Pharmacokinetics of gestodene and ethinyl estradiol after oral administration of a monophasic contraceptive

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The pharmacokinetic and protein-binding properties of gestodene and ethinyl estradiol have been investigated after single and multiple dosing in several studies in 83 healthy, young women. After oral administration, gestodene is completely absorbed and bioavailable and exhibits dose-linear pharmacokinetics. During long-term pill use, serum levels of gestodene were four to five times higher than after single administration, showing a periodic increase from day 1 to day 10 during each cycle. Ultrafiltration studies revealed that 75.3% of total serum gestodene is bound to sex hormone-binding globulin, 24.1% is bound to albumin, and only 0.6% is not protein bound. Thus gestodene levels during steady state are explained by an increase in sex hormone-binding globulin as a result of concomitant administered ethinyl estradiol and a specific binding of gestodene to this protein. Serum levels of ethinyl estradiol during single and multiple administration were identical and were not different from those observed with another preparation containing 30 μg of ethinyl estradiol. (AM J OBSTET GYNECOL 1990;163:1414-20.)

Key words: Ethinyl estradiol, gestodene, monophasic contraceptive

Progestins and estrogens in oral contraceptives are either drugs, which are, per se, pharmacologically active, or prodrugs, which must be converted into the active compound by the organism. Most progestins used in oral contraception are of the 19-nortestosterone type (Fig. 1). Norethisterone, as the first compound available, is still one of the most widely used progestins and is the active principle of several prodrugs (noretisterone acetate, norethynodrel, ethynodiol diacetate, and lynestrenol).

Changing the methyl residue at C13 to an ethyl group led to norgestrel and its solely active enantiomer levonorgestrel (α (-) norgestrel), whose progestogenic activity is approximately 10-fold higher than that of norethisterone.1,4 The progestins of the so-called third generation are desogestrel, norgestimate, and the latest development, gestodene. Desogestrel and norgestimate are both prodrugs. Desogestrel is activated in the body by conversion into 3-ketodesogestrel; norgestimate is converted by biotransformation into several metabolites—one, of which the most important is probably levonorgestrel.

After oral administration of a contraceptive pill, a series of events precede or run in parallel while the active ingredients reach their site of action. A necessary prerequisite for drug absorption is the disintegration of the tablet in the gastrointestinal tract and the dissolution of the active ingredients. After absorption and first passage in the liver, the active ingredients are bound to transport proteins in the plasma and are distributed throughout the body by way of the circulation. Parallel to these distribution processes, the compounds are metabolically degraded and excreted with the urine and the bile. Pharmacokinetics describes these processes quantitatively by monitoring drug and metabolite levels in blood and excreta.

This article presents the pharmacokinetic behavior of gestodene in humans.

Material and methods

Subjects and design of trials. Tables I and II summarize the most important pharmacokinetic studies with gestodene in human volunteers.

Single-dose studies. In the single-dose study by Düsterberg et al., absorption, distribution, biotransformation, and excretion were investigated after intravenous and oral administration of 50 and 300 μg of carbon 14–gestodene (14C-label in the ethinyl group) as a solution in propanediol physiologic saline solution (10/90 v/v) and as micronized substance together with lactose.

In the study by Täuber et al.,2 basic pharmacokinetic parameters of gestodene, absolute bioavailability, and dose linearity of pharmacokinetics were investigated in a fourfold changeover design in six young women. In a third trial plasma levels of ethinyl estradiol were studied in 18 young female volunteers receiving a single dose of Femovan (gestodene, 75 μg + ethinyl estradiol, 30 μg; Schering Ag, Berlin, West Germany) and Marvelon (desogestrel, 150 μg + ethinyl estradiol, 30 μg; Organon, Oss, The Netherlands) in a crossover design.3 Both preparations contained 30 μg of ethinyl estradiol.

