# INTRAINDIVIDUAL COMPARISON OF PHARMACOKINETIC PARAMETERS OF d-NORGESTREL, LYNESTRENOL AND CYPROTERONE ACETATE IN 6 WOMEN

M. Hümpel, H. Wendt, G. Dogs, Chr. Weiß, S. Rietz and U. Speck

Research Laboratories, Schering AG, Berlin/Bergkamen

## ABSTRACT

2.5 mg lynestrenol-$^{14}$C (Lyn), 2.0 mg cyproterone acetate-$^{14}$C (CPA) and 0.25 mg d-norgestrel-$^{3}$H (d-Ng), each together with 50 µg ethinyloestradiol, were each administered once - consecutively in a randomised sequence - orally to 6 women. The substance combinations were administered as a micronisate with lactose in gelatine capsules at intervals of 14 days. The course of the substance concentration (NET for Lyn) and of the total radioactivity in plasma, and the elimination of the labelled substances were recorded up to the 5th and 8th day after ingestion.

The progestogens were absorbed completely and at a comparable rate. The respective postmaximum course of the substance level in plasma was characterized by two disposition phases, of which the first phase with a half-life of about 3 hours displayed no substance-specific differences. Significant differences in the pharmacokinetics of the three progestogens could be demonstrated in the rate of the terminal disposition of the active substance (NET $>$ d-Ng $>$ CPA) and total radioactivity in plasma (d-Ng, CPA $>$ Lyn), in the rate of elimination with urine and faeces (Lyn, d-Ng $>$ CPA) and in the portion of the dose eliminated with the urine (d-Ng, Lyn $>$ CPA) and faeces (CPA $>$ d-Ng $>$ Lyn).

Accepted for publication June 14, 1977

## INTRODUCTION

The contraceptive reliability of combined oral preparations of synthetic sex steroids is extremely high when they are taken according to instructions. Differences in the contraceptive reliability of various preparations which contain different steroid combinations only become apparent when they are taken incorrectly (missed pill). The oestrogen contained in most preparations is ethinyloestradiol or its 3-methyl ether, mestranol, so the question about a varying reliability of the preparations really only concerns the progestogen used or its pharmacokinetic behaviour in man.

Various studies are available on the kinetics of the most important synthetic progestogens, e.g. norethisterone, lynestrenol and d-norgestrel, which have led to some nicely coinciding results with respect to the extent and rate of elimination in the urine (total radioactivity) (1-8). However, neither different study methods (total radioactivity, RIA) nor the observation of different periods of time after administration have led to a uniform picture of the course of the plasma concentration of progestogens (2, 7-17).

The object of the present study was to observe the course of the total radioactivity and of the substance in plasma and to determine the elimination of the total activity of d-norgestrel, lynestrenol and cyproterone acetate (in each case combined with 50 µg ethinyloestradiol) in 6 women in a controlled intraindividual comparison.

## EXPERIMENTAL PROCEDURE, MATERIAL AND METHODS

### Experimental design

Six clinically healthy women (age 21-39 years, weight 47-61 kg) volunteered for the experiments. The women had not taken any oral contraceptives for at least one month before this investigation started. The substance combinations were administered in the morning with a standardised breakfast according to a randomisation schedule (Table I).

Table I. Specification of Treatments and Scheme of Application

| treatment | substance combination of |
|---|---|
| A = 2.0 mg cyproterone acetate-methylene-$^{14}$C<br>0.05 mg ethinyl oestradiol-6,7-$^{3}$H | SH B 209 AB |
| B = 0.25 mg d-norgestrel-15,16-$^{3}$H<br>0.05 mg ethinyl oestradiol | Neogynon® |
| C = 2.5 mg lynestrenol-4-$^{14}$C<br>0.05 mg ethinyl oestradiol-6,7-$^{3}$H | widely used commercial preparation |

| Study No. | TS 1 | TS 2 | TS 3 | TS 4 | TS 5 | TS 6 |
|---|---|---|---|---|---|---|
| 1* | A | B | B | C | A | C |
| 2* | B | C | C | A | B | A |
| 3* | C | A | A | B | C | B |

TS = test subject
* = The different studies were conducted at intervals of 14 days.

After dilution with the respective unlabelled substance, the radiolabelled compounds were absorbed from benzene solution onto lactose, which was then micronized to a particle size of $< 20$ µm. Each gelatine capsule contained 300 µg of that lactose micronisate.

Urine and faeces were collected quantitatively and the radioactivity determined up to the 8th day after administration. In every individual study, plasma was obtained from the peripheral venous blood at the same points in time (Figure 2) and stored at -18 °C ready for determination of the radioactivity and the substance concentration. The substance levels of ethinyloestradiol are being (18) and of cyproterone acetate have already been (17) reported. The method for the determination of the radioactivity in plasma, urine and faeces has been described (8).

