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Enterohepatic Cycling and Pharmacokinetics of Oestradiol in Postmenopausal Women

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Abstract

The pharmacokinetics and enterohepatic cycling of oestradiol have been studied after three oral, single-dose administrations of equimolar doses of oestradiol alone, oestradiol plus desogestrel and oestradiol valerate, in a 3-way cross-over mode in 18 healthy postmenopausal women.

Oestradiol was readily absorbed and metabolized to oestrone, which reached much higher serum concentrations ($140 pg mL^{-1}$) than its parent compound ($35 pg mL^{-1}$). All three formulations had the same kinetic profile and were bioequivalent on testing. Noticeable first and second absorption phases were apparent from the oestradiol and oestrone serum concentration–time curves for all oestradiol formulations. The mean serum concentration–time curves of the metabolite oestrone (corrected for endogenous oestrone) showed a second maximum at approximately 25 h. By means of line feathering, serum concentration–time curves were constructed which belonged to the first, second and third phases of absorption. The maximum serum concentration, C_{max}, of the second absorption or recirculation of oestrone was 20% that of the first, and the C_{max} of the third circulation was 50% that of the second. The areas under the serum-concentration–time curves (AUC) for the second and third recirculations were similar—each comprised 12–13% of the total AUC. The oral clearance values of the recirculations were constant ($590 L h^{-1}$).

Enterohepatic recirculation of endogenous compounds is aimed at maintaining a steady-state serum concentration for immediate use and hydrolysis in the target organs. It is concluded that exogenously added oestradiol and its metabolites follow the recirculation pathways of the endogenous oestrogen pool.

Hormone replacement therapy (HRT) has been used for many years for the treatment of the postmenopausal syndrome (Borglin & Staland 1975; Clisham et al 1991). The use of oestrogens is efficient in reducing climacteric symptoms and preventing osteoporosis. One drawback is that the use of oestrogen alone is associated with an increased risk for endometrial hyperplasia and endometrial carcinoma (Gambrell 1986; Persson et al 1989). To protect the endometrium against hyperplasia and malignancy, progestagens are added to the oestrogen regimen.

In oestrogen–progestagen combinations in HRT a sequential dosage regimen is popular in pre- and perimenopausal women. With this regimen oestrogen is given in the first half of the medication cycle followed by an oestrogen–progestagen combination in the second half. Each medication cycle is followed by a tablet-free period (Saure et al 1993). Recently, a new sequential oestrogen–progestagen combination has been developed for HRT. The composition of this combination (Liseta, Org 32818) is 12 tablets containing 1·5 mg micronized oestradiol, followed by 12 tablets containing 1·5 mg micronized oestradiol + 0·15 mg desogestrel, and four placebo tablets. Desogestrel is a potent progestagen with only weak androgenic effects. It is expected that this combination of desogestrel and oestradiol will not only reduce climacteric symptoms but also prevent osteoporosis and protect the endometrium against hyperplasia. Moreover, because of the low androgenicity of the progestogenic component, lipid metabolism is also little affected (Kloosterboer et al 1986; Lufkin et al 1988).

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No data are available about the bioavailability and pharmacokinetics of oestradiol after the oral administration of Org 32818 tablets. In a bioavailability study it was shown that after oral administration of Org 32818 a second absorption or recirculation peak of rather long duration was apparent from the serum concentration–time curves of both oestradiol and the metabolite oestrone (Timmer & Geurts personal communication).

In this part of the investigation we have studied the pharmacokinetics and enterohepatic cycling of oestradiol after administration of three oral, equimolar, single-doses of oestradiol, oestradiol plus desogestrel, and oestradiol valerate in postmenopausal women.

