PHARMACOLOGY OF ESTROGENS AND GESTAGENS

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Replacement therapy with estrogens and gestagens serves the purpose of avoiding the unfavorable consequences of the loss of endogenous estradiol and progesterone production. It is not of primary importance to restore the physiological conditions of an ovulatory cycle, but much rather to realize the intended purpose of the treatment in an optimal way. Various preparations are available for this purpose, allowing the individual situation to be taken into account to a large extent. The choice of estrogen depends on whether only certain complaints (e.g. atrophic symptoms) are to be treated, or whether the entire therapeutic and preventive potential of hormone replacement therapy (HRT) is to be exploited, on whether bleeding will be tolerated, and which side effects are acceptable. With regard to the risk of serious complications, ethinyl estradiol is considered unsuitable for HRT, since the available natural estrogens estradiol, estrone sulfate and estriol are sufficiently effective preparations for which there are hardly any contraindications today. These preparations are supplemented by the equine conjugated estrogens, which have a stronger effect on the hepatic metabolism than estradiol. In the case of certain health limitations (e.g. liver disorders, gastrointestinal complaints, hypertriglyceridemia), the various alternative methods of application help to choose the optimal therapy. Estriol, which does not have any hepatic effects, is unsuitable for osteoporosis prevention, and it does not have any effect on the lipid metabolism. In order to assess the advantages and disadvantages of the various therapy regimens, it is important to know the pharmacokinetics and metabolism of the preparation used. Thereby it must be noted that there are great inter-individual differences in absorption and metabolism that account for the individual variations in serum level, effects and side effects. Attention to the time-related differences in estrogen levels after administration and their accumulation or decrease during long-term application are a prerequisite for correct interpretation of the hormone analysis, should these be considered necessary in certain cases for monitoring or prevention.

EFFECTIVENESS OF ESTROGENS

There are numerous natural and synthetic estrogens, all of which vary quite considerably in terms of their effectiveness (Fig. 1). The prerequisite for a strong estrogenous effect is a strong binding with the estrogen receptor (Table 1), whereby the resulting complex must have the “correct” steric configuration in order to remain bound to the steroid-sensitive element on the DNA for a sufficiently long time and to trigger the biological effect.

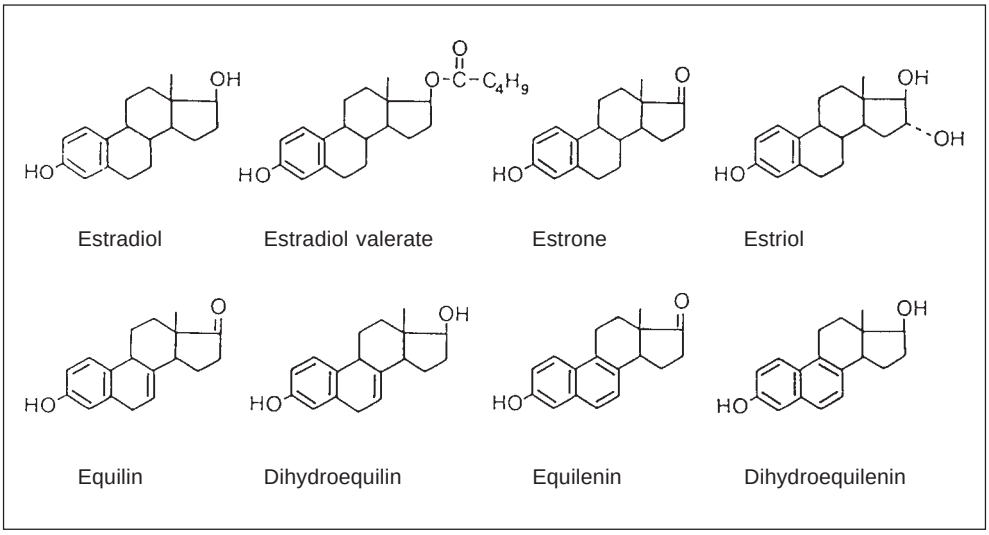

Figure 1. Structural formulas of the estrogens used in HRT

Table 1. Relative binding affinities (RBA) of some estrogens to the estrogen receptors ERα and ERβ (from Kuiper et al. [1]). Since they depend on the incubation conditions, they are not consistent. They are not a measure of biological effect.

Estrogen	RBA to ERα	RBA to ERβ
Estradiol-17β	100	100
Estradiol-17α	58	11
Estrone	60	37
Estriol	14	21
4-hydroxyestradiol	13	7
2-hydroxyestradiol	7	11
Estrone sulfate	< 1	< 1
Tamoxifen	7	6
4-hydroxytamoxifen	178	339
Diethylstilbestrol	468	295
Coumestrol	94	185
Genistein	5	36

Meanwhile, it has been demonstrated that there are two different estrogen receptors, ERα and ERβ, which occur in different concentrations in the various organs and tissues. The so-called organ-specific effects of certain estrogens or anti-estrogens (e.g. estriol, tamoxifene, raloxifene) can be explained by the fact that the relevant estrogen-estrogen receptor complexes can induce different effects in the individual tissues. A high affinity alone does not necessarily mean a strong estrogen effect, as the example of the anti-estrogens shows. Moreover, the application must lead to sufficiently high concentrations in the target cell, which depends primarily on the serum levels and local metabolization in the cell.

Of the physiological estrogens, estradiol has the strongest effect, whilst estrone has only a slight effect due to its low binding affinity. The significance of estrone lies in the fact that it is a metabolite and precursor of estradiol at the same time (Fig. 2). It is conjugated into estrone sulfate, which circulates in high concentrations, and into estrone glucuronide, most of which is eliminated.

Estriol is a weak estrogen, which, at the normal dose, has only a low proliferative effect on the endometrium. This is due to the fact that estriol is an estrogen with a short-term effect, and although it is bound by the receptor with the same association rate as estradiol, it only remains bound for 1 to 4 hours due to the rapid dissociation.