Radioimmunological determinations
Specific radioimmunoassays were available for cyproterone acetate and d-norgestrel for the determination of the respective substance in plasma. The substance level after administration of lynestrenol was determined with the aid of a norethisterone RIA (see below):

a) d-Norgestrel (d-Ng) was determined with the aid of an anti-d-Ng-3-(O-carboxy-methyl)oxim-BSA-serum* (rabbit) using d-norgestrel-15,16-$^{3}$H (specific activity: 56 Ci/mMol** (19).

b) Norethisterone (NET) was determined with the aid of an anti-NET-11α-hemisuccinate-BSA-serum* (rabbit) using norethisterone-6,7-$^{3}$H (specific activity: 40 Ci/mMol*** (20).

c) Cyproterone acetate (CPA) was determined with the aid of an anti-CPA-11α-hemisuccinate-BSA-serum* (rabbit) using CPA-11α-hemisuccinyl-$^{125}$iodohistamine* (21).

The cross-reactions (22) of the antisera with endogenous steroids could be ignored in every case. The NET antiserum displayed an 8 % cross-reaction (22) with lynestrenol. The main metabolite of CPA in human plasma, 15β-OH-CPA (33), displayed a 15 % cross-reaction with the CPA anti-serum.

Substance measurement after administration of lynestrenol

So far no measurement of the plasma level of substance after oral administration of lynestrenol in man are available. To develop such a determination, the steroid fraction which can be freely extracted from plasma with diethyl ether was studied by thin-layer chromatography. Aliquot portions of plasma of all 6 test subjects were pooled (2-h pool and 5-h pool) and extracted under the conditions of RIA sample preparation. The extracts were separated by thin-layer chromatography (Figure 1).

At both points in time after the administration of $^{14}$C-lynestrenol, only about 10 % of the extracted $^{14}$C activity behave chromatographically like lynestrenol, whereas about 80 % like norethisterone. In view of the opinion expressed in the literature of an in vivo conversion of lynestrenol to norethisterone (23-27), these findings appeared to be adequate to justify the measurement in the following of norethisterone as the substance following administration of lynestrenol. As an active ingredient of which concentration in plasma correlates with the biological effects, Weiner and Johansson (35) measured norethisterone after subcutaneous application of lynestrenol-containing implants.

---

* prepared in the Department of General Biochemistry, Schering AG

** synthesized in the Department for Isotope Chemistry, Schering AG

*** NEN Corporation

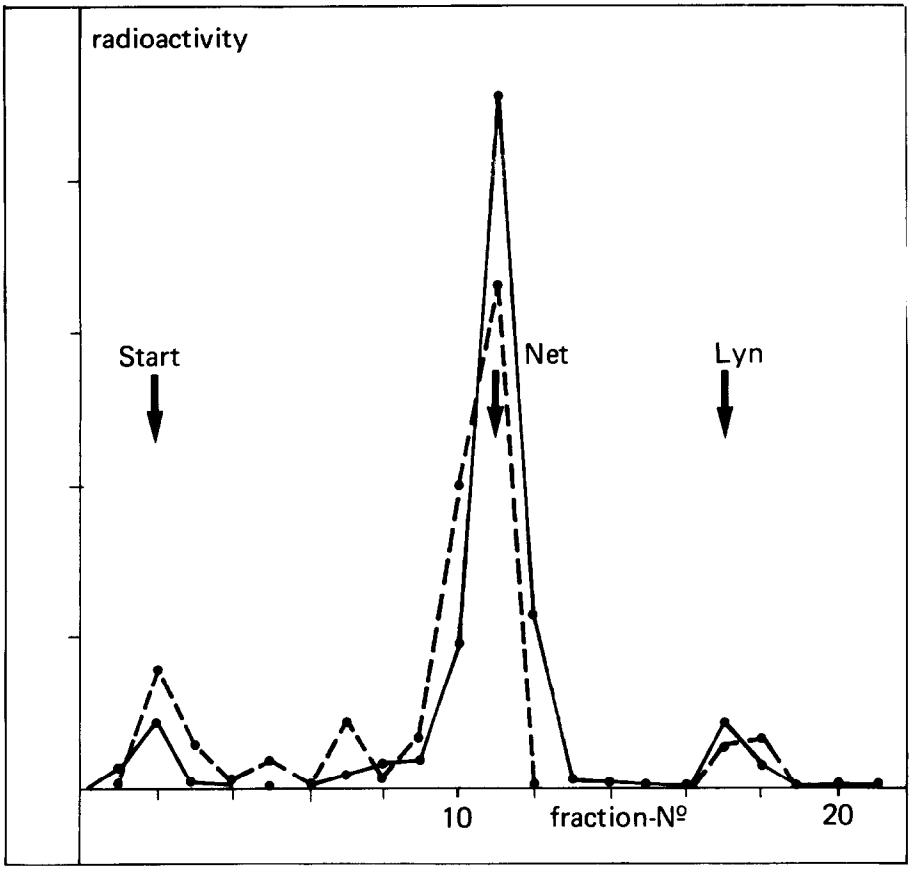



Figure 1.
Thin-layer chromatogram of a diethylether extract of plasma which was obtained 2 hours (•——•) and 5 hours (•– –•) after oral administration of 2.5 mg lynestrenol 4-$^{14}$C in 6 women;system: chloroform /acetone: 9/1, ascending DC 60 F 254 (Merck, Darmstadt). 0.5 cm of each of the supports were scraped off and measured in dioxane scintillator; the arrows denote the runs of authentic norethisterone (NET) and lynestrenol (Lyn).