Materials and Methods

Pharmaceutical formulations

Oestradiol hemihydrate, complying with the requirements of the Ph. Eur. and USP, and desogestrel, Org 2969, were obtained from NV Organon (Oss, The Netherlands). Oestradiol valerate tablets (batch 24115) containing 2 mg oestradiol valerate (Progynova 21, Schering), equivalent to 1·53 mg oestradiol, were obtained from commercial sources. Oestradiol tablets (batch CP094064) were white-coloured tablets containing 1·5 mg micronized oestradiol formulated (dry-mix procedure) with corn starch, colloidal silicon dioxide, magnesium stearate, povidone, lactose M100, hydroxypropylmethylcellulose, poly(ethylene glycol) 400, titanium dioxide and talc. Oestradiol + desogestrel tablets (batch CP 093138) were white-coloured tablets containing 1·5 mg micronized oestradiol and 0·15 mg desogestrel formulated (dry-mix procedure for oestradiol, wet-mix procedure for desogestrel) with corn starch, colloidal silicon dioxide, tocopherol, stearic acid, povidone, lactose M100, hydroxypropylmethylcellulose taken from commercial sources and used as such (batch code 24115).

Subjects

Eighteen postmenopausal women were enrolled in this study. Subjects were numbered consecutively and were randomly allocated to three groups each receiving a different treatment sequence (Table 1).

Inclusion criteria

Postmenopausal volunteers, 50–70 years, were in good physical and mental health, between 80% and 130% of ideal body weight (Metropolitan Life Insurance Company Tables for Women), with lack of spontaneous vaginal bleeding for at least 12 months. Serum oestradiol concentrations were $< 100\,pmol\,L^{-1}$ (i.e. $< 27\,pg\,mL^{-1}$) and serum follicle-stimulating hormone concentrations $> 50\,IU\,units\,L^{-1}$. Concomitant medication not allowed during the course of the study was sex steroids other than the study medication, hydantoins, barbiturates, primidone, carbamazepine, rifampicin, griseofulvin, active carbon, smoking more than 10 cigarettes day^{-1} and alcohol or drug abuse within the last 12 months.

Study design

Three groups of six postmenopausal volunteers were each treated as shown in Table 1. The washout period between treatments was 7 days. Blood samples were collected −0·25 (pre-dose), 0·25, 0·5, 0·75, 1, 1·25, 1·5, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, 48 and 72 h after dosing. Serum was separated and stored at −18°C pending analysis.

Assay of oestradiol and oestrone

Free oestradiol (E_2, CAS 50-28-2, MW 272·39) and free oestrone (E_1, CAS 53-16-7, MW 270·37) serum concentrations were determined by use of commercially available immunoassay kits. The analysis was performed by ABL (Assen, The Netherlands).

Oestradiol was assayed by time-resolved fluorimetric immunoassay (Delfia Estradiol, Delphia, Wallac Oy, Turku, Finland; Kabi Pharmacia; cat. no. 1244-056) with a sensitivity of $0{\cdot}050\,nmol\,L^{-1}$. For oestradiol three different quality-control samples (0·20, 0·37 and $1{\cdot}03\,nmol\,L^{-1}$) of Lyphocheck (Bio-Rad, Anaheim, CA) were used in duplicate. Intraday precision ranged between 2·8 and 4·0% and interday precision between 3·8 and 5·8%. Accuracy ranged between 104 and 106%.

Oestrone was assayed by radioimmunoassay (^{125}I, Kit DSL-8700; Diagnostica Systems Laboratories (DSL), Webster, TX) with a sensitivity of $5{\cdot}00\,pg\,mL^{-1}$. For oestrone two different quality-control samples from DSL (35 and $300\,pg\,mL^{-1}$) were used in triplicate. Intraday precision was 5·3 and 6·2%, and interday precision 9·1 and 6·4% for the low- and high-concentration values. Accuracy was 96·0 and 98·6%.

Pharmacokinetic parameters

Pharmacokinetic parameters were calculated from the fitted mean plasma concentration–time curve ($r^2 > 0{\cdot}98$) according to a three-compartment model after oral administration using the MW/Pharm computer package (Mediware, Groningen, The Netherlands) (Proost & Meijer 1992).

Terminal elimination half-lives ($t^{1}/_{2Z}$) were calculated from $\ln 2/\lambda$, where λ was calculated by

Table 1. Subject demographics.