As a result, the biological effects that rely on binding of the estrogen receptor complex to the DNA for 8 to 12 hours cannot be triggered. Estriol is an end product of metabolization that cannot be transformed back into estradiol and is also eliminated as a conjugate. Although the serum levels of the estrogens and their metabolites correlate with the dose administered, the individual effects – like the serum levels on administration of the same dose – are very different, even if the measured estrogen levels are identical. Accordingly, the question of an optimal estradiol level cannot be answered and the value of an estradiol determination to monitor the therapy success is doubtful. Similarly, the effectiveness of the various estrogens can only be understood as an average estimate with considerable individual deviations. Thereby, it must be noted that the effects of the estrogens depend on the relevant organ or test system, so that e.g. the effect on the karyopyknotic index does not necessarily correlate with bone density, hot flushes or hepatic angiotensinogen synthesis [2].

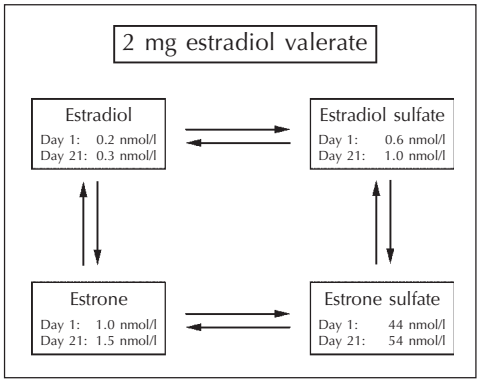

Figure 2. Mutual transformation of estradiol, estrone, estrone sulfate and estradiol sulfate during treatment with estradiol and estrone sulfate (after Aedo et al. [4])

In terms of their clinical effect, the dose of 1 to 2 mg estradiol or estradiol valerate corresponds with a dose of 0.6 to 1.25 mg equine conjugated estrogens, which is generally considered to be the minimum effective dose for the therapy and prevention of complaints and disorders caused by an estrogen deficiency. It is roughly comparable with a transdermal treatment with 100 µg estradiol [2].

By contrast, estradiol and the conjugated estrogens differ considerably in their effect on the hepatic metabolism (Table 2). Equine conjugated estrogens, a mixture of various estrogen conjugates, have a considerably stronger stimulating effect on the synthesis of many proteins (e.g. angiotensinogen, SHBG) than estradiol, which is primarily due to the equilins. In addition, oral

Table 2. Relative effectiveness of certain estrogens with regard to various clinical and metabolic parameters (from Kuhl [3]).

Estrogen	Hot flushes	FSH	HDL-CH	CBG	SHBG	Angio-tensinogen
Estradiol-17β	100	100	100	100	100	100
Estriol	30	30	20			
Estrone sulfate		90	50	70	90	150
Conjugated estrogens	120	110	150	150	300	500
Equilin sulfate			600	600	750	750
Ethinyl estradiol	12,000	12,000	40,000	60,000	50,000	35,000

treatment has a stronger effect than parenteral administration due to the high local concentrations in the liver during the first passage [2]. Accordingly, transdermal estradiol therapy is preferable to oral therapy in patients suffering from severe liver function disorders or disorders of the hepatic metabolism, and equine conjugated estrogens should not be administered. Estriol, on the other hand, has no effect on the liver at the recommended doses.

Estradiol and Estradiol Ester

Oral Administration

When administered orally, the micronized estradiol is metabolized into estrone, estrone sulfate and estradiol sulfate to a large part in the duodenum and jejunum, as well as in the liver. Due to the large surface of the microcrystals, however, a sufficient quantity of estradiol is absorbed rapidly and thus escapes metabolization.

Similar conditions are found in treatment with estradiol valerate, which is split rapidly after administration, whereby estradiol is released. Within a short time of administration of e.g. 2 mg estradiol valerate, the estrogen serum concentration rises to a maximum of about 40 pg/ml on average on the first day, and up to 80 to 100 pg/ml after daily administration. The serum levels of estrone reach values that are about four to six times as high as those of estradiol, whilst estrone sulfate, which is produced in large quantities, reaches concentrations that are 30 to 40 times as high as those of estrone (Fig. 3) [4]. Estradiol sulfate also increases, although to a far lesser degree than estrone sulfate. The half-life of estradiol in the serum is around 35, that of estrone around 20, that of estradiol sulfate around 20 and that of estrone sulfate around 12 hours [4]. Compared with micronized estradiol, slightly lower estrone levels are found after administration of the same dose of estradiol valerate, although the estradiol concentrations are similar [5]. This means that valerate slows down the intestinal metabolization of estradiol. In the further course of treatment with estradiol valerate, estradiol and its metabolites accumulate in the serum, so that on day 21 of treatment the serum levels of estradiol and estrone are about 50 %, that of estrone sulfate 25 % and that of estradiol sulfate 65 % higher than on day 1 (Fig. 3) [4].

In contrast to ethinyl estradiol or estriol, where a rapid increase to a maximum and a similarly rapid decrease in serum levels is observed after administration, estradiol has a special status with regard to pharmacokinetics. The maximum estradiol concentration is not reached until after about 5 hours, and the decrease is also gradual, so that an increased estradiol level can be found for several hours (Fig. 3) [4]. Accordingly, the terminal half-life time ($t_{1/2\beta}$) of estradiol is fairly long at 35 hours. The reason for this lies in the fact that estrone, estrone sulfate and estradiol sulfate must be regarded not only as metabolites but also as precursors of estradiol, and they can be transformed back into estradiol (Fig. 2). These relationships become clear when the concentrations of estradiol, estrone and estrone sulfate after administration of estradiol valerate are compared with those after administration of estrone sulfate (Fig. 3). Since estrone and estrone sulfate circulate in considerably higher concentrations, they represent a

