone in the present study, which are all lower than 0.01 $\mu g \cdot ml^{-1}$, it is valid to assume that the hydrolysis rate of nandrolone decanoate in human blood is relatively fast; presumably the half-life of this process is of the order of one h or less.

There is very little information in the literature about the fate of nandrolone in man. Raynaud (1970) reported a central volume of distribution of 36 litres of plasma and a metabolic clearance rate of 80 litres of plasma per hour. From the rate constants in the two-compartment body model used by this author, we derived a half-life of distribution of 10 min, a half-life of elimination of 1.2 h and a total (steady-state) volume of distribution of 82 litres, obtained from mean intersubject data of four healthy male volunteers.

The nandrolone levels in serum obtained in the

Table 2.

Nandrolone levels ($ng \cdot ml^{-1}$) in serum before and after intramuscular injection of nandrolone decanoate. The first blood sample was taken before drug administration.

Day	Time of blood sampling	Group I (females) 1 injection of 100 mg nandrolone decanoate				Group II (males) 1 injection of 200 mg nandrolone decanoate			
		Patient No.							
		1	2	4	8	5	6	7	9
1	08.00	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06
	09.00	1.1	1.4	0.6	0.4	1.1	0.8	0.3	0.2
	10.00	2.2	2.7	1.3	1.1	1.9	0.7	0.2	0.4
	12.00	2.9	3.9	1.8	1.0	2.5	1.0	0.9	0.7
	14.00	2.5	4.6	1.4	2.8	4.2	1.3	1.3	0.8
	16.00	3.3	4.4	3.8	3.4	4.0	1.6	2.0	1.2
	18.00	4.0	4.7	2.5	2.6	3.2	6.5	1.7	1.2
	20.00	6.0	4.9	2.5	3.2	3.7	5.7	1.7	2.2
2	08.00	3.6	3.2	2.3	3.3	3.8	6.3	1.2	1.5
4	08.00	2.8	2.1	2.3	2.5	3.5	3.3	0.7	1.3
6	08.00	2.3	3.0	2.0	2.6	3.3	3.6	2.1	0.6
8	08.00	2.4	1.7	0.3	2.5	2.3	3.1	1.1	2.5
10	08.00	2.3	1.6	0.3	1.4	2.0	2.7	0.6	1.9
12	08.00	1.3	1.3	0.5	1.3	1.2	1.4	2.5	1.5
14	08.00	0.9	0.9	0.3	0.8	0.9	1.1	2.0	1.0
16	08.00	0.8	0.7	0.2	0.3	0.6	0.7	1.6	1.0

Table 3.

Nandrolone levels (ng · ml^{-1}) in serum before and after intramuscular injection of nandrolone decanoate. The first blood sample was taken before drug administration.

Day	Time of blood sampling	Group III (males) 2 injections of 100 mg nandrolone decanoate on day 1 and 5				Group IV (males) 4 injections of 50 mg nandrolone decanoate on day 1, 3, 5 and 7			
		Patient No.							
		10	11	12	13	14	15	16	17
1	08.00	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06
2	08.00	2.4	6.0	3.8	5.1	1.2	1.6	1.0	1.6
3	08.00	2.6	5.2	2.1	5.3	1.2	1.3	0.8	0.9
4	08.00	2.7	5.2	1.6	4.6	1.7	2.5	1.5	2.1
5	08.00	2.7	2.8	2.0	3.4	2.4	2.1	1.9	1.9
6	08.00	3.7	9.6	2.6	6.3	2.3	3.1	2.1	2.9
7	08.00	4.2	8.6	2.2	5.3	2.2	2.9	2.2	2.2
8	08.00	2.6	2.8	2.4	3.2	2.5	3.4	2.4	3.4
9	08.00	1.7	2.6	1.6	6.4	3.4	1.0	2.1	2.2
10	08.00	2.2	2.5	1.8	5.4				

present study show a relatively rapidly ascending phase with an apparent half-life of the order of a few hours, and a relatively slowly descending phase with a half-life of the order of a few days to approximately one week. Based on these nandrolone levels and the references mentioned above, we propose the following model: nandrolone decanoate is slowly released from its muscular depot following a first-order process with a half-life of up to approximately one week. As long as the ester is in the muscular depot, it as assumed not to be hydrolyzed; as soon as the ester enters into the general circulation it is rapidly hydrolyzed with a half-life of the order of one hour or less. The time course of the resulting nandrolone exhibits two-compartmental disposition kinetics with half-lives of distribution and elimination of 10 min and approximately one hour respectively. Since, however, the process of drug release from the injection depot to the general circulation is the slowest process of all, it will be rate-limiting in the overall result: in the time course of nandrolone serum levels the descending phase will characterize the process of 'prodrug' (the decanoate) release from the injection depot and the ascending phase will characterize the combined processes of hydrolysis of the ester and of distribution and elimination of nandrolone.

