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Comparison of ethinylestradiol pharmacokinetics in three hormonal contraceptive formulations: the vaginal ring, the transdermal patch and an oral contraceptive

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Abstract

This open-label, randomized study compared the pharmacokinetics of ethinylestradiol (EE) from the contraceptive vaginal ring NuvaRing (15 μg EE/day), the transdermal patch (20 μg EE/day) and a combined oral contraceptive (COC) containing 30 μg EE. After 2–8 weeks of synchronization by COC treatment, subjects were randomized to 21 days of treatment with NuvaRing, patch or COC. Analysis of area under the EE concentration-versus-time curve (AUC) during 21 days of treatment showed that exposure to EE in the NuvaRing group was 3.4 times lower than in the patch group ($p<.05$) and 2.1 times lower than in the pill group ($p<.05$). Serum EE levels of subjects showed much lower variation with NuvaRing than with the patch or the COC. Thus, exposure to EE was significantly lower with NuvaRing than with the patch and pill methods, demonstrating that NuvaRing is a low-estrogen-dose contraceptive method that also results in low estrogen exposure.

Keywords: NuvaRing; Oral contraceptive; Transdermal contraceptive patch; Ethinylestradiol; Pharmacokinetics

1. Introduction

NuvaRing® (NV Organon, Oss, The Netherlands) is a monthly contraceptive vaginal ring that releases 15 μg of ethinylestradiol (EE) and 120 μg of etonogestrel (ENG) daily. Vaginal administration of contraceptive hormones allows low, steady and continuous dosing and results in stable serum concentrations. NuvaRing has been shown to produce mean serum EE concentrations of 19 pg/mL and maximum serum concentrations (C_{max}) of 35 pg/mL [1]. The benefits of this low, precise dosing include lower systemic exposure to EE and a low incidence of estrogen-related side effects [2,3].

The transdermal patch is a weekly combined contraceptive method designed to deliver 20 μg EE and 150 μg norelgestromin daily. Transdermal administration using an abdominal application site has been reported to produce steady-state EE concentrations of 58–71 pg/mL and C_{max} values of 74–96 pg/mL [4]. It is notable that although the patch delivers more EE daily than NuvaRing, its pharmacokinetic profile suggests that serum EE concentrations are higher than might be expected based solely on the amount of EE delivered by each formulation.

The oral route of administration of contraceptive hormones is very well established. The pharmacokinetic profile of EE from a combined oral contraceptive (COC) containing 30 μg EE and 150 μg desogestrel (Marvelon®) has previously been compared with that of NuvaRing. This COC delivers twice as much EE as NuvaRing and, as would be expected, produced mean serum EE concentrations that were approximately twice as high as those produced by NuvaRing [1]. Daily dosing produces characteristic peaks and troughs in contraceptive hormone serum concentrations, which accounts for the C_{max} values of the COC being more than twice as high as that of NuvaRing in the study by Timmer and Mulders [1].

A widely used COC containing 30 μg of EE and 150 μg levonorgestrel (Microgynon®, Schering, Berlin, Germany) has been reported to produce mean area-under-the-curve

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(AUC) values over 24 h at steady state (AUC_{0-24}) of 728–778 pg·h/mL, which approximates the mean steady-state serum EE concentrations of 30–32 pg/mL [5]. The pharmacokinetics of this COC have not been directly compared with those of NuvaRing, but it would be reasonable to expect that exposure to EE with this COC would be approximately twice as high as that with NuvaRing.

The objective of this study was to directly compare the pharmacokinetics of EE released from three hormonal contraceptive methods that use different routes of administration (vaginal, transdermal and oral). Such a three-way pharmacokinetic comparison has not previously been reported and it will be of interest to gain an insight into EE exposure from these different contraceptive formulations.

