

Pharmacokinetics of Etonogestrel and Ethinylestradiol Released from a Combined Contraceptive Vaginal Ring

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Abstract

Objective: To assess the pharmacokinetics of etonogestrel and ethinylestradiol released from a novel combined contraceptive vaginal ring (NuvaRing[®]) releasing etonogestrel 120µg and ethinylestradiol 15µg per day and compare them with those of a combined oral contraceptive containing desogestrel 150µg/ethinylestradiol 30µg (DSG/EE COC).

Design and setting: This was a nonblind, randomised, crossover study in 16 healthy women.

Methods: All volunteers received one cycle of DSG/EE COC before being randomised to 1 of 2 treatment groups. The participants in group 1 received 1 cycle of DSG/EE COC, a treatment period with NuvaRing[®] and an intravenous bolus injection of etonogestrel/ethinylestradiol (150µg/30µg). Those in group 2 received a NuvaRing[®] treatment period, 1 cycle of DSG/EE COC and the same intravenous bolus injection.

Results and conclusions: After the insertion of NuvaRing[®], maximum serum concentrations of etonogestrel and ethinylestradiol were achieved in approximately 1 week. The concentrations subsequently showed a gradual linear decrease in time. The maximum serum concentrations of etonogestrel and ethinylestradiol were approximately 40 and 30%, respectively, of those for the DSG/EE COC. In comparison with the DSG/EE COC, the absolute bioavailability for NuvaRing[®] was higher for etonogestrel (102.9 vs 79.2%) and similar for ethinylestradiol (55.6 vs 53.8%). Taking the difference in daily doses into account, systemic exposure to etonogestrel was similar for NuvaRing[®] and the DSG/EE COC, whereas systemic exposure to ethinylestradiol with NuvaRing[®] was only approximately 50% of that for the DSG/EE COC.

Steroid-releasing contraceptive vaginal rings were first described in 1970.^[1] These rings showed several advantages over oral contraceptives. Due to the controlled release mechanism, contraceptive vaginal rings achieved steroid concentrations that were more uniform throughout the day as distinct from the daily fluctuations in steroid concentrations associated with oral contraceptive use. Further-

more, peak steroid concentrations occurred only once per cycle.^[1] In addition, the vaginal route of administration avoids hepatic first-pass metabolism and gastrointestinal interference with the absorption of steroids, allowing lower steroid doses to be used.^[2,3]

N.V. Organon has developed a combined contraceptive vaginal ring containing the progestagen

etonogestrel and the estrogen ethinylestradiol (NuvaRing®). NuvaRing® is a flexible, soft, transparent ring made of ethylene vinyl acetate copolymer, with an outer diameter of 54mm and a cross-sectional diameter of 4mm. Each ring has a declared daily release rate of etonogestrel 120µg and ethinylestradiol (EE) 15µg over a period of 3 weeks of use. Both etonogestrel and ethinylestradiol are well established as the biologically active steroids in a number of contraceptive products.^[4]

NuvaRing® is to be used for 1 cycle, which consists of a 3-week period of continuous ring use followed by a 1-week ring-free period. The present study evaluated the pharmacokinetics and pharmacodynamics of etonogestrel and ethinylestradiol as released by NuvaRing® under normal use conditions (3 weeks) as well as prolonged use, where the ring was left in place for an additional 2 weeks (i.e. a total of 35 days of use). The additional period allowed evaluation of the effects if women do not remove NuvaRing® after the recommended period of use.

The objectives of the study were to assess the pharmacokinetics of etonogestrel and ethinylestradiol for NuvaRing® and to compare them with those of a desogestrel 150µg/ethinylestradiol 30µg combined oral contraceptive (DSG/EE COC). The pharmacodynamic results will be presented elsewhere.

Methods

This nonblind, randomised, crossover pharmacokinetic study was conducted at the Kendle Clinical Pharmacology Unit in Utrecht, The Netherlands, between January and May 1998. The study was performed in accordance with the Declaration of Helsinki, the International Committee for Harmonisation for Good Clinical Practice and current regulatory regulations. All participants entering the trial provided written informed consent.

Study Population

16 women, aged 18 to 35 years, in good physical and mental health and with a body mass index of 18 to 29 kg/m² were enrolled. Prior to onset of any

oral contraceptive use, participants were required to have had a usual cycle duration of 24 to 35 days \pm 3 days. Participants had to have good venous accessibility and good visibility of both ovaries upon ultrasonography.