A 'full model' to adequately describe these processes is given in the Appendix. It is shown in the Appendix that the simple one-compartmental open body model provides a very good approximation of the theoretically more correct full model. It

Table 4.

Peak times and peak levels of nandrolone in serum after intramuscular administration of nandrolone decanoate. Data taken from Table 2 for single-dose groups (I and II).

Group	Volunteer	t_{max} (h)	C_{max} (ng/ml)
I	1	12	6.0
	2	12	4.9
	4	8	3.8
	8	8	3.4
		10	4.5
II	5	6	4.2
	6	10	6.5
	7	8	2.0
	9	12	2.2
		9	3.7

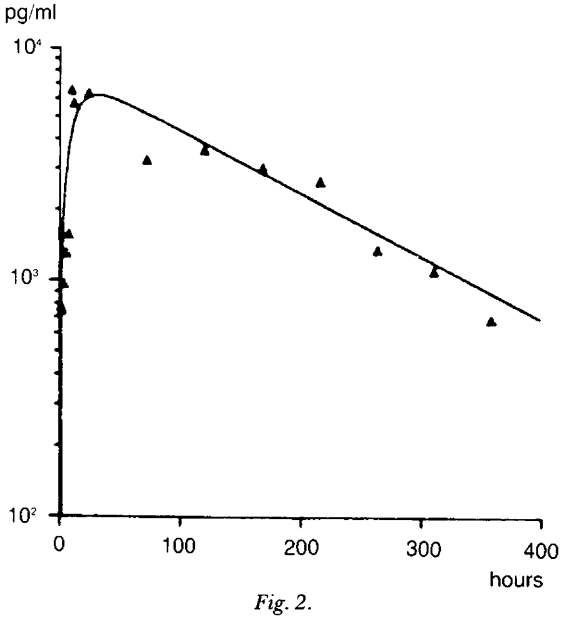


Fig. 2.
Nandrolone levels in serum after intramuscular injection of 200 mg of nandrolone decanoate. Group II, Volunteer 6 (male).

is also shown in the Appendix by computerized simulation (Fig. 3) that in order to obtain a nandrolone peak level in serum at 9 to 10 h following intramuscular administration of the ester (see Table 4), the hydrolysis half-life must be taken as approximately one hour. For shorter peak times of nandrolone, this hydrolysis half-life may be taken to be considerably smaller.

Estimation of pharmacokinetic parameters

The data were fitted to equation 8 of the Appendix, using a Random Search non-linear least squares program (Wijnand & Timmer 1979). Some series of the single-dose groups (I and II) could not be used for meaningful parameter estimation; due to large variability in the data computerized parameter estimation resulted in very large coefficients of variation of strongly intercorrelated parameter estimates. Of the two single-dose groups, the following series could not be used: Group I, volunteer 4; Group II, volunteer 7 and 9. It should be noted that the peak times and peak levels of nandrolone could be taken directly from the empirical data (Table 4).

An important point in parameter estimation is data weighting. Theoretically, given an assay which exhibits relatively constant coefficients of variation over the whole concentration range of interest, the data should be weighted proportionally to their reciprocal squares, or even better, proportionally to the reciprocal square of the fitted value. This resulted, however, in 'best-fitted' curves which in some cases were unacceptably low. Based on comparison of the residuals obtained using various weighting factors, it was found that the data should be equally weighted in order to obtain the smallest sum of residual squares and the absence of systematic patterns in the residual plots.

The parameter estimates obtained by using the curve-fitting program are given in Table 5. For convenience, the rate constants are not designated k_a and k_e, but k_{asc} and k_{desc} (for the ascending and descending part of the curves respectively), since the numerical values of the model parameters present a typical 'flip-flop' case, in which the smaller rate constant (being associated with the longer half-life) is rate-limiting. As pointed out in the Appendix, this implies that the ascending part of the curves represents the combined processes of ester hydrolysis, nandrolone distribution and nandrolone elimination, and that the descending part