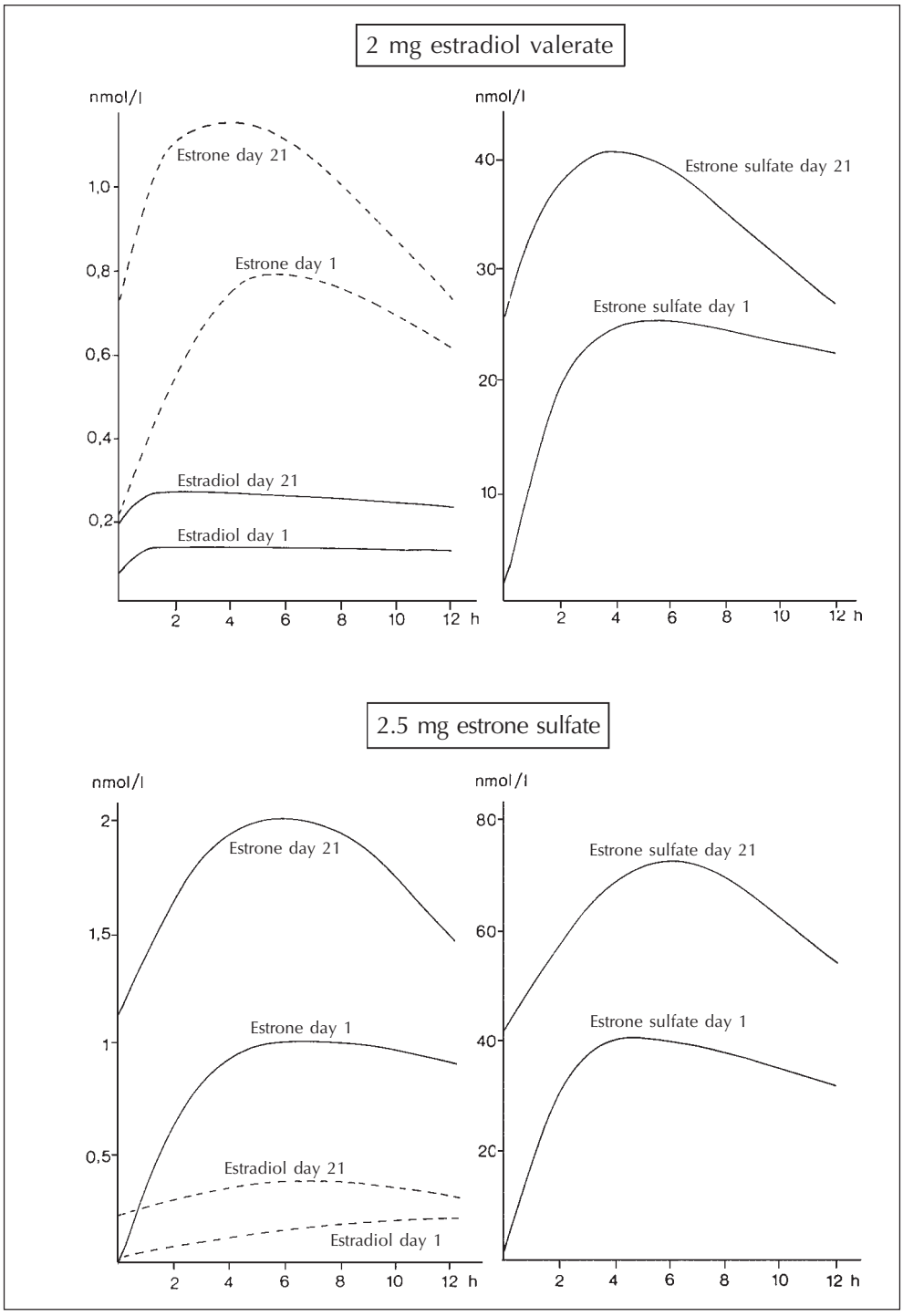

Figure 3. Average serum concentration curve for estradiol, estrone and estrone sulfate following oral administration of 2 mg estradiol valerate (above) or 2.5 mg estrone sulfate (below). Modified from Aedo et al. [4].

large, hormonally inactive reservoir that is responsible for the estradiol level still being raised 24 hours after administration. The ratio of estrone to estradiol, which is often used as a criterion for a "more physiological" or "more unphysiological" therapy and which is 5:1 in oral therapy, 1:1 in transdermal therapy, 1:2 in young women and 2:1 in postmenopausal women, is without any clinical relevance.

Transdermal Administration

Transdermal treatment avoids the strong metabolization in the intestinal tract and during the first passage through the liver. It is particularly suitable for women suffering from gastrointestinal or liver disorders. There are two types of patches containing estradiol, namely the reservoir patch and the matrix patch.

The ***reservoir patch*** contains an alcoholic gel with 2, 4 or 6 mg estradiol. After application, the estradiol dissolved in alcohol diffuses through the membrane into the *horny layer* and reaches the capillaries in the *dermis*. The diffusion depends on the concentration gradient between the reservoir and the capillaries, whereby the alcohol not only facilitates diffusion but also reduces metabolization of the estradiol in the skin. The system is only efficient as long as the patch sticks and the alcohol solution is present. The reservoir patch is available with different doses, whereby release rates of 25, 50 or 100 µg per day are indicated. After the application of a 50 µg patch, the estradiol levels increase rapidly and reach a maximum of 40–60 pg/ml after 30 hours. Then they decrease again, reaching a level of 30 pg/ml after 48 hours and the baseline value after 72 hours (Fig. 4) [6, 7]. When the first patch is applied, the levels are slightly lower, but the steady state is already reached with the second patch. With the 25 µg patch, the estradiol levels are 30–40 pg/ml, and with the 100 µg patch they are between 60 and 110 pg/ml. With transdermal treatment, there are also strong intra-individual fluctuations of the estradiol level, ranging from 30 to 65 pg/ml with the 50 µg patch and from 60 to 100 pg/ml with the 100 µg patch. Usually, a strong decrease in estradiol is observed on the third day, since diffusion becomes weaker with the disappearance of the alcohol. In about 30% of the women, the values are fairly low due to poor absorption.

