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# Pharmacokinetics of estradiol valerate and medroxyprogesterone acetate in different age groups of postmenopausal women

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**Abstract**

*Objectives:* To study whether ageing affects the pharmacokinetics of estradiol valerate ($E_2V$) or medroxyprogesterone acetate (MPA) in postmenopausal women. *Methods:* Forty-six postmenopausal women from two essentially similar pharmacokinetic studies were divided into three age categories: under 60 years ($n = 15$), between 60 and 65 years ($n = 18$) and over 65 years ($n = 13$). They all were treated for 12 days or 14 days with four galenically identical tablets containing combinations of 1 mg or 2 mg $E_2V$ and 2.5 mg or 5 mg MPA. The studies followed an open, randomised cross-over design with no washout between the periods. Serum estradiol and MPA concentrations were measured at steady state on study day 12 or 14 of each period. *Results:* No statistically significant differences were observed in the peak concentration ($C_{max}$), time to peak ($t_{max}$), AUC or elimination half-life for estradiol or MPA between the different age groups. In spite of the lack of statistical significance the AUC was on an average 1.6-fold and $C_{max}$ 1.40-fold higher in the oldest group of women than in the youngest group and age was found significant as a continuous variable for AUC and $C_{max}$ for MPA but not for estradiol. *Conclusions:* The results suggest that there would be no significant changes in the pharmacokinetics of estradiol between women under 60 and over 65 years of age. However, a significant trend towards higher MPA concentrations and bioavailability was observed with increasing age. The results suggest that from the pharmacokinetic point of view the relationship between estradiol and MPA dose to be used in elderly could be different from that in younger postmenopausal women, while no pharmacokinetic reasons to use lower estradiol doses in the elderly were observed.


*Keywords:* Pharmacokinetics; Estradiol valerate; Medroxyprogesterone acetate; Elderly

## 1. Introduction

The increased use of postmenopausal hormone replacement therapy (HRT) frequently leads to situations in which the physician has to decide whether to continue HRT in an elderly patient. The risks and benefits of HRT in women aged 65 or above have not been studied as thoroughly as in younger postmenopausal women but HRT has been suggested to benefit also women of advanced postmenopausal status [1,2]. Therefore, counselling about HRT has been recommended for all postmenopausal women and

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initiation of treatment may become actual even at an older age [1]. In addition to the conventional indications of HRT, such as treatment of estrogen deficiency symptoms and prevention of osteoporosis, some further indications for HRT in older women might be found, such as treatment of urinary incontinence or recurrent urinary tract infections [1,3].

The elderly population is generally more susceptible to drug-related adverse effects and treatment with any drug is recommended to be started with a lower dose [4]. In accordance, low-dose HRT regimens have been suggested for women in late postmenopausal period [2,5]. Adequate symptom control and beneficial effects on serum lipids, coagulation factors and bone have been observed with lower estrogen and progestogen doses in younger postmenopausal women with even better bleeding control than with higher doses [5–8]. However, it has not been studied whether lower estrogen doses would be sufficient for elderly women in particular, or whether the pharmacokinetics of estrogens or progestogens would be changed by ageing.

If the many ageing-related physiological changes that may lead to altered absorption, distribution or metabolism of a drug would be true also for compounds used in HRT, low-dose HRT in elderly women would be even more justified [4]. Although the liver content of cytochrome P450 enzymes does not seem to alter with ageing, liver blood flow is reduced in the elderly and this could decrease the clearance of drugs with a high metabolic ratio [9]. These drugs generally have a high first-pass metabolic effect, which is evident with estrogens as a high conversion rate to estrone [10].

High first-pass metabolism is observed also with progesterone and such metabolism is most likely shared by its derivatives such as medroxyprogesterone acetate (MPA) [11,12]. Furthermore, the clearance of the steroid hormone prednisolone was decreased in postmenopausal women as compared with premenopausal women [13]. A change in the pharmacokinetics of either the estrogen or the progestogen component of HRT in the elderly would lead to the need of dose adjustment of both components. Therefore, we have compared the pharmacokinetics of estradiol valerate and medroxyprogesterone acetate in three different age groups of postmenopausal women at different dose levels.