2. Materials and methods

This randomized, open-label, parallel-group trial was conducted at a single center in the Netherlands between March and June 2004. The study protocol was approved by the Independent Ethics Committee of the trial center and was conducted in accordance with the Declaration of Helsinki and the ICH Guideline for Good Clinical Practice. All subjects provided written informed consent before screening.

The primary objective of this trial was to compare the pharmacokinetics of EE released from NuvaRing, the transdermal contraceptive patch and a COC.

2.1. Subjects

It was intended that 24 healthy women aged 18–40 years would be recruited and evaluated for pharmacokinetic analysis. Major inclusion criteria included a body weight of ≤90 kg (upper weight limit for the patch), a body mass index of <30 kg/m^2 and a willingness to refrain from consuming food or drink containing caffeine, xanthine or alcohol from 24 h before the administration of trial medication until the last blood sample for pharmacokinetic analysis had been obtained. Subjects also had to be willing to refrain from smoking from 7 days prior to the study start until after the last blood sample had been taken and from consuming food or drink containing grapefruit from 14 days before the first administration of trial medication until the last blood sample for pharmacokinetic analysis had been obtained. Major exclusion criteria included known or suspected pregnancy; contraindications to the use of the contraceptive vaginal ring, patch or COC; breast-feeding within the last 2 months before the trial; use of a contraceptive injection, implant or intrauterine device during the 6 months prior to the start of the trial; use of any systemic medication during the 14 days prior to the trial or any substance known to induce liver enzyme metabolism (including over-the-counter medication) during the 2 months prior to the trial; smoking more than five cigarettes or one pipe or one cigar per day; a cervical smear result of Papanicolaou class III or higher; and acute or chronic hepatitis B/C or HIV infection.

For the sample size calculation, it was assumed that mean EE concentrations would be 20, 40 and 60 pg/mL during one 21-day cycle of treatment with NuvaRing, the COC and the patch, respectively [1,4,6] The number of subjects required to detect a difference of 20 pg/mL between groups with a power of ≥90% at $\alpha = 0.05$, assuming a between-subjects coefficient of variation of 40%, was eight per group.

2.2. Interventions

Subjects were screened and then entered (within 21 days) a synchronization period in which they received a COC containing 30 μg EE and 150 μg levonorgestrel (Microgynon) daily for 2–8 weeks. Subjects who were already using a COC were given instructions on starting synchronization by the investigator and those who were not already using a COC started their synchronization on days 1–3 of their normal menstrual cycle. After synchronization, subjects underwent a 7-day pill-free period before entering the active treatment phase of the study. The active phase started with the random allocation of subjects to 21 days of treatment with a contraceptive vaginal ring releasing 15 μg EE and 120 μg ENG (NuvaRing), three consecutive 7-day applications of a contraceptive transdermal patch releasing 20 μg EE and 150 μg norelgestromin daily (Evra™, Ortho-McNeil Pharmaceutical, Raritan, NJ) or 21 days of treatment with the COC (Microgynon).

The contract research organization, Farma Research BV, was responsible for the conduct of the trial, including allocation of subjects to treatment by means of computer randomization using SAS/STAT® computer software. The trial was carried out at the trial center of Farma Research BV in Nijmegen, the Netherlands.

All subjects remained in the trial center from the evening of the day before the start of active treatment (day −1) to the morning of day 2. In addition, subjects remained in the center from the evening of day 21 until the morning of day 23 in the NuvaRing group, between the evenings of days 7 and 8 and days 14 and 15 and from the evening of day 21 until the morning of day 23 in the patch group and from the evening of day 20 to the morning of day 22 in the COC group. In addition, subjects visited the trial center on days 3, 4, 6, 8, 10, 12 14, 16, 18, 20, 24 and 25 in the NuvaRing group, on days 3, 4, 6, 7, 9, 10, 11, 13, 14, 16, 17, 18, 20, 21, 24 and 25 in the patch group and on days 3, 4, 5, 7, 9, 11, 13, 15, 17, 19, 22, 23 and 24 in the COC group. A posttreatment follow-up examination took place between days 26 and 30 in all groups.