The women were excluded if they had any contraindications for contraceptive steroid use as described in the current labelling of COC products. There were also some specific NuvaRing®-related exclusion criteria, which comprised cervicitis, vaginitis or a bleeding erosio portionis; diagnosis at screening of a cervical smear Papanicolaou class III, IV or V; prolapse of uterine cervix, cystocele, and/or rectocele; severe or chronic constipation; and dyspareunia or other coital problems.

Study Design

All trial medication was supplied by N.V. Organon, Oss, The Netherlands. All participants had received at least 1 DSG/EE COC cycle (21 days of pill intake followed by a 7-day pill-free period) before the start of the treatment period. This step was required for pharmacodynamic assessments. Participants were then randomised to 1 of 2 treatment groups; both groups received the same treatments but in different orders.

The women in group 1 received 21 days of DSG/EE COC intake, a 7-day pill-free period and then a 35-day treatment period with NuvaRing® followed by a ring-free period. An intravenous bolus injection of etonogestrel/ethinylestradiol (150µg/30µg) was administered in the morning of the third day after removal of NuvaRing®.

Those in group 2 received 35 days of treatment with NuvaRing® followed by a 7-day ring-free period and then 21 days of DSG/EE COC intake followed by a pill-free period. The intravenous bolus injection of etonogestrel/ethinylestradiol was administered in the morning of the fourth day after the last tablet intake.

After the last pill of a COC regimen, steady-state concentrations of both steroids are maintained for the following 24 hours, whereas steroid concentrations for ring users decrease from the moment of ring removal. Therefore, the timing of the intra-

venous bolus injections (the third day after ring removal in group 1 and the fourth day after last pill intake in group 2) was effectively similar. The wash-out periods before the intravenous bolus administration were deliberately chosen to be short in order to maintain sufficiently elevated sex hormone-binding globulin (SHBG) serum levels: SHBG levels are known to influence the serum concentrations of etonogestrel.^[5] The total duration of the study was 72 days.

During screening, but before the start of the NuvaRing[®] treatment period, participants were instructed how to insert and remove the ring and also received written instructions. After insertion, the ring was kept inserted continuously until the scheduled removal day. Removal occurred at approximately the same time of day as insertion. If necessary, the ring could be removed before intercourse, as long as it was reinserted within 3 hours. The use of condoms as a protective method against sexually transmitted diseases was permitted. Furthermore, condoms were to be used in case the pharmacodynamic assessments (vaginal ultrasonography) indicated the presence of a follicle with a diameter of 13mm or higher.

The women were instructed to take their DSG/EE COC tablets in the morning (in view of pharmacokinetic assessment). If a participant forgot to take a tablet, she was instructed to take it as soon as she remembered.

The intravenous bolus injection of etonogestrel/ethinylestradiol (etonogestrel 150µg and ethinylestradiol 30µg) dissolved in 10ml of NaCl 0.9% was administered – within 1 minute – in the morning of day 67 of the study period.

At screening, the women provided a medical and gynaecological history. They underwent a medical and gynaecological examination, evaluation of routine laboratory parameters and a drug screen. A home pregnancy test was performed just before the first pill was taken or insertion of the ring; trial medication was started only if the test was negative. Blood samples were collected for both the pharmacokinetic (serum concentrations of etonogestrel and ethinylestradiol) and pharmaco-

dynamic (serum hormone levels) assessments. Questioning as to the occurrence of adverse events and use of concomitant medication took place throughout the trial. In addition to the medications listed in the labelling of COC products, concomitant use of sex steroids other than the trial medication was prohibited. A medical and gynaecological examination, and evaluation of routine laboratory parameters, were also performed on the last study day.

Blood samples (4.5ml) for assessments of serum concentrations of etonogestrel and ethinylestradiol were taken at the following times:

- 5 minutes before the last DSG/EE COC tablet (i.e. day 21 in group 1, day 63 in group 2) and 15 and 30 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48 and 72 hours after the last tablet
- 5 minutes before the insertion of NuvaRing[®] (i.e. day 29 in group 1, day 1 in group 2) and 6, 8, 12, 16, 24, 48, and 72 hours thereafter, then on alternate days for the remainder of the NuvaRing[®] treatment period (i.e. days 34 to 62 for group 1 or days 6 to 34 for group 2)
- 5 minutes before the removal of NuvaRing[®] (i.e. day 64 in group 1, day 36 in group 2) and 3, 6, 12, 24 and 48 hours after removal
- 5 minutes before the bolus injection of etonogestrel/ethinylestradiol (day 67 in both groups 1 and 2) and 5, 10, 15, 30 and 45 minutes and 1, 1.5, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 120 hours after the injection.