In the ***matrix patch***, the estradiol is distributed in the adhesion layer consisting of an acryl or vinyl acetate polymer, and it diffuses into the skin when the matrix is applied, whereby various absorption enhancers (fatty acids, fatty acid esters, lecithin) facilitate the penetration. The diffusion rate of the matrix system is fairly constant, so that the estradiol levels are still around 50% of the maximum value after 4 days (Fig. 4) [6]. Therefore, the matrix patch lasts seven days, even though some manufacturers recommend changing it twice a week. Once the matrix patch has been applied, the maximum estradiol level is reached after only 12 hours, whereby the values are 30–45 pg/ml

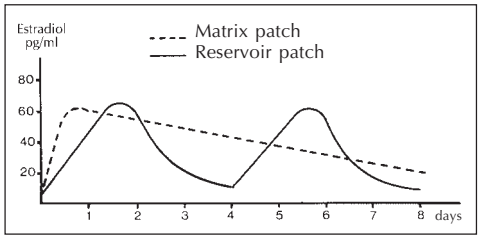

Figure 4. Schematic illustration of the serum concentration curve for estradiol following single administration of a matrix patch and after two administrations of a reservoir patch (after Baracat et al. [6])

with the 25 µg patch, 40–80 pg/ml with the 50 µg patch, and 90–140 pg/ml with the 100 µg patch. In addition, there are matrix patches with a release rate of 37.5 µg and 75 µg per day. The observation that the estradiol level is higher in the evening than in the morning, possibly due to circadian fluctuations in the circulation of the skin, is interesting [8].

The administration of an alcohol-water ***gel*** containing estradiol, which is applied to a certain area of the abdomen or upper arm, follows a different principle. The hormone penetrates very rapidly, until the gel has dried (within 2 minutes). Thereby, the *horny layer* acts as a store from which the estradiol gradually diffuses into the capillaries of the *dermis* and reaches the circulation.

There are two different types of such preparations. One of them contains a dose of 1.5 mg estradiol in 2.5 g gel (0.06 % estradiol) and is always applied to the same area of skin. As a result, the *horny layer* is saturated with estradiol, and the estradiol level correlates with the surface of the treated skin. Consequently, an increase in estradiol level is observed during the first four or five days, until the steady state is reached. When 1.5 mg estradiol is applied to 400 cm^2 skin surface daily, serum levels of 70 to 90 pg/ml are reached [9]. The other preparation contains 0.1 % estradiol hemi-hydrate (crystal water), and it is applied to different areas of skin. After application of 1.5 g gel with 1.5 mg estradiol, the estradiol level increases to a peak value of about 30 pg/ml within 6 hours [10]. After repeated daily administration, a steady state with a maximum estradiol level of 80 pg/ml is reached after 4 hours. Here, too, the *horny layer* serves as a store, but the skin is not saturated with estradiol since the area of application is changed every day. Therefore, the estradiol levels do not correlate with the treated skin surface.

Subcutaneous Administration

In England and in the USA, pellets of crystalline estradiol are available for subcutaneous implantation, which release the hormone in fairly equal rates over a period of several months. With a pellet of 100 mg estradiol, estradiol levels of between 150 and 250 pg/ml are reached, which decrease only slowly and are still at about 50 pg/ml after 12 months. Therefore, an accumulation of estradiol must be expected after repeated implantation. There have been reports on estrogen deficiency syndromes that occurred between 3 and 16 weeks after the implantation of 50 or 100 mg estradiol, although the estradiol levels were within a range from 400 to 1000 pg/ml [11]. It is possible that extremely high estradiol concentrations cause desensitization, so that even the start of a decrease in estradiol level may lead to the recurrence of hot flushes.

Intramuscular Administration

The intramuscular injection of an estradiol ester produces a microcrystalline primary deposit at the injection site or a secondary deposit in the fatty tissue, from which the ester is released gradually and broken down into estradiol in the liver. The deposit effect is all the more marked, the more lipophilic the fatty acid contained is. After the injection of 4 mg estradiol valerate, a maximum estradiol level of about 400 pg/ml is reached within two days, which decreases again gradually and reaches a level of about 150 pg/ml after 10 days. If, on the other hand, the more lipophilic estradiol cipionate (estradiol

cyclopentyl propionate) is used, the peak estradiol level of 340 pg/ml is lower, but the increase and decrease last much longer than after an injection with estradiol valerate [12].

Vaginal Administration

After the vaginal administration of 0.5 mg estradiol, the good absorption and fairly low metabolization rate lead to estradiol levels of about 900 mg, i.e. 10 to 20 times as high as after oral administration, but which drop again rapidly. With regard to the serum concentrations of estrone, estrone sulfate and estradiol sulfate, however, there are no differences between vaginal and oral administration [13]. Accordingly, topical administration of estrogen at a sufficient dose is not only a strong local therapy but also a systemic therapy with much higher effectiveness than that of oral administration of the same dose. When a ***vaginal ring*** is used, which contains 4% estradiol in a matrix of silicon elastomer, a gradual release of 100–200 µg per day is achieved, resulting in systemic estradiol levels of between 60 and 150 pg/ml. At a release rate of 140 µg per day, an estradiol level of 85 pg/ml is reached [13].

Limitation to a purely topical effect on the vaginal epithelium is only possible if the applied estradiol dose is very low. After vaginal application of 25 µg ***tablets***, there is a slight rise in estradiol level to 50 pg/ml on the first day only, but after 14 days of treatment a systemic effect is no longer to be expected [14]. This is presumably due to the fact that at the beginning of local therapy the atrophic vaginal epithelium has virtually no metabolic capacity, but with increasing proliferation and normalization it inactivates a large part of the absorbed estradiol [15]. Systemic effects can even be avoided with a vaginal ring that contains 2 mg estradiol in its hollow core and releases only 7.4 µg estradiol per day. The ring lasts for an application period of 85 days [16].

Intranasal Administration

Intranasal administration of estradiol with the help of an aqueous ***spray*** containing estradiol – conjugated with methylated β-cyclodextrin – results in a significantly raised estradiol level for a short time within 10–30 minutes due to rapid absorption in the strongly vascularized nasal mucosa, followed by an equally rapid decrease to about 10% of the peak value after 2 hours [17]. With a daily dose of 300 µg estradiol, which is adequately effective in 80% of women, a peak serum estradiol level of 1150 pg/ml is reached, that drops to 150 pg/ml again within 2 hours. The therapeutic effectiveness of this method is proof that even large daily fluctuations in estradiol level do not necessarily have to exert unfavorable effects, and that an even distribution of the estradiol concentration does not have any particular benefits.

Sublingual Administration

Due to the rapid absorption and low metabolization rate, very high bolus-like estradiol levels are observed after sublingual administration of estradiol. A maximum estradiol level of about 300 pg/ml and an estrone level of 60 pg/ml is reached within one hour of sublingual administration of a tablet containing 0.25 mg micronized estradiol. This is followed by a rapid decrease in estrogen level. After sublingual administration of 1 mg estradiol, an estradiol peak of 450 pg/ml is reached [18].