## RESULTS

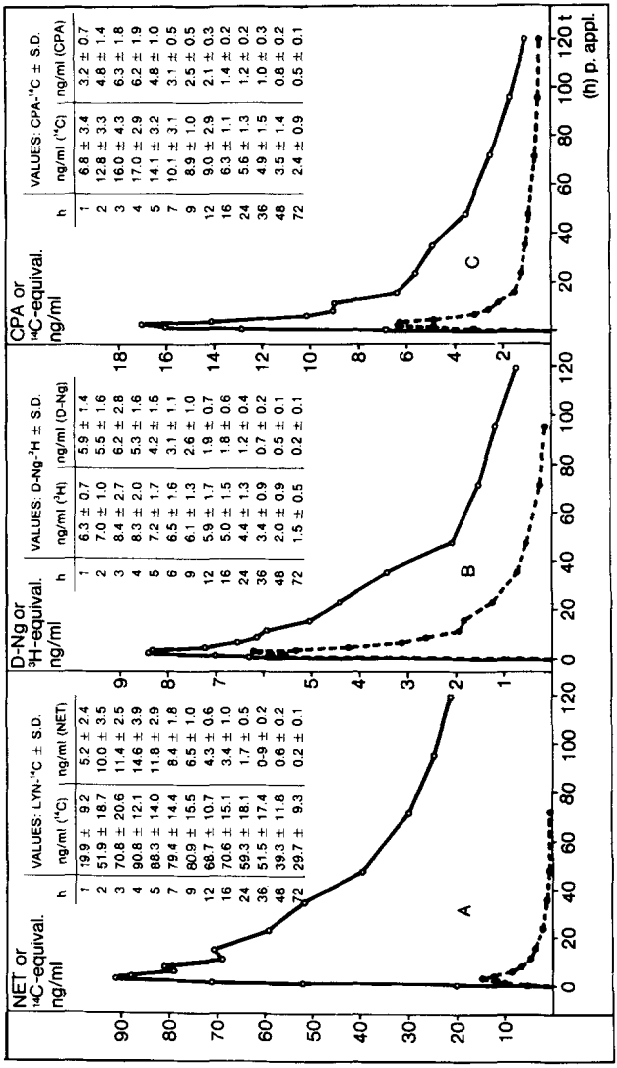
Three progestogens were studied pharmacokinetically in an intraindividual comparison in 6 women within a randomised trial design. Following oral administration of 2.0 mg cyproterone acetate-methylene-$^{14}$C (CPA), 2.5 mg lynestrenol-4-$^{14}$C (Lyn) or 0.25 mg d-norgestrel-$^{3}$H (d-Ng), the course of the total activity in plasma, the elimination of the total activity with urine and faeces and the course of the substance concentration in plasma (RIA) were determined. Each progestogen was administered together with 50 µg ethinyloestradiol in an identical galenic formulation.

The mean (n = 6) plasma level of the total radioactivity and of the radioimmunologically determined substance following administration of each of the progestogens is presented in Figure 2. The maximum radioactivity in the total plasma volume was 8.6 ± 2.3 % (d-Ng), 10.4 ± 1.7 % (Lyn) and 2.0 ± 0.3 (CPA) of the dose. 24 hours after the administration, 3.9 ± 1.2 % of the dose, 6.7 ± 2.4 % of the dose and 0.63 ± 0.14 % of the dose, respectively, could still be demonstrated in the total plasma.

As measured against the area under the mean plasma curve of the total activity (days 0 - 5), the mean area under the substance curve was 31.2 % (d-Ng), 3.8 % (Lyn) and 26.7 % (CPA).

As could be observed from the semilogarithmic plot of the values, the fall in the plasma concentration of each of the three progestagens took place in two disposition phases. Disposition phase 1 was recognisable in the period of time between the maximum plasma level and 12 - 16 hours after administration, and passed for all three substances with half-lives between 3 and 4 hours. In the period of time from 24 hours to day 3 (5), the plasma concentration fell more slowly and with a half-life characteristic for each substance (disposition phase 2: $t_{1/2}$d-Ng = 1.1 ± 0.3 d, $t_{1/2}$NET = 0.69 ± 0.03 d, $t_{1/2}$CPA = 2.0 ± 0.4 d).