Treatment sequence	Age (years)	Height (cm)	Weight (kg)	n
B-C-A	57±6	164±4	63±2	6
A-B-C	59±5	167±9	64±10	6
C-A-B	61±4	160±8	65±8	6
Total	59±5	164±8	64±7	18

Data are means±s.d. Treatments: A. single oral dose of 2 mg oestradiol valerate (equivalent to 1·5 mg oestradiol); B. single oral dose of 1·5 mg 17β-oestradiol; C. single oral dose of 1·5 mg 17β-oestradiol + 0·15 mg desogestrel. The wash-out period between the treatments was seven days.

Table 2. Mean corrected serum concentrations ($pg\,mL^{-1}$) of oestradiol after administration of the three pharmaceutical formulations containing 1·5 mg oestradiol.

Time (h)	Oestradiol	Oestradiol + desogestrel	Oestradiol valerate
−0·25	–	–	–
0·25	18·6±12·9	23·8±10·2	–
0·50	19·9±15·0	23·9±9·0	20·2±11·5
0·75	16·9±12·5	22·1±7·5	20·9±9·3
1·0	19·2±9·2	20·9±5·7	23·8±7·8
1·25	20·7±8·3	18·9±5·3	23·4±6·2
1·50	20·2±8·1	20·5±3·3	24·0±4·8
2·0	22·5±6·9	21·2±5·0	25·4±6·2
3·0	24·9±5·8	24·5±7·3	27·7±5·0
4	25·5±5·1	26·0±7·6	26·9±5·6
6	29·6±6·7	28·1±6·1	29·3±6·9
8	35·1±8·2	32·2±8·0	34·5±9·1
12	32·4±9·1	31·5±8·4	33·4±8·6
18	25·4±7·8	23·7±8·1	24·0±6·4
24	22·1±7·7	21·8±10·0	22·4±6·1
30	15·8±7·5	17·9±7·8	17·5±6·6
36	16·2±8·2	–	17·3±7·0
48	–	–	14·1±4·9
72	–	–	–

Data are means±s.d. The limits of quantification for oestradiol and oestrone were 10 and 20 $pg\,mL^{-1}$, respectively.

log–linear regression analysis of the terminal log–linear phase. The area under the serum concentration–time curve (AUC_{0-t}) was calculated using the linear trapezoidal rule, where t is the time of the last concentration measurement. Total body clearance (CL) was described as $CL = F \times Dose/AUC_{0-t}$, assuming the overall bioavailability, F=1. For each separate absorption phase, the amount (%) of AUC_{0-t}/AUC_{total} represented the fraction of the dose that was absorbed during that period, assuming F = 1. Mean residence time (MRT) = $AUMC_{0-\infty}/AUC_{0-\infty}$[2], where $AUMC_{0-\infty}$ is the area under the moment curve from time zero to ∞. The MRT of each absorption = MRT − t_{lag}, where t_{lag} is the lag time. The difference in MRTs between each absorption was described as $MRT_{II} - MRT_{I}$.

Table 3. Mean corrected serum concentrations ($pg\,mL^{-1}$) of the metabolite oestrone after administration of the three pharmaceutical formulations containing 1·5 mg oestradiol.

Time (h)	Oestradiol	Oestradiol + desogestrel	Oestradiol valerate
−0·25	21·7±6·4	21·9±7·4	21·6±6·8
0·25	27·9±7·6	26·0±8·0	21·7±5·3
0·50	38·6±14·6	35·8±12·0	37·8±13·5
0·75	52·5±18·0	45·7±13·5	54·2±20·3
1·0	62·3±21·0	53·8±17·3	71·5±33·8
1·25	72·3±26·6	62·6±19·3	81·9±32·5
1·50	81·2±36·5	75·7±25·3	89·9±33·8
2·0	95·0±34·7	88·5±26·8	96·2±37·9
3·0	114·±40·2	111±32·1	119±35·7
4	119·±34·6	117±34·3	120±42·3
6	124±42·1	127±44·2	124±31·7
8	143±46·0	148±47·8	143±36·3
12	121±52·8	121±41·7	118±34·4
18	65·9±28·3	62·3±24·2	59·1±17·5
24	61·9±23·2	61·8±25·6	57·1±17·1
30	44·8±15·3	46·4±17·8	42·2±10·3
36	40·1±14·9	40·3±12·9	37·6±9·9
48	32·4±8·5	33·7±10·5	30·5±6·6
72	26·8±9·8	25·8±9·1	24·2±6·3

Data are means±s.d. The limits of quantification for oestradiol and oestrone were 10 and 20 $pg\,mL^{-1}$, respectively.