Conjugated Estrogens

The sulfuric acid and glucuronic acid esters of the estrogens, which are water-soluble and circulating in high concentrations – especially the sulfates –, are generally referred to as conjugated estrogens or estrogen conjugates. They are particularly important for the metabolism and elimination of endogenous steroids. It is less well known that steroid conjugates occupy numerous enzyme systems directly, i.e. without prior hydrolysis, as a substrate, and can thus influence the steroid synthesis. However, since they only have a mild affinity to the receptor, they do not have any hormonal effect until after being split into the free steroid.

The conjugated estrogens that are used for substitution therapy are the sulfates of various estrogens that are available as sodium salt. In the USA, the sodium may be replaced by piperazine, a strong organic base. The most important conjugates used in therapy are estrone sulfate and equilin sulfate (Fig. 1). Equine conjugated estrogens are a mixture of 9 different conjugates, whereby the total dose consists of about 50% estrone sulfate, 25% equilin sulfate, and 15% 17α-dihydroequilin sulfate (Table 3). Mainly the estradiol produced from the estrone sulfate and the 17β-dihydroequilin produced from the equilin sulfate are responsible for the estrogen effect. 17α-dihydroequilin, on the other hand, has hardly any hormonal effect, although it is bound by the estrogen receptor with a fairly high affinity (Table 1) [19].

After administration of the conjugated estrogens, a large part of the estrone sulfate and the other conjugates is absorbed without modification. Within 5 hours of administration of 2.5 mg estrone sulfate, the estrone level increases to about 250 pg/ml, and with continued daily administration it increases to over 400 pg/ml (Fig. 3). The estrone sulfate concentration is 30 to 40 times as high as the estrone concentration [4]. The estradiol serum level increases only slowly on the first day of treatment, reaching a value of about 50 pg/ml after 12 hours. In the further course of treatment, an increase in estradiol to an average of 100 pg/ml can be observed [4]. Part of the estrone sulfate is converted directly into estradiol sulfate, which reaches serum levels that are 3 to 4 times as high as those of estradiol [4, 20]. About 3 hours after the administration of 10 mg conjugated equine estrogens, a maximum equilin serum level of about 530 pg/ml and a maximum estrone level of 1400 pg/ml is observed [21]. It may be assumed that daily administration of equilin and equilin sulfate will also result in an accumulation in the serum.

The conjugated estrogens do not have a hormonal effect until after hydrolysis of the sulfuric acid and conversion into the active substances. Thereby, hydrolysis of the sulfates takes place not only in the liver, which they pass through largely without modification, but also in the peripheral tissue [20]. As with the conversion of estrone into 17β-estradiol, the formation of 17β-dihydroequilin and 17β-dihydroequilenin from equilin and equilenin is an important factor for their effectiveness (Fig. 1). Due to the fairly strong binding to albumin, the half-life of equilin sulfate in the blood is considerably longer than that of equilin [2]. However, both equilin and equilin sulfate are eliminated much faster than estrone and estradiol or estrone sulfate [23].

Table 3. Composition of conjugated estrogens, and relative estrogen effectiveness and relative binding affinity to the estrogen receptor (RBA) of the individual components [3, 19, 22]. The substances are contained in the preparation as the sodium salt of the relevant sulfuric acid conjugate (sulfate). The relative effectiveness is with reference to growth of the rat uterus [19, 22].

Substance	Share (%)	Relative effectiveness (%)	Relative binding affinity (%)
Total preparation	100	100	32
Estrone	49.1	32	41
Equilin	22.8	80	40
Dihydroequilin	13.5	2.6	6
8,9-dehydro estrone	3.9		
Estradiol-17α	3.7	3.5	32
Equilenin	2.8	11.4	7
Dihydroequilenin-17α	1.6	1.3	18
Dihydroequilin-17β	1.5	200	47
Dihydroequilenin-17β	0.7	9.4	46
Estradiol-17β	0.5	246.2	100

Estriol

Oral Administration

Following oral administration, most of the estriol is metabolized rapidly within the intestinal tract, so that only 1–2 % of the dose reaches the circulation without modification [2]. Within 1 to 4 hours of administration of 4 mg, a peak serum level of 35 pg/ml is reached, followed by a fairly rapid decrease. The greater part of the administered estriol circulates in the form of glucuronides and sulfates with concentrations that are 500 times as high as those of unconjugated estriol. Daily administration leads to an accumulation, however, and the estriol serum levels rise up to 130 pg/ml [24]. Since estriol is subject to a marked enterohepatic circulation, a second peak serum level may be reached within one hour after eating [2]. Since this may extend the retention of estriol in the target cell and interaction with the receptor, proliferation of the endometrium in the long term cannot be excluded. The same holds true for very high estriol doses or for dividing the daily dose into two or three applications. Therefore, the entire estriol dose should be taken at one time, preferably in the evening.

Oral estriol succinate (estriol-16,17-dihemisuccinate) is absorbed almost without modification and much more slowly than estriol, since the intestinal mucosa hardly hydrolyses the ester. In the liver, however, the substance is splitted much faster and then metabolized further [25]. After the first administration of 8 mg, the estriol level reaches a maximum of 40 pg/ml only after 12 hours, but with daily administration it rises to 80 pg/ml within 5 days [26].

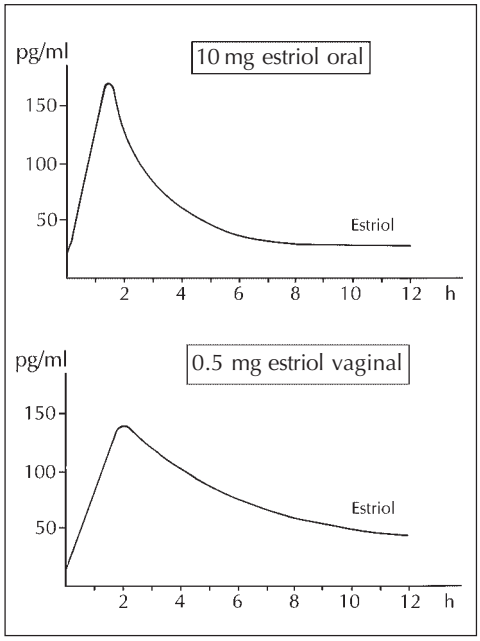

Figure 5. Average serum concentration curve for estriol following oral administration of 10 mg estriol (above) or vaginal administration of 0.5 mg estriol (below).