The terminal half-life of the total activity in plasma was 1.5 ± 0.2 d (d-Ng), 2.5 ± 0.6 d (Lyn) and 1.7 ± 0.5 d (CPA).




| h | VALUES: LYN-$^{14}$C ± S.D. ng/ml ($^{14}$C) | ng/ml (NET) |
|---|---|---|
| 1 | 19.9 ± 9.2 | 5.2 ± 2.4 |
| 2 | 51.9 ± 18.7 | 10.0 ± 3.5 |
| 3 | 70.8 ± 20.6 | 11.4 ± 2.5 |
| 4 | 90.8 ± 12.1 | 14.6 ± 3.9 |
| 5 | 88.3 ± 14.0 | 11.8 ± 2.9 |
| 7 | 79.4 ± 14.4 | 8.4 ± 1.8 |
| 9 | 80.9 ± 15.5 | 6.5 ± 1.0 |
| 12 | 68.7 ± 10.7 | 4.3 ± 0.6 |
| 16 | 70.6 ± 15.1 | 3.4 ± 1.0 |
| 24 | 59.3 ± 18.1 | 1.7 ± 0.5 |
| 36 | 51.5 ± 17.4 | 0.9 ± 0.2 |
| 48 | 39.3 ± 11.8 | 0.6 ± 0.2 |
| 72 | 29.7 ± 9.3 | 0.2 ± 0.1 |

| h | VALUES: D-Ng-$^{3}$H ± S.D. ng/ml ($^{3}$H) | ng/ml (D-Ng) |
|---|---|---|
| 1 | 6.3 ± 0.7 | 5.9 ± 1.4 |
| 2 | 7.0 ± 1.0 | 5.5 ± 1.6 |
| 3 | 8.4 ± 2.7 | 6.2 ± 2.8 |
| 4 | 8.3 ± 2.0 | 5.3 ± 1.6 |
| 5 | 7.2 ± 1.7 | 4.2 ± 1.6 |
| 6 | 6.5 ± 1.6 | 3.1 ± 1.1 |
| 9 | 6.1 ± 1.3 | 2.6 ± 1.0 |
| 12 | 5.9 ± 1.7 | 1.9 ± 0.7 |
| 16 | 5.0 ± 1.5 | 1.8 ± 0.6 |
| 24 | 4.4 ± 1.3 | 1.2 ± 0.4 |
| 36 | 3.4 ± 0.9 | 0.7 ± 0.2 |
| 48 | 2.0 ± 0.9 | 0.5 ± 0.1 |
| 72 | 1.5 ± 0.5 | 0.2 ± 0.1 |

| h | VALUES: CPA-$^{14}$C ± S.D. ng/ml ($^{14}$C) | ng/ml (CPA) |
|---|---|---|
| 1 | 6.8 ± 3.4 | 3.2 ± 0.7 |
| 2 | 12.8 ± 3.3 | 4.8 ± 1.4 |
| 3 | 16.0 ± 4.3 | 6.3 ± 1.8 |
| 4 | 17.0 ± 2.9 | 6.2 ± 1.9 |
| 5 | 14.1 ± 3.2 | 4.8 ± 1.0 |
| 7 | 10.1 ± 3.1 | 3.1 ± 0.5 |
| 9 | 8.9 ± 1.0 | 2.5 ± 0.5 |
| 12 | 9.0 ± 2.9 | 2.1 ± 0.3 |
| 16 | 6.3 ± 1.1 | 1.4 ± 0.2 |
| 24 | 5.6 ± 1.3 | 1.2 ± 0.2 |
| 36 | 4.9 ± 1.5 | 1.0 ± 0.3 |
| 48 | 3.5 ± 1.4 | 0.8 ± 0.2 |
| 72 | 2.4 ± 0.9 | 0.5 ± 0.1 |

Figure 2: Mean plasma levels of the total activity (o—o) and the radioimmunologically determined active substance (●--●) after a single oral administration of 2.5 mg lynestrenol-4-$^{14}$C (A), 0.25 mg d-norgestrel-$^{3}$H (B) and 2.0 mg cyproterone acetate-$^{14}$C-methylene (C) in 6 women; each of the progestogens was administered together with 50 µg ethinyl oestradiol in an identical galenic preparation (intraindividual comparison with a randomised trial design); the mean values ± SD are presented in the tables.

The elimination (urine, faeces) of the 19-nor progestogens took place with a shorter half-life ($t_{1/2} \approx 1$ d) than that of cyproterone acetate ($t_{1/2} \approx 1.9$ d). d-Ng and Lyn were eliminated to a greater extent (48.5 ± 7.5 and 49.9 ± 9.5 % of the dose) in urine than cyproterone acetate (30.4 ± 7.4 % of the dose). The quotient of the elimination urine:faces was 1.1 for d-Ng, 1.3 for Lyn and 0.5 for CPA, with comparable mean balances of 94.8 ± 4.4 % of the dose (d-ng), 88.5 ± 6.2 % of the dose (Lyn) and 88.2 ± 11.5 % of the dose (CPA) (Figure 3, Table II).

Table III presents the results of the statistical evaluation of the individual pharmakokinetic data, the mean values of which are given in Table II.

## DISCUSSION

The pharmacokinetic data (Table II) of the three progestogens examined are in good agreement with values from the literature (d-Ng: 3, 4, 5, 6, 11, 12, 13, 14; CPA: 7, 8, 9, 10, 16; Lyn: 1, 2, 15) and with our own unpublished results (d-Ng).