Statistical analysis

Analysis of variance was performed according to standard procedures. The level of significance was set at $P = 0{\cdot}05$.

Results

Subjects

The demographic data and group (sequence) allocation of the 18 postmenopausal volunteers included in the pharmacokinetic analysis are shown in Table 1. Their mean age (s.d.) was 59±5 years and their mean weight was 64·1±7·3 kg. Fifteen subjects reported at least one adverse effect; none of the adverse effects was serious. Assessments of blood chemistry, haematology, urine analysis and vital signs did not reveal any changes of clinical significance.

Pharmacokinetics

Oestradiol. Table 2 shows the mean (s.d.) corrected serum concentrations of oestradiol for the three formulations; those for the metabolite oestrone are listed in Table 3. Figure 1 shows the free serum concentration–time curves of oestradiol and oestrone after oral administration of the three pharmaceutical formulations. Oestradiol was readily absorbed and metabolized to oestrone, the serum concentrations of which (C_{max} 140 $pg\,mL^{-1}$) were much higher than those of the parent compound (C_{max} 30 $pg\,mL^{-1}$). All three oestradiol formulations gave the same kinetic profile and were

Table 4. Pharmacokinetic parameters of oestradiol after administration of 1·5 mg oestradiol in three pharmaceutical formulations.

Parameter	Oestradiol		Oestradiol + desogestrel		Oestradiol valerate	
	Uncorrected	Corrected†	Uncorrected	Corrected	Uncorrected	Corrected
$AUC_{0-\infty}$ ($ng\,L^{-1}h$)	1244	560	1141	571	2174	535
$AUC_{0-30trap}$ ($ng\,L^{-1}h$)	866	508	751	452	804	445
AUC_{trap} (%)	69·6	90·7	65·8	79·2	37·0	83·2
CL* (Lh^{-1})	1210	2670	1320	2630	690	2800
CL (Lh^{-1})	1730	2950	2000	3320	1870	3370
$t^{1}/_{2\alpha}$ (h)	0·011	0·013	0·012	0·008	0·034	0·03
$t^{1}/_{2\beta}$ (h)	17·7	7·13	10·7	8·33	3·91	3·40
$t^{1}/_{2Z}$ (h)	67·3	14·9				
MRT (h)	30·1	19·4	26·7	21·6	89·6	21·4
$t^{1}/_{2abs}$ (h)	4·71	7·12	10·7	8·33	4·22	3·75
t_{lag} (h)	0·010	0·010	0·01	0·05	0·01	0·003
t_{max} (h)	9·40	8·94	9·75	8·6	5·66	5·58
C_{max} ($ng\,L^{-1}$)	30·7	20·2	28·7	18·0	31·3	21·0

$AUC_{0-\infty}$ is the total area under the serum concentration–time curve; $AUC_{0-30trap}$ is the area under the serum concentration–time curve between 0 and 30 min calculated according to trapezoidal rule; AUC_{trap} (%) is the percentage of $AUC_{0-\infty}$; CL is the clearance = dose/$AUC_{0-\infty}$; CL* = Dose/AUC_{trap}; $t^{1}/_{2\alpha}$, $t^{1}/_{2\beta}$ and $t^{1}/_{2Z}$ are the half-lives of the first, second and terminal phase of the serum concentration–time curve, respectively; MRT is the mean residence time; $t^{1}/_{2abs}$ is the half-life of absorption; t_{lag} is the lag time; C_{max} is the calculated maximum serum concentration and t_{max} the time at which C_{max} is reached. †Serum concentration corrected for endogenous concentration of oestradiol ($10\,pg\,mL^{-1}$).

bio-equivalent on testing. The individual oestradiol serum concentration–time curves for all oestradiol formulations showed noticeable first and second absorption phases, which levelled out in the overall mean curves, except for the oestradiol + desogestrel formulation (Figure 2). The calculated pharmacokinetic parameters for oestradiol are summarized in Table 4.