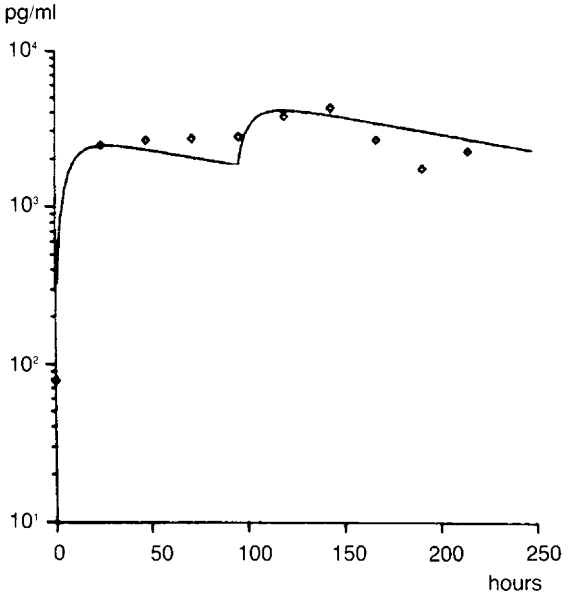


Fig. 3.
Nandrolone levels in serum after intramuscular injection of 2 × 100 mg of nandrolone decanoate, with fixed half-life of 6 days for descending phase. Group III, Volunteer 10 (male).

of the curves represents the process of ester release from the muscular depot.

For estimating the parameters of the volunteers of Group III and IV a linear summation algorithm was used. No valid parameter estimates could be obtained due to the fact that the data spacing in time chosen for this first study cannot provide sufficient information for estimating the rate constants k_{asc} and k_{desc} correctly. There are almost no sampling points available on the ascending part of the curves, and this does not allow one to estimate k_{asc} precisely. Moreover, serum levels of nandrolone in these groups are relatively constant as a consequence of the repeated dosing of nandrolone decanoate, which does not allow one ot estimate k_{desc} from the descending curve either. There is, however, no reason to suppose that the rate constants for Groups III and IV differ systematically from those in groups I and II. We have therefore taken the mean value for k_{desc} of 0.00484 h^{-1} (corresponding to a half-life of 143 h) of volunteers 1, 2, 8, 5 and 6 of Groups I and II, as fixed value in estimating the parameters k_{asc} and Z (see equation 10 of the Appendix) for the volunteers of Groups III and IV. The results, which are included in Table 5, show a satisfying homogeneity for the numerical values of k_{asc} over the four groups, despite the fact that the empirical information about the ascending phase is poor. It should be noted that these results represent single-dose parameters, due to using the summation algorithm for Groups III and IV.

All derived parameters such as half-lives for the descending phase and the (composite) ascending phase, areas under the curve and serum clearances, are shown in Table 6. The most relevant parameter for further consideration is the serum clearance. When subjected to a one-way analysis of variance,

Table 5.

Parameter estimates of nandrolone after i.m. administration of nandrolone decanoate. Groups III and IV were obtained using a fixed value of 0.004837 h^{-1} for k_{desc}, being the mean of groups I and II.

Used function: $C_t = Z \cdot \{ e^{-k_{desc}t} - e^{-k_{asc}t} \}$

Group	Volunteer	Dose of nandrolone decanoate	k_{asc} (h^{-1})	k_{desc} (h^{-1})	Z ($ng \cdot ml^{-1}$)
I	1	1 × 100 mg	0.2453	0.004156	4.6
(females)	2	1 × 100 mg	0.4634	0.005417	4.6
	8	1 × 100 mg	0.1637	0.004363	3.9
			0.2908	0.004645	4.4
II	5	1 × 200 mg	0.2981	0.004132	4.3
(males)	6	1 × 200 mg	0.0906	0.006119	7.5
			0.1898	0.005123	5.9
III	10	2 × 100 mg	0.1272	0.004837 (fixed)	2.8
(males)	11	2 × 100 mg	0.3170	0.004837	5.2
	12	2 × 100 mg	0.3233	0.004837	2.2
	13	2 × 100 mg	0.2000	0.004837	4.9
			0.2419	0.004837	3.8
IV	14	4 × 50 mg	0.0513	0.004837 (fixed)	1.3
(males)	15	4 × 50 mg	0.3116	0.004837	1.2
	16	4 × 50 mg	0.3867	0.004837	1.0
	17	4 × 50 mg	0.3711	0.004837	1.2
			0.2802	0.004837	1.2

Table 6.
Derived parameters using numerical values of primary parameters specified in Table 5.

Group	Volunteer	Dose of nandrolone decanoate (mg)	$T_{½}$ (asc) (h)	$T_{½}$ (desc) (d)	AUC ($\mu g \cdot h \cdot l^{-1}$)	Plasma clearance for single dose	
						($l \cdot h^{-1}$)	($l \cdot h^{-1} \cdot kg^{-1}$)
I	1	1 × 100	2.8	6.9	1081	59.2	1.10
(females)	2	1 × 100	1.5	5.3	846	75.7	1.51
	8	1 × 100	4.2	6.6	871	73.5	1.29
			2.9	6.3	933	69.5	1.30
II	5	1 × 200	2.4	7.0	1034	123.8	1.67
(males)	6	1 × 200	7.7	4.7	1146	111.7	1.60
			5.0	5.9	1090	117.7	1.63
III	10	2 × 100	5.4	6.0*	549	116.6	1.82
(males)	11	2 × 100	2.2	6.0	1059	60.4	0.80
	12	2 × 100	2.1	6.0	440	145.5	1.99
	13	2 × 100	3.5	6.0	440	64.8	0.88
			3.3	6.0	759	96.8	1.37
IV	14	4 × 50	13.5	6.0*	252	126.9	1.79
(males)	15	4 × 50	2.2	6.0	251	127.5	1.75
	16	4 × 50	1.8	6.0	204	156.9	2.16
	17	4 × 50	1.9	6.0	252	127.0	1.79
			4.8	6.0	238	134.6	1.87