Vaginal Administration

Since the strong intestinal metabolization is bypassed, vaginal administration results in estriol levels that are 10 to 20 times higher than after oral administration of the same dose [2]. This means that similar estriol levels and similar systemic effects are achieved with local therapy with e.g. 0.5 mg estriol as with oral treatment with 10 mg estriol (Fig. 5). Following vaginal administration of 0.5 mg estriol, a maximum serum level of 100 to 160 pg/ml is reached after 1 to 2 hours. If the vaginal dose is doubled, the estriol level only increases by 10%, however. Accordingly, the maximum effect of vaginal estriol therapy is achieved with 0.5 mg, and doubling the dose does not lead to any significant improvement. During long-term local treatment – in contrast to oral administration – there is a continuous decrease in estriol levels, which are 30–50% lower than on the first day of treatment after 4 weeks [27]. This is presumably due to normalization of the vaginal epithelium, which has a metabolic activity similar to that of the endometrium [15]. Since in this route of administration the production of estriol conjugates is very low compared with oral administration, the enterohepatic circulation of estriol does not play a role. The same applies to the vaginal administration of estriol succinate, which is hydrolyzed in the liver after absorption, as for estriol.

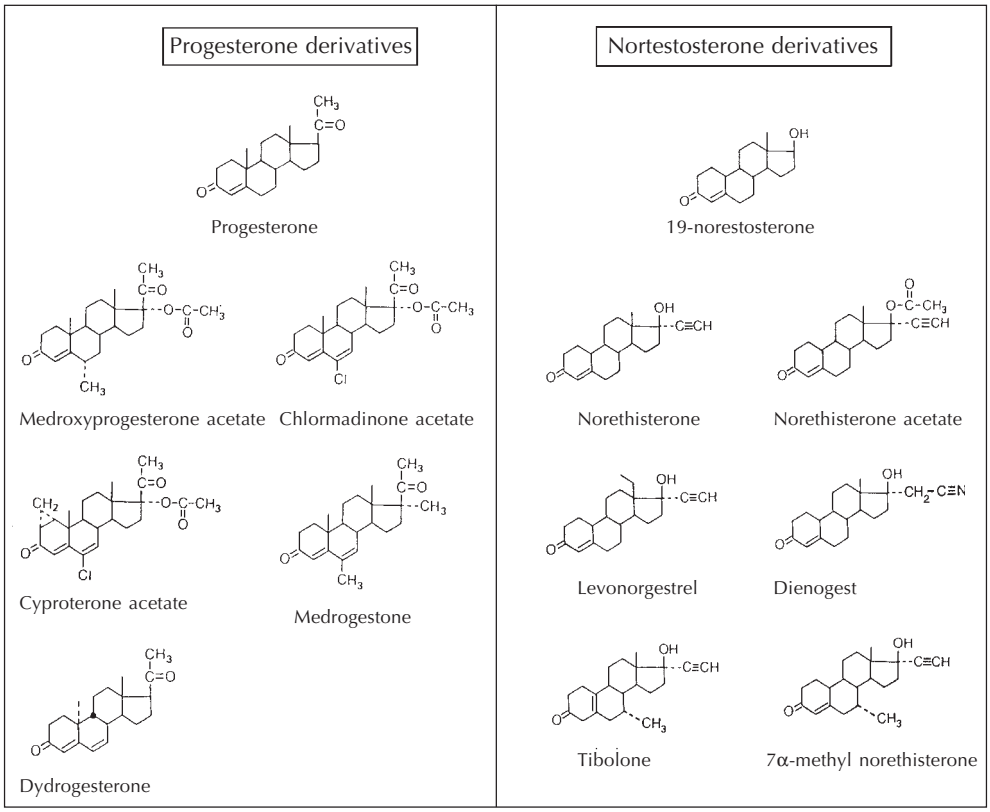

Figure 6. Structural formulas of the gestagens used in HRT

Structure and Hormonal Pattern of Gestagens

The only indication for the use of a gestagen in HRT is to reduce the risk of endometrial carcinoma, so that gestagen addition is not necessary for women after hysterectomy. Exceptions are benign breast disorders, the Raynaud syndrome, (former) cycle-related epilepsy, and osteoporosis, in which cases the addition of gestagen may have beneficial effects. With regard to the effect on bone, however, norethisterone is the only gestagen for which a significant effect has been shown. In patients for whom estrogens are contraindicated, hot flushes can often be improved with sufficient doses of progesterone derivatives. The gestagens also include tibolone, a nortestosterone derivative that is effective for climacteric complaints and suitable for the prevention of osteoporosis.

Since the natural gestagen progesterone is inactivated very rapidly by reduction of the carbonyl groups on C3 and C20 and the double bond between C4 and C5, synthetic gestagens have been developed that are metabolized much more slowly and can therefore be administered orally at fairly low doses. We distinguish between the progesterone derivatives and the nortestosterone derivatives (Fig. 6). Due to their origin, the two gestagen types have different hormonal action patterns. With the exception of dienogest, the nortestosterone derivatives have weak androgenic properties, but in combination with an effective estrogen these are without clinical relevance. They also have a stronger effect on the various hepatic parameters, some of which are considered beneficial, others less beneficial. Progesterone and the progesterone derivatives have a weak glucocorticoid effect that may be of importance in association with the cardiovascular risk. The most important effect of the gestagens is their strong anti-estrogenic and differentiating effect on the endometrium, which inhibits estrogen-induced proliferation. The anti-estrogenic effect can also be observed in the cervical mucus and vaginal epithelium, whilst it tends to enhance the proliferative effect of estrogens in the mammary gland tissue. With the exception of dydrogesterone, the gestagens have a central effect, they reduce gonadotropin secretion and raise the basal temperature. The varying hormonal pattern of the gestagens is based on their binding ability to the androgen, glucocorticoid and mineral corticoid receptor, whereby there are considerable differences with regard to the binding affinity and the resulting effects (Table 4).