2.2.1. Ring insertion

Vaginal rings were inserted by subjects (under supervision) in the morning of day 1 of active treatment and removed at the same time on day 22. Subjects were not

allowed to remove the rings during treatment and made daily records of the number of hours of ring use in a diary. Subjects made daily checks to ensure that the ring was in place. If the ring was accidentally removed, this was to be recorded and the ring reinserted or replaced.

2.2.2. Patch application

The first patch was applied on day 1 and removed on day 8; second patch, days 8 and 15, respectively; and third patch, days 15 and 22, respectively. Patches were applied and removed under supervision at the study center with the abdomen used as the application site. Subjects made daily records of the number of hours of patch use in a diary. Subjects also made daily checks to ensure that the patch was in place. In case of accidental removal, this was recorded and the patch reapplied (if possible) or replaced.

2.2.3. Pill intake

Pills were taken under supervision in the study center on days 1–5, 7, 9, 11, 13, 15, 17, 19 and 21. On other days, subjects took the pill at home, without supervision, and used a diary card to record the time and date of intake. After the intake of the first pill, all subsequent pills were taken at 24-h intervals at the same time of day.

2.3. Assessments

2.3.1. Pharmacokinetic analysis

Serial blood samples (10 mL) for pharmacokinetic analysis were taken in the NuvaRing group immediately prior to and at 6, 8, 12, 16, 24, 48, 72, 120, 168, 216, 264, 312, 360, 408, 456 and 504 h after ring insertion and at 3, 6, 12, 16, 24, 48 and 72 h after ring removal. In the patch group, blood samples were taken immediately prior to and at 6, 12, 24, 48, 72, 120, 144 and 168 h after each patch application as well as 6, 12, 24, 48 and 72 h after the last (third) patch was removed. In the pill group, blood samples were collected immediately prior to and at 0.5, 1, 1.5, 2, 3, 4, 6, 9 and 12 h after tablet intake on days 1 and 21, immediately prior to and 1.5 h after tablet intake on days 2, 3, 4, 5, 7, 9, 11, 13, 15, 17 and 19 and at 24, 36, 48 and 72 h after the last tablet intake.

After collection, blood samples were processed to serum and frozen. Concentrations of EE were measured by a previously described radioimmunoassay [1] following high-performance liquid chromatography purification (limit of quantification 2.25 pg/mL). Assessment of serum concentrations of EE was performed by PPD Development (Richmond, VA).

2.3.2. Other assessments

Compliance and extent of exposure to study medication were assessed using diary cards. The time and date of NuvaRing insertion and removal, patch application and removal and COC intake were all recorded using diary cards. Subjects were not allowed to remove the ring or the patch during the treatment period. If this happened, it had to be documented using the diary card.

Subjects provided a medical history and underwent a cervical smear test and an electrocardiographic examination at screening. Pregnancy tests were carried out at screening, during synchronization and on day −1.

2.3.3. Tolerability

At screening and follow-up, subjects underwent a physical examination, assessment of vital signs and laboratory parameters. Information on adverse events was collected by regular questioning and by examining subjects.

2.4. Statistical analysis

Serum EE concentrations were plotted using concentration-versus-time plots for each subject. The arithmetic mean concentrations (with 95% confidence intervals for mean values) were graphically depicted by treatment.

The pharmacokinetic parameters that were evaluated for EE concentrations for each treatment were AUC, average serum concentration over the 21-day treatment period (C_{av}), the peak concentration (C_{max}), its time of occurrence (t_{max}) and the elimination half-life during washout ($t_{½}$). The AUC parameters investigated covered the periods days 0–21 ($AUC_{0–21}$, i.e., AUC during treatment period), day 0 until the time of the last measurable concentration ($AUC_{0–tlast}$, i.e., AUC including washout until t_{last}) and day 0 to infinity ($AUC_{0–\infty}$, i.e., AUC including washout until infinity). The $AUC_{0–21}$ and $AUC_{0–tlast}$ were calculated using the linear trapezoidal rule. The $AUC_{0–\infty}$ was calculated as $AUC_{0–tlast}$ extrapolated to infinity using the regression line from which $t_{½}$ was calculated.