Table 1
Baseline demographics of postmenopausal women in each age group (mean ± S.E.M.)

| | <60 years | 60–65 years | >65 years |
|---|---|---|---|
| Age (years) | 55.1 ± 0.7 | 62.9 ± 0.4 | 67.9 ± 2.0 |
| Height (cm) | 162.3 ± 1.1 | 162.3 ± 1.5 | 155.8 ± 0.9[a] |
| Weight (kg) | 62.9 ± 2.2[b] | 69.2 ± 2.2[c] | 58.0 ± 1.3 |
| Body mass index (kg/m$^2$) | 23.9 ± 0.9 | 26.2 ± 0.5[d] | 23.8 ± 0.5 |
| *N* | 15 | 18 | 13 |

[a] $P \leq 0.05$ as compared to <60 years and 60–65 years.
[b] $P \leq 0.05$ as compared to 60–65 years.
[c] $P \leq 0.05$ as compared to >65 years.
[d] $P \leq 0.05$ as compared to <60 years and >65 years.

## 2. Methods

### 2.1. Subjects

Forty-six postmenopausal women (age 50–73 years, weight 50–89 kg, height 150–172 cm, BMI 19.8–30.5), participants of two essentially similar pharmacokinetic studies, were divided into three categories according to their age: under 60 years, between 60 and 65 years or above 65 years (Table 1). They all had at least 1 month since previous estrogen or progestogen therapy before the study. They had at least 3 years since their last spontaneous menstruation and all had serum estradiol below 80 pmol/l and serum FSH above 36 IU/l.

Their medical history was reviewed and physical status including gynecological examination was controlled before the study. Some elementary laboratory tests were analysed before and after the study. Known contraindications for estrogen or progestogen therapy formed the exclusion criteria. These exclusion criteria consisted of undiagnosed vaginal bleeding, thickness of endometrium more than 4 mm, history of menorragia, recent blood donation, hepatosis during pregnancy and predisposition to vascular thrombosis. In addition, a history of serious hepatic, renal, cardiovascular or mental disease or history of any malignancy, insulin dependent diabetes, asthma or drug allergy or prior blood donation were included in exclusion criteria. The subjects were all non-smokers. Seven subjects had medication for hypertension (four subjects metoprolol, one verapamil, one felodipine, two enalapril and one atenolol), two subjects were treated with thyroxin

supplementation and one with pilocarpine eyedrops. Occasional medication during the study consisted of cephalexin antibiotic course in one subject, topical miconazole treatment in one and vaginal metronidazole in one subject, whereas one subject took some nitroglycerin tablets and one got a steroid injection in shoulder and in total 15 subjects took some pain killer (paracetamol, ibuprofen, ketoprofen, meloxicam, aspirin or diclofenac).

The subjects gave a written informed consent and the study protocols were reviewed by the local ethics committee and followed the guidelines of the Declaration of Helsinki.

### 2.2. Study design

Two essentially similar pharmacokinetic studies were performed. Both studies followed an open, randomised, cross-over design where the subjects were treated with four galenically similar combination formulations of estradiol valerate ($E_2V$) and medroxyprogesterone acetate tablets (Indivina®, Orion Pharma, Espoo, Finland) without a washout period between the study periods. The combination formulations contained: (1) 1 mg $E_2V$ and 2.5 mg MPA; (2) 1 mg $E_2V$ and 5 mg MPA; (3) 2 mg $E_2V$ and 2.5 mg MPA; and (4) 2 mg $E_2V$ and 5 mg MPA. The tablets were taken once daily in the morning for 12 days or 14 days. On the 1st, 11th and 12th or on the 1st, 13th and 14th study days the tablets were taken at the study site and the last dose after an overnight fast (10 h).

Venous blood samples were taken for serum estradiol and MPA measurements immediately before the study medication on the 1st and 11th or 1st and 13th study day of each period and before the dose and 1, 2, 3, 4, 6, 8, 12 and 24 h after it on the 12th or 14th study day of each period.