* Fixed value. Overall mean clear. (± SD) 1.55 ± 0.41.

the difference between groups is significant at the 5% level (P = 0.048). Upon inspection of the individual clearances and their group means, it is tempting to postulate that this significance is caused by a systemically lower value of Group I towards Group II, III and IV, suggesting systematic differences between the male and the female volunteers with respect to serum clearance. When, however, the clearances are corrected for body weight, the results of which are included in Table 6, no significant differences can be demonstrated in a one-way analysis of variance (P = 0.25). It is therefore extremely likely that the differences in serum clearance between groups are caused by differences in body weight only. The overall mean serum clearance (± SD) is 1.55 ± 0.41 $l \cdot h^{-1} \cdot kg^{-1}$.

It should be noted that the available data do not allow one to distinguish between the extent of absorption, F, and the volume of distribution, V, in the expression for the parameter Z (equation 10 of the Appendix), since no intravenous studies in the same volunteers were performed. The serum clearance found by us and the clearance reported by Raynaud (1970), however, are very similar. For an assumed mean body weight of 67 kg for Raynaud's young male volunteers, the mean clearance of 80 $l \cdot h^{-1}$ would correspond to 1.19 $l \cdot h^{-1} \cdot kg^{-1}$. A point estimate of nandrolone bioavailability from nandrolone decanoate, by combining the results of Raynaud's study and the present study, is therefore $100 \cdot 1.19/1.55 = 77\%$. It is indicated in the Appendix how individual estimates of nandrolone biovailability from nandrolone decanoate can be obtained in future studies.

The mean half-life for the descending phase in

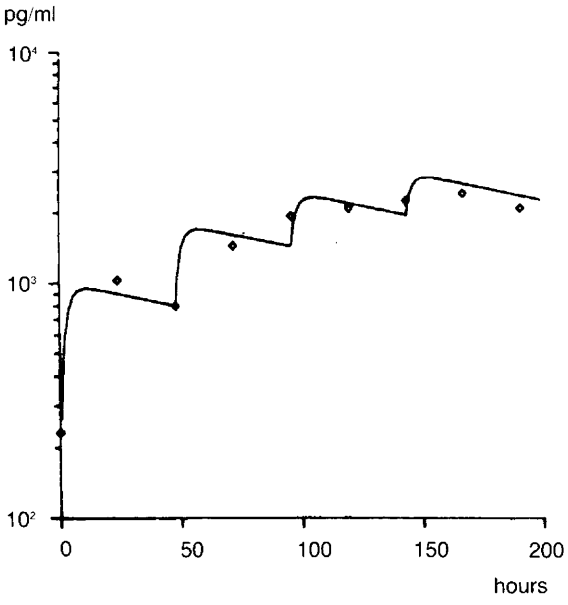


Fig. 4.
Nandrolone levels in serum after intramuscular injection of 4 × 50 mg of nandrolone decanoate, with fixed half-life of 6 days for descending phase. Group IV, Volunteer 16 (male).

Groups I and II (subjects 1, 2, 8, 5 and 6) is 6 days, representing the process of drug release from the muscular depot into the general circulation. The mean half-life for the ascending part of the curve, calculated from the individual values given in Table 6, excluding volunteer 14, is 4.3 h. This represents the combined processes of hydrolysis of nandrolone decanoate and of distribution and elimination of nandrolone.

Typical examples of the individual serum levels of nandrolone as well as the best-fitted curve based on the parameters of Table 5 are given in Figs. 1–4. The curves show that after single dose administration peak serum levels are obtained within the first day after intramuscular administration of nandrolone decanoate. The large variability in the data and the practical difficulties to estimate the rate constants of the curves for Groups III and IV, are clearly illustrated. Nevertheless it has been possible to establish a valid model which adequately describes the available data.

The absence of significant differences in serum clearance between the four groups of volunteers (when corrected for body weight) indicates linear pharmacokinetics for the dose range studied.

Acknowledgments

We thank Mr. J. I. J. van Casteren and Mrs. B. T. M. Rutjes for their expert performance of the radioimmunoassay of nandrolone, and Drs. R. G. A. van Wayjen and A. van den Ende for performing the clinical part of the study.