To calculate the AUC for the COC group, a compartmental model was fitted to the measured EE data using nonlinear mixed effects modeling. For the best data fit, a two-compartmental model was used with first-order absorption and first-order elimination from the central compartment with (log-normally distributed) interindividual variability on clearance (CL), volume of distribution of central (V2) and peripheral (V3) compartment and on the intercompartmental clearance (Q). Lag time was added to model the delay in absorption, and addition of body weight further improved the fit of the model. Individual model parameters were estimated by applying the estimated COC model to individual serum concentrations. These model parameters were used to predict complete concentration-versus-time profiles for each subject using the time points from the actual sampling schedule on days 1 and 21 to fill in the same sampling time points on days 2–20. These predicted concentration-versus-time profiles were used to calculate the AUC parameters for subjects in the COC group.

The pharmacokinetic parameters AUC and C_{max} were logarithmically transformed and then analyzed using one-way analysis of variance (ANOVA) with treatment as a factor. Treatments were compared in pairs by calculating the ratio of geometric means and producing point estimates with 95% confidence intervals. Effects were considered statistically significant if $p \leq .05$.

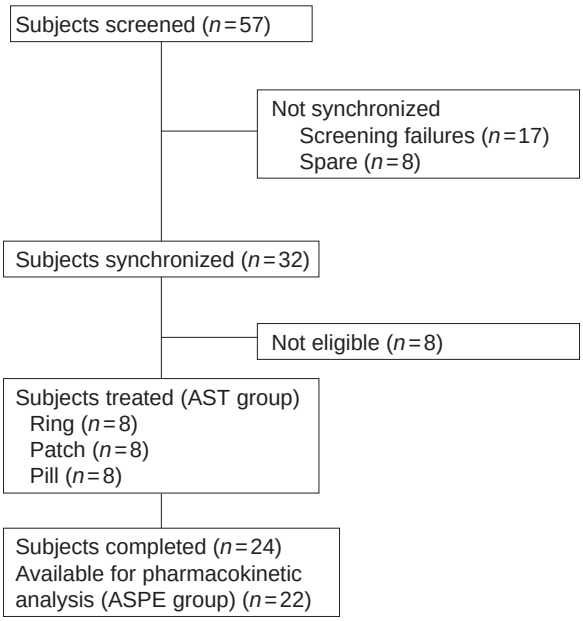

Fig. 1. Subject disposition.

Pharmacokinetic evaluations were carried out on the all-subjects-pharmacokinetically evaluable (ASPE) group, which comprised all treated subjects who did not have any protocol variations and for whom the pharmacokinetic parameter $AUC_{0–21}$ could be calculated.

Tolerability analysis was restricted to descriptive statistics and was performed on the all-subjects-treated (AST) group, which comprised all subjects who took at least one dose of study medication.

3. Results

3.1. Study population

Of the 24 subjects who were randomized to treatment, all completed the study and comprised the AST group. Two subjects in the patch group had to use replacement patches after experiencing problems with patch detachment and were excluded from the pharmacokinetic analysis. The ASPE group therefore comprised 22 subjects (Fig. 1).

The three groups were well matched in terms of demographic and baseline characteristics (Table 1). All subjects were Caucasian except for two who were black (one in the patch group and one in the COC group).

Table 1
Demographic and baseline characteristics at screening (ASPE group)

	NuvaRing (n=8)	Patch (n=6)	COC (n=8)
Age (years)	23.3±3.6	25.3±7.6	25.8±5.3
Weight (kg)	61.2±6.4	70.4±9.6	67.4±13.9
Height (cm)	167±5.5	171±9.3	169±5.9
Body mass index (kg/m^2)	21.9±2.3	24.0±2.7	23.3±3.7

Values are means with standard deviations.