Blood samples (1.5ml per sample) for assessment of serum SHBG levels were only collected once daily per sampling day. Throughout the study, the total amount of blood collected per participant was approximately 400ml. Blood samples were processed to serum and stored at -20°C until assays were performed.

Etonogestrel and Ethinylestradiol Assays

Etonogestrel and ethinylestradiol were isolated from serum (1 ml) by solid-phase extraction using C-18 columns. The extract was concentrated and further purified by high-performance liquid chromatography (HPLC) employing a silica col-

umn to remove potentially cross-reacting compounds. The HPLC-purified fractions were assayed for etonogestrel and ethinylestradiol by radioimmunoassay, using polyclonal rabbit antisera specific for each compound as the primary antibodies. The quantification range was 30 to 720 ng/L for etonogestrel and 2 to 48 ng/L for ethinylestradiol; interassay coefficients of variation were 7.23 to 11.0% for etonogestrel and 6.08 to 20.8% for ethinylestradiol.

A validation study established that there were no endogenous components that interfered with the quantification assays; cross-reactivities of the etonogestrel assay [at the 50% effective dose (ED_{50})] were <0.01% for ethinylestradiol, testosterone, estrone, pregnenolone and cortisol. For the ethinylestradiol assay (at the ED_{50}), cross-reactivity was 0.04% for etonogestrel and $\leq 0.004\%$ for testosterone, estrone, progesterone and cortisol.

Assay of Sex Hormone-Binding Globulin

SHBG was determined by time-resolved fluoroimmunoassay (AutoDELFLIA SHBG Kit, Wallac Oy, Turku, Finland). The overall precision of the assay, expressed as the total coefficient of variation of the quality control samples, was 4.7 to 5.7%. The accuracy of the quality control samples ranged from 103.8 to 112.9%. The lower and higher limits of quantification were 6.25 and 200 nmol/L, respectively.

Assay of Residual Etonogestrel and Ethinylestradiol in Rings

A used vaginal ring was cut into pieces of <2mm. The pieces were extracted into 160ml of methanol for 20 hours. An aliquot of the solution was then analysed by HPLC, using C18 columns; absorbance was monitored at 210nm. The relative standard deviations of the injections for etonogestrel and ethinylestradiol were $\leq 1.5\%$.

Pharmacokinetic Assessments

From the plot of the serum concentrations of etonogestrel and ethinylestradiol versus time, the

maximum serum concentration (C_{max}) and the time of its occurrence (t_{max}) were assessed for each of the 3 routes of administration. Concentrations measured during the terminal log-linear phase were used to estimate the elimination half-life ($t_{1/2\beta}$) for all 3 routes of administration. The area under the concentration-time curve (AUC) for all routes of administration was calculated by means of the linear trapezoidal rule.

Use of NuvaRing[®] resulted in gradually decreasing serum concentrations for both etonogestrel and ethinylestradiol. Therefore, instead of steady-state concentrations, the mean serum concentrations were calculated for each week of NuvaRing[®] use. Furthermore, the slope of the individual regression lines fitted to the serum concentrations from day 7 to 35 of NuvaRing[®] was calculated. Steady-state serum concentrations (C_{ss}) as well as minimum steady-state concentrations ($C_{ss,min}$) for both etonogestrel and ethinylestradiol were calculated for the DSG/EE COC. The apparent plasma clearance (CL/F) was calculated as the total amount released from NuvaRing[®] during the insertion period (determined from the residual hormone content of used rings) divided by the AUC to infinity (AUC_{∞}), or as the daily dose/ AUC_{24} for DSG/EE COC. The absolute bioavailability of etonogestrel and ethinylestradiol for NuvaRing[®] and the DSG/EE COC were determined using the intravenous data as reference. For the intravenous bolus injection, the volume of distribution was also calculated. SHBG serum levels were plotted against time. Except for descriptive statistics, the pharmacokinetic parameters of SHBG serum levels were not determined.