Progesterone

In the luteal phase, progesterone reaches serum concentrations of between 10 and 25 ng/ml. It is an effective aldosterone antagonist, but this effect is compensated by an increase in aldosterone level. Progesterone is also available in micronized form for oral administration, and it is particularly suitable for high risk patients (e.g. with severe liver disorders). With regard to its use in women with cardiovascular disorders, however, a number of issues is still unanswered.

In the circulation, 17% of progesterone is bound to CBG and 80% to albumin. Due to the strong metabolism, the half-life of 6 ($t_{1/2\alpha}$) and 42 ($t_{1/2\beta}$) minutes is very short. Therefore, in oral and

vaginal administration daily doses of 200–300 mg are required. With regard to the produced metabolites and their serum concentrations, there are considerable individual differences. The most important inactive metabolite of progesterone is pregnanediol, which is eliminated mainly as a conjugate.

Oral Administration

In oral therapy with progesterone, metabolites with a sedative effect may be produced. Therefore, administration in the evening is recommended. Following the administration of 200 mg, a maximum progesterone level of 10–20 ng/ml is reached after 3–4 hours. In some women the sedative, ring A-reduced metabolites 5α- and 5β-pregnanolone may reach serum concentrations of 35 and 20 ng/ml [28]. Other major metabolites are 20α-dihydroprogesterone, which accounts 25–50% of the gestagen effect of progesterone, and 11-deoxycorticosterone (DOC), which is a strong mineral corticoid that can partly compensate the anti-aldosterone effect of progesterone. Due to the considerable inter-individual variations, only a part of the patients are affected by these side effects.

Vaginal Administration

In vaginal treatment with progesterone, administration in the evening is recommended for practical reasons. Within 5 hours of vaginal administration of 400 mg, a maximum progesterone level of about 16 ng/ml is reached, whilst the various metabolites are produced in small quantities only. After administration of 45 and 90 mg gel with 4% or 8% progesterone, the natural gestagen is released quite evenly and with delay, so that administration twice a week is sufficient. Thereby, it seems to be a direct connection between vaginal tissue and endometrium (uterine first-pass effect).

Progesterone Derivatives

In the progesterone derivatives, the steroid frame has been modified by introducing a methyl or chlorio substitute at C6 and a methyl or acetyl group at C17α, so that the reduction reactions are strongly inhibited and the effectiveness is thus enhanced considerably. The progesterone derivatives are usually administered orally, but depot

Table 4. Relative binding affinities of gestagens to the steroid receptors. The values are compiled from literature, are not consistent and correlate only in part with the biological effects. PR = progesterone receptor (promegestone = 100), AR = androgen receptor (metribolone = 100), ER = estrogen receptor (estradiol = 100), GR = glucocorticoid receptor (dexamethasone = 100), MR = mineral corticoid receptor (aldosterone = 100).

Gestagen	PR	AR	ER	GR	MR
Progesterone	50	0	0	10	100
Medroxyprogesterone acetate	115	5	0	29	160
Chloromadinone acetate	67	3	0	8	0
Cyproterone acetate	90	6	0	6	8
Medrogestone					
Dydrogesterone	75				
Dienogest	5	10	0	1	0
Norethisterone	75	15	0	0	0
Levonorgestrel	150	45	0	2	70
Δ 4-tibolone	90	35	1		2

preparations with medroxyprogesterone acetate or hydroxyprogesterone caproate for intramuscular injection are also available. The progesterone derivatives are less suitable for transdermal therapy.

Medroxyprogesterone Acetate

Medroxyprogesterone acetate is administered orally at doses of 5 or 10 mg daily, or as microcrystalline depot preparation (injection of 150 mg every three months). The gestagen has weak androgenic properties and low glucocorticoid effects. The bioavailability is 100%, and a maximum medroxyprogesterone acetate serum level of 4–5 ng/ml is reached 1–2 hours after administration of a dose of 5 mg [5]. In the serum, it is bound only to albumin. The half-life is 2.2 ($t_{1/2\alpha}$) and 33 ($t_{1/2\beta}$) hours. The most important inactivation steps are hydroxylation reactions on C6β and C21.

Chlormadinone Acetate

At a dosage of 1 or 2 mg, chlormadinone acetate has a bioavailability of almost 100%. A maximum chlormadinone acetate serum level of about 4 ng/ml is reached between 1 and 2 hours after administration of 4 mg. In the serum, it binds only to albumin, with weak affinity. Chlormadinone acetate has mild anti-androgenic properties that correspond to about 30% with those of cyproterone acetate. In view of the fairly low concentrations and low binding affinity, however, the clinical relevance is doubtful. The substance is stored in the fatty tissue and eliminated very slowly, with a half-life of 2.4 ($t_{1/2\alpha}$) and 89 ($t_{1/2\beta}$) hours. The most important inactivation steps are reduction of the 3-oxo group, whereby the double bond is maintained, and hydroxylation reactions. 3β-hydroxychlormadinone acetate has 70% of the anti-androgenic effect of chlormadinone acetate.

Cyproterone Acetate

When administered orally at a dose of 1 to 2 mg, cyproterone acetate has a bioavailability of almost 100%. It has fairly strong anti-androgenic and mild glucocorticoid effects. For the treatment of androgenic symptoms, higher dosages are often necessary. Following the administration of 2 mg, the cyproterone acetate serum concentration increases to about 11 ng/ml, whereby 93% are bound to albumin. It is stored in the fatty tissue and eliminated very slowly, with a half-life of 2–8 ($t_{1/2\alpha}$) and 60 ($t_{1/2\beta}$) hours. Daily administration of higher doses may therefore lead to accumulation and a depot effect. The most important metabolic steps are hydroxylation reactions and de-acetylization, whilst the C4 double bond is maintained. Of the metabolites, 15β-hydroxycyproterone acetate has a similar anti-androgenic effectiveness, but only 10% of the gestagen effect of cyproterone acetate.