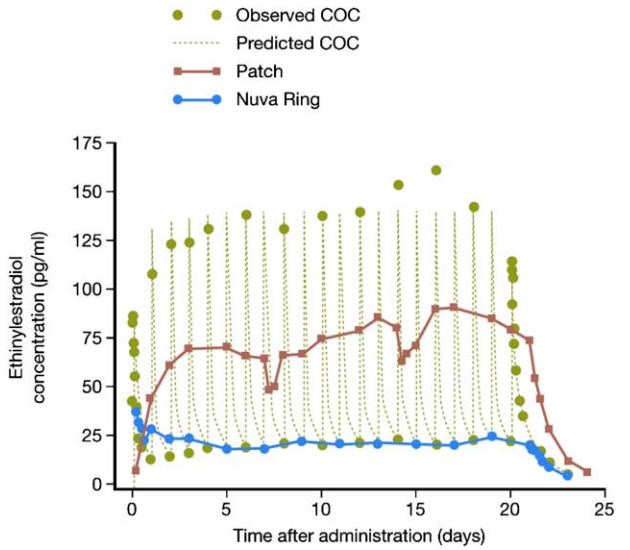

Fig. 2. Mean EE C-t curves for subjects (ASPE group) treated with NuvaRing (n=8), the transdermal contraceptive patch (n=6) and the COC (n=8).

3.2. Pharmacokinetics

The mean concentration-versus-time curves (C-t curves) revealed markedly different patterns in serum EE concentrations with the three contraceptive formulations (Fig. 2). The pharmacokinetic profiles shown in Fig. 2 are in line with those reported previously in separate studies of the three methods [1,4,5].

The pharmacokinetic parameters for EE are summarized in Table 2. Statistical analysis of the primary pharmacokinetic parameters using ANOVA showed that the differences between treatments were statistically significant for all treatment comparisons (Table 3). Of the three contraceptive methods, exposure to EE was highest for the patch group. The mean $AUC_{0–21}$ in the patch group was 3.4 times higher than in the NuvaRing group and 1.6 times higher than in the pill group ($p<.05$ for both comparisons). The same observation (same order of magnitude) was made for the mean C_{av} values (Table 2). The highest mean C_{max} was seen in the contraceptive pill group, which was 4.5 times higher than in the NuvaRing group and 1.6 times higher than in the patch group ($p<.05$ for both comparisons). The mean C_{max} for the patch group was 2.8 times higher compared with the NuvaRing group ($p<.05$).

Table 2
Summary of EE pharmacokinetic parameters (ASPE group)

	NuvaRing (n=8)	Patch (n=6)	COC (n=8)
C_{max} (pg/mL)	37.1±5.1	105±12.4	168±29.5
t_{max} (h)	6.0 (6.0–11.8)	372.0 (240–456)	386 (337–434)
$t_{½}$ (h)	20.7± 4.1	20.2±2.9	24.4±7.0
$AUC_{0–21}$ (ng · h/mL)	10.6±2.5	35.8±5.5	21.9±2.9
$AUC_{0-tlast}$ (ng · h/mL)	11.1±2.7	37.5±5.7	22.5±2.9
$AUC_{0-\infty}$ (ng · h/mL)	11.2±2.7	37.7±5.6	22.7±2.8
C_{av} (pg/mL)	21.1±5.01	70.9±11.0	43.5±5.66

Values are arithmetic means with standard deviations, except for t_{max}, which is presented as median values (with ranges).