Statistics

Descriptive statistics were used for the serum concentrations (etonogestrel, ethinylestradiol and SHBG) as well as the pharmacokinetic parameters by route of administration. Serum concentrations of etonogestrel and ethinylestradiol were analysed separately over the recommended period of NuvaRing[®] use (the first 21 days) and the period of extended use (days 22 to 35). The values of $t_{1/2\beta}$ for

Table I. Demographics and vital signs

Parameter	Group 1		Group 2	
	mean (SD)	range	mean (SD)	range
Age (years)	26.5 (3.2)	22-30	23.0 (2.9)	18-26
Bodyweight (kg)	66.8 (8.3)	51-76	62.3 (9.1)	51-79
Height (cm)	172.1 (5.9)	160-179	166.0 (5.1)	159-174
BMI (kg/m ²)	22.5 (1.8)	20-25	22.5 (2.4)	19-27
SBP (mm Hg)	117.3 (6.7)	110-130	125.3 (9.3)	110-134
DBP (mm Hg)	77.8 (5.9)	70-88	77.3 (6.1)	68-88
Heart rate (bpm)	65.8 (11.4)	44-80	65.3 (8.3)	44-80

BMI = body mass index; **bpm** = beats per minute; **DBP** = diastolic blood pressure; **SBP** = systolic blood pressure; **SD** = standard deviation.

the 3 routes of administration were compared using an analysis of variance (ANOVA) for repeated-measures design applied to the log-transformed values. Results were considered significant if $p \leq 0.05$. The slope of the individual regression lines fitted to the concentrations from day 7 to 35 of NuvaRing[®] use was tested for difference from zero using Student's t-test.

Results

Demographics and Baseline Characteristics

16 women were randomised to treatment group 1 ($n = 8$) or 2 ($n = 8$). All completed the total treat-

ment period. There was no clinically relevant difference between the 2 groups in demographics and vital signs at screening (table I). Most participants were Caucasian with the exception of 2 women allocated to group 2 who were mixed Caucasian/Asian. Neither the general medical history nor the physical examination revealed any clinically relevant findings in any of the participants. All the women had a normal cervical smear (Papanicolaou class I) and pelvic examinations that did not reveal any abnormalities. In addition, the results of the drug screening and urinary pregnancy tests performed before inserting the ring

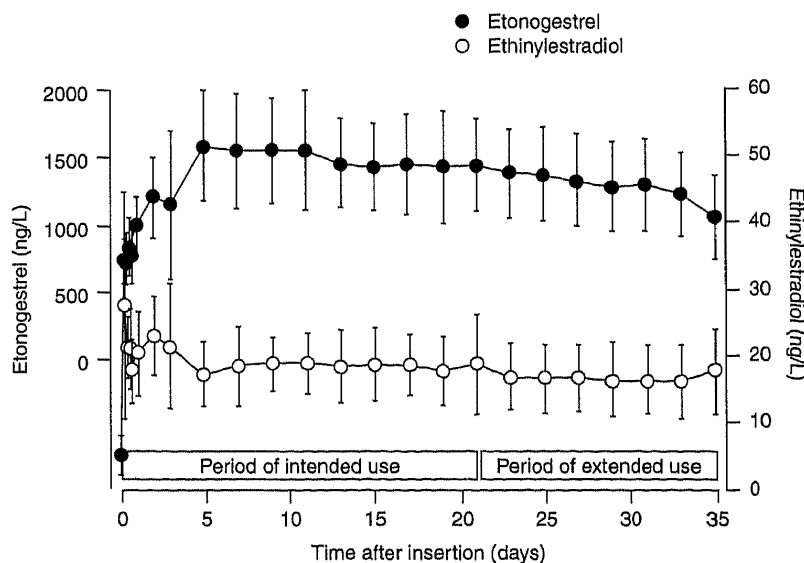


Fig. 1. Serum concentration–time curve (mean \pm standard deviation; $n = 16$) of etonogestrel and ethinylestradiol during treatment with NuvaRing[®] [days 1 to 21 (intended use) and days 22 to 35 (extended use)].

Table II. Mean serum concentrations (\pm standard deviation) of etonogestrel and ethinylestradiol at the end of weeks 1 to 3 (intended use) and 4 to 5 (extended use) of NuvaRing[®]

Concentration (ng/L)	Intended use			Extended use	
	week 1	week 2	week 3	week 4	week 5
Etonogestrel	1578 \pm 408	1476 \pm 362	1374 \pm 328	1272 \pm 311	1170 \pm 313
Ethinylestradiol	19.1 \pm 4.5	18.3 \pm 4.3	17.6 \pm 4.3	16.8 \pm 4.6	16.1 \pm 5.1

(group 2) or taking the first pill (group 1) were negative for all participants.