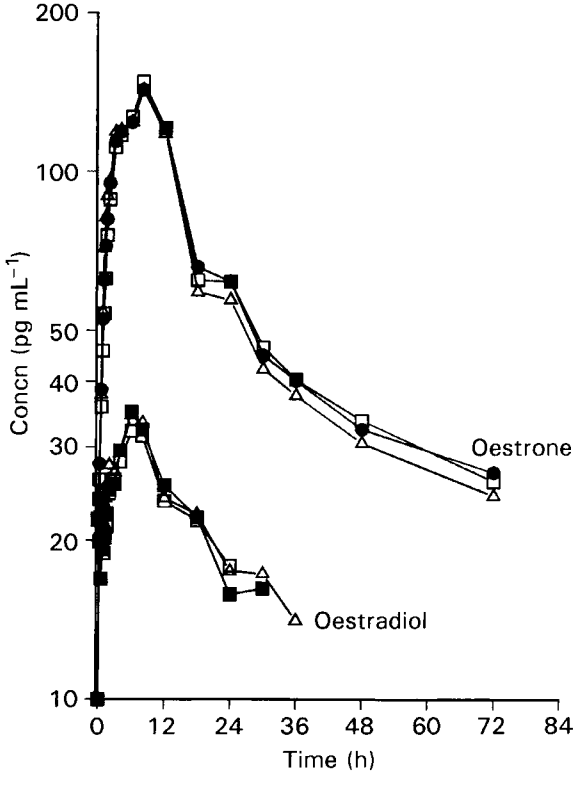

Figure 1. Mean serum concentration–time curves for oestradiol and its metabolite oestrone after oral administration of three pharmaceutical formulations containing 1·5 mg oestradiol to healthy postmenopausal women (n = 18): ●, oestradiol; □, oestradiol + desogestrel; △, oestradiol valerate.

Oestrone. The serum concentration–time curves of the metabolite oestrone showed a second maximum at approximately 20 h. Figure 3 shows the mean plasma concentration–time curves for total free oestrone (endogenous + exogenous) and oestrone corrected for endogenous oestrone. By means of line feathering as shown in Figure 4 serum concentration–time curves were constructed which belonged to the first, second and third phase of absorption. Table 5 lists the mean serum concentration data for oestrone in the absorption and recircu-

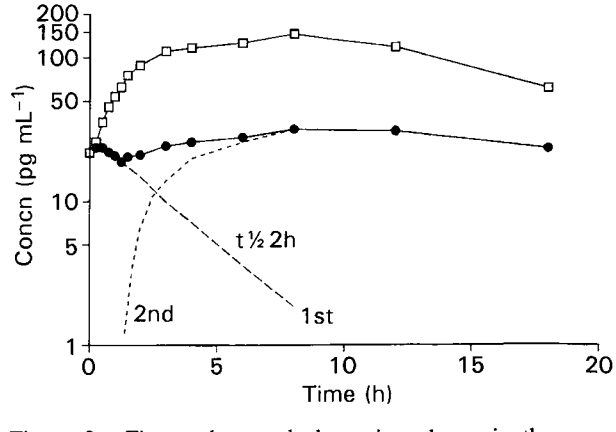

Figure 2. First and second absorption phases in the mean serum concentration–time curves for oestradiol (●) and its metabolite oestrone (□) after oral administration of the pharmaceutical formulation oestradiol + desogestrel containing 1·5 mg oestradiol to healthy postmenopausal women (n = 18).

Table 5. Mean corrected serum concentrations ($pgmL^{-1}$) for the three absorption phases of oestrone (for oestradiol administration as an example).