### 2.3. Analytical methods

Serum was separated by centrifugation and the samples were stored at $-20\,^{\circ}C$ until analysis. Validated methods were used for the determination of estradiol and MPA. Concentrations below the linear range were reported as zero.

Serum estradiol concentration was determined by commercially available radioimmunoassay (RIA) reagent kit (Sorin Biomedica Diagnostics, Italy). The linear concentration range for estradiol was 37–3670 pmol/l. The between-run precision ranged from 4.4 to 8.0% ($n = 6$) and the within-run precision from 3.1 to 10.1% ($n = 6$). The accuracy was between $-1.9$ and $+1.8$%.

Serum MPA concentrations were determined by liquid-chromatography–tandem mass spectrometry (LC–MS/MS). MPA was extracted from 1 ml of serum by liquid–liquid extraction to *n*-hexane:isobutanol (98:2). ($^2H_3$)-MPA was used as the internal standard. The determinations were carried out by using the selected reaction monitoring technique. The reactions followed were at $m/z$ 387 $\rightarrow$ 123 for MPA and at $m/z$ 390 $\rightarrow$ 123 for ($^2H_3$)-MPA. The calibrated range was 0.04–2.0 ng/ml. The between-run precision ranged from 3.5 to 7.7% ($n = 20$–36) and the within-run precision from 1.9 to 19% ($n = 6$). The accuracy was between $-1.0$ and $+3.0$%.

### 2.4. Pharmacokinetic and statistical analyses

Peak serum estradiol and MPA concentrations ($C_{max}$), time to reach it ($t_{max}$) and trough concentration ($C_{min}$) were read from individual time–concentration data. Area under the time concentration curve from zero to the last observation point ($AUC^{0-24}$) was calculated according to the trapezoidal rule with WinNonlin Professional, version 3.1 (Pharsight Corporation, Mountain View, CA, USA). Apparent elimination half-life ($t_{1/2}$) was calculated from the terminal slope if at least three sample points were on the descending line of the time–concentration curve and if the correlation coefficient for the terminal slope was at least 0.95.

The results of all parameters are summarised as means with S.E.M. For statistics the logarithm transformed AUC, $C_{max}$ and $t_{1/2}$ were analysed using analysis of variance for repeated measurements. The statistical model included period, formulation and age by formulation interaction as fixed effects and subject as a random effect. Two separate analyses were performed in the first of which age was used as a categorical variable and in the second as a continuous variable in the statistical model. Pairwise comparisons between different age groups for $t_{max}$ were analysed using a non-parametric Mann–Whitney *U*-test. The level of statistical significance was set at an $\alpha$-error

level of 0.05. SAS statistical software (SAS Institute Inc., Cary, NC, USA) was used in the analyses.

## 3. Results

In general, trough estradiol and MPA concentrations did not differ between the 11th and 12th or 13th and 14th study days indicating that steady state was reached and that the data of subjects from the two different studies could be combined. However, a statistically significant difference in trough estradiol concentrations was observed with both formulations containing 1 mg $E_2V$ but only in the group of women over 65 years with an increase of 10–12% of the value on the latter day and with only one of the two formulations containing 2 mg $E_2V$ in the group of women between 60 and 65 years old. The postmenopausal women aged between 60 and 65 years had a slightly higher body mass index than the groups of younger or older women (Table 1). However, the body mass index also in this group was on an average within normal limits. There were no differences in the number of concomitant diseases or the use of chronic medication between the groups.

### 3.1. Estradiol

There were no significant differences in the pharmacokinetic parameters AUC, peak level ($C_{max}$), time to peak ($t_{max}$) or apparent elimination half-life ($t_{1/2}$) of estradiol between the three age groups of postmenopausal women (Table 2). These results were similar with both 1 and 2 mg estradiol doses combined with the lower or higher dose of MPA. However, the peak estradiol level was slightly higher in women under 65

Table 2
Pharmacokinetic parameters of estradiol after 12 days' or 14 days' treatment in three different age groups of postmenopausal women with four different combination tablets of estradiol valerate ($E_2V$) and medroxyprogesterone acetate in an open randomized cross-over study (mean ± S.E.M.)