References

Bosch A M G (1983): A radioimmunoassay of 19-nortestosterone using Celite column chromatography. J Clin Chem Clin Biochem 22: 22–34.

Byrne G D & Hindmarsh A C (1974): A polyalgorithm for the numerical solution of ordinary differential equations. Lawrence Livermore Laboratory Report UCRL-75652.

Dost F H (1968): Grundlagen der Pharmacokinetik 2. Auflage: pages 38–47. Georg Thieme Verlag, Stuttgart, GFR.

Raynaud J P (1970): Metabolism of contraceptive steroids in man. Excerpta Medica International Congress Series No. 219, Hormonal Steroids. Proceedings of the Third International Congress Hamburg, GFR.

Van der Vies J (1965): On the mechanism of action of nandrolone phenylpropionate and nandrolone decanoate in rats. Acta Endocrinol (Copenh) 49: 271–282.

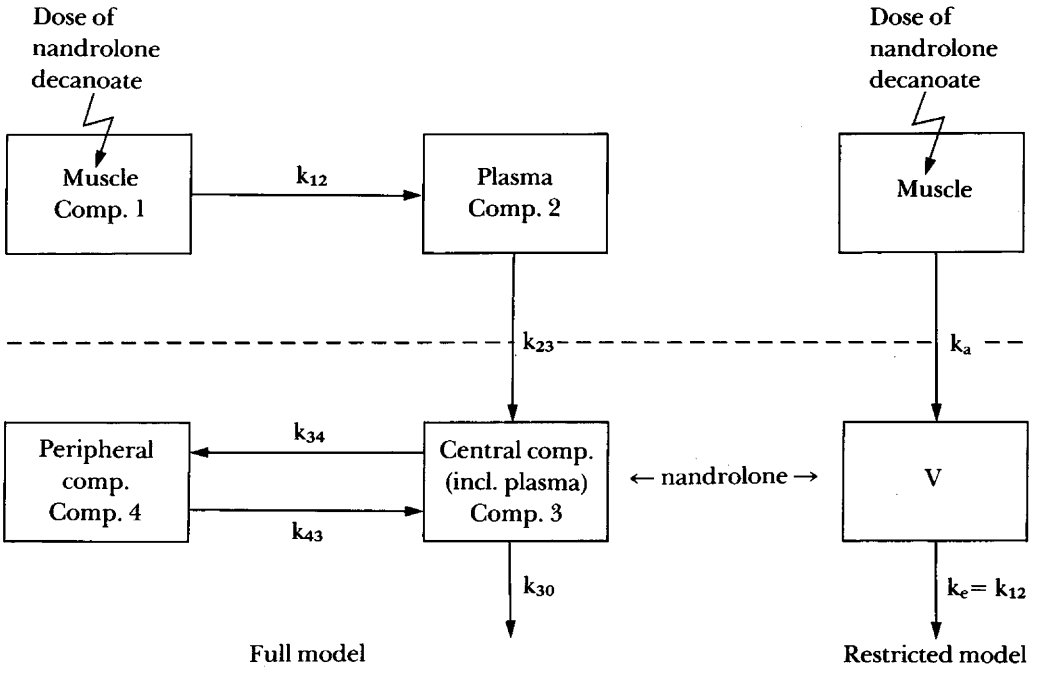
Van der Vies J (1970): Model studies in vitro with long-acting hormonal preparations. Acta Endocrinol (Copenh) 64: 656–669.

Wagner J G (1975): Fundamentals of Clinical Pharmacokinetics: p 244–245. Drug Intelligence Publ Inc Hamilton, USA.

Wijnand H P & Timmer C J (1979): Curve-fitting and modeling in pharmacokinetics: all programs are equal, but some programs are more equal than others. J Pharmacokinet Biopharm 7: 681–684.

Appendix

The model considerations in the text lead to the distinction between a 'full model', in which the processes of release and hydrolysis of the ester and disposition of the resulting nandrolone can be distinguished, and a restricted 'flip-flop' model. This can schematically be represented as follows:



In the full model, k_{12} represents the first-order process of release of the ester into the general circulation, k_{23} represents the first-order process of hydrolysis into nandrolone, and k_{34}, k_{43} and k_{30} represent the first-order processes of distribution and elimination of nandrolone. The differential equations describing the changes in drug masses Q_i in each compartment (with i = 1, 2, 3 and 4), given the first-order rate constants k_{ij} between compartments i and j, are as follows:

$$dQ_1/dt = -k_{12}Q_1 \quad (1)$$

$$dQ_2/dt = k_{12}Q_1 - k_{23}Q_2 \quad (2)$$

$$dQ_3/dt = k_{23}Q_2 + k_{43}Q_4 - (k_{30} + k_{34})Q_3 \quad (3)$$

$$dQ_4/dt = k_{34}Q_3 - k_{43}Q_4 \quad (4)$$

The general solution for such a set of equations is known in the form of Laplace transforms (Wagner 1975). Back transformation by Heaviside expansion into the time domain yields the following equation for the concentration of drug in compartment No. 3, which is the reference compartment when sampling plasma or serum for nandrolone levels:

$$C_3(t) = \frac{Q_3(t)}{V_3} = \frac{Dk_{12}k_{23}}{V_3} \cdot \left\{ \frac{k_{43}-k_{12}}{(k_{23}-k_{12})(\alpha-k_{12})(\beta-k_{12})} \cdot e^{-k_{12}t} + \frac{k_{43}-k_{23}}{(k_{12}-k_{23})(\alpha-k_{23})(\beta-k_{23})} \cdot e^{-k_{23}t} + \frac{k_{43}-\alpha}{(k_{12}-\alpha)(k_{23}-\alpha)(\beta-\alpha)} \cdot e^{-\alpha t} + \frac{k_{43}-\beta}{(k_{12}-\beta)(k_{23}-\beta)(\alpha-\beta)} \cdot e^{-\beta t} \right\} \quad (5)$$

in which V_3 represents the central volume of distribution in the disposition model of nandrolone, D represents the equimolar dose of nandrolone from nandrolone decanoate, and α and β are the rate constants for distribution and elimination respectively in the dispostition model of nandrolone:

$$\alpha = \tfrac{1}{2}\{k_{34} + k_{43} + k_{30} + \sqrt{(k_{34} + k_{43} + k_{30})^2 - 4k_{43}k_{30}}\} \quad (6)$$

$$\beta = \tfrac{1}{2}\{k_{34} + k_{43} + k_{30} + \sqrt{(k_{34} + k_{43} + k_{30})^2 - 4k_{43}k_{30}}\} \quad (7)$$

The plasma (or serum) levels of nandrolone can be simulated by inserting the following numerical values into equations 5, 6 and 7:
k_{12} = 0.00484 h^{-1} (corresponding to a half-life of approximately 6 days);
k_{23} = 41.6 h^{-1}, 8.32 h^{-1}, 1.386 h^{-1}, 0.693 h^{-1}, 0.462 h^{-1} and 0.347 h^{-1} (corresponding to hypothetical hydrolysis half-lives of 1 min, 5 min, 30 min, 1 h, 1.5 h and 2 h respectively);
k_{34} = 1.4 h^{-1}, k_{43} = 1.1 h^{-1}, k_{30} = 2.2 h^{-1} } mean nandrolone rate constants reported by Raynaud (1970)

Another was of handling models of this type is by numerically integrating the set of differential equations 1−4. Since, however, the numerical values of the rate constants differ by several orders of magnitude, this set of equations represents a 'stiff system'. Such a system can be solved by using a special algorithm, the variable-step variable-order backward differentiation formula method (Byrne & Hindmarsh 1974).

The two methods resulted in identical curves representing the time course of nandrolone levels in serum. In the simulations, the intramuscular dose of nandrolone decanoate was taken as 100 mg, corresponding to 64 mg of nandrolone. The results are shown in Figs. 1 and 2 for hypothetical hydrolysis half-lives of 1 min, 5 min and 30 min, and in Figs. 3 and 4 for hypothetical hydrolysis half-lives of 1 min, 30 min, 1 h, 1.5 h and 2 h. The descending part of all curves has the same slope and is essentially log-linear for times longer than 12 h; this log-linear phase has a half-life of approximately 6 days, corresponding to k_{12} = 0.00484 h^{-1} in the model. The ascending part of the curves