Multiple-dose studies. Unlike most other drugs,
plasma levels of 19-nortestosterone–type progestins during multiple dosing cannot be predicted from single-dose pharmacokinetics. This is due to the induction of sex hormone–binding globulin (SHBG) by the concomitant administration of ethinyl estradiol and specific binding of 19-nortestosterone–type progestins to SHBG.\(^1\)

In three studies the plasma or serum levels of gestodene and also those of SHBG and cortisol-binding globulin have been followed over longer time spans.\(^7\)–\(^9\) In the last study the protein-binding characteristics of progestins were also analyzed, comparing gestodene with 3-ketodesogestrel.\(^9\)

**Assays.** Total concentrations of gestodene and ethinyl estradiol in plasma or serum were determined after diethyl ether extraction by specific radioimmunoassays developed in the research laboratories of Schering AG.\(^5\)–\(^9\) SHBG, cortisol-binding globulin, and cortisol levels were measured with commercial kits.\(^9\)

Free fraction, albumin, and SHBG-bound proportions of sex steroids were determined after spiking of ex vivo samples with \(^3\)H-gestodene, \(^3\)H-ketodesogestrel, or \(^3\)H–ethinyl estradiol (specific radioactivity >1.5 TBq/mmol) by means of an ultrafiltration method similar to that described by Kuhnz et al.\(^9\) and Hammond et al.\(^11\)

**Results**

**Gestodene: Single-dosing.** Distribution and elimination processes can be studied undisturbed by absorption phenomena only after intravenous administration. After single intravenous administration of 75 \(\mu\)g as solution, the concentration of gestodene in the plasma declined in three different phases for which half-lives of 10 ± 7 minutes, 1.5 ± 1.4 hours, and 10 ± 2.3 hours have been calculated (Fig. 2). First and second disposition half-lives mainly reflect distribution processes: the terminal half-life reflects the elimination of the drug from the plasma. Gestodene is highly bound to plasma proteins. The apparent volume of distribution of the central compartment \((V_c)\) was determined as 0.15 ± 0.06 L/kg. The volume of distribution during the terminal phase \((V_z)\) was 0.66 ± 0.43 L/kg.\(^2\)

Gestodene is almost entirely metabolized before it leaves the body. Less than 1% of the dose has been found unchanged in the urine. As with many other steroids, gestodene is metabolized into a large number of metabolites. Biotransformation pathways comprise reduction processes at the 3-keto group as well as at the \(\Delta^5\)-double bond, hydroxylation at various points of the molecule (including C1, C6, and C11), and conjugation (Fig. 3). By cochromatography of a metabolite isolated from dog urine, it was estimated that <4% of the dose was excreted in the form of a deethinylated,
Table I. Single-dose pharmacokinetic studies with gestodene and ethinyl estradiol in humans

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Dose (µg)</th>
<th>Route of administration</th>
<th>Pharmaceutical formulation</th>
<th>No. of subjects</th>
<th>Aim of study</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twofold crossover with 14C-ethinyl-GTD</td>
<td>50</td>
<td>IV</td>
<td>Propylene glycol Saline 10/90 v/v Capsule with lactose</td>
<td>3</td>
<td>14C-radioactivity in plasma and excreta Balance Metabolite pattern in plasma and urine</td>
<td>Düsterberg et al.²</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>PO</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fourfold crossover</td>
<td>75</td>
<td>IV</td>
<td>Propylene glycol Saline 10/90 v/v Tablet</td>
<td>6</td>
<td>GTD plasma levels Pharmacokinetic parameters Absolute bioavailability Dose dependency</td>
<td>Tauber et al.³</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>PO</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>75</td>
<td>PO</td>
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<tr>
<td></td>
<td>125</td>
<td>PO</td>
<td></td>
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<tr>
<td>Twofold crossover comparison Femovan</td>
<td>75</td>
<td>PO</td>
<td>Coated tablet</td>
<td>18</td>
<td>Serum levels of EE</td>
<td>Kühnz et al.⁴</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Marvelon</td>
<td>150*</td>
<td>PO</td>
<td>Tablet</td>
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</tr>
</tbody>
</table>

EE, Ethinyl estradiol; GTD, gestodene; IV, intravenous; PO, by mouth.
*Desogestrel.