| | Estradiol | | |
|---|---|---|---|
| | <60 years ($N = 15$) | 60–65 years ($N = 18$) | >65 years ($N = 13$) |
| $AUC_\tau$ ((pmol×h)/l)[a] | | | |
| 1 mg $E_2V$ + 2.5 mg MPA | 2740 ± 326 | 2635 ± 301 | 2587 ± 256 |
| 1 mg $E_2V$ + 5 mg MPA | 2890 ± 331 | 2503 ± 278 | 2575 ± 289 |
| 2 mg $E_2V$ + 2.5 mg MPA | 5191 ± 485 | 4941 ± 661 | 4510 ± 495 |
| 2 mg $E_2V$ + 5 mg MPA | 5341 ± 727 | 4526 ± 548 | 4687 ± 542 |
| $C_{max}$ (pmol/l)[b] | | | |
| 1 mg $E_2V$ + 2.5 mg MPA | 163 ± 15 | 146 ± 13 | 143 ± 12 |
| 1 mg $E_2V$ + 5 mg MPA | 161 ± 17 | 139 ± 13 | 139 ± 14 |
| 2 mg $E_2V$ + 2.5 mg MPA | 293 ± 23 | 280 ± 34 | 260 ± 27 |
| 2 mg $E_2V$ + 5 mg MPA | 310 ± 36 | 251 ± 26 | 263 ± 29 |
| $t_{max}$ (h)[c] | | | |
| 1 mg $E_2V$ + 2.5 mg MPA | 5.5 ± 0.6 | 5.2 ± 0.8 | 5.2 ± 0.9 |
| 1 mg $E_2V$ + 5 mg MPA | 4.5 ± 0.5 | 4.4 ± 0.6 | 4.6 ± 0.6 |
| 2 mg $E_2V$ + 2.5 mg MPA | 5.7 ± 0.5 | 4.1 ± 0.6 | 5.3 ± 0.9 |
| 2 mg $E_2V$ + 5 mg MPA | 5.3 ± 0.4 | 4.6 ± 0.7 | 5.9 ± 0.9 |
| $t_{1/2}$(h)[d] | | | |
| 1 mg $E_2V$ + 2.5 mg MPA | 19.4 ± 3.1 ($N = 12$) | 21.7 ± 3.4 ($N = 9$) | 18.7 ± 1.5 ($N = 12$) |
| 1 mg $E_2V$ + 5 mg MPA | 22.5 ± 3.9 ($N = 14$) | 18.3 ± 1.8 ($N = 14$) | 19.2 ± 2.1 ($N = 9$) |
| 2 mg $E_2V$ + 2.5 mg MPA | 17.7 ± 3.4 ($N = 12$) | 17.8 ± 1.2 ($N = 16$) | 14.7 ± 1.2 ($N = 11$) |
| 2 mg $E_2V$ + 5 mg MPA | 17.2 ± 2.5 ($N = 10$) | 19.9 ± 1.8 ($N = 12$) | 15.8 ± 1.0 ($N = 12$) |

[a] $P = 0.6539$.
[b] $P = 0.4839$.
[c] NS.
[d] $P = 0.7361$.