Differences between the present data and those published by other authors can be attributed to different formulations ($t_{max}$, $C_{max}$) (e.g. CPA: 7, 8; d-Ng: 12, 13; Lyn: 2, 15) or can be explained by an altered pharmacokinetic evaluation of the plasma levels (11, 14, 28, 29).

The absorption of the substances from the chosen galenic formulation took place somewhat more slowly than from the original preparations with the same dose. However, the elimination of the total activity in urine indicates complete absorption of the substances in every case.

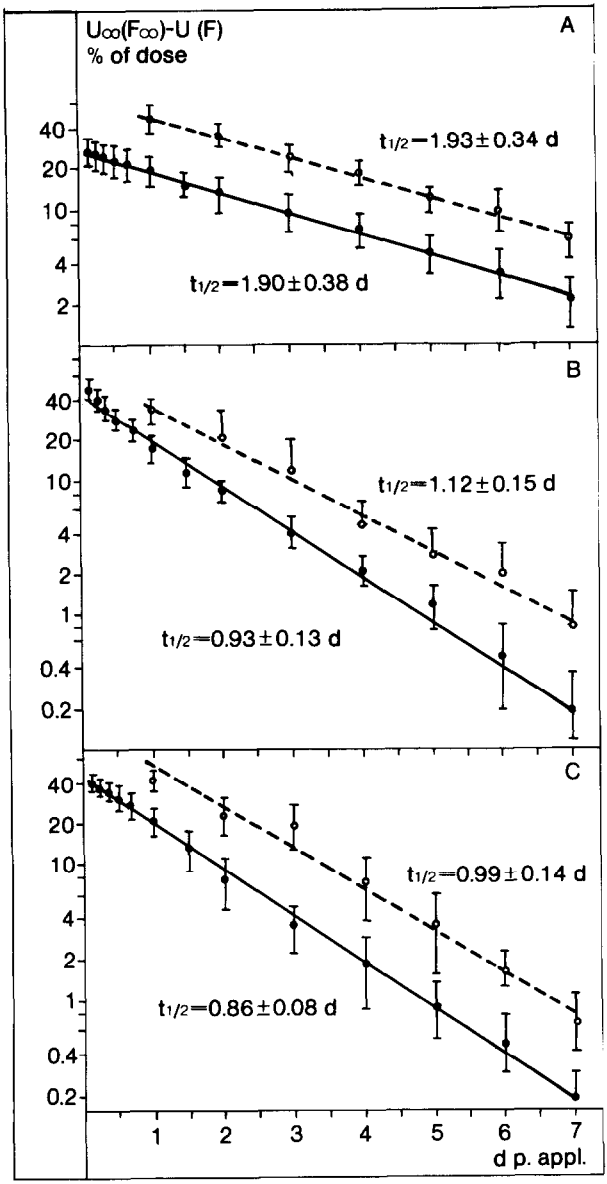



Figure 3. Semilogarithmic presentation of the elimination of the total activity with urine (•—•) and faeces (o-o) after a single oral administration of CPA-$^{14}$C (A), Lyn-$^{14}$C (B) and D-Ng-$^{3}$H (C); Mean values of 6 women; cf. figure 2 and table I for doses and trial design.

Table II. Intraindividual comparison of pharmacokinetic data after single oral application of three synthetic progestional compounds to six healthy women; the compounds were applied each together with 50 µg ethinyloestradiol as identical galenic formulation (gelatine capsules) in biologically relevant dosages, i.e. 0.25 mg d-norgestrel, 2.5 mg lynestrenol, 2.0 mg cyproterone acetate; values are given as mean ± S.D. (n = 6); application was randomised according to a latin square design

| Compound Label (Position) Measurement | d-Norgestrel 15 - 16 $^{3}H$ | | Lynestrenol 4 - $^{14}C$ | | Cyproterone acetate $^{14}C$-Methylene | |
|---|---|---|---|---|---|---|
| | Total Activity | Drug (d-NG) | Total Activity | Drug (NET) | Total Activity | Drug (CPA) |
| Plasma Level | | | | | | |
| t max (h) | 3.3± 0.5 | 2.2± 1.3 | 4.0± 0.6 | 3.8± 1.0 | 3.5±0.5 | 3.7± 0.8 |
| C max (ng/ml) | 9.2± 2.2 | 7.1± 2.0 | 92.8± 11.4 | 15.1± 4.2 | 18.6± 3.8 | 7.2± 1.4 |
| $t_{1/2}$D.Phase 1 (h) | * | 3.0± 0.6 | * | 3.7± 0.4 | 3.0± 1.6 | 3.0± 1.8 |
| Range of calculation (h) | – | 2± 1-14± 2 | – | 5-16 | 4± 1-9± 2 | 4± 1-16± 5 |
| $t_{1/2}$D.Phase 2 (d) | 1.5± 0.2 | 1.10± 0.30 | 2.5± 0.6 | 0.69± 0.03 | 1.7± 0.5 | 2.00± 0.40 |
| Range of calculation (d) | 0.5–5.0 | 1–5 | 0.5–5.0 | 1–3 | 0.5–5.0 | 1–5 |
| Elimination | | | | | | |
| $t_{1/2}$urine (d) | 0.86± 0.08 | * | 0.93± 0.13 | * | 1.90± 0.38 | * |
| % of dose urine | 48.5± 7.5 | * | 49.9± 9.5 | * | 30.4± 7.4 | * |
| $t_{1/2}$faeces (d) | 0.99± 0.14 | * | 1.12± 0.15 | * | 1.93± 0.34 | * |
| % of dose faeces | 46.3± 6.5 | * | 38.6± 6.1 | * | 57.8± 6.9 | * |
| Balance (% of dose) | 94.8± 4.4 | * | 88.5± 6.2 | * | 88.2± 11.5 | * |