Time	Uncorrected total	Corrected total	Absorption		
			1st	2nd	3rd
−0·25	21·7±6·4	0	0		
0·25	27·9±7·6	8	8		
0·50	38·6±14·6	19	19		
0·75	52·5±18·0	32	32		
1·0	62·3±21·0	42	42		
1·25	72·3±26·6	52	52		
1·50	81·2±36·5	61	61		
2·0	95·0±34·7	75	75		
3·0	114·±40·2	94	94		
4	119·±34·6	99	99		
6	124±42·1	104	104		
8	143±46·0	123	123		
12	121±52·8	101	101		
18	65·9±28·3	46	46	1	
20		34	10		
22				19	
24	61·9±23·2	42	20	22	
26				23	
28				21	
30	44·8±15·3	24	2·3	15·5	1
32				12	3
34				9·5	6·5
36	40·1±14·9	20	0·46	7·5	8
40				4·5	10
44				2·6	11
48	32·4±8·5	12		1·6	11
52				10	
72	26·8±9·8	6			6

Data are means±s.d. (n=18). The limit of quantification for oestrone was $20pgmL^{-1}$.

lation phases after administration of the oestradiol formulation (as a representative example of all three oestradiol formulations). The corresponding pharmacokinetic parameters were calculated for each mean oestrone serum concentration–time curve. The mean kinetic parameters of the 1st, 2nd and 3rd phases of absorption of the three pharmaceutical formulations are shown in Table 6. The mean residence time (MRT) values of oestrone increased (100%) with each recirculation and are governed by the lag time. The C_{max} of the second recirculation ($22·5\pm1·8pgmL^{-1}$) was 20% of that of the first ($115\pm7·8pgmL^{-1}$), and the C_{max} of the third recirculation ($10·4\pm0·4pgmL^{-1}$) was 50% that of the second. The AUC values for the second and third recirculations were similar; each comprised 12–13% of the total AUC. The oral clearance values of the recirculations were constant ($590Lh^{-1}$).

Discussion

Oestradiol is absorbed from the gastrointestinal tract, the vagina, and through the skin (Nilsson & Heimer 1992a, b; Boyd et al 1996). Oestradiol has been administered as tablets, implants, by intramuscular injection and by topical gel application. It is partly bound to plasma proteins and is rapidly metabolized in the liver to the less active oestriol and oestrone. The compound is excreted in the urine as the sulphate and glucuronide esters with a small amount of unchanged oestradiol (Martindale 1982; Siddle & Whitehead 1983; Lobo & Cassidenti 1992).

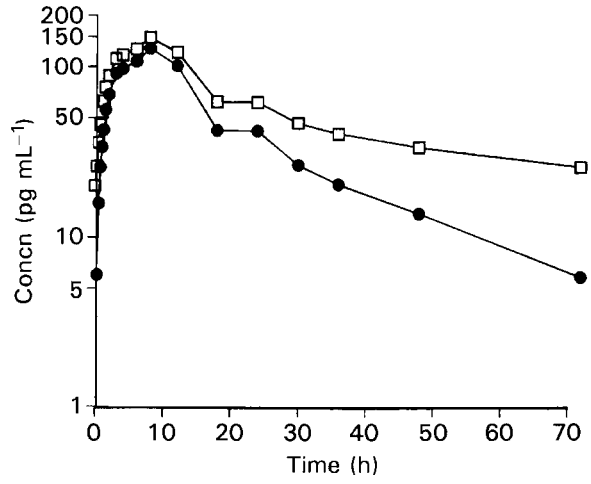

Figure 3. Example of the mean total (□) and baseline-value-corrected (●) serum concentration–time curves for the metabolite oestrone after oral administration of the pharmaceutical formulation oestradiol + desogestrel containing 1·5 mg oestradiol to healthy postmenopausal women (n = 18).

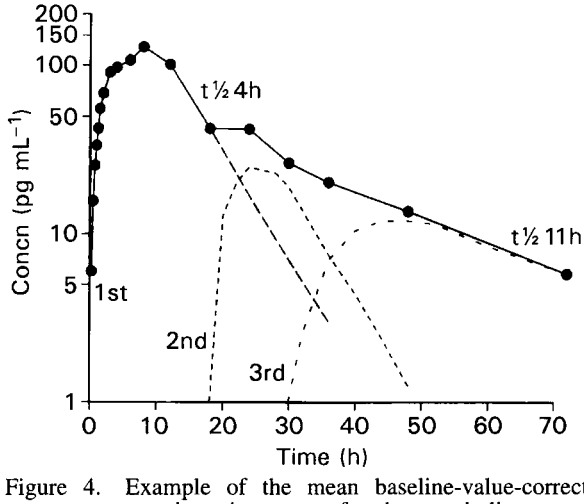

Figure 4. Example of the mean baseline-value-corrected serum concentration–time curve for the metabolite oestrone and the first absorption and the recirculation phases (second and third) after oral administration of the pharmaceutical formulation oestradiol + desogestrel containing 1·5 mg oestradiol to healthy postmenopausal women (n = 18).