Serum Etonogestrel and Ethinylestradiol Concentrations

Serum etonogestrel concentrations during NuvaRing[®] use increased during the first week and then gradually decreased (fig. 1). The individual regression lines fitted to the etonogestrel concentrations from day 7 up to day 35 of NuvaRing[®] use showed a mean slope of -14.57 ng/L per day ($p = 0.0001$). This equated to a decreasing trend of the mean serum etonogestrel concentration of approximately 100 ng/L per week (table II). The C_{\max} of etonogestrel with NuvaRing[®] was 40% of that for the DSG/EE COC (table III). In contrast to the daily peak concentrations found with COCs, peak concentrations only occur once per cycle with NuvaRing[®].

The mean etonogestrel concentration at the end of the first week of NuvaRing[®] use (1578 ng/L;

table II) was similar to the average steady-state concentration of etonogestrel for the DSG/EE COC (1617 ng/L; table III). Etonogestrel concentrations during the remaining period of NuvaRing[®] use were found to be lower than the average steady-state concentration for the DSG/EE COC, but still higher than the $C_{ss,\min}$ of DSG/EE COC.

Figure 1 also shows the mean serum concentration of ethinylestradiol during NuvaRing[®] use. These concentration reached a peak 2 to 3 days after insertion and then gradually decreased by 0.77 ng/L per week (table II). The individual regression lines fitted to the ethinylestradiol concentrations from day 7 to 35 of NuvaRing[®] use showed a mean slope of -0.11 ng/L per day ($p = 0.0063$). The C_{\max} of NuvaRing[®] was 30% of that for DSG/EE COC (table IV). As with etonogestrel, peak ethinylestradiol concentrations only occur once per cycle with NuvaRing[®].

The mean ethinylestradiol concentrations after the first week of NuvaRing[®] use (19.1 ng/L; table

Table III. Pharmacokinetic parameters for etonogestrel (means \pm standard deviation)

Parameter	NuvaRing [®] (n = 16)	DSG/EE COC (n = 16)	IV (n = 9 ^a)
t_{\max} (h)	200.3 \pm 69.6	1.3 \pm 0.8	0.1 \pm 0.0
C_{\max} (ng/L)	1716 \pm 445	4273 \pm 830	10 298 \pm 2585
$C_{ss,\min}$ (ng/L)	NA	1004 \pm 405	NA
C_{ss} (ng/L) ^b	NA	1617 \pm 491	NA
$t_{1/2\beta}$ (h) ^c	29.3 \pm 6.1	30.2 \pm 5.2	28.4 \pm 3.4
Apparent clearance (L/h)	3.4 \pm 0.8	4.4 \pm 1.2	3.7 \pm 0.9
Bioavailability (%)	102.9 \pm 12.8	79.2 \pm 7.7	100

a Because of a blood sampling error, the intravenous data of 7 of the women could not be used. Blood was sampled from the same cannula as used for the bolus injection, and therefore these samples were contaminated with residues of etonogestrel and ethinylestradiol from the surface of the cannula.

b Calculated as $(AUC_{24})/24$ on day 21 of the oral preparation.

c The median values of $t_{1/2\beta}$ were 29.4h (NuvaRing[®]), 29.4h (DSG/EE COC) and 29.5h (IV).

AUC = area under the concentration-time curve; **AUC₂₄** = area under the concentration-time curve to 24 hours; **C_{max}** = peak serum drug concentration; **C_{ss}** = steady-state drug concentration; **C_{ss,min}** = minimum steady-state drug concentration; **DSG/EE COC** = combined oral contraceptive containing desogestrel 150 μ g/ethinylestradiol 30 μ g; **IV** = intravenous bolus of etonogestrel 150 μ g/ethinylestradiol 30 μ g; **NA** = not applicable; $t_{1/2\beta}$ = elimination half-life; t_{\max} = time to C_{\max} .