Table 3
ANOVA for primary pharmacokinetic parameters (ASPE group)

	Geometric mean			Ratio of point estimates (95% confidence interval)		
	NuvaRing ($n=8$)	Patch ($n=6$)	COC ($n=8$)	COC/NuvaRing	Patch/NuvaRing	Patch/COC
C_{max} (pg/mL)	36.8	104.0	165	4.5 (3.9–5.3)*	2.8 (2.4–3.4)*	0.63 (0.53–0.75)*
AUC_{0-21} (ng · h/mL)	10.4	35.4	21.7	2.1 (1.7–2.6)*	3.4 (2.8–4.2)*	1.6 (1.3–2.0)*
$AUC_{0-tlast}$ (ng · h/mL)	10.8	37.2	22.3	2.1 (1.7–2.5)*	3.4 (2.8–4.3)*	1.7 (1.3–2.1)*
$AUC_{0-\infty}$ (ng · h/mL)	10.9	37.4	22.5	2.1 (1.7–2.5)*	3.4 (2.8–4.3)*	1.7 (1.3–2.1)*

* $p<.05$.

When the mean C-t curves with 95% confidence intervals for mean values are presented (Fig. 3), it can be seen that subjects using NuvaRing had the least variation in EE serum levels and that variations in serum levels with the patch were far greater than with NuvaRing. As expected, the COC group showed the greatest degree of variation in serum concentrations.

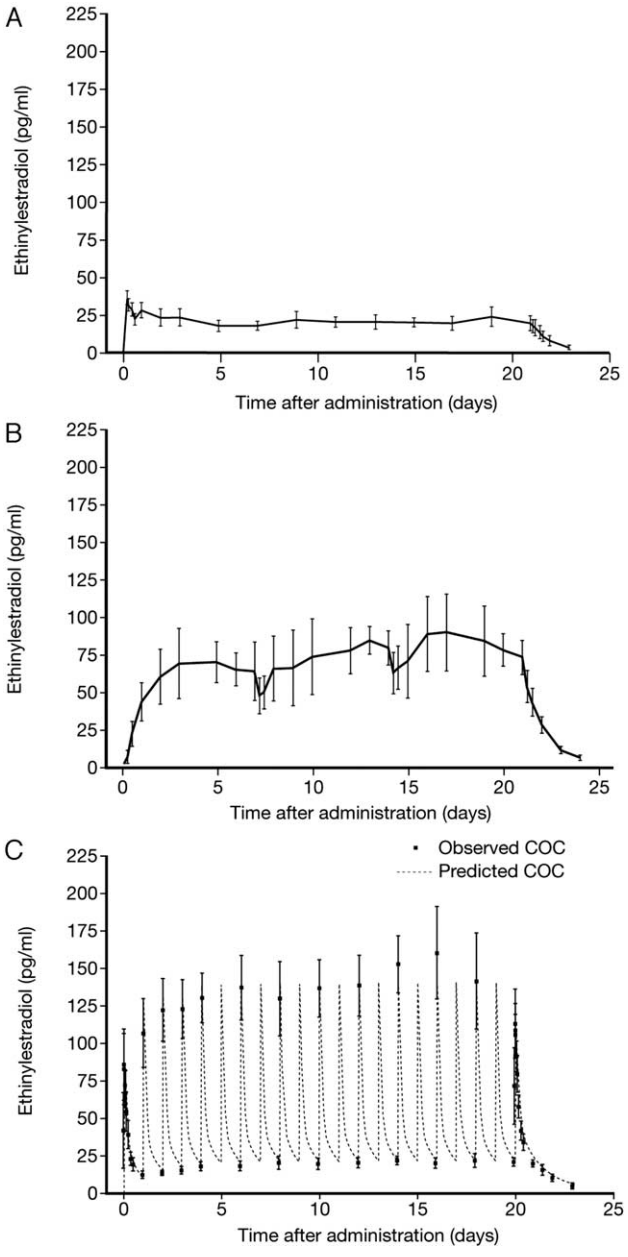

Fig. 3. Mean EE C-t curves for subjects treated with (A) NuvaRing ($n=8$), (B) the transdermal contraceptive patch ($n=6$) and (C) COC ($n=8$) including 95% confidence intervals for mean values (ASPE group).