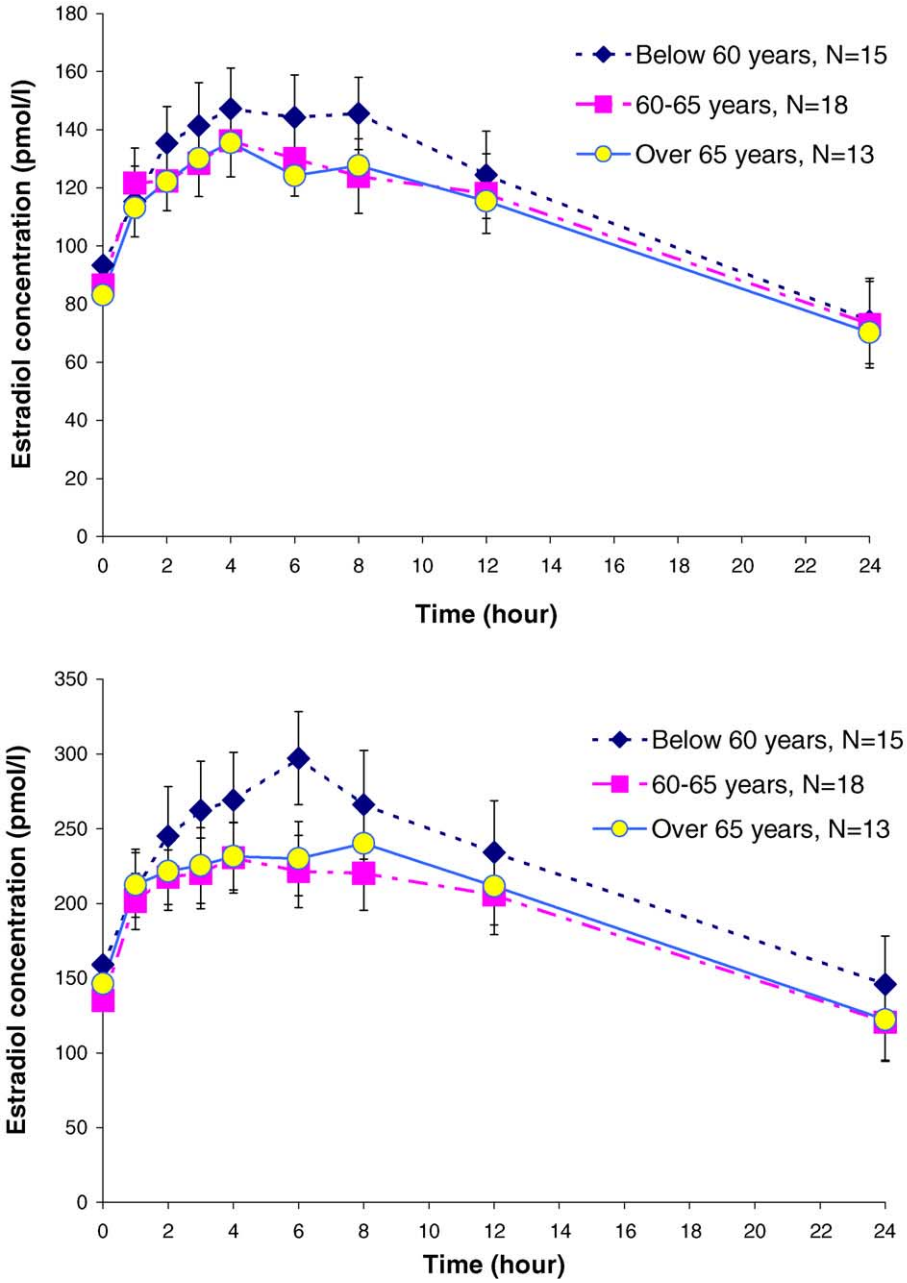


Fig. 1. Serum estradiol concentration (mean ± S.E.M.) at steady state in different age groups of postmenopausal women after a once daily treatment of $E_2V$ 1 mg + MPA 2.5 mg tablet (upper) and $E_2V$ 2 mg + MPA 5 mg tablet (lower).

years of age which was observed also in the estradiol concentration 6 h after the dose (Fig. 1). In addition, $t_{1/2}$ tended to be 2 h shorter in the oldest than in the two younger groups but this difference was not statistically significant and the terminal slopes were parallel in all groups (Table 2 and Fig. 1).

Neither was any significant trend in the pharmacokinetic parameters observed when age was used as

Table 3
Pharmacokinetic parameters of medroxyprogesterone acetate (MPA) after 12 days' or 14 days' treatment in three different age groups of postmenopausal women with four different combination tablets of estradiol valerate ($E_2V$) and MPA in an open randomized cross-over study (mean ± S.E.M.)