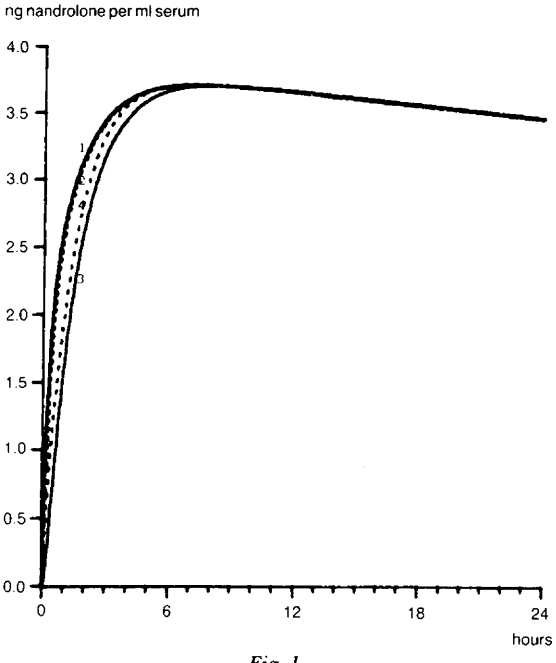


Fig. 1.
Influence of rate of hydrolysis on serum levels of nandrolone, from intramuscular dose of 100 mg of nandrolone decanoate, and approximatoin of full model by restricted 'flip-flop' model. Full model (—1—) $t_{½\,(hydrol)}$ = 1 min. Full model (−−2−−) $t_{½\,(hydrol)}$ = 5 min. Full model (—3—) $t_{½\,(hydrol)}$ = 30 min. Restricted model (−−4−−) $t_{½\,(abs)}$ = 1 h.

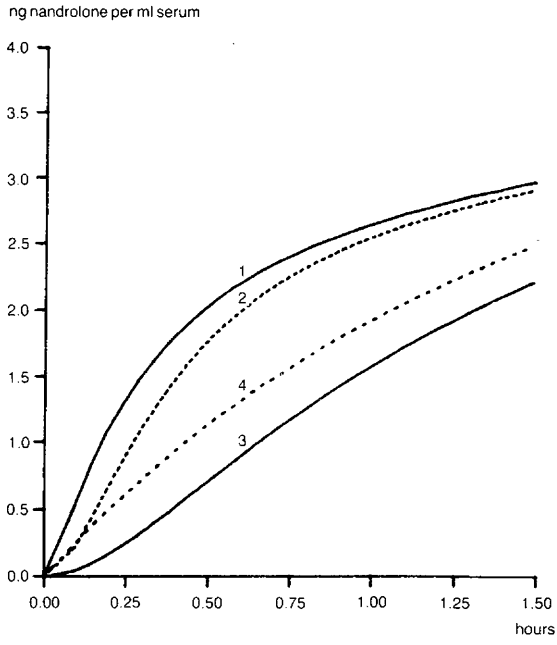


Fig. 2.
Influence of rate of hydrolysis on serum levels of nandrolone, from intramuscular dose of 100 mg of nandrolone decanoate, and approximation of full model by restricted 'flip-flop' model. Full model (—1—) $t_{½\,(hydrol)}$ = 1 min. Full model (−−2−−) $t_{½\,(hydrol)}$ = 5 min. Full model (—3—) $t_{½\,(hydrol)}$ = 30 min. Restricted model (−−4−−) $t_{½\,(abs)}$ = 1 h.

is slightly S-shaped with a point of inflection within the first hour after drug administration, for hydrolysis half-lives up to 1.5 h; this point occurs as earlier times as the hydrolysis half-life is smaller.

It is also shown in Fig. 1 that the time course of nandrolone levels from the full model can be very well approximated by those from the restricted 'flip-flop' model. In the latter model, the rate constant of elimination is taken as 0.00484 h^{-1}; the rate constant of absorption is (in this example) 0.693 h^{-1}, corresponding to a half-life of 1 h. The distribution volume is to be taken much larger (approx. 16 600 litres) due to the 'flip-flop' nature of reversed input and output rate constants. Similarly, the simulated curves from the full model can be equally well approximated by the restricted model, using other numerial values; in order not to complicate Fig. 3 too much, the curves from the

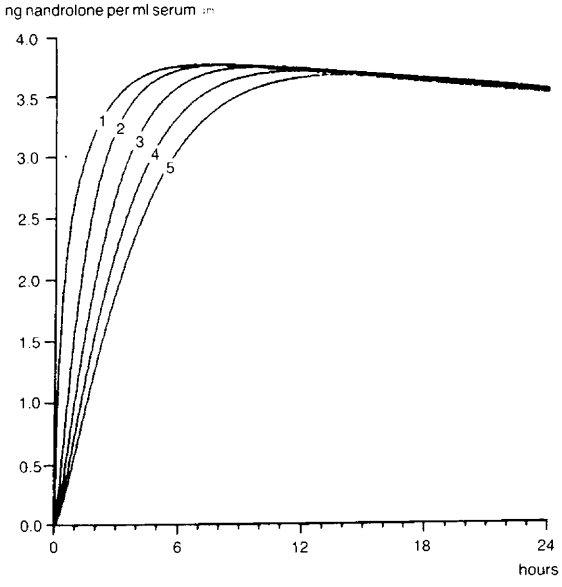


Fig. 3.
Influence of half-life of ester hydrolysis on serum levels of nandrolone from intramuscular dose of 100 mg of nandrolone decanoate, by simulation using full model.