Table IV. Pharmacokinetic parameters for ethinylestradiol (means \pm standard deviation)

Treatment	NuvaRing [®] (n = 16)	DSG/EE COC (n = 16)	IV (n = 9 ^a)
t_{\max} (h)	59.3 \pm 67.5	1.2 \pm 0.4	0.1 \pm 0.0
C_{\max} (ng/L)	34.7 \pm 17.5	124.9 \pm 46.3	598 \pm 191
$C_{\text{ss,min}}$ (ng/L)	NA	17.2 \pm 7.0	NA
C_{ss} (ng/L) ^b	NA	34.5 \pm 10.8	NA
$t_{1/2\beta}$ (h) ^c	44.7 \pm 28.8	29.5 \pm 16.7	37.2 \pm 20.0
Apparent clearance (L/h)	34.8 \pm 11.6	39.6 \pm 12.2	19.0 \pm 4.9
Bioavailability (%)	55.6 \pm 12.9	53.8 \pm 17.6	100

a Because of a blood sampling error, the intravenous data of 7 of the women could not be used. Blood was sampled from the same cannula as used for the bolus injection, and therefore these samples were contaminated with residues of etonogestrel and ethinylestradiol from the surface of the cannula.

b Calculated as $(\text{AUC}_{24})/24$ on day 21 of the oral preparation.

c The median values of $t_{1/2\beta}$ were 33.9h (NuvaRing[®]), 24.6h (DSG/EE COC) and 25.1h (IV).

AUC = area under the concentration-time curve; **AUC₂₄** = area under the concentration-time curve to 24 hours; **C_{max}** = peak serum drug concentration; **C_{ss}** = steady-state drug concentration; **C_{ss,min}** = minimum steady-state drug concentration; **DSG/EE COC** = combined oral contraceptive containing desogestrel 150 μ g/ethinylestradiol 30 μ g; **IV** = intravenous bolus of etonogestrel 150 μ g/ethinylestradiol 30 μ g; **NA** = not applicable; **t_{1/2 β}** = elimination half-life; **t_{max}** = time to **C_{max}**.

II) were lower than the average steady-state concentrations achieved with the DSG/EE COC (34.5 ng/L; table IV). The ethinylestradiol concentrations during NuvaRing[®] use were similar to the $C_{\text{ss,min}}$ of the DSG/EE COC (table IV).

The etonogestrel and ethinylestradiol concentration time-curves during the ring-free period were approximately log-linear from 6 hours onwards for most participants. Ethinylestradiol concentrations 72 hours after the removal of the NuvaRing[®] were frequently below the lowest level of quantification

and therefore were not used for the estimation of $t_{1/2\beta}$ (fig. 2). For DSG/EE COC, the terminal log-linear phase for both etonogestrel and ethinylestradiol started at approximately 16 hours after administration (fig. 2).

For the intravenous injection, the terminal log-linear phase for both etonogestrel and ethinylestradiol began approximately 36 hours after administration (fig. 2). The ethinylestradiol concentrations at 96 and 120 hours after the intravenous bolus were frequently found to be below the lowest lev-

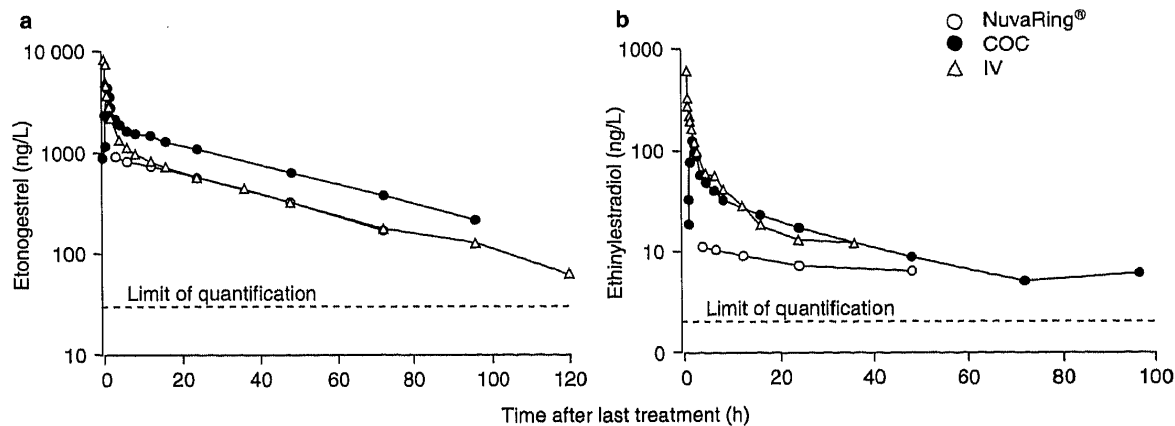


Fig. 2. Serum concentration-time curves (mean values) of (a) etonogestrel and (b) ethinylestradiol immediately after treatment with NuvaRing[®] (n = 16), the last tablet of a combined oral contraceptive (COC) containing desogestrel 150 μ g/ethinylestradiol 30 μ g (n = 16) or a single intravenous injection (IV) of etonogestrel 150 μ g/ethinylestradiol 30 μ g (n = 9).