Pharmacokinetic parameters

The three pharmaceutical formulations in this study are bioequivalent (Timmer & Geurts 1998).

Table 6. Mean pharmacokinetic parameters for the three phases of absorption of oestrone after administration of 1·5 mg oestradiol in three pharmaceutical formulations.

Parameter	Overall corrected	Absorption		
		1st	2nd	3rd
$AUC_{0-72\ trap}$ ($ng\,L^{-1}h$)	2540±95	1831±16	333±24	356±29
AUC (%)	100	74·6	12·9	13·3
CL (Lh^{-1})	570±30	940±60	4570±310	3230±550
CL* (Lh^{-1})	593±23	820±60	4510±310	4230±360
CL** (Lh^{-1})	593±23	590±17	593±23	590±21
$t^{1}/2_{\alpha}$ (h)	0·16±0·25	0·11±0·17	1·04±0·79	0·81±0·65
$t^{1}/2_{\beta}$ (h)	3·56±0·23	3·93±0·73	3·77±0·23	11·5±1·4
$t^{1}/2_{z}$ (h)	17·6±1·2	3·93±0·73	3·77±0·23	11·5±1·4
MRT (h)	24·4±2·3	10·5±1·0	28·8±0·66	62·7±4·2
MRT_{I-II} (h)	18·3±1·6	34·0±3·8		
t_{lag} (h)	0·12±0·11	0·16±0·06	17·8±0·10	29·5±0·1
t_{max} (h)	5·97±0·51	5·23±0·50	23·3±0·4	46·1±2·0
C_{max} ($ng\,L^{-1}$)	113±3·5	115±7·8	22·2±1·8	10·4±0·4

Data are means±s.d. $AUC_{0-72trap}$ is the area under the serum concentration–time curve between 0 and 72 min calculated according to trapezoidal rule; AUC (%) is the percentage of total AUC; CL is the clearance = dose/$AUC_{0-\infty}$; CL* = Dose/AUC_{trap}; CL** = Dose corrected AUC_{abs}/AUC_{total}; $t^{1}/2_{\alpha}$, $t^{1}/2_{\beta}$ and $t^{1}/2_{Z}$ are the half-lives of the first, second and terminal phase in the serum concentration–time curve, respectively; MRT is the mean residence time; MRT_{I-II} is the difference between the oestrone MRT for each cycle; t_{lag} is the lag time; C_{max} is the calculated maximum serum concentration and t_{max} the time at which C_{max} is reached.

Pharmacokinetic parameters were calculated with baseline correction because most of the oestradiol pre-dose concentrations were lower than or equal to the lower limit of quantitation (LOQ), but are still present in the blood of postmenopausal women and of men (Powers et al 1985; Marslew et al 1991; Albertsson-Wikland et al 1997). The method for baseline correction is to subtract the pre-dose serum concentration from all subsequent concentrations. This was done for the three mean serum concentration–time curves of the 18 subjects and for all three formulations.

Because the validity of baseline correction depends on the periodicity of the circadian or biorhythm of oestrone and oestradiol (Matsumoto et al 1991), this method is not valid for women who have a complete cycle with high values of oestradiol and oestrone (Kuhnz et al 1993). In these women, intrinsic oestradiol kinetics must be investigated with [^{2}H]oestradiol and GC-MS analysis (Shou et al 1997) or with radiolabelled oestradiol (Longcope et al 1994). Even if the time-course of the sampling period is limited compared with the whole oestrous cycle, the whole group of female volunteers will not be monophasic in their cycles. The serum concentration of oestradiol and oestrone is constant in men and in postmenopausal women (Powers et al 1985; Marslew et al 1991; Albertsson-Wikland et al 1997) and the method used for baseline correction is therefore valid in this study.