Table II. Multiple-dose pharmacokinetic studies with gestodene and ethinyl estradiol in humans

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Dose (µg)</th>
<th>Route of administration</th>
<th>Pharmaceutical formulation</th>
<th>No. of subjects</th>
<th>Aim of study</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steady-state kinetics over 1 cycle</td>
<td>75</td>
<td>PO</td>
<td>Coated tablet</td>
<td>6</td>
<td>GTD, SHBG levels</td>
<td>Düsterberg et al.¹</td>
</tr>
<tr>
<td>Steady-state kinetics over 12 cycles</td>
<td>75</td>
<td>PO</td>
<td>Coated tablet</td>
<td>11</td>
<td>GTD, CBG, SHBG, days 1, 10, and 21</td>
<td>Kuhl et al.¹²</td>
</tr>
<tr>
<td>Long-term study† Group comparison, day 14 of cycle Femovan</td>
<td>75</td>
<td>PO</td>
<td>Coated tablet</td>
<td>39</td>
<td>Free and bound GTD, KDG, EE, CBG, SHBG, cortisol</td>
<td>Hümpele et al.⁷⁴</td>
</tr>
<tr>
<td></td>
<td>30</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Marvelon</td>
<td>150*</td>
<td>PO</td>
<td>Tablet</td>
<td>30</td>
<td></td>
<td>Kühnz et al.⁴</td>
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<td>30</td>
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</tbody>
</table>

CBG, Cortisol-binding globulin; EE, ethinyl estradiol; GTD, gestodene; KDG, 3-ketodesogestrel; SHBG, sex hormone–binding globulin; PO, by mouth.
*Desogestrel.
†Women had been taking Femovan or Marvelon for a period of 11 ± 5 months or 38 ± 24 months, respectively.

D-ring homoannulated metabolite. The metabolites of gestodene were mainly excreted with the urine with a half-life of approximately 24 hours. Total plasma clearance of gestodene, which represents metabolic clearance, was 0.80 ± 0.53 ml/min/kg (Table III).

After oral administration, gestodene is rapidly absorbed into the systemic circulation. Maximum concentrations are reached after 30 minutes to 3 hours. No absorption problems have been observed after dosage of the tablet formulation. One-hundred percent of the dose reaches the systemic circulation unchanged, as seen from a comparison of areas under the plasma concentration-time curve after oral and intravenous administration; that is, gestodene undergoes no mentionable first-pass metabolization during the absorption process. Plasma concentration-time profiles for gestodene after oral and intravenous administrations are strikingly similar and are essentially superimposable after the absorption process is finished (i.e., 2 to 3 hours after dosing).

The pharmacokinetics of gestodene are dose linear over the whole therapeutic range and cover all dosage forms of both monophasic and triphasic preparations; that is, underlying pharmacokinetic processes obey first-order mechanisms. Plasma levels of gestodene and areas under the plasma level curves increased linearly with the dose, whereas all other pharmacokinetic parameters, such as time of maximum concentration,

Table III. Pharmacokinetic parameters of gestodene after single intravenous administration of 75 µg to six women (mean ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>First disposition half-life (t_{1/2a})</td>
<td>0.16 ± 0.12 hr</td>
</tr>
<tr>
<td>Second disposition half-life (t_{1/2b})</td>
<td>1.53 ± 1.35 hr</td>
</tr>
<tr>
<td>Half-life (t_{D})</td>
<td>10.01 ± 2.33 hr</td>
</tr>
<tr>
<td>Total plasma clearance (CL)</td>
<td>0.80 ± 0.53 ml/min/kg</td>
</tr>
<tr>
<td>Area under curve (AUG)</td>
<td>35.2 ± 15.1 ng·hr/ml</td>
</tr>
<tr>
<td>Volume of distribution of central compartment (V_{cl})</td>
<td>0.15 ± 0.06 L/kg</td>
</tr>
<tr>
<td>Volume of distribution during terminal phase (V_{z})</td>
<td>0.66 ± 0.43 L/kg</td>
</tr>
</tbody>
</table>


half-lives, volumes of distribution, clearance rate, and bioavailability, were independent of the dose (Fig. 4 and Table IV).