els of quantification and, therefore, were not used for the estimation of $t_{1/2\beta}$. As expected, there were no statistically significant differences between the 3 routes of administration in the $t_{1/2\beta}$ of etonogestrel or ethinylestradiol.

The absolute bioavailability of etonogestrel for NuvaRing[®] was 102.9% versus 79.2% for DSG/EE COC (table III). The absolute bioavailability for ethinylestradiol was similar for NuvaRing[®] and the DSG/EE COC (55.6% and 53.8%, respectively) (table IV).

The mean SHBG levels versus time by group are depicted in figure 3. As expected, SHBG levels decreased during the pill- and ring-free periods as a result of lack of exposure to ethinylestradiol. Approximately 1 week after exposure to NuvaRing[®], plateau levels for SHBG were achieved. The SHBG levels measured during NuvaRing[®] use were found to be slightly higher for group 1 than for group 2 throughout the whole treatment period. At the time of administration of the intravenous bolus injection, similar levels were found for participants in both treatment groups.

Safety

Treatments with NuvaRing[®], DSG/EE COC and the etonogestrel/ethinylestradiol intravenous bolus injection were all well tolerated. Physical and pelvic examination after the treatment period revealed no clinically relevant abnormalities or changes in any of the women. Furthermore, assessment of routine laboratory and vital signs did not reveal any clinically relevant abnormalities or changes compared with the screening values.

None of the women discontinued treatment during this study.

Discussion

NuvaRing[®] is a novel combined contraceptive vaginal ring releasing on average etonogestrel 120µg and ethinylestradiol 15µg per day. Each ring is intended to be used for 1 cycle which consists of a 3-week period of continuous use followed by a 1-week ring-free period. The present study evaluated the pharmacokinetics of etonogestrel and

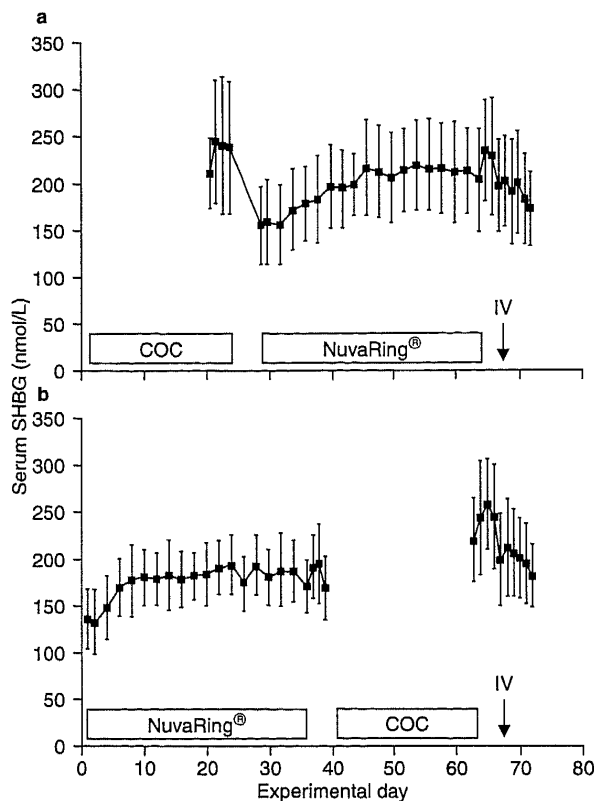


Fig. 3. Mean serum sex hormone-binding globulin (SHBG) concentrations (\pm standard deviation) in (a) group 1 ($n = 8$) and (b) group 2 ($n = 8$) during treatment with NuvaRing[®], a combined oral contraceptive (COC) containing desogestrel 150µg/ethinylestradiol 30µg or following a single intravenous injection (IV) of etonogestrel 150µg/ethinylestradiol 30µg.

ethinylestradiol as released by NuvaRing[®] under both normal use conditions (3 weeks) as well as prolonged use for 2 additional weeks. The latter allowed evaluation of the pharmacokinetics in women who would accidentally not remove the ring after the recommended 3 week period of use. The pharmacokinetics of NuvaRing[®] were compared with those of a desogestrel 150µg/ethinylestradiol 30µg COC.