3.3. Tolerability

Twenty-two of the 24 subjects in the AST group reported adverse events; the majority of these events were of mild intensity. No serious adverse events were reported and no subjects discontinued treatment during the trial. Of the 105 reported adverse events, 23 were reported in the NuvaRing group, 73 in the patch group and 9 in the COC group. Treatment-related adverse events were also more frequent ($n=57$) in the patch group compared with the NuvaRing ($n=18$) and COC groups ($n=1$), as shown in Table 4. Headache was the most frequently reported drug-related adverse event and affected 5 of 8 subjects in the patch group, 4 of 8 subjects in the NuvaRing group and 1 of 8 subjects in the COC group. The estrogen-related adverse events, nausea and breast tenderness, were reported more

Table 4
Frequency of adverse events judged to be at least possibly related to treatment (AST group)

	NuvaRing ($n=8$)	Patch ($n=8$)	COC ($n=8$)
Headache	10 (4)	9 (5)	1 (1)
Breast tenderness	–	7 (5)	–
Abdominal pain	2 (1)	6 (4)	–
Nausea	1 (1)	6 (3)	–
Vaginal hemorrhage	1 (1)	4 (1)	–
Application site pruritus	–	4 (3)	–
Fatigue	–	3 (3)	–
Application site irritation	–	2 (2)	–
Dizziness	–	2 (1)	–
Loose stools	–	2 (2)	–
Dysmenorrhea	–	2 (2)	–
Genital pain	–	2 (1)	–
Dry mouth	1 (1)		–
Flatulence	–	1 (1)	
Vomiting	–	1 (1)	–
Application site dermatitis	–	1 (1)	–
Peripheral edema	–	1 (1)	–
Menorrhagia	–	1 (1)	–
Pelvic pain	1 (1)	–	–
Vaginal discharge	1 (1)	–	–
Altered mood	–	1 (1)	–
Myalgia	–	1 (1)	–
Acne	1 (1)	–	–
Erythema nodosum	–	1 (1)	–
Total	18	57	1

Actual numbers of events (numbers of subjects who experienced events).

frequently in the patch group (by 3 of 8 and 5 of 8 subjects, respectively) than in the NuvaRing (1 of 8 and 0 of 8 subjects, respectively) and COC groups (0 subjects for each event). Local adverse events, such as application site dermatitis and irritation, were confined to the patch group.

No clinically relevant changes in blood chemistry or blood pressure were observed in any group. Three subjects were found to have low hemoglobin counts at follow-up and were referred to their general practitioners. Urine test abnormalities were noted in three subjects at screening and two subjects at follow-up and were found to be either of mild intensity or not clinically relevant. Pelvic and ultrasound examinations revealed no significant abnormalities, and one subject was found to have a Papanicolaou class II smear at screening but this had improved to a class I smear at follow-up.

4. Discussion

The results of this study show that for subjects who used NuvaRing, exposure to EE was on average 3.4 times lower than for those who used the transdermal patch and approximately twice as low as those who used the COC. This pattern of results was seen for each of the EE concentration-versus-time parameters analyzed, and these differences were statistically significant.

The pharmacokinetic results obtained for the three methods are supported by previously reported studies using these formulations [1,4,5]. Furthermore, the results with the COC, which delivers 30 μg EE daily, twice as much as NuvaRing, are similar to those from a previous pharmacokinetic comparison between NuvaRing and a COC containing 30 μg EE (Marvelon) [1]. That study showed that exposure to EE in the COC group was twice as great as that seen in the NuvaRing group and that the bioavailability of EE was similar (approximately 55%) for both formulations. In contrast, although the transdermal patch delivers only 33% more EE daily than NuvaRing, the exposure to EE in the patch group was approximately 250% greater than in the NuvaRing group.