Curve	$t_{½}$ hydrol	$t_{½}$ max
1	1 min	7.2 h
2	0.5 h	8.1 h
3	1.0 h	9.8 h
4	1.5 h	11.9 h
5	2.0 h	14.2 h

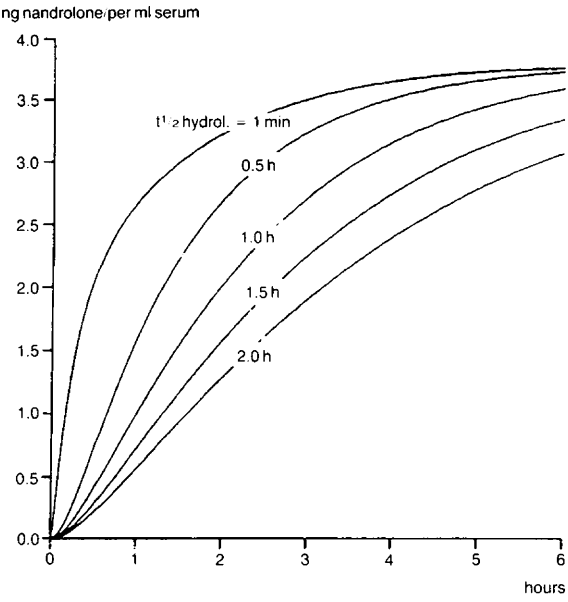


Fig. 4.
Influence of half-life of ester hydrolysis on serum levels of nandrolone drom intramuscular dose of 100 mg of nandrolone decanoate, by simulation using full model.

restricted model are not shown. Mathematically, the well-known Bateman function (Dost 1968) describes the restricted model:

$$C(t) = \frac{F \cdot D}{V} \cdot \frac{k_a}{k_a - k_e} \cdot \{e^{-k_e t} - e^{-k_a t}\} \qquad (8)$$

in which F represents the fraction of drug absorbed (the extent of absorption), D represents the dose, V represents the volume of distribution, and k_a and k_e represent first-order rate constants for absorption and elimination respectively.

The half-lives of absorption and elimanation are obtained as:

$$t_{½\,(abs)} = \frac{\ln 2}{k_a} = \frac{0.69315...}{k_a} \qquad (9)$$

and

$$t_{½\,(elim)} = \frac{0.69315...}{k_e} \qquad (9)$$

The area under the plasma or serum level vs time curve is obtained by integration of C(t), resulting in:

$$AUC_{0\to\infty} = \frac{F \cdot D}{V} \cdot \frac{k_a}{k_a - k_e} \cdot \left\{ \frac{1}{k_e} - \frac{1}{k_a} \right\}$$

$$= Z \cdot \left\{ \frac{1}{k_a} - \frac{1}{k_e} \right\} \qquad (10)$$

The plasma or serum clearance is calculated as follows, including a correction for the difference in molecular mass between nandrolone decanoate (M = 428.63) and nandrolone (M = 274.39):

$$Cl = \frac{274.39}{428.63} \cdot \frac{D}{AUC_{0\to\infty}} = 0.6302 \cdot \frac{D}{AUC_{0\to\infty}} \qquad (11)$$

From the curves given Figs. 1–4 it follows that:

1) Relatively large differences in hydrolysis half-life of the ester exert relatively little influence on the time course of nandrolone levels in plasma or serum. For hydrolysis half-lives ranging from 1 to 30 min, the differences can only be seen during the first few hours following intramuscular administration. Even for hydrolysis half-lives up to 2 h, the resulting nandrolone serum levels are essentially the same from 12 h after administration onwards.

2) Theoretically, in the curves from the full model four exponentials should be detectable. Since, however, the descending part of the curve represents the release of the ester from the muscular depot into the general circulation, the half-lives of ester hydrolysis and of nandrolone distribution and elimination are to be estimated in the ascending part of the curve. It would be practically impossible to design an experimental set-up which is able to discriminate between these three processes during the first few hours after drug administration. The only possibility would be to administer nandrolone intravenously and to estimate its kinetic profile. After a sufficiently long wash-out period (presumably not exceeding one day) the ester can be administered intramuscularly. Using the individual kinetic parameters of nandrolone as preset values in the full model, the rate constants of ester release and of ester hydrolysis, as well as the bioavailability of nandrolone from the ester, can then be estimated from the time course of nandrolone serum (or plasma) levels.

3) It follows from Fig. 3 that hydrolysis half-lives up to one hour are sufficient to produce serum peak levels of nandrolone from nandrolone decanoate at up to 10 h following i.m. administration of the ester.

4) The restricted 'flip-flop' model gives an excellent approximation of the theoretically more correct time course of nandrolone levels obtained with the full model. After the first few hours following drug administration, differences between the curves from the two models are negligible. For a great number of parameter combinations the restricted model will also give very good approximations even for the first few hours following administration of the ester.