After insertion of NuvaRing[®], maximum serum concentrations of etonogestrel were achieved after approximately 1 week. The serum concentration for etonogestrel subsequently showed a gradual, linear decrease in time from day 7 to 21. This linear decrease continued in the period of prolonged use,

that is up to day 35. The ethinylestradiol concentrations showed a similar pattern, but reached their maximum around day 2 or 3.

The C_{\max} values for etonogestrel and ethinylestradiol were approximately 40 and 30%, respectively, of those for the DSG/EE COC and, because of the controlled release formulation, occurred only once per cycle.

The absolute bioavailability of etonogestrel for NuvaRing[®] was higher (103%) than that for the DSG/EE COC (79%). Taking the difference in daily etonogestrel dose into account for NuvaRing[®] and the DSG/EE COC (120 vs 150 µg, respectively), the difference in absolute bioavailability results in similar systemic exposure to etonogestrel for both routes of administration. In contrast, the absolute bioavailability of ethinylestradiol for NuvaRing[®] was similar to that of the DSG/EE COC (approximately 55% for both routes of administration). This means that the difference in daily ethinylestradiol dose between NuvaRing[®] and the DSG/EE COC (15 vs 30 µg) is also reflected in the systemic exposure. It is most likely that the approximately 55% absolute bioavailability of ethinylestradiol with NuvaRing[®] is due to incomplete absorption in the vagina.

Despite the lower systemic exposure to ethinylestradiol for NuvaRing[®] compared with DSG/EE COC, the pharmacodynamics, that is, suppression of ovarian function, of the 2 methods were comparable (unpublished observations). Apparently, the controlled release profiles obtained with NuvaRing[®] offer a clinical advantage.

As was expected, the elimination half-lives for both etonogestrel and ethinylestradiol associated with each of the 3 routes of administration were found to be similar.

The synthesis of SHBG by the liver is known to be increased by estrogens and decreased by both androgens and progestogens.^[6] SHBG levels increased during the treatment periods with both NuvaRing[®] and the DSG/EE COC, and decreased in the subsequent ring- and pill-free periods. Most probably because of the difference in ethinylestradiol exposure between the 2 routes of admin-

istration, mean SHBG levels were significantly higher after 1 cycle of DSG/EE COC use (211 nmol/L) than after 3 weeks of NuvaRing[®] use (186 nmol/L; $p = 0.0056$).

Since etonogestrel is known to be extensively bound to serum proteins, predominantly SHBG and albumin,^[5] the serum concentrations of etonogestrel are dependent on SHBG levels. The latter is, among others, reflected in the difference in t_{\max} for etonogestrel and ethinylestradiol during NuvaRing[®] use (8 vs 3 days, respectively). The t_{\max} of 8 days for etonogestrel is comparable with the time needed for SHBG levels to reach its maximum. Furthermore, the washout period prior to the intravenous bolus injection with the etonogestrel/ethinylestradiol solution was deliberately chosen to be short so that sufficiently elevated serum SHBG levels were maintained. At the time of administration of the intravenous injection, the SHBG levels in both groups were similar, thereby avoiding the need for corrections of the 'intravenous' pharmacokinetic parameters for etonogestrel.

In conclusion, the pharmacokinetics of NuvaRing[®] show that steroid serum concentrations are highest at the end of the first week of use, after which they show a gradual linear decrease over time. The C_{\max} values for etonogestrel and ethinylestradiol were approximately 40 and 30%, respectively, of those for the DSG/EE COC. In comparison with the DSG/EE COC, the absolute bioavailability for NuvaRing[®] was higher for etonogestrel (102.9 vs 79.2%) and similar for ethinylestradiol (55.6 vs 53.8%). As a consequence, taking the difference in daily doses for etonogestrel and ethinylestradiol into account, the systemic exposure to etonogestrel was similar for NuvaRing[®] and DSG/EE COC, whereas the systemic exposure with NuvaRing[®] to ethinylestradiol was only approximately 50% of that for the DSG/EE COC.

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