Medrogestone

Medrogestone differs from the other progesterone derivatives in that it has a methyl group instead of an acetyl group at C17α. The bioavailability is about 100%, and following the administration of 10 mg medrogestone serum-concentrations of 10–15 ng/ml are reached. The half-life is 4 ($t_{1/2\alpha}$) and 36 ($t_{1/2\beta}$) hours. In the serum, it is bound mainly to albumin. The most important metabolic steps are hydroxylation reactions. Data on its binding to the various steroid receptors are not available, therefore possible side effects cannot be estimated (Table 4).

Dydrogesterone

Dydrogesterone is a so-called retroprogesterone where rings A and B do not lie on the same plane as rings C and D, and the steric configuration differs from that of the other steroids. This is presumably the reason why there are virtually no central effects, i.e. no gonadotropin-inhibiting, thermo-genetic and sedating properties. Due to the unusual steric structure, the 3-carbonyl group and the C4 double bond are not reduced. Even so, the half-life is short, so that doses of 10–20 mg are required. The most important metabolization steps are reduction of the 20-carbonyl group and hydroxylation reactions. Apart from the binding affinity to the progesterone receptor, no data are available on the binding to other steroid receptors (Table 4).

Nortestosterone Derivatives

The mild androgenic properties of the nortestosterone derivatives, which are derived from 19-nortestosterone (nandrolone), are normally without clinical significance, since the gestagens are applied at a fairly low dosage and in combination with estrogens. As with the anabolic agent nandrolone, reduction of the C4 double bond decreases rather than enhancing the androgenic effect – as is seen with dihydrotestosterone. A patch with norethisterone acetate is available for transdermal substitution.

Norethisterone and Norethisterone Acetate

Since norethisterone acetate is hydrolized to norethisterone in the gastrointestinal tract and in the liver soon after administration, the pharmacokinetics and pharmacodynamics of the two substances are quite similar. Norethisterone does not have any glucocorticoid or anti-mineralocorticoid effects, and the mild androgenic properties are not effective at a dose of 0.5 mg or 1 mg, if the substance is combined with an estrogen. When administered orally, the bioavailability is between 50 and 77%. Following the administration of 1 mg, norethisterone levels of 5–10 ng/ml are measured. In the serum, 36% of the norethisterone binds to SHBG and 61% to albumin. The half-life is 2.5 ($t_{1/2\alpha}$) and 8 ($t_{1/2\beta}$) hours. The most important metabolic step is reduction of the 3-oxo group and the double bond in ring A. A small part of the norethisterone (0.35%) is aromatized in the fatty tissue, but the ethinyl estradiol levels produced after administration of 1 mg norethisterone are usually close to or below the detection limit and – in the presence of high estradiol levels – without clinical relevance [29]. At higher dosages, e.g. 5 mg or 10 mg, ethinyl estradiol concentrations similar to those after administration of ovulation inhibitors can be found [30].

After transdermal administration of 0.25 mg norethisterone acetate, the norethisterone concentration increases to 0.5–1 ng/ml within 2 days, and then decreases to about half this level when the next change of patch is due (every 3.5 days).

Levonorgestrel and DL-Norgestrel

DL-norgestrel is a racemate and consists of equal parts of the strong gestagen levonorgestrel and the hormonally ineffective dextronorgestrel. Therefore, only 0.25 mg levonorgestrel are effective when 0.5 mg DL-norgestrel are administered. Because of the mild

androgenic properties, levonorgestrel should be administered at the lowest possible dose. The bioavailability is almost 100%. Following the administration of 0.125 mg levonorgestrel, a levonorgestrel level of about 3.5 ng/ml is reached. In the serum, 48% of the levonorgestrel is bound to SHBG and 50% to albumin. The half-life is 1 ($t_{1/2\alpha}$) and 24 ($t_{1/2\beta}$) hours. The most important metabolic step is reduction of the 3-oxo group and of the C4 double bond.

When an intrauterine device containing levonorgestrel is administered, 20 µg levonorgestrel are released daily. High local concentrations of gestagen in the endometrium occur, which cause atrophy of the endometrium even during estrogen treatment. Since the levonorgestrel serum levels remain very low at 0.1–0.2 ng/ml, systemic effects are hardly noticeable.

Dienogest

Dienogest differs from the other nortestosterone derivatives in that it has a cyanomethyl group at C17α instead of an ethinyl group (Fig. 6). It has an antiandrogenic effect rather than an androgenic effect, equivalent to about 40% of the effect of cyproterone acetate. In the serum, it does not bind to SHBG or CBG; 90% are bound to albumin. Even so, the dienogest serum levels following administration of 2 mg reach very high values of about 50 ng/ml, which decrease again with a fairly short half-life of 9 hours ($t_{1/2\beta}$). The most important metabolic steps are reduction of the 3-oxo group, hydroxylation reactions, and conversion of the cyano group into a hydroxy or carbonic acid group. Dienogest is also aromatized to a very minor extent.

Tibolone

Tibolone is the 7α-methyl derivative of the old gestagen norethynodrel and, like this substance, a prodrug. Whilst norethynodrel is converted into norethisterone after administration, tibolone is converted into 7α-methyl norethisterone (Fig. 6). Like norethynodrel, tibolone has a mild androgenic and marked estrogenic effect. The estrogenic effects are thought by the manufacturer to be due to the metabolites 3α- and 3β-hydroxy tibolone, which have a low binding affinity to the estrogen receptor. Since the serum levels of the two metabolites are unknown and it must be assumed that they are largely present as ineffective conjugates, their clinical significance is doubtful. Since both norethynodrel and norethisterone are aromatized to a minor degree, it cannot be excluded that tibolone and the resulting 7α-methyl norethisterone are also converted into an effective estrogen. Tibolone has no glucocorticoid or anti-mineralocorticoid effects, and no or very little proliferative effect on the endometrium. Following the administration of 2.5 mg, the unmodified tibolone reaches a maximum serum level of about 1 ng/ml. In the serum, tibolone and its metabolites are bound mainly to albumin only. The terminal half-life ($t_{1/2\beta}$) is 45 hours. Inactivation is caused primarily by hydroxylation reactions. Although the 7α-methyl group blocks reduction of the double bond on C4, it does not block aromatization – as was shown in the example of 7α-methyl nortestosterone [31].

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