Abrevations:
t max = time (h) after application, when maximal concentration occurred
C max = concentration (ng/ml Plasma) at t max
$t_{1/2}$ = half life
D.Phase 1 = first visible disposition phase
D.Phase 2 = terminal disposition phase
Drug = radioimmunological data as specified
S.D. = standard deviation according to S.D. = $\sqrt{\frac{\sum x^2 - \frac{(\sum x)^2}{n}}{n-1}}$
* = no calculation possible

Table III. Study of the pharmacokinetic parameters of d-norgestrel, lynestrenol and cyproterone acetate for significant differences* (intraindividual comparison in 6 women)

| | Significance between | | | |
|---|---|---|---|---|
| | D-Ng and Lyn | D-Ng and CPA | Lyn and CPA | boundary difference |
| Parameter | | | | |
| $t_{1/2}$ D.Ph. 1 (Drug) | 0 | 0 | 0 | – |
| $t_{1/2}$ D.Ph. 2 (T.A.) | – | 0 | + | 0.8 d |
| $t_{1/2}$ D.Ph. 2 (Drug) | + | – | – | 0.4 d |
| $t_{1/2}$ urine (T.A.) | 0 | – | – | 10.3 h |
| $t_{1/2}$ faeces (T.A.) | 0 | – | – | 11.5 h |
| % of D. urine (T.A.) | 0 | + | + | 14.2 % of D. |
| % of D. faeces (T.A.) | + | – | – | 3.8 % of D. |
| Balance | 0 | 0 | 0 | – |

Legend

$\pm$) significance: first value $\begin{matrix}\text{larger}\\ \text{smaller}\end{matrix}$) second value; risk of error $\alpha = 0.05$ %

T.A.: total activity
D.Ph.: disposition phase
$t_{1/2}$: half life
% of D.: percent of dose

*The null hypothesis A= B=C was tested with the aid of the F-test. In the case of rejection of the hypothesis, it was decided by means of the Tukey-test between which treatments differences can be assumed.

The literature contains only little if any reference data on the size and course of the respective substance level in plasma. Gerhards et al. (4) reported peak values of about 3 ng d-norgestrel/ml plasma after administration of 250 µg d-norgestrel to one male volunteer. Weiner et al. (12) recently reported d-Ng levels following oral administration of 250 µg d-Ng to five women, which are in very good agreement with the present values. The linearity of the area under the CPA plasma level following oral administration of 2 and 50 mg cyproterone acetate has already been discussed (17). Because of the "prodrug character" of lynestrenol (23, 25, 26, 27), no substance level of the orally administered substance can be measured. However, the concentrations of norethisterone determined in plasma following oral administration of lynestrenol are in very good agreement with NET plasma levels determined after oral administration of norethisterone (28, 29, 30, 31).

Some remarkable differences with respect to the pharmacokinetics of the three progestogens can be recognised from the present intraindividual comparison:

1) Plasma levels (total activity)
   In comparison to d-norgestrel or cyproterone acetate, the plasma level of total activity following oral administration of lynestrenol-$^{14}$C falls only slowly.

   The terminal fall in the concentration took three times longer than the elimination of the total activity with urine, while the corresponding values for d-Ng and CPA almost coincide. 5 days after the administration of Lyn-$^{14}$C, the concentration of radioactive metabolites in plasma was still higher than at the point of time of maximum plasma level following administration of CPA-$^{14}$C. The high concentration of $^{14}$C-Lyn metabolites in plasma is also highlighted by the small amount of the substance relative to the $^{14}$C-plasma level in comparison to d-Ng or CPA. On daily administration of the three progestogens (steady state), the plasma concentration of metabolites in the case of lynestrenol will increase as a result of accumulation to about 20 - 15-fold higher values than in the case of d-norgestrel or cyproterone acetate.

2) Plasma levels (substance)
   Disposition phase 1, which should be characterized principally by distribution processes, passes with approximately the same

speed for all three progestogens ($t_{1/2}$ = 3 - 4 hours). However, significant differences exist between the three substances with respect to the speed of the terminal fall in the plasma level from 24 hours after administration. Within the variation, the half-life of this process also corresponds to the half-life of the respective elimination of the total activity with urine and faeces. The active substance of lynestrenol, norethisterone, accordingly displays the shortest ($t_{1/2}$ = 0.69 ± 0.03 d), d-norgestrel a medium ($t_{1/2}$ = 1.1 ± 0.3 d) and cyproterone acetate the longest half-life ($t_{1/2}$ = 2.0 ± 0.4 d). The absolute values established are in good agreement with the values of Weiner et al. (12) for d-norgestrel and those of Hümpel et al. (16) for CPA. For norethisterone, Fotherby and Warren (28) found a half-life of about 6 hours, whereby the varying values (6 hours in comparison to 16 - 17 hours) can be explained by a changed evaluation of the measured data.