| | MPA | | |
|---|---|---|---|
| | <60 years ($N = 15$) | 60–65 years ($N = 18$) | >65 years ($N = 13$) |
| $AUC_\tau$ ((ng×h)/ml)[a] | | | |
| 1 mg $E_2V$ + 2.5 mg MPA | 1.95 ± 0.31 | 2.73 ± 0.33 | 3.46 ± 0.80 |
| 1 mg $E_2V$ + 5 mg MPA | 4.59 ± 0.66 | 5.19 ± 0.50 | 7.22 ± 1.61 |
| 2 mg $E_2V$ + 2.5 mg MPA | 2.16 ± 0.42 | 2.86 ± 0.46 | 3.37 ± 0.75 |
| 2 mg $E_2V$ + 5 mg MPA | 4.15 ± 0.60 | 4.93 ± 0.55 | 6.90 ± 1.63 |
| $C_{max}$ (ng/ml)[b] | | | |
| 1 mg $E_2V$ + 2.5 mg MPA | 0.31 ± 0.04 | 0.42 ± 0.04 | 0.44 ± 0.07 |
| 1 mg $E_2V$ + 5 mg MPA | 0.60 ± 0.07 | 0.68 ± 0.06 | 0.88 ± 0.13 |
| 2 mg $E_2V$ + 2.5 mg MPA | 0.32 ± 0.04 | 0.41 ± 0.06 | 0.45 ± 0.08 |
| 2 mg $E_2V$ + 5 mg MPA | 0.56 ± 0.08 | 0.63 ± 0.07 | 0.86 ± 0.17 |
| $t_{max}$ (h)[c] | | | |
| 1 mg $E_2V$ + 2.5 mg MPA | 1.8 ± 0.2 | 1.3 ± 0.1 | 1.5 ± 0.1 |
| 1 mg $E_2V$ + 5 mg MPA | 1.9 ± 0.2 | 1.7 ± 0.2 | 1.8 ± 0.4 |
| 2 mg $E_2V$ + 2.5 mg MPA | 2.0 ± 0.4 | 1.6 ± 0.2 | 1.3 ± 0.1 |
| 2 mg $E_2V$ + 5 mg MPA | 1.7 ± 0.2 | 1.4 ± 0.2 | 1.8 ± 0.2 |
| $t_{1/2}$ (h)[d] | | | |
| 1 mg $E_2V$ + 2.5 mg MPA | 6.1 ± 2.5 ($N = 6$) | 10.7 ± 2.5 ($N = 10$) | 8.8 ± 2.1 ($N = 6$) |
| 1 mg $E_2V$ + 5 mg MPA | 15.7 ± 5.2 ($N = 5$) | 12.3 ± 0.9 ($N = 9$) | 16.3 ± 1.1 ($N = 6$) |
| 2 mg $E_2V$ + 2.5 mg MPA | 4.6 ± 1.3 ($N = 7$) | 14.1 ± 5.3 ($N = 7$) | 9.6 ± 2.2 ($N = 7$) |
| 2 mg $E_2V$ + 5 mg MPA | 10.1 ± 1.8 ($N = 10$) | 16.2 ± 1.5 ($N = 7$) | 18.9 ± 2.5 ($N = 4$) |

[a] $P = 0.0621$.
[b] $P = 0.0763$.
[c] Mann–Whitney $U$-tests, NS.
[d] $P = 0.1516$.

a continuous variable: $P = 0.307$ for AUC, $P = 0.2128$ for $C_{max}$ and $P = 0.1966$ for $t_{1/2}$, respectively.

### 3.2. MPA

No statistically significant differences were observed in the pharmacokinetic parameters for MPA between the age groups either (Table 3). However, the MPA levels in the oldest group of women were on an average clearly higher than in the younger women (Fig. 2). In the oldest group, also AUC was on an average 1.6-fold and peak level on an average 1.4-fold higher than those in women under 60 years of age (Table 3). Age was also significant as a continuous variable for AUC ($P = 0.0231$) and $C_{max}$ ($P = 0.0299$) but not for $t_{1/2}$ ($P = 0.1399$).