Usually there is only one binding protein for drugs; that is, albumin, which is available in high concentrations in plasma or serum. Certain basic drugs are bound to the α-acidic glycoprotein. In 19-nortestosterone progestins but not in 21-progestins, another binding protein, the so-called SHBG that physiologically binds testosterone and estradiol, plays an important role.

Intake of ethinyl-containing oral contraceptives can lead to a gradual increase in SHBG concentration in the plasma. The extent of the SHBG increase depends on the estrogen-progestogen balance of a preparation, that is, on the dose of ethinyl estradiol and on the dose and nature of the progestin. Table V shows the nonprotein-bound fraction and the albumin- and SHBG-bound fraction of gestodene in women with basal (77 ± 28 nmol/L) and induced (186 ± 57 nmol/L) SHBG levels. A 2.4-fold increase in SHBG levels led to a decrease in the free fraction of gestodene, from 1.9% ± 0.3% to 0.6% ± 0.1%. This change in the
Table IV. Pharmacokinetic parameters of gestodene after single oral administration of 25, 75, and 125 µg as tablets together with 30 µg ethinyl estradiol (mean ± SD, n = 6)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25 µg</td>
</tr>
<tr>
<td>Maximum concentration (C_max), ng/ml</td>
<td>1.0 ± 0.4</td>
</tr>
<tr>
<td>Time of maximum concentration (t_max), hr</td>
<td>1.9 ± 1.2</td>
</tr>
<tr>
<td>Half-life of absorption (A) (t_(1/2)_A), hr</td>
<td>1.2 ± 0.65</td>
</tr>
<tr>
<td>Second disposition half-life (t_(1/2)_A2), hr</td>
<td>0.97 ± 0.7</td>
</tr>
<tr>
<td>Half-life (t_{1/2}), hr</td>
<td>13.94 ± 2.9</td>
</tr>
<tr>
<td>Area under curve (AUC), ng · hr/ml</td>
<td>10.6 ± 5.2</td>
</tr>
<tr>
<td>Fraction of dose systemically available (F)</td>
<td>0.88 ± 0.18</td>
</tr>
</tbody>
</table>


nonprotein-bound fraction is obviously caused by a redistribution of gestodene in the human body. At low SHBG levels, almost equal proportions were bound to albumin and SHBG, whereas in the induced SHBG state, the proportion bound to SHBG was more than threefold higher than the proportion bound to albumin.

A competition experiment with the serum of pregnant women confirms the results of the ex vivo-binding studies. The serum of pregnant women containing high levels of SHBG was loaded with ³H-dihydrotestosterone as ligand. The replacement of ³H-radioactivity by various progestins was measured as a function of their concentrations. Relative-binding affinity decreased in the order of gestodene > levonorgestrel > 3-ketodesogestrel (Muhn-Seipoldy HP. Unpublished results) (Fig. 5).

Gestodene: Multiple dosing. Oral contraceptives are taken long term in a regimen of a once daily for 3 weeks followed by a pill-free interval of 1 week. Because of the periodic increase of SHBG over each cycle and the specific binding of gestodene to this protein, serum levels of gestodene cannot be predicted by computer simulation from single-dose pharmacokinetic parameters.

Fig. 6 shows the time course of total gestodene trough levels and SHBG levels in a subject receiving the monophasic preparation over one cycle. Both compounds increased in the plasma up to days 8 to 10, at which time steady state was reached. During the intake-free intervals, gestodene but not SHBG achieved pretreatment values, owing to their different half-lives of 18 hours and 10 to 14 days, respectively.