3) Elimination (total activity)
The elimination of the total activity in urine following administration of lynestrenol and d-norgestrel took place at a comparable rate (half-life approx. 1 day). Just as this value is well documented for 19-nor progestogens (e.g. 1, 2, 11, 14, 24), the rate of elimination of $^{14}$C-CPA can be compared with the elimination of chlormadinone acetate (32).

The same is also true with respect to both substances for the absolute portion of the dose eliminated with urine. The portion of the dose eliminated with faeces supplemented the portion of the dose eliminated with urine to an average of about 90 % of the dose in each case, which, in view of the problems involved in obtaining and measuring the samples, can be regarded as almost complete elimination in the period of observation.

4) Biological consequences
An oral progestogen for daily administration should not be eliminated or metabolically inactivated so quickly that it cannot provide a substance level adequate for the biological effect for as long as 36 or 48 hours after the last ingestion. Because of their half-lives, d-norgestrel and particularly cyproterone acetate have this desirable property. Lynestrenol or its conversion product,

norethisterone, can fulfill this requirement to only a very much lower extent because of the extremely short terminal half-life. On the other hand, metabolites of lynestrenol will accumulate in plasma to a considerable extent and, in comparison to the other two substances, out of all proportion to the active substance (NET). Why such a high concentration of plasma metabolites is present after administration of lynestrenol but not after d-norgestrel or CPA has not yet been elucidated. One possible interpretation consists in the assumption that the conversion of Lyn to NET is not 100 % and does not take place without competing side reactions, and leads to the formation of polar metabolites of lynestrenol. Because of the presumably low fictive distribution volume of these metabolites in comparison to the active substance, even the formation of a small amout could lead to a high plasma level of these compounds. The slow terminal half-life ($t_{1/2}$ 2.5 d) would speak in favour of a lower clearance of the components which cannot be extracted from plasma by means of ether.

As measured by the dose administered and in a comparison of the three substances, d-Ng leads to the highest substance concentration in plasma, which is probably attributable to high plasma protein binding (34). The extent to which this observation is connected with the biological activity of d-norgestrel has not yet been clarified.

## REFERENCES

1. Kamyab, S., Fotherby, K. and Klopper, A.I. Metabolism of (4-$^{14}$C)-lynestrenol in man. J Endocrinol 42: 337-343 (1968)

2. van der Molen, H.J., Hart, P.G. and Wijmengen, H.G. Studies with 4-$^{14}$C-lynestrenol in normal and lactating women. Acta Endocrinol 61: 255-274 (1969)

3. Littleton, P., Fotherby, K. and Dennis, K.J. Metabolism of ($^{14}$C)-norgestrel in man. J Endocrinol 42: 591-598 (1968)

4. Gerhards, E., Hecker, W., Hitze, H., Nieuweboer, B. and Bellmann, O. Zum Stoffwechsel von Norethisteron (17α-Aethinyl-4-östren-17β-ol-3-on) und dl- sowie d-Norgestrel (18-Methyl-17α-äthinyl-4-östren-17β-ol-3-on) beim Menschen. Acta Endocrinol 68: 219-248 (1971)

5. Zaldivar, A. and Gallegos, A.J. Metabolism and tissue localization of (14,15-$^{3}$H)-d-norgestrel in the human. Contraception 4: 169-182 (1971)

6. Hendeles, S.M., Galand, N. and Schwers, J. Metabolism of orally administered d-norgestrel in women. Acta Endocrinol 71: 557-568 (1972)

7. Speck, U., Jentsch, D., Kühne, G., Schulze, P.E. and Wendt, H. Bioverfügbarkeit und Pharmakokinetik von Cyproteronacetat-$^{14}$C nach Applikation als 50-mg-Tablette. Arzneim Forsch 26: 1717-1720 (1976)

8. Speck, U., Wendt, H., Schulze, P.E. and Jentsch, D. Bioavailability and pharmacokinetics of cyproterone acetate-$^{14}$C and ethinyloestradiol-$^{3}$H after oral administration as a coated tablet (SH B 209 AB). Contraception 14: 151-163 (1976)

9. Gerhards, E., Gutsche, H. and Riemann, I. Biodynamik von 1,2α-Methylen-6-chlor-pregna-4,6-dien-17α-acetoxy-3,20-dion (Cyproteronacetat) nach oraler Verabreichung beim Menschen. Arzneim Forsch 23: 1550-1555 (1973)

10. Kolb, K.H. and Roepke, H. Die Pharmakokinetik von Cyproteronacetat. Eine vergleichende Untersuchung bei Mensch und Pavian. Int J Clin Pharmacol 1: 184-190 (1968)