## 4. Discussion

The pharmacokinetics of estrogens or progestogens have not been studied in elderly postmenopausal women although they are becoming more likely to receive HRT. Decreased clearance of prednisolone in postmenopausal women as compared to premenopausal women suggests that steroid hormone metabolism could be altered by ageing [13]. Decreased liver blood flow could cause a decrease in metabolism of drugs with a high first-pass metabolism such as estrogens or progestins [9–12]. Therefore we decided to analyse the results from two similar pharmacokinetic studies comparing four similar estradiolvalerate and medroxyprogesterone acetate combination tablets by dividing the subjects into three different age groups. It has to be pointed out that

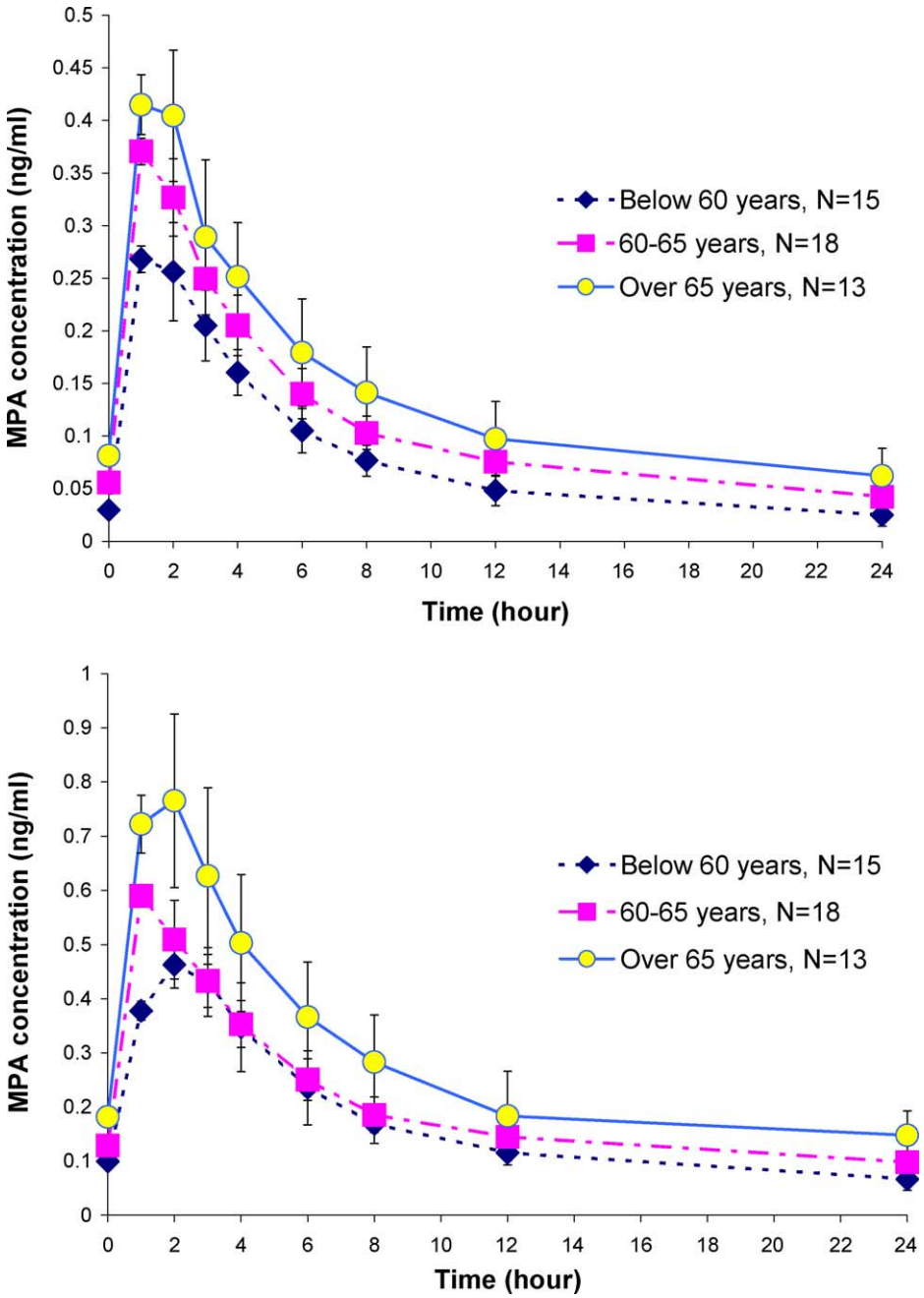


Fig. 2. Serum MPA concentration (mean ± S.E.M.) at steady state in different age groups of postmenopausal women after a once daily treatment of $E_2V$ 1 mg + MPA 2.5 mg tablet (upper) and $E_2V$ 2 mg + MPA 5 mg tablet (lower).