In Fig. 7 average area under the curve values of total and free gestodene serum level curves determined in 11 women on days 1, 10, and 21 in cycles 1, 3, 6, and 12 are presented. The free levels are in a dynamic equilibrium with concentrations at the target tissues. The periodic increases in total gestodene concentrations and area under the curve values during each cycle are higher than the accumulation determined by the half-life and the dosing interval. Increases observed can be easily explained by the periodic increase in SHBG up to 300% above pretreatment levels and the high-specific binding of gestodene to this binding protein.

Ethinyl estradiol. Fig. 8 shows mean time course of
Table V. Binding of gestodene to human plasma proteins in women with basal and induced SHBG levels

<table>
<thead>
<tr>
<th></th>
<th>Single administration (n = 18)</th>
<th>Multiple administration (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonprotein bound, % unbound</td>
<td>1.9 ± 0.3</td>
<td>0.6 ± 0.1</td>
</tr>
<tr>
<td>Albumin, % bound</td>
<td>47.8 ± 7.5</td>
<td>24.1 ± 0.1</td>
</tr>
<tr>
<td>SHBG, % bound</td>
<td>50.3 ± 7.8</td>
<td>75.3 ± 9.1</td>
</tr>
<tr>
<td>SHBG concentration (nmol/L)</td>
<td>77 ± 28</td>
<td>180 ± 61</td>
</tr>
</tbody>
</table>


Table VI. AUC values of ethinyl estradiol after single dose and during long-term use of Femovan and Marvelon in pg · hr/ml

<table>
<thead>
<tr>
<th></th>
<th>Single-dose, intraindividual comparison</th>
<th>Long-term use, group comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Femovan</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (0-4 hr)</td>
<td>308 ± 83 (n = 18)</td>
<td>305 ± 115 (n = 39)</td>
</tr>
<tr>
<td>AUC (0-24 hr)</td>
<td>1002 ± 332† (n = 18)</td>
<td>1246 ± 468§ (n = 39)</td>
</tr>
<tr>
<td><strong>Marvelon</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (0-4 hr)</td>
<td>315 ± 77 (n = 18)</td>
<td>354 ± 139 (n = 30)</td>
</tr>
<tr>
<td>AUC (0-24 hr)</td>
<td>1001 ± 311† (n = 18)</td>
<td>1360 ± 541‡ (n = 30)</td>
</tr>
</tbody>
</table>

AUC, Area under the curve.
*Measured per average on day 14 of cycle after an average intake period of 11 (Femovan) and 38 (Marvelon) months.
†AUC calculations based on sampling points, 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours.
§AUC calculations based on sampling points 0, 0.5, 1, 2, 3, 4, and 24 hours.

Comment

The monophasic oral contraceptive combining gestodene and ethinyl estradiol provides complete and rapid absorption and bioavailability of gestodene with dose-linear pharmacokinetics. Plasma levels of ethinyl estradiol are no different from those observed with another preparation containing the same amount of ethinyl estradiol.

Periodic increases in the serum levels of gestodene are seen from day 1 through day 8 during each cycle. Gestodene is highly bound to plasma proteins. Slightly more than three fourths of total serum gestodene is bound to SHBG and nearly all the balance to albumin.

REFERENCES
Fig. 7. Areas (0 to 4 hours) under serum level curves of total (left ordinate) and free (right ordinate) concentration of gestodene on days 1, 10, and 21 of cycles 1, 3, 6, and 12 during intake of monophasic gestodene-coated tablets over a 1-year period (mean ± SD, n = 11). (Total AUC [0-4 hr] values from Kuhl H, Jung-Hoffman C, Heidt F. Contraception 1988;38:477-86.)

Fig. 8. Plasma levels of ethinyl estradiol in a group of 18 women taking a single dose of either Femovan (upper figure) or Marvelon (lower figure) in a crossover design (mean ± SD). (From Kuhnz W, Hümpel M, Schütt B, Louton T, Steinberg B, Gansau C. Horm Res 1990;33:35-9. by permission of S. Karger AG, Basel.)