Exposure to EE following transdermal patch application has been compared for different sites [7]. The abdomen, which was used as the application site in this study, was shown to result in 20% less absorption of EE compared with the arm, buttock or torso, which were all equivalent [7]. Hence, the higher EE serum levels observed in the patch group in this study might be even more pronounced when other sites for patch application are chosen. Furthermore, daily life exposure may be higher if users experience adhesion problems and have to replace their patches. Two subjects in this study were excluded from the pharmacokinetic evaluation because of detached patches that had to be replaced, resulting in additional exposure to study medication and higher serum EE levels.

NuvaRing and the patch are both designed to deliver EE to the systemic circulation. Comparison of these two methods reveals a large difference in EE exposure that would seem to indicate greater bioavailability of EE with the patch. The reason for this is unclear, especially considering the good correlation between the doses of EE delivered by NuvaRing and the COC and their respective C_{av} values. Another interesting difference between NuvaRing and the transdermal patch regarding the systemic delivery of EE was that variations in individual subject serum EE levels were far greater with the patch than with NuvaRing. As would be expected, individual serum levels with the COC showed the greatest variability as a result of its dosing regimen. Overall, these data show that vaginal administration of EE with NuvaRing affords much lower, more stable and far more precise dosing than both the transdermal and oral routes.

In combined hormonal contraceptives, efficacy is provided by the progestogenic component, which suppresses ovulation, while the estrogenic component maintains cycle control. The development of new contraceptive formulations has been typically characterized by progressively lower dosages of estrogen in an attempt to reduce EE exposure [8]. However, lowering the EE dose of oral formulations to below 20 μg EE has been shown to compromise cycle control [9]. With a daily dose of 15 μg EE and 120 μg ENG, NuvaRing has been shown to be highly effective and to provide excellent cycle control [3], which is superior to that produced by a COC containing 30 μg of EE [10,11]. Vaginal administration, therefore, appears to uniquely allow lower dosing and exposure to EE while achieving excellent cycle control.

Minimizing exposure to EE is desirable as this reduces estrogen-related side effects such as nausea and breast tenderness. One of the main implications of these results is that contraceptive formulations that deliver low daily doses of EE do not automatically guarantee that exposure to EE will be reduced. Of the three contraceptive formulations evaluated here, NuvaRing and the COC showed a clear correlation between dosage and EE exposure. The patch, however, which is designed to deliver a relatively low dose of EE, was found to produce EE serum levels higher than those expected with a COC containing 30 μg of EE [1,5].

The overall incidence of reported adverse events in this study was relatively high. This may be related to the stress involved in a study that requires multiple blood samples to be taken and to the high level of contact between subjects and investigators over the short time scale of this study. It should be noted that the majority of events were of mild intensity and that there were no serious adverse events or withdrawals due to adverse events. A notably lower incidence of adverse events was observed in the COC group, which is most likely related to the fact that the protocol required all subjects to be treated for 2–8 weeks with the COC during synchronization prior to the study period. Most adverse events occur during initial exposure to a hormonal contraceptive method, and continued use of the COC as study medication would explain the lower incidence of adverse events in this group during the actual study cycle compared with the patch and ring groups.

Finally, minimizing exposure to EE is desirable because it reduces estrogen-related adverse events such as nausea and breast tenderness. However, although this study was not designed to compare adverse events, it was noted that the frequency of adverse events such as nausea and breast tenderness was highest in the patch group.

5. Conclusion

This pharmacokinetic comparison has shown that NuvaRing produces lower exposure to EE than the transdermal patch and a COC containing 30 μg EE. Although the transdermal patch is designed to deliver a low daily dose of EE, this does not appear to result in low exposure. The vaginal route of administration appears to be the best route for administering low, steady and precise doses of contraceptive hormones, resulting in stable serum concentrations and low exposure to EE.

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M. van den Heuvel, M. Kaptein and A. van Bragt are employees of Organon.

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