The pharmacokinetic parameters of oestradiol and oestrone obtained in this study and summarized in Tables 4 and 6 are similar to those reported earlier for oral administration (Aedo et al 1990; Lobo & Cassidenti 1992; Kuhnz et al 1993; Price et al 1997; Thomas et al 1997). The overall $t^{1}/2_{Z}$ of oestradiol after oral administration varied, and increased with dose from 14·2±8·0 h after 0·5 mg to 20·1±14·2 h after 1·0 mg. The ratio of the serum concentrations of oestrone and oestradiol was found to be approximately 10, which is in accordance with that found by Thomas et al (1997) and by Kuhnz et al (1993). Mean serum concentrations of oestrone and its sulphate were found to be 150 $pg\,mL^{-1}$ and 4 $ng\,mL^{-1}$, respectively. The oestrone sulphate concentration was, therefore, 25 times that of oestrone (Thomas et al 1997) and this metabolite might serve as a large circulating pool of available oestrogen to tissues with sulphatase activity (Lobo & Cassidenti 1992).

Enterohepatic recirculation

The second maximum of oestrone at t = 25 h (Figures 1 and 4) in the overall serum concentration–time curve can be considered as a result of enterohepatic cycling. The overall oestrone serum curve is then the result of sequential cycling, each cycle of which can be described according to a bi- or monoexponential equation as illustrated in Figure 4. The damping of each cycle is reflected in MRT_{I-II} (the difference between the oestrone MRT of each cycle) which doubles each cycle (Table 6). The more cycles the more the oestrone concentration reaches a steady state and approaches the endogenous level.

Heimer & Englund (1986a) demonstrated that when activated charcoal is administered 3 h after an oral dose of oestriol, no second peak plasma concentration is observed. Oestriol shows a peak plasma concentration 2 h after oral administration and declines with a $t^{1/2}$ of approximately 1 h. No second plasma oestriol rise was seen after a meal. Intravenously administered [^{3}H]oestriol shows a biexponential decrease in the plasma concentration–time curves with a $t^{1/2}_{\alpha}$ of $3{\cdot}6 \pm 0{\cdot}9$ min and a $t^{1/2}_{\beta}$ of 64 ± 11 min. Oestriol was not metabolized to oestrone and oestradiol (Longcope et al 1994). A second peak in an oestrone serum concentration–time curve was also reported by Kuhnz et al (1993). A second peak plasma concentration for orally administered oestriol was seen after a meal (no charcoal co-medication). This effect is minimal after vaginal application (Englund et al 1984; Heimer & Englund 1986b).

First-pass metabolism

Oral administration of oestradiol induces a very large increment of oestrone, far in excess of physiological levels. With Estraderm TTS, oestrone levels increase only slightly, the ratio of oestrone to oestradiol remaining below 1, i.e. in the physiological range similar to that observed during the follicular phase of the cycle (Laufer et al 1983). After transdermal absorption oestradiol serum concentrations reach high values ($50-100\,pg\,mL^{-1}$; Harrison et al 1997). Thus oral oestradiol dosages show a high first-pass effect.

Clinical implications

The three different tablets tested (two pharmaceutical formulations containing oestradiol with or without desogestrel and one pharmaceutical formulation containing oestradiol valerate) were well tolerated after single-dose administration to postmenopausal volunteers. In clinical terms there were no relevant differences between the three tablets in respect of safety. For all oestradiol formulations the mean oestrone serum concentration–time curve was indicative of noticeable first and a second absorption phases. Although the second absorption phase was also seen in most of the individual oestradiol curves, owing to high variation it levelled out in the overall mean curves except for the oestradiol kinetic profile of the oestradiol + desogestrel formulation. The serum concentration curves of the metabolite oestrone contained a second maximum at approximately 25 h. The C_{max} of the second recirculation was 20% that of the first, and the C_{max} of the third recirculation was 50% that of the second. The oral clearance values of the recirculations were constant ($590\,L\,h^{-1}$). Extrahepatic recirculation of endogenous compounds is aimed at maintaining a steady-state serum concentration for immediate use and hydrolysis in the target organs. It is concluded from this study that exogenously administered oestradiol and its metabolites follow the recirculation pathways of the endogenous oestrogen pool.

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