11. Fotherby, K., Kamyab, S., Littleton, P. and Klopper, A.I. Metabolism of synthetic progestational compounds in humans. J Reprod Fertil Suppl. 5: 51-61 (1968)

12. Weiner, E., Victor, A. and Johansson, E.D.B. Plasma levels of d-norgestrel after oral administration. Contraception 14: 563-570 (1976)

13. Stanczyk, F.Z., Hiroi, M., Goebelsmann, U., Brenner, P.F., Lumkin, M.E. and Mishell, D.R., Jr. Radioimmunoassay of serum d-norgestrel in women following oral and intravaginal administration. Contraception 12: 279-298 (1975)

14. Warren, R.J. and Fotherby, K. Metabolism of d- and l-norgestrel in humans. Arzneim Forsch 25: 964-965 (1975)

15. Littleton, P., Phil, M. and Bhamarapravati, Y. Metabolism of 4-$^{14}$C-lynestrenol in Thai women. J Int Med Res 2: 409-417 (1974)

16. Hümpel, M., Dogs, G., Wendt, H. and Speck, U. Plasmaspiegel und Pharmakokinetik von Cyproteronacetat nach oraler Applikation als 50-mg-Tablette bei 5 Männern. Arzneim Forsch, in press (1977)

17. Hümpel, M., Wendt, H., Dogs, G., Weiβ, Chr. and Speck, U. Bioavailability and pharmacokinetics of cyproterone acetate after oral administration of 2.0 mg cyproterone acetate in combination with 50 μg ethinyloestradiol to 6 young women. Contraception, 15:579 (1977)

18. Hümpel, M., Wendt, H., Kühne, C. and Dogs, G. Pharmacokinetics of ethinyloestradiol given in combination with d-norgestrel, lynestrenol and cyproterone acetate. In preparation

19. Spona, J., Weiner, E., Nieuweboer, B., Hümpel, M., Schneider, W. H.F. and Johansson, E.D.B. Injectable depot contraceptives on d-norgestrel basis. II. Clinical pharmacokinetic studies with d-norgestrel-undecylate in women. Contraception, 15:413 (1977)

20. Morris, S.E., Nieuweboer, B. and Cameron, E.H.D. In preparation

21. Nieuweboer, B. and Lübke, K. Radioimmunological determination of cyproterone acetate. Horm Res, in press

22. Abraham, G.E. Solid-phase radioimmunoassay of estradiol-17β. J Clin Endocrinol Metab 29: 866 (1969)

23. Fotherby, K. Metabolism of synthetic steroids by animals and man. In: Pharmacological models in contraceptive development, WHO Symposium, Geneva, 1973, p. 119-147

24. Mazaheri, A., Fotherby, K. and Chapman, J.R. Metabolism of lynestrenol to norethisterone by liver homogenate. J Endocrinol 47: 251-252 (1970)

25. Ishihara, S. Experimental studies on the aromatization of some synthetic progestins. Folia Endocrinol Japon 42: 55-68 (1966/67)

26. Mutara, S. Metabolism of 17α-ethinyl-19-nortestosterone and 17α-ethinyl-estrenol *in vivo*. Folia Endocrinol Japon 43: 1083-1096 (1967/68)

27. Yamamoto, J. Metabolism of 17α-ethinyl-estrenol in rabbit. Folia Endocrinol Japon 44: 1309-1319 (1968/69)

28. Fotherby, K. and Warren, R.J. Bioavailability of contraceptive steroids from capsules. Contraception 14: 261-267 (1976)

29. Warren, R.J. and Fotherby, K. Radioimmunoassay of synthetic progestogens, norethisterone and norgestrel. J Endocrinol 62: 1-14 (1974)

30. Morris, S.E. and Cameron, E.H.D. Radioimmunoassay system for norethisterone using $^{3}H$- and $^{125}I$-labbeld radioligands. J Steroid Biochem 6: 1145-1150 (1975)

31. Nygren, K.G., Lindberg, P., Martinsson, K., Bosu, W.T.K. and Johansson, E.D.B. Radioimmunoassay of norethindrone: peripheral plasma levels after oral administration to humans and rhesus monkeys. Contraception 9: 265-278 (1974)

32. Dorfman, R.I. Chlormadinone acetate: some pharmacological, toxicological and pharmacokinetic aspects in various species, in Kewitz, H. Nebenwirkungen kontrazeptiver Steroide, Symposium in Berlin, 1971, p. 139-171

33. Bhargava, A.S., Seeger, A. and Guenzel, P. Isolation and identification of 15β-hydroxy-cyproterone acetate as a new metabolite of cyproterone acetate in dog, monkey and man. In preparation

34. Victor, A., Weiner, E. and Johansson, E.D.B. Sex hormone binding globulin: the carrier protein for d-norgestrel. J Clin Endocrinol Metab 43: 244-247 (1976)

35. Weiner, E. and Johansson, E.D.B. Effects on the ovarian function of subcutaneous implants containing lynestrenol. Acta Obstet Gynecol Scand Suppl 47: 50 (1976)