the studies were not particularly designed to study age-related changes and that the number of subjects in the present analysis was rather small. However, each subject received each dose of $E_2V$ and MPA twice, which increases the reliability of the observations although it does not increase the statistical power of the study.

Regarding both estradiol and MPA, the pharmacokinetic parameters AUC, $C_{max}$ and $t_{max}$ were on an average numerically almost identical within each age group with the two periods at the same dose level. This suggests that the two drugs are reliably and reproducibly absorbed from the used formulations. Furthermore, when the dose of one drug substance was changed it did not affect the pharmacokinetic parameters of the other drug substance. Together these results confirm our unpublished results which showed that neither $E_2V$ nor MPA affected the absorption of each other from combination tablets. However, this similarity could not be observed in elimination half-lives between the two treatments with the same dose. This most probably reflects the fact that the elimination half-life could not be very reliably measured due to few sampling points in the elimination phase and due to endogenous estrogen production. For this reason more sophisticated pharmacokinetic estimates such as volume of distribution were not calculated.

For clinical purposes estradiol or MPA concentrations and AUC define the drug exposure of the patient and significant age dependent changes would become evident in these parameters. No significant differences were observed between the early or late postmenopausal women in these parameters for estradiol. In fact, AUC was numerically even lower in the oldest age group than in the group of youngest women. This is in contrast with decreased metabolic clearance observed for another steroid hormone, prednisolone, in postmenopausal women as compared to premenopausal women [13]. However, the decreased clearance of prednisolone was restored to premenopausal level in one woman who received HRT. This would suggest that HRT might affect the metabolism of steroid hormones, which was not revealed by the results of the present study.

Our results, however, clearly indicate that no significant changes in the pharmacokinetics of estradiol in postmenopausal women between under 60 and 65–70 years are likely, and that dose adjustments in these age groups cannot be justified by pharmacokinetic reasons. However, this does not exclude the need to individualise the estradiol regimen and dose or to possibly use lower doses to avoid adverse drug reactions in the elderly [1,5].

The results suggest that MPA pharmacokinetics is affected by ageing since a significant trend was observed with increasing age in both AUC and $C_{max}$. MPA concentrations were also clearly higher and AUC was 36–44% higher in the group of oldest women than in the youngest group although these differences did not quite reach statistical significance. These results suggest that the relationship between the estradiol and MPA dose to be used in elderly could be different from that in younger postmenopausal women. In particular, the dose combinations with the lower MPA doses could be suitable for women in more advanced age.

Lower estradiol and MPA doses of the combination formulation used in this study have been observed to be sufficient to control the menopausal symptoms and to prevent bone loss in women under 65 years of age [8,14–16]. Bleeding control was better with lower estradiol doses than with higher doses [8,15]. Similar results have been obtained with lower doses of conjugated equine estrogens combined with lower MPA doses in women of the same age group [7,16]. However, bleeding control with the higher 2 mg $E_2V$ dose was improved when it was combined to 5 mg MPA as compared to 2.5 mg MPA dose [8,15]. This suggests that at least in these women under 65 years of age this relationship between $E_2V$ and MPA doses would be the most suitable for most women. The trend towards higher bioavailability and higher serum concentrations of MPA in older women suggests that lower MPA doses might be sufficient in older women even together with the higher 2 mg $E_2V$ dose if proven adequate in clinical studies. However, in clinical practice the doses of $E_2V$ and MPA must be decided on clinical basis according to the needs of each patient.

In conclusion, our results suggest that there would be no significant changes in the pharmacokinetics of estradiol valerate between women under 60 and over 65 years of age. However, a significant trend towards higher MPA concentrations and bioavailability was observed with